EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2022
EMA/155595/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0107

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

ADA	anti-drug antibodies
AE	adverse event
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
Cavg(WX)	average concentration at Week X
CFR	Code of Federal Regulations
chemo	chemotherapy
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax(WX)	maximum concentration at Week X
CMBP	LabCorp Center for Molecular Biology and Pathology
Cmin(WX)	minimum concentration at Week X
CMH	Cochran-Mantel-Haenszel
CRC	colorectal cancer
CSR	clinical study report
CTC	common terminology criteria
CTLA-4	cytotoxic T-lymphocyte associated protein-4
DMC	data monitoring committee
dMMR	mismatch repair deficient
DOR	duration of response
EAC/OAC	Esophageal/oesophageal adenocarcinoma
EC/OC	esophageal cancer
ECOG	Eastern Cooperative Oncology Group
ECS	esophageal cancer subscale
eCRF	electronic case report form
EMA	European Medicines Agency
E-R	exposure-response
ESMO	European Society for Medical Oncology
FA	final analysis
FACT-E	Functional Assessment of Cancer Therapy-Esophageal
FACT-G7	Functional Assessment of Cancer Therapy - General cancer-related 7-item core mea
FDA	Food and Drug Administration
5-FU	5-fluorouracil
GC	gastric cancer
GEJC	gastroesophageal junction cancer
HCC	hepatocellular carcinoma
HR	hazard ratio
IA	interim analysis
ICH	International Conference on Harmonization
IHC	immunohistochemistry
IMAE	immune-mediated adverse event

ADA	anti-drug antibodies
IND	Investigational New Drug
ipi	ipilimumab
iPSP	initial pediatric study plan
IRRC	independent radiology review committee;
IRT	interactive response technology
IV	intravenous(ly)
KM	Kaplan-Meier
1L	first-line
2L	second-line
LEG	legally binding procedure
LPLV	last patient's last visit
MedDRA	Medical Dictionary for Regulatory Activities
MPM	malignant pleural mesothelioma
MSI-H	microsatellite instability-high
N	number of subjects
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute-Common Terminology
nivo	nivolumab
NSCLC	non-small cell lung cancer
OESIs	other events of special interest
ORR	objective response rate
OS	overall survival
OSCC	oesophageal squamous cell carcinoma
PD-(L)1	programmed death-(ligand) 1
PFS	progression-free survival
PFS2/TSST	progression-free survival after next line of treatment/time to second subsequent lin
PK	pharmacokinetics
PPK	population pharmacokinetics
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PS	performance status
QXW	every X weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
RMST	restricted mean survival time
ROW	rest of the world
SAE	serious adverse event
SAP	statistical analysis plan
(s)BLA	(supplemental) biologics license application
SAWP	Scientific Advice Working Party
SCCHN	squamous cell carcinoma of the head and neck
TCGA	The Cancer Genome Atlas Program
UC	urothelial carcinoma

ADA	anti-drug antibodies
US	United States
USPI	United States Prescribing Information
VAS	visual analog scale
WHO	World Health Organization

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 28 July 2021 an application for a variation.

The following changes were proposed:

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 in combination with fluoropyrimidine- and platinum-based combination chemotherapy the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) for OPDIVO based on study CA209648; 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 25.0 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision(s) 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/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 in oesophageal cancer from the CHMP on 28 May 2020 (EMEA/H/SA/2253/12/2020/II). The Scientific Advice pertained to the following clinical aspects:

Regarding amendments to an ongoing randomized Phase 3 study in adult patients with unresectable advanced, recurrent, or metastatic OSCC:

- Whether OS as a sole primary endpoint would enable a benefit/risk assessment;
- A change in the primary population from PD-L1 expressors to all randomized, for analysis of overall survival in the nivolumab in combination with ipilimumab arm.

At that time the MAH was strongly discouraged to amend the analysis plan as proposed/planned, bearing in mind that the trial was at a very late stage (i.e. a few months prior to the planned database

lock). The fact that the study is open label and its pivotal nature were also arguments against the proposed late changes that, even if followed from a statistical point of view (e.g. in terms of gain in power for the newly proposed primary comparisons), were anticipated to give raise to major issues in terms of credibility/integrity of the study at the time of assessment of the corresponding type II variation; notwithstanding the Applicant's claims that all changes were proposed based on external data. The MAH followed the scientific advice received and did not implement the changes they proposed during this SA.

1.1. Steps taken for the assessment of the product

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

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 July 2021
Start of procedure	14 August 2021
CHMP Rapporteur's preliminary assessment report circulated on	22 October 2021
PRAC Rapporteur's preliminary assessment report circulated on	22 October 2021
PRAC RMP advice and assessment overview adopted by PRAC on	28 October 2021
CHMP Rapporteur's updated assessment report circulated on	5 November 2021
Request for supplementary information adopted by the CHMP on	11 November 2021
MAH's responses submitted to the CHMP on	21 December 2021
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	28 January 2022
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	31 January 2022
PRAC RMP advice and assessment overview adopted by PRAC on	10 February 2022
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	18 February 2022
CHMP Opinion	24 February 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Oesophageal cancer (OC) is the eighth-most common cancer and the sixth-most common cause of death worldwide, with an estimated 604,100 new cases (3.1% of all cancers) and 544,076 cancer deaths (5.5% of all cancer deaths) (GLOBOCAN 2020). In the UE, oesophageal cancer is the 19th most common cancer (1.2% of all new cancers), although variability between countries is high and may reflect different prevalence of risk factors, use of screening and diagnostic methods. Around 53,000 new cases of OC were registered in Europe in 2020.

State the claimed therapeutic indication

Proposed indication

The MAH initially applied for the following indication:

"OPDIVO, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma."

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

"OPDIVO, in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression≥1%."

Dosage and administration

The recommended dose of nivolumab is 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W) administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy. Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Epidemiology and risk factors, screening tools/prevention

The two distinct histologic types of OC are squamous cell carcinoma (SCC) and adenocarcinoma (AC) (Abnet CC 2018). Globally, OSCC remains the predominant histological subtype (approximately 90% of total cases but around 65% in most European countries) (Wong MCS, 2018); however, the incidence of OSCC has been decreasing, while the incidence of OAC has been increasing rapidly, particularly in Western Europe, North America, and Australia. SCC continues to be the more common OC in Asia. Mortality rates associated with AC are rising and have surpassed those of SCC in several regions in the EU.

Oesophageal carcinoma is rare in young people and increases in incidence with age, peaking in the seventh and eighth decades of life. AC is three to four times as common in men as it is in women, whereas the sex distribution is more equal for SCC.

The main risk factors for OSCC in Western countries are smoking and alcohol consumption, whereas OAC predominantly occurs in patients with chronic gastro-oesophageal reflux disease and their risk is correlated with the patient's body mass index with a higher risk for obese people.

Aetiology and pathogenesis

Alcohol consumption, smoking and poor socioeconomical status represent major risk factors for OSCC. Differences in exposure to well established common risk factors, such as smoking and alcohol, genetic polymorphism in alcohol metabolism genes, and different levels of exposure to suspected risk factors, such as polycyclic aromatic hydrocarbons, may contribute to the observed regional differences in OSCC incidence.

The molecular biology of OSCC is not yet fully understood. Of note, comprehensive molecular analyses of OC by The Cancer Genome Atlas Program (TCGA) have shown that OSCC is molecularly distinct from OAC (Kim J. 2017). Based on these analyses, OSCC has stronger resemblance to other squamous tumours like SCCHN than to OAC, and consequently, OAC resembles gastric cancer more than OSCC. Squamous cell carcinomas are different from adenocarcinoma in genetic alterations, gene expression and DNA methylation profiles. Frequent alterations in cell cycle regulators, RTK/RAS/PI(3)K pathways and chromatin-modifying enzymes have been observed in OSCC and the patterns were different from those of OAC.

Clinical presentation, diagnosis and stage/prognosis

All patients with new dysphagia, gastrointestinal bleeding, recurrent aspiration or emesis, weight loss and/or loss of appetite should undergo an upper intestinal endoscopy. Approximately three-quarters of all ACs are found in the distal oesophagus, whereas SCCs occur more frequently in the proximal to middle oesophagus. The differentiation between SCC and AC is of prognostic and clinical relevance. Immunohistochemical stainings are recommended in poorly and undifferentiated cancers (G 3/4) according to WHO to differentiate between SCC and AC.

Approximately 50% of OCs will be locally or locoregionally advanced at diagnosis, and thus amenable to potentially curative loco-regional therapy. Five-year survival rates for all patients with OC have shown modest improvements over the past 35 years, from 5% in 1975 to approximately 20% for patients diagnosed in 2004. Five-year survival rates for loco-regionally advanced disease treated with surgery alone have been consistently poor, ranging from 6% to 26%.

Management

The management of OC often requires a multi-disciplinary approach, with treatment decisions involving surgical, radiation, and medical oncology expertise. Recommendations by treatment guidelines for OC are based on histology (i.e., SCC vs. AC). Patients with advanced or metastatic OSCC are generally treated with palliative intent with chemotherapy to extend survival, and with localized treatments, such as radiotherapy (including external radiation or brachytherapy), or endoscopic therapies, such as stents, for the symptomatic treatment of obstruction and dysphagia. Chemotherapy is typically offered to selected patients with good performance status, although its value is less proved than in AC, according to ESMO clinical practice guidelines (2016).

Cytotoxic chemotherapy has remained the mainstay treatment for advanced OSCC for many years. In the first-line (1L) setting, combination chemotherapies are routinely used. Although there are some differences, global guidelines are generally consistent and recommend the combination of a fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) with a platinum agent (cisplatin or oxaliplatin). The combination of cisplatin and fluorouracil is the only chemotherapy option which is supported by

data from a randomized Phase 2 trial in OSCC. In that trial which was conducted in Europe, patients (n=88) with locally advanced or metastatic OSCC were treated with cisplatin 100 mg/m^2, combined with 5-FU at a dose of 1000 mg/m^2 as a continuous infusion from days 1-5 or with cisplatin alone. Cisplatin in combination with 5-FU (vs. cisplatin alone) conferred a response rate of 35% (95% CI: 20, 54%) vs. 19% (95% CI: 8, 35%) and median survival of 7.6 vs. 6.4 months. Cisplatin may be substituted in clinical practice by oxaliplatin because of a more favourable safety profile and fluorouracil may be substituted by alternative fluoropyrimidines, such as capecitabine. This is encouraged by international treatment guidelines such as NCCN.

Recent findings from the KEYNOTE 590 study (median follow-up 10.8 months) showed that immune checkpoint inhibitor pembrolizumab in combination with chemotherapy in the 1L setting was superior to chemotherapy for OS and PFS in patients with locally advanced/unresectable or metastatic EAC, OSCC (73% of the study population), or Siewert type 1 GEJ adenocarcinoma. In the overall KEYNOTE-590 population, median OS was 12.4 months (95% CI: 10.5, 14.0) vs. 9.8 months (95% CI: 8.8, 10.8) with pembrolizumab plus chemotherapy vs. chemotherapy (HR=0.73 [95% CI: 0.62, 0.86]) and median PFS was 6.3 months (95% CI: 6.2, 6.9) vs. 5.8 months (95% CI: 5.0, 6.0), respectively (HR=0.65 [95% CI: 0.55, 0.76]). Based on these study findings, pembrolizumab (in combination with platinum- and fluoropyrimidine-based chemotherapy) received a Commission Decision on 24 June 2021 for the 1L treatment of locally advanced or metastatic oesophageal carcinoma (including OSCC) that is not amenable to surgical resection or definitive chemoradiation in patients whose tumours express PD-L1 with a CPS≥10 (Keytruda II/97).

Unmet medical need

OSCC is an aggressive disease with a poor prognosis; the global 5-year relative survival rate is <20%. For decades, platinum plus fluoropyrimidine-based chemotherapy was the only recommended 1L treatment for advanced or metastatic OSCC, resulting in poor survival (median OS <1 year). Despite the recent approval of pembrolizumab plus chemotherapy for 1L treatment of OSCC, there are still opportunities to advance new modalities and regimens that improve survival in this setting.

2.1.2. About the product

Nivolumab is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2. Tumours use PD-L1 expression as a defense or escape mechanism against the host's anti-tumour T-cell response; inhibiting PD-(L)1 restores the function of these anti-tumour T-cells which have become ineffective or suppressed. Therefore, the efficacy of PD-(L)1 inhibition relies on a pre-existing immune response. Nivolumab, as monotherapy, is approved for multiple indications, including for the treatment of patients with advanced or recurrent OSCC who received prior fluoropyrimidine- and platinum-based chemotherapy in the EU.

In the EU, nivolumab as monotherapy has been approved for the treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin's lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, oesophageal squamous cell carcinoma and adjuvant treatment of OC or GEJC. The combination of nivolumab with ipilimumab (Yervoy) has been approved for the treatment of melanoma, RCC, malignant pleural mesothelioma and dMMR or MSI-H colorectal cancer, and in combination with platinum-based chemotherapy for the first-line treatment of metastatic NSCLC. The combination of nivolumab with fluoropyrimidine- and platinum-based combination chemotherapy has been approved for the treatment of first-line HER-2 negative gastric, GEJ or oesophageal adenocarcinoma whose tumours express PD-L1 with CPS ≥ 5%, and the combination of nivolumab with cabozantinib has been approved for the first-line treatment of RCC.

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

Study CA209648, a Phase 3, open-label, randomized trial of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated oesophageal squamous cell carcinoma is the pivotal study for the current application (see section 4.4.2. Main study).

The MAH did seek Scientific Advice at the CHMP on the design of study CA209648, the pivotal trial for this application (EMEA/H/SA/2253/12/2020/II). Questions referred to the choice of endpoints and primary population (see section 1). The MAH overall followed the recommendations of the CHMP scientific advice.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

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.

- Tabular overview of clinical studies

Study/ Status	Population	Design	Endpoints	Test Drugs and Dose	Number of Subjects
CA209648 Ongoing Database lock: 01-Mar-2021 for the pre-specified analysis of the primary endpoints	Adults (≥ 18 years) with previously untreated advanced or metastatic OSCC	Phase 3, randomized, open-label, 3-arm study of **nivo+ipi** or **nivo+chemo** (fluorouracil+ cisplatin) vs **chemo** (fluorouracil+ cisplatin)	***Primary***: OS and PFS (per BICR) in all randomized subjects with tumor cell PD-L1 ≥ 1% ***Secondary:*** OS and PFS by BICR in all randomized subjects, ORR by BICR in all randomized subjects with tumor cell PD-L1 ≥ 1% and in all randomized subjects ***Key Exploratory:*** PFS, ORR, DOR, and PFS2/TSST by investigator, DOR by BICR Safety, Immunogenicity, PRO	**Nivo+Chemo Arm** Nivo 240 mg IV Q2W + fluorouracil 800 mg/m^2/day IV on Days 1-5 Q4W + cisplatin 80 mg/m^2 IV on Day 1 Q4W **Nivo+Ipi Arm** Nivo 3 mg/kg IV Q2W + ipi 1 mg/kg IV Q6W **Chemo Arm** Fluorouracil 800 mg/m^2/day IV on Days 1-5 Q4W + cisplatin 80 mg/m^2 IV on Day 1 Q4W	970 randomized subjects: 325 to nivo+ipi, 321 to nivo+chemo, and 324 to chemo

Abbreviations: Chemo - chemotherapy, DOR - duration of response, ipi - ipilimumab, IV - intravenous, nivo - nivolumab, ORR - objective response rate, OS - overall survival, OSCC - oesophageal squamous cell carcinoma, PFS - progression-free survival, PFS2/TSST - PFS after next line of treatment/ time to second subsequent line therapy, PRO - patient-reported outcomes, QXW - every X weeks

This clinical pharmacology document summarizes the human pharmacokinetics (PK), exposure-response (E-R), and immunogenicity data of nivolumab (OPDIVO®, BMS-936558, MDX-1106, ONO-4538) in support of the efficacious and safe use of nivolumab in combination with fluorouracil plus cisplatin for the first-line (1L) treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC).

2.3.2. Pharmacokinetics

The purpose of the pharmacometric analyses described in this document is to characterize the pharmacokinetics (PK) of nivolumab (BMS-936558, MDX-1106, ONO-4538) when administered in combination with ipilimumab (BMS-734016) or fluorouracil plus cisplatin and to characterize the PK of ipilimumab when administered in combination with nivolumab as the first-line (1L) treatment in subjects with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (OSCC) based on the data from Phase 3 Study CA209648.

Study CA209648 was a randomized, global Phase 3 study of nivolumab plus ipilimumab (nivo+ipi hereafter) or nivolumab in combination with fluorouracil plus cisplatin (nivo+chemo hereafter) versus fluorouracil and cisplatin chemotherapy (chemo hereafter) as 1L-therapy in unresectable advanced, recurrent, or metastatic OSCC.1 The clinical database lock occurred on 01-Mar-2021 and included data for subjects randomized to the nivo+ipi, nivo+chemo and chemo arms.

The treatment used in this study was nivolumab 3 mg/kg as a 30-minute infusion every 2 weeks (Q2W) plus ipilimumab 1 mg/kg as a 30-minute infusion every 6 weeks (Q6W), or nivolumab 240 mg as a 30-minute infusion Q2W in combination with fluorouracil 800 mg/m2/day as an intravenous (IV) continuous infusion on Day 1 through Day 5 (for 5 days) and cisplatin 80 mg/m2 as a 30- to 120-minute infusion on Day 1 of a 4-week cycle (every 4 weeks [Q4W]).

Pharmacokinetics in the target population

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

Protocol #: Title Study Population	Treatment	Planned Sample Size[a,b]	Nominal PK/PD Sampling Schedule	Analysis
MDX1106-01 (**CA209001**): Phase 1, open-label, multicenter, dose escalation study to evaluate the safety and pharmacokinetics of BMS936588 in subjects with selected refractory or relapsed malignancies *Adult subjects with pathologically verified and recurrent or treatment refractory colorectal adenocarcinoma, melanoma, NSCLC, castration-resistant prostate adenocarcinoma, and RCC*	Single-dose Phase (Cycle 1): 0.3, 1, 3, or 10 mg/kg IV infusion administered over 60 minutes Re-treatment Phase (Cycle 2): 0.3, 1, 3, or 10 mg/kg IV infusion administered over 60 minutes on Days 1 and 29; eligible subjects were treated with the same dose level as in the Single-dose Phase and could receive additional re-treatment cycles	39	Single-dose Phase: Predose, 30 minutes into dosing, immediately post-infusion, and 30 minutes, and 1, 2, 4, 6, 8, 24, 48, and 72 hours post-infusion end time; on Days 8, 15, 22, 29, 43, 57, 71, and 85 Re-treatment Phase: Predose and peak on treatment Days 1 and 29; single samples on Days 8, 15, 22, 36, 43, 57, 85, and 113	Nivo PPK
MDX1106-03 (**CA209003**): Phase 1, open-label, multicenter, multidose, dose-escalation study to evaluate the safety and tolerability of BMS-936588 in subjects with selected advanced or recurrent malignancies *Adult subjects with pathologically verified and advanced or recurrent and progressing colorectal adenocarcinoma, melanoma, NSCLC, castration-resistant prostate adenocarcinoma, and RCC*	0.1, 0.3, 1, 3, or 10 mg/kg IV infusion depending upon tumor type, administered over 60 minutes Q2W for up to twelve 8-week cycles	306	Pre-Amendment: Cycle 1: End of Infusion and pre-infusion levels on infusion days: Days 1, 15, 29, and 43 and Cycle 2: Single samples were collected Post-Amendment: Serial PK samples were collected from all subjects enrolled in 0.1, 0.3, and 1 mg/kg melanoma cohorts and first 16 subjects each from 3 and 10 mg/kg NSCLC cohorts. Cycle 1: Day 1 (after 60-minute infusion, 4, 8 hr), Days 2, 3, 5, 8, and 15; Cycle 2: Day 1 (pre-infusion); Cycle 3: Day 1 (pre-infusion, after 60-minute infusion), and Days 2, 3, 5, 8, and 15 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. Cycle 1: Day 1 (after 60-minute infusion) and Days 3, 8, and 15; Cycle 2: Day 1 (pre-infusion); Cycle 3: Day 1 (pre-infusion, after 60-minute infusion), and Days 3, 8, and 15 Each treatment cycle is comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 of the cycle	Nivo PPK Only include subjects with melanoma, NSCLC, and RCC
CA209017: An open-label, randomized Phase 3 trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic SQ NSCLC *Subjects with SQ NSCLC*	Dose: 3 mg/kg, 1-hr IV infusion Regimen: Q2W	132	Day 1 (Cycle 1) and Day 99 (Cycle 8), pre-infusion, after 60-minute infusion and pre-infusion at Cycles 2 and 3 and every 8th cycle after Cycle 8 Day 1 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 NSQ NSCLC *Subjects with NSQ NSCLC*	Dose: 3 mg/kg, 1-hr IV infusion Regimen: Q2W	287	Day 1 (Cycle 1) and Day 99 (Cycle 8), pre-infusion, after 60-minute infusion and pre-infusion at Cycles 2 and 3 and every 8th cycle after Cycle 8 Day 1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle	Nivo PPK
ONO-4538-07: A Phase 2, multicenter, open-label, uncontrolled study in patients with esophageal cancer *Subjects with esophageal cancer*	Dose: 3 mg/kg, 1-hr IV infusion Regimen: Every 2 weeks	60	Cycle 1: Predose and immediately post dose on Day 1, predose on Days 15 and 29 Cycles 2, 4, 5, 7, and 9: Predose on Day 1 and immediately post dose on Day 1 (Cycle 4) Follow-up visits Each cycle consists of 6 weeks	Nivo PPK
ONO-4538-24/CA209473: A Phase 3, multicenter, randomized, open-label study in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs *Subjects with esophageal cancer*	Dose: 240 mg, 30-min IV infusion Regimen: Every 2 weeks	195	Cycle 1: Predose on Day 1 and Day 29 Cycles 4 and 9: Predose on Day 1 Follow-up visits Each cycle consists of 6 weeks	Nivo PPK
CA209577: A randomized, multicenter, double blind, Phase III study of adjuvant nivolumab or placebo in subjects with resected esophageal, or gastroesophageal junction cancer *Subjects with resected esophageal, or gastroesophageal junction cancer*	Dose: 240 mg, 30-min IV infusion, every 2 weeks for 16 weeks followed by 480 mg Q4W	506	Cycles 1, 3, 10, 13, and 17: Predose on Day 1 Cycle 9: Predose on Day 1 and EOI	Nivo PPK
CA184008: A multi-center, single arm Phase 2 study of MDX-010 (BMS-734016)	Ipilimumab 10 mg/kg Q3W during induction period (Week 1, 4, 7, and 10), followed by Q12W during	144	Schedule A: On D1 and D43, pre-infusion and 90-min post-infusion. 3 additional samples were taken between D3-7 after Week 7 dose, D10-15	Ipi PPK

monotherapy in patients with previously treated unresectable stage III or IV melanoma *Previously treated unresectable Stage III or IV melanoma*	maintenance period (starting on Week 24)		after Week 7 dose and the predose sample on D64 Schedule B: On D1 and D43, predose and 90-min post-infusion, 24, 72 hr post-infusion, D8 (± 27 hrs), D15 (± 48 hrs); 2 additional predose samples were taken on D22 and D64	
CA184022: A randomized, double-blind, multi-center, Phase 2 fixed dose study of multiple doses of ipilimumab (MDX-010) monotherapy in patients with previously treated unresectable stage III or IV melanoma *Advanced Stage III or Stage IV melanoma, who were previously treated with any regimen except a CD-137 agonist or a CTLA4 inhibitor or agonist*	Ipi 0.3, 3, or 10 mg/kg Q3W during induction period (Weeks 1, 4, 7, and 10), followed by Q12W during maintenance period (starting on Week 24)	210	On D1 and D43 pre-infusion and 90-min post-infusion; 3 additional samples were taken between D3-7 (post dose) after Week 7 dose, D10-15 (post dose) after Week 7 dose and the predose sample on D64	Ipi PPK
CA209227: An open-label, randomized phase 3 trial of nivolumab, or nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in subjects with chemotherapy-naïve stage IV or recurrent non-small cell lung cancer (NSCLC) (CheckMate 227, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 227). Only Part 1 data will be used. *Chemotherapy-naïve stage IV or recurrent NSCLC*	**Arm A:** nivo 240 mg (30-min infusion) Q2W **Arm B/D:** nivo 3 mg/kg (30-min infusion) Q2W + ipi 1 mg/kg (60-min infusion) Q6W **Arm G:** nivo 360 mg (30-min infusion) Q3W in combination with chemotherapy **Arm H**: nivo 360 mg (30-min infusion) Q3W in combination with chemotherapy	1514	Arms B/D for ipi: Blood samples were collected at C1D1 (ipi dose 1), C2D1 (ipi dose 2), C4D1 (ipi dose 2), C10D1 (ipi dose 4), D1 of every 9th cycle after C10D1 until end of study treatment (or ipi doses 7, 10, 13 etc). First 2 follow-up visits (approximately up to 100 days from discontinuation of study drug)	Nivo and Ipi PPK
CA209743: A Phase III, randomized, open label trial of nivolumab in combination with ipilimumab versus pemetrexed with cisplatin or carboplatin as first line therapy in unresectable pleural mesothelioma (CheckMate 743: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 743) *Subjects with histologically proven diagnosis of advanced, unresectable malignant pleural mesothelioma (MPM) with determination of epithelioid vs non-epithelioid histology*	**Arm A:** nivolumab 3 mg/kg Q2W combined with ipilimumab 1 mg/kg Q6W until progression, unacceptable toxicity, or other reasons specified in the protocol	300	Blood samples were collected from Arm A at predose and EOI time points on C1D1, and at predose only on C1D15, C2D15, and C4D15 and at D15 of every 4th cycle (18 weeks) thereafter, until discontinuation or up to a maximum of 2 years of treatment (each cycle=6 weeks)	Nivo and Ipi PPK
CA209648: A randomized, multicenter, open-label, Phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine (hereafter referred to as nivo+chemo) versus oxaliplatin plus fluoropyrimidine (hereafter referred to as chemo) in subjects with previously untreated advanced or metastatic gastroesophageal junction cancer (GEJC), gastric cancer (GC) or esophageal adenocarcinoma cancer (EAC). *Subjects with advanced or metastatic gastric or gastroesophageal junction or esophageal adenocarcinoma*	Dose for Arm A: nivo 3 mg/kg, 30-min infusion, Q2W and ipi 1 mg/kg, 30-min infusion, Q6W Or Dose for Arm B: nivo 240 mg, 30-minute infusion, Q2W, fluorouracil 800 mg/m²/day IV continuous infusion on Day 1 through Day 5 (for 5 days), and cisplatin 80 mg/m², 30- to 120-min infusion[c] on Day 1 of 4-week cycle	313 per arm (nivolumab plus chemotherapy, nivolumab plus ipilimumab)	For Arm A (nivo 3 mg/kg Q2W+ ipi 1 mg/kg Q6W): One Cycle = Every 2 weeks (nivo Q2W, ipi Q6W) Cycles 1, 2, 4,5, 7, 9, 15, 23, 35, and 47: Predose on Day 1 For Arm B (nivo 240 mg, Q2W + fluorouracil 800 mg/m²/day and cisplatin 80 mg/m²): One Cycle = Every 4 weeks (nivo Q2W) Cycles 1, 2, 3, 7, 9, 17, and 25: Predose on Day 1	Nivo and Ipi PPK, E-R efficacy, and E-R safety

[a] As per protocol.

[b] Only nivolumab treated subjects are included

[c] Subjects are allowed to receive treatment with cisplatin 80 mg/m² as an IV infusion over a period of longer than 120 minutes if it is in accordance with local standard of care/local label.

Abbreviations: C = cycle; D = day; DBL = database lock; EOI = end of infusion; E-R = exposure-response; GC = gastric cancer; hr = hour(s); IV = intravenous; min = minute(s); Ipi = ipilimumab, Nivo = nivolumab; NSCLC = non-small cell lung cancer; NSQ NSCLC = non-squamous cell non-small cell lung cancer; PK = pharmacokinetic(s); PK/PD = pharmacokinetic/pharmacodynamic; PPK = population pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks; Q12W = every 12 weeks; RCC = renal cell carcinoma; SCLC = small cell lung cancer; SQ NSCLC = squamous cell non-small cell lung cancer.

Nivolumab

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

Study	# Subjects			
	Nivolumab Treated	PK Database (eToolbox)[a]	Flagged	Included (% of Subjects in eToolbox)
MDX1106-01 (CA209001)	39	39	0	39 (100)
MDX1106-03 (CA209003)	306	310	6	304 (98.1)
ONO-4538-07	65	65	0	65 (100)
CA209017	125	127	2	125 (98.4)
CA209057	280	282	2	280 (99.3)
CA209227	1514	1418	112	1306 (92.1)
ONO-4538-24 (CA209473)	186	186	0	186 (100)
CA209577	494	526	32	494 (93.9)
CA209648	632	626	51	575 (91.9)
CA209743	300	300	3	297 (99)
Total	3941	3879	208	3671 (94.6)

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

Abbreviations: PK = pharmacokinetic; PPK = population pharmacokinetic.

Analysis-Directory: /global/pkms/data/CA/209/ec-11/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-11-escc-pmr-tfl-section-3.Rmd

Source: Analysis-Directory/d1pk-nivo/tables/rmd-rtf/data-disposition-table-subjects-v01.rtf

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

Study	Number of Samples In PK Database[a]	Number of Samples Excluded						Samples Included in Analysis (%)[d]
		LLOQ[b]	Day 1 Predose	Missing Dose or Sample Information	Conc > 2000 µg/mL	Duplicate Samples at Same Time (Set Up for NCA)	Other[c]	
MDX1106-01 (CA209001)	915	42	40	33	0	0	0	800 (87.4)
MDX1106-03 (CA209003)	3733	74	331	32	2	76	0	3218 (86.2)
ONO-4538-07	431	3	65	0	0	1	0	362 (84.0)
CA209017	585	8	119	4	0	0	0	454 (77.6)
CA209057	1355	15	264	16	0	0	0	1060 (78.2)
CA209227	4828	30	1170	76	0	0	6	3546 (73.4)
ONO-4538-24 (CA209473)	618	0	184	0	0	0	0	434 (70.2)
CA209577	2503	2	507	8	1	1	0	1984 (79.3)
CA209648	2413	2	608	5	0	0	0	1798 (74.5)
CA209743	1518	31	286	25	0	0	0	1176 (77.5)
Total	18899	207	3574	199	3	78	6	14832 (78.5)

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

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

[c] PK samples collected using incorrect kit and PK samples from a subject with indication different from the protocol.

[d] % samples included in analysis =100 * (number of samples in PK database - number of samples excluded)/ number of samples in PK database for each respective study.

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

Analysis-Directory: /global/pkms/data/CA/209/ec-11/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-11-escc-pmr-tfl-section-3.Rmd

Source: Analysis-Directory/d1pk-nivo/tables/rmd-rtf/data-disposition-table-samples-v01.rtf

Table 3.3.1.5-1: Summary of Baseline Covariates by Subject Population in the Nivolumab Population Pharmacokinetic Analysis Dataset

Subject Characteristics		2L NSCLC	2L+ EC	ADJ EC/GEJC	1L ESCC	1L NSCLC	1L MESO	Others[a]	Overall
Age (years)	Mean (SD)	62.2 (9.18)	62.6 (8.23)	60.5 (9.25)	62.5 (9.18)	63 (9.79)	68.7 (8.53)	60.9 (12.2)	62.8 (9.68)
	Median	62	63	62	63	64	69	61	64
	Min, Max	37, 85	37, 82	26, 82	28, 90	26, 87	32, 85	29, 85	26, 90
	n	539	251	474	575	1306	297	209	3651
	Missing, n (%)	0 (0)	0 (0)	20 (4.05)	0 (0)	0 (0)	0 (0)	0 (0)	20 (0.545)
Baseline Body Weight (kg)	Mean (SD)	73.9 (16.3)	55.2 (10)	71.5 (16.2)	58.6 (11.9)	70.8 (15.8)	73.1 (14.9)	85 (20)	69.4 (16.9)
	Median	71.6	55.1	70.8	58	69	71.9	82.4	67.7
	Min, Max	41.6, 158	34.1, 83.1	34.5, 119	25.7, 125	36.8, 131	40, 123	44.1, 153	25.7, 158
	n	538	251	494	575	1304	297	209	3668
	Missing, n (%)	1 (0.186)	0 (0)	0 (0)	0 (0)	2 (0.153)	0 (0)	0 (0)	3 (0.0817)
Baseline GFR (mL/min/1.73 m^2)	Mean (SD)	82.7 (19.6)	86.8 (17.1)	94.7 (14.4)	95.8 (12.6)	90.8 (16.9)	86.5 (15.4)	79.4 (20.3)	89.6 (17.3)
	Median	84.5	91.4	95.7	95.9	93.5	88.8	82.6	92.4
	Min, Max	31.2, 135	31.2, 123	39.3, 136	50.1, 145	25.1, 158	35, 125	34.5, 132	25.1, 158
	n	537	251	471	574	1301	296	206	3636
	Missing, n (%)	2 (0.371)	0 (0)	23 (4.66)	1 (0.174)	5 (0.383)	1 (0.337)	3 (1.44)	35 (0.953)
Baseline Serum Albumin (g/dL)	Mean (SD)	3.92 (0.487)	3.94 (0.429)	3.96 (0.388)	3.9 (0.519)	3.91 (0.496)	3.66 (0.612)	4.09 (0.507)	3.91 (0.5)
	Median	4	3.9	4	4	4	3.8	4.1	4
	Min, Max	1.9, 5.2	2.7, 5.2	2.7, 5.1	2.2, 5.2	1.5, 5.2	1.7, 5	2.3, 5.1	1.5, 5.2
	n	526	251	466	554	1292	293	206	3588
	Missing, n (%)	13 (2.41)	0 (0)	28 (5.67)	21 (3.65)	14 (1.07)	4 (1.35)	3 (1.44)	83 (2.26)
Baseline Lactate Dehydrogenase (U/L)	Mean (SD)	330 (264)	230 (225)	186 (70.7)	243 (190)	297 (232)	221 (97.5)	317 (378)	269 (224)
	Median	238	192	167	195	232	193	199	206
	Min, Max	98, 3080	101, 3420	81, 567	67, 3410	74, 3600	99, 701	91, 2980	67, 3600
	n	534	251	484	571	1293	294	204	3631
	Missing, n (%)	5 (0.928)	0 (0)	10 (2.02)	4 (0.696)	13 (0.995)	3 (1.01)	5 (2.39)	40 (1.09)

Subject Characteristics		2L NSCLC	2L+ EC	ADJ EC/GEJC	1L ESCC	1L NSCLC	1L MESO	Others[a]	Overall
Combination Treatment, n (%)	Nivo	539 (100)	251 (100)	494 (100)	0 (0)	328 (25.1)	0 (0)	209 (100)	1821 (49.6)
	Nivo+Ipi	0 (0)	0 (0)	0 (0)	289 (50.3)	484 (37.1)	297 (100)	0 (0)	1070 (29.1)
	Nivo+Chemo	0 (0)	0 (0)	0 (0)	286 (49.7)	494 (37.8)	0 (0)	0 (0)	780 (21.2)
Baseline Performance Status, n (%)	0	136 (25.2)	122 (48.6)	292 (59.1)	278 (48.3)	478 (36.6)	113 (38)	113 (54.1)	1532 (41.7)
	1	399 (74)	129 (51.4)	202 (40.9)	297 (51.7)	824 (63.1)	184 (62)	92 (44)	2127 (57.9)
	2	4 (0.742)	0 (0)	0 (0)	0 (0)	3 (0.23)	0 (0)	4 (1.91)	11 (0.3)
	3	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.0766)	0 (0)	0 (0)	1 (0.0272)
Race, n (%)	White	489 (90.7)	5 (1.99)	403 (81.6)	135 (23.5)	976 (74.7)	260 (87.5)	190 (90.9)	2458 (67)
	Black/African American	23 (4.27)	0 (0)	4 (0.81)	3 (0.522)	11 (0.842)	0 (0)	14 (6.7)	55 (1.5)
	Asian	14 (2.6)	246 (98)	77 (15.6)	421 (73.2)	291 (22.3)	26 (8.75)	3 (1.44)	1078 (29.4)
	Others	9 (1.67)	0 (0)	10 (2.02)	12 (2.09)	25 (1.91)	5 (1.68)	2 (0.957)	63 (1.72)
	Unknown	2 (0.371)	0 (0)	0 (0)	4 (0.696)	3 (0.23)	6 (2.02)	0 (0)	15 (0.409)
	Missing	2 (0.371)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.0545)
Sex, n (%)	Male	326 (60.5)	212 (84.5)	417 (84.4)	471 (81.9)	898 (68.8)	229 (77.1)	144 (68.9)	2697 (73.5)
	Female	213 (39.5)	39 (15.5)	77 (15.6)	104 (18.1)	408 (31.2)	68 (22.9)	65 (31.1)	974 (26.5)
Immunogenicity [b] by Visit Level, N (%)	Negative	1988 (75.7)	0 (0)	1226 (61.8)	1651 (91.8)	3110 (87.7)	859 (73)	1529 (52.6)	10363 (69.9)
	Positive	166 (6.32)	0 (0)	32 (1.61)	130 (7.23)	408 (11.5)	120 (10.2)	69 (2.38)	925 (6.24)
	Missing	473 (18)	796 (100)	726 (36.6)	17 (0.945)	28 (0.79)	197 (16.8)	1307 (45)	3544 (23.9)

[a] Others include subjects with colorectal cancer (CRC), melanoma (MEL), prostate cancer, renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC) in Studies CA209001, CA209003, and CA209227.

[b] Immunogenicity was not a baseline covariate and was summarized by visit level.

Abbreviations: 1L = first-line; 2L = second-line; Adj = adjuvant; Chemo = chemotherapy; EC = esophageal cancer; EC/GEJC = esophageal cancer or gastroesophageal junction cancer; ESCC = esophageal squamous cell carcinoma; Ipi = ipilimumab; GFR = glomerular filtration rate; Max = maximum; MESO = mesothelioma; Min = minimum; N = number of observations; n = number of subjects; Nivo = nivolumab; NSCLC = non-small cell lung cancer; SD = standard deviation.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-3.Rmd

Source: Analysis-Directory/d1pk-nivo/tables/rmd-rtf/stat-covs-bypop-v01.rtf

Table 3.3.1.5-2: Summary of Baseline Covariates by Nivolumab Treatment in Study CA209648

Subject Characteristics		Nivo 240 mg Q2W + Chemo	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W	Overall
Age [years]	Mean (SD)	62.6 (9.18)	62.4 (9.19)	62.5 (9.18)
	Median	63	63	63
	Min, Max	40, 90	28, 81	28, 90
	5th, 95th	47, 76	47, 75	47, 76
	n	286	289	575
	Missing, n (%)	0 (0)	0 (0)	0 (0)
Baseline Body Weight [kg]	Mean (SD)	58.2 (12.5)	59 (11.2)	58.6 (11.9)
	Median	57.4	58.2	58
	Min, Max	29.6, 125	25.7, 104	25.7, 125
	5th, 95th	41.5, 79	43.4, 78.9	42.1, 79
	n	286	289	575
	Missing, n (%)	0 (0)	0 (0)	0 (0)
Baseline GFR [mL/min/1.73 m^2]	Mean (SD)	96.3 (12.6)	95.2 (12.7)	95.8 (12.6)
	Median	96.7	94.7	95.9
	Min, Max	62.6, 145	50.1, 145	50.1, 145
	5th, 95th	73.6, 116	75.4, 116	73.9, 116
	n	285	289	574
	Missing, n (%)	1 (0.35)	0 (0)	1 (0.174)
Baseline Serum Albumin [g/dL]	Mean (SD)	3.89 (0.515)	3.9 (0.524)	3.9 (0.519)
	Median	3.9	4	4
	Min, Max	2.2, 5.02	2.3, 5.2	2.2, 5.2
	5th, 95th	3, 4.61	2.9, 4.6	2.9, 4.6
	n	270	284	554
	Missing, n (%)	16 (5.59)	5 (1.73)	21 (3.65)
Baseline Lactate Dehydrogenase [U/L]	Mean (SD)	242 (160)	243 (215)	243 (190)
	Median	193	198	195
	Min, Max	87, 1980	67, 3410	67, 3410
	5th, 95th	130, 468	128, 452	128, 456
	n	285	286	571
	Missing, n (%)	1 (0.35)	3 (1.04)	4 (0.696)
Age Group, n (%)	< 65 years	154 (53.8)	161 (55.7)	315 (54.8)
	≥ 65 years	132 (46.2)	128 (44.3)	260 (45.2)

Table 3.3.1.5-2: Summary of Baseline Covariates by Nivolumab Treatment in Study CA209648

Subject Characteristics		Nivo 240 mg Q2W + Chemo	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W	Overall
Body Weight Group, n (%)	≤ 50 kg	80 (28)	59 (20.4)	139 (24.2)
	> 50 - 70 kg	160 (55.9)	185 (64)	345 (60)
	> 70 kg	46 (16.1)	45 (15.6)	91 (15.8)
Race, n (%)	Asian	210 (73.4)	211 (73)	421 (73.2)
	Others	3 (1.05)	9 (3.11)	12 (2.09)
	Unknown	3 (1.05)	1 (0.346)	4 (0.696)
	White	70 (24.5)	65 (22.5)	135 (23.5)
	Black/African American	0 (0)	3 (1.04)	3 (0.522)
Primary Chinese Ethnicity, n (%)	Chinese (Primary)	48 (16.8)	43 (14.9)	91 (15.8)
	Non-Chinese Asian	141 (49.3)	144 (49.8)	285 (49.6)
	Non-Asian	73 (25.5)	77 (26.6)	150 (26.1)
	Chinese (Non-Primary)	21 (7.34)	24 (8.3)	45 (7.83)
	Missing	3 (1.05)	1 (0.346)	4 (0.696)
Secondary Chinese Ethnicity, n (%)	Chinese (Secondary)	67 (23.4)	65 (22.5)	132 (23)
	Non-Chinese Asian	141 (49.3)	144 (49.8)	285 (49.6)
	Non-Asian	73 (25.5)	77 (26.6)	150 (26.1)
	Chinese (Non-Secondary)	2 (0.699)	2 (0.692)	4 (0.696)
	Missing	3 (1.05)	1 (0.346)	4 (0.696)
Japanese Ethnicity, n (%)	Japanese	116 (40.6)	120 (41.5)	236 (41)
	Non-Japanese Asian	94 (32.9)	91 (31.5)	185 (32.2)
	Non-Asian	73 (25.5)	77 (26.6)	150 (26.1)
	Missing	3 (1.05)	1 (0.346)	4 (0.696)
Region, n (%)	Japan/Korea/Taiwan	169 (59.1)	169 (58.5)	338 (58.8)
	Rest of Asia	40 (14)	40 (13.8)	80 (13.9)
	Rest of World	77 (26.9)	80 (27.7)	157 (27.3)
Sex, n (%)	Male	228 (79.7)	243 (84.1)	471 (81.9)
	Female	58 (20.3)	46 (15.9)	104 (18.1)
Baseline Performance Status, n (%)	0	139 (48.6)	139 (48.1)	278 (48.3)
	1	147 (51.4)	150 (51.9)	297 (51.7)

Table 3.3.1.5-2: Summary of Baseline Covariates by Nivolumab Treatment in Study CA209648

Subject Characteristics		Nivo 240 mg Q2W + Chemo	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W	Overall
Disease Status at Current Diagnosis, n (%)	Recurrent-Loco-Regional	18 (6.29)	24 (8.3)	42 (7.3)
	Recurrent-Distant	63 (22)	64 (22.1)	127 (22.1)
	De Novo Metastatic	164 (57.3)	171 (59.2)	335 (58.3)
	Unresectable Advanced	41 (14.3)	30 (10.4)	71 (12.3)
Smoking Status, n (%)	Never	51 (17.8)	43 (14.9)	94 (16.3)
	Current/Former	235 (82.2)	246 (85.1)	481 (83.7)
Alcohol Status, n (%)	Never	60 (21)	55 (19)	115 (20)
	Current/Former	226 (79)	234 (81)	460 (80)
Number of Organs With Metastases at Base, n (%)	≤ 1	143 (50)	141 (48.8)	284 (49.4)
	≥ 2	143 (50)	148 (51.2)	291 (50.6)
Prior Surgery, n (%)	Yes	191 (66.8)	197 (68.2)	388 (67.5)
	No	95 (33.2)	92 (31.8)	187 (32.5)
Prior Radiotherapy, n (%)	Yes	45 (15.7)	67 (23.2)	112 (19.5)
	No	241 (84.3)	222 (76.8)	463 (80.5)
PD-L1 Expression (1% Cutoff), n (%)	Negative	145 (50.7)	145 (50.2)	290 (50.4)
	Positive	141 (49.3)	141 (48.8)	282 (49)
	Missing	0 (0)	3 (1.04)	3 (0.522)
Immunogenicity[a] by visit level, N (%)	Negative	775 (96.6)	876 (88)	1651 (91.8)
	Positive	19 (2.37)	111 (11.1)	130 (7.23)
	Missing	8 (0.998)	9 (0.904)	17 (0.945)

[a] Immunogenicity was not a baseline covariate and was summarized by visit level.

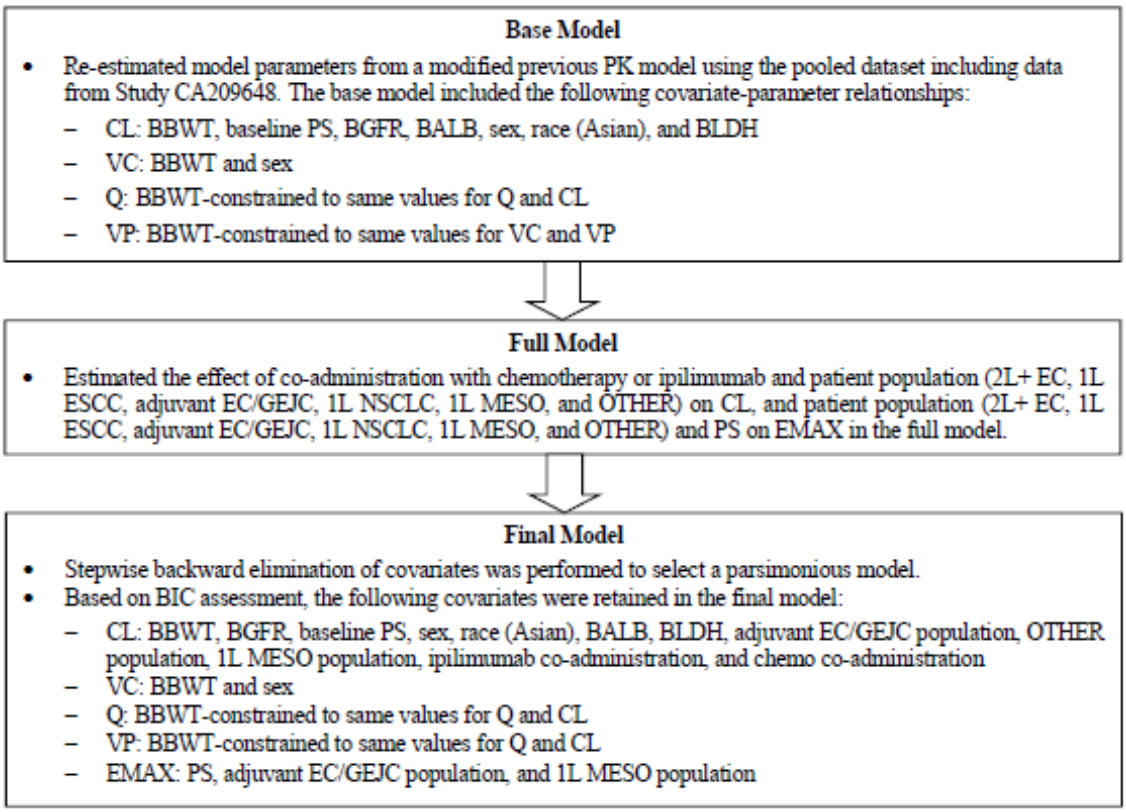
Abbreviations: Chemo = chemotherapy; GFR = glomerular filtration rate; Ipi = ipilimumab; Max = maximum; Min = minimum; n = number of subjects; Nivo = nivolumab; PD-L1 = Programmed death ligand-1; Q2W = every 2 weeks; Q6W = every 6 weeks; SD = standard deviation.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-3.Rmd

Source: Analysis-Directory/d1pk-nivo/tables/rmd-rtf/stat-covs-s648-v01.rtf

Figure 5.1.1-1: Schematic Overview of the Population Pharmacokinetic Model Development for Nivolumab



Final model of Nivolumab

The final model for nivolumab was developed from the full model by performing a stepwise backward elimination of the covariate effects of the full model (co-administration with chemotherapy or ipilimumab and subject population on CL, and subject population and PS on Emax) to determine a parsimonious model. Parameter estimates of the final model following backward elimination are presented in Table 5.1.1.3-1. The condition number of the final model was 309, indicating there was no evidence for ill-conditioning.

Table 5.1.1.3-1: Parameter Estimates of the Nivolumab Final Population Pharmacokinetic Model

Name [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval (Bootstrap Derived)[d]
		Fixed Effects		
$CL0_{REF}$ [mL/h][e]	θ_1	12.1	0.359 (2.96)	11.4 - 12.8
VC_{REF} [L][e]	θ_2	4.39	0.0457 (1.04)	4.3 - 4.48
Q_{REF} [mL/h][e]	θ_3	39.6	4.46 (11.2)	31.3 - 49.7
VP_{REF} [L][e]	θ_4	2.59	0.121 (4.66)	2.37 - 2.83
CL_{BBWT}[f]	θ_7	0.489	0.0308 (6.31)	0.432 - 0.552
CL_{BGFR}[f]	θ_8	0.153	0.0274 (17.9)	0.0969 - 0.205
CL_{SEX}[g]	θ_9	-0.181	0.0142 (7.84)	(-0.207) - (-0.153)
CL_{PS}[g]	θ_{10}	0.126	0.0167 (13.2)	0.0931 - 0.163
CL_{RAAS}[g]	θ_{11}	-0.116	0.0143 (12.3)	(-0.142) - (-0.088)
CL_{BALB}[f]	θ_{12}	-0.861	0.047 (5.46)	(-0.951) - (-0.763)
CL_{BLDH}[f]	θ_{13}	0.287	0.0681 (23.7)	0.153 - 0.427
CL_{POPOTH}[g]	θ_{14}	0.0976	0.0324 (33.3)	0.0296 - 0.158
$CL_{POPADJEC/GEJC}$	θ_{15}	-0.137	0.0232 (16.9)	(-0.186) - (-0.0888)
VC_{BBWT}[f]	θ_{16}	0.621	0.0293 (4.72)	0.562 - 0.674
VC_{SEX}[g]	θ_{17}	-0.187	0.0222 (11.9)	(-0.233) - (-0.144)
$EMAX_{REF}$	θ_{18}	-0.387	0.0355 (9.16)	(-0.457) - (-0.317)
T50 [h]	θ_{19}	1400	69.1 (4.94)	1270 - 1550
HILL	θ_{20}	2.12	0.167 (7.88)	1.81 - 2.46
$CL_{POP1LMESO}$[g]	θ_{21}	0.116	0.0289 (25)	0.0553 - 0.169
CL_{CO-IPI}[g]	θ_{22}	0.0766	0.0159 (20.7)	0.0471 - 0.11

Table 5.1.1.3-1: Parameter Estimates of the Nivolumab Final Population Pharmacokinetic Model

Name [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval (Bootstrap Derived)[d]
$CL_{CO\text{-}CHEMO}$[g]	θ_{23}	-0.123	0.0164 (13.3)	(-0.158) - (-0.0909)
$EMAX_{PS}$[g]	θ_{24}	-0.109	0.0229 (21)	(-0.159) - (-0.0644)
$EMAX_{POPADJEC/GEJC}$[g]	θ_{25}	-0.0956	0.0237 (24.8)	(-0.142) - (-0.0456)
$EMAX_{POP1LMESO}$[g]	θ_{26}	-0.124	0.0395 (31.8)	(-0.201) - (-0.0428)
Random Effects[h,i]				
ω^2-CL [-]	$\omega_{1,1}$	0.0728 (0.27)	0.00535 (7.35)	0.0626 - 0.0847
ω^2-VC [-]	$\omega_{2,2}$	0.0896 (0.299)	0.014 (15.6)	0.064 - 0.119
ω^2-VP [-]	$\omega_{3,3}$	0.261 (0.511)	0.0405 (15.5)	0.187 - 0.343
ω^2-EMAX [-]	$\omega_{4,4}$	0.042 (0.205)	0.00869 (20.7)	0.0246 - 0.0596
ω^2-CL: ω^2-VC [-]	$\omega_{1,2}$	0.0352 (0.188)	0.00481 (13.7)	0.0272 - 0.0469
Residual Error				
Proportional RV [-]	θ_6	0.219	0.00617 (2.82)	0.208 - 0.232

[a] Random effects and residual error parameter names containing a colon (:) denote correlated parameters.

[b] Random effect and residual error parameter estimates are shown as variance (standard deviation) for diagonal and off-diagonal elements.

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

[d] Confidence Interval values are taken from bootstrap calculations (989 successful out of a total of 1,000).

[e] CL_{REF}, VC_{REF}, Q_{REF}, VP_{REF}, and $EMAX_{REF}$ are typical values of CL, VC, Q, VP, and EMAX at the reference covariate values. Covariate effects were estimated relative to a reference subject who is a male, with BALB of 4.0 g/dL, BLDH of 200 IU/L, BBWT of 80 kg, estimated BGFR of 90 mL/min/1.73 m^2, PS of 0, race = non-Asian, defined as White, Black/African American, Other, Unknown, or missing.

[f] The typical values of CL, VC, Q, and Vp corresponding to continuous valued covariates of subject i are modeled as:

$$CL_{TV,i} = CL_{REF} \times \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} \times \left(\frac{BGFR_i}{BGFR_{REF}}\right)^{CL_{BGFR}} \times \left(\frac{BLDH_i}{BLDH_{REF}}\right)^{CL_{BLDH}} \times \left(\frac{BALB_i}{BALB_{REF}}\right)^{CL_{BALB}}$$

$$VC_{TV,i} = VC_{REF} \times \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}}$$

$$Q_{TV,i} = Q_{REF} \times \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}}$$

$$VP_{TV,i} = VP_{REF} \times \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}}$$

[g] The typical values of CL, VC, and EMAX corresponding to categorical valued covariates of subject i are modeled as:

$$CL_{TV,i} = CL_{REF} \times (e^{CL_{SEX}})^{SEX_i} \times (e^{CL_{PS}})^{PS_i} \times (e^{CL_{RAAS}})^{RAAS_i} \times \left(e^{CL_{POPADJEC/GEJC}}\right)^{POPADJEC/GEJC_i} \times (e^{CL_{POP1LMESO}})^{POP1LMESO_i} \times (e^{CL_{POPOTH}})^{POPOTH_i} \times (e^{CL_{COIPI}})^{COIPI_i} \times (e^{CL_{COCHEMO}})^{COCHEMO_i}$$

$$VC_{TV,i} = VC_{REF} \times (e^{VC_{SEX}})^{SEX_i}$$

$$EMAX_{TV,i} = EMAX_{REF} + \left(EMAX_{POPADJEC/GEJC}\right) + \left(EMAX_{POP1LMESO}\right) + \left(EMAX_{PS}\right)$$

[h] Eta shrinkage: ETA_CL: 17.7%, ETA_VC: 41.3%, ETA_VP: 53.0%, ETA_EMAX: 52.9%; Epsilon shrinkage: 16.8%.

[i] The calculated correlation coefficient (r) of the off-diagonal omega was 0.436 for cov(IIV in VC, IIV in CL).

Note: The Others population (POPOTH) was comprised of subjects with colorectal cancer (CRC), melanoma (MEL), prostate cancer, and renal cell carcinoma (RCC) in Studies CA209001 and CA209003.

Note: The condition number was 309 indicating there was no evidence for ill-conditioning.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-5-model-development.Rmd

Source: Analysis-Directory/KIWI Run ID 299402

The final model was described as 2-compartment model, with zero-order IV infusion and time-varying CL (sigmoidal-Emax function), with a proportional residual error model. Random effects were estimated for CL, VC, and Emax, including the covariance between CL and VC. The covariate effects of BBWT on Q and VP were constrained to be the same as the effects of BBWT on CL and VC, respectively.

The final model estimated (typical value) Emax (-0.387) indicates that nivolumab CL decreases with time, and that the maximal decrease is approximately 32.1% [calculated as: 1 −exp(Emax)]. The typical half-maximal change is estimated to occur at approximately 2 months (T50 = 1,400 hours).

Figure 5.1.1.3-1: Goodness-of-Fit Plots for the Nivolumab Final Population Pharmacokinetic Model, Overall, and by Population Groups

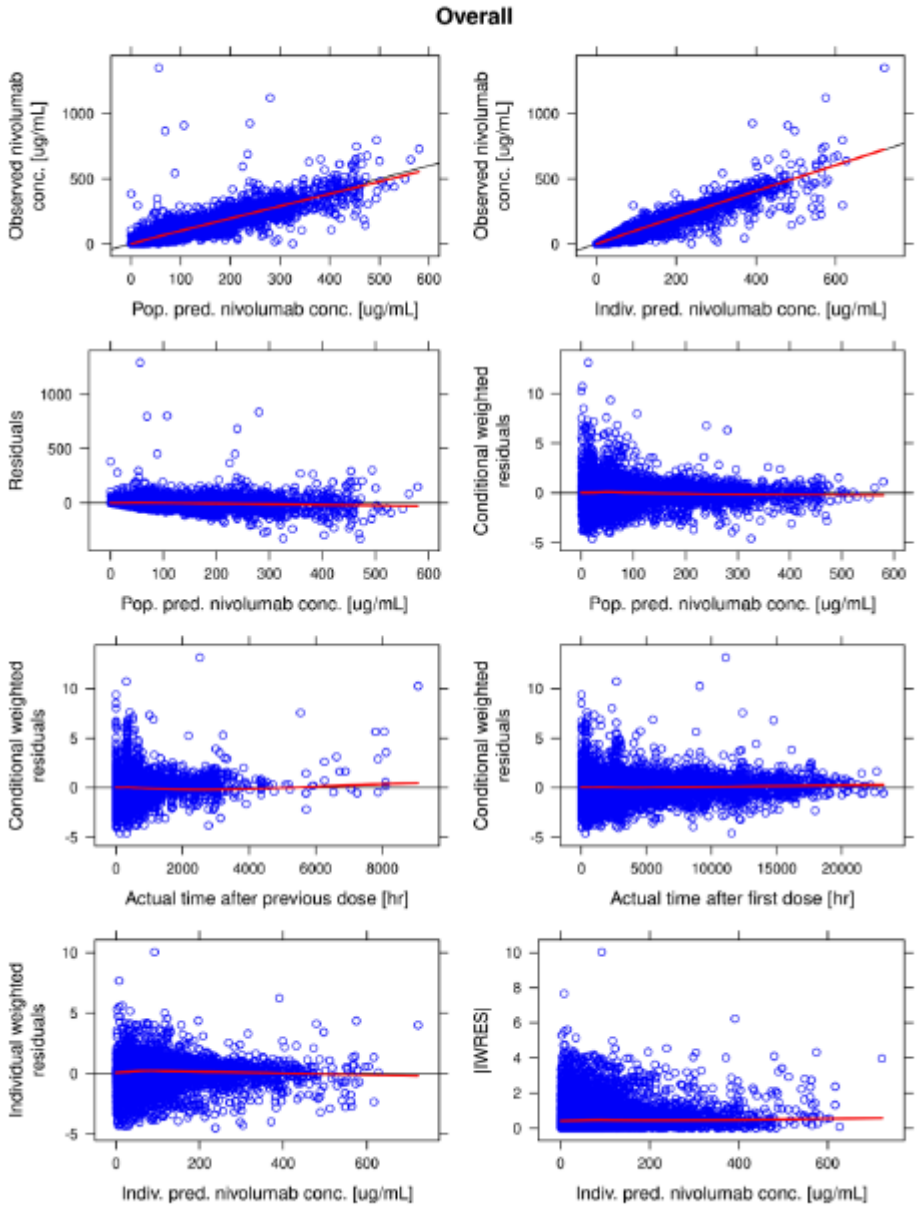
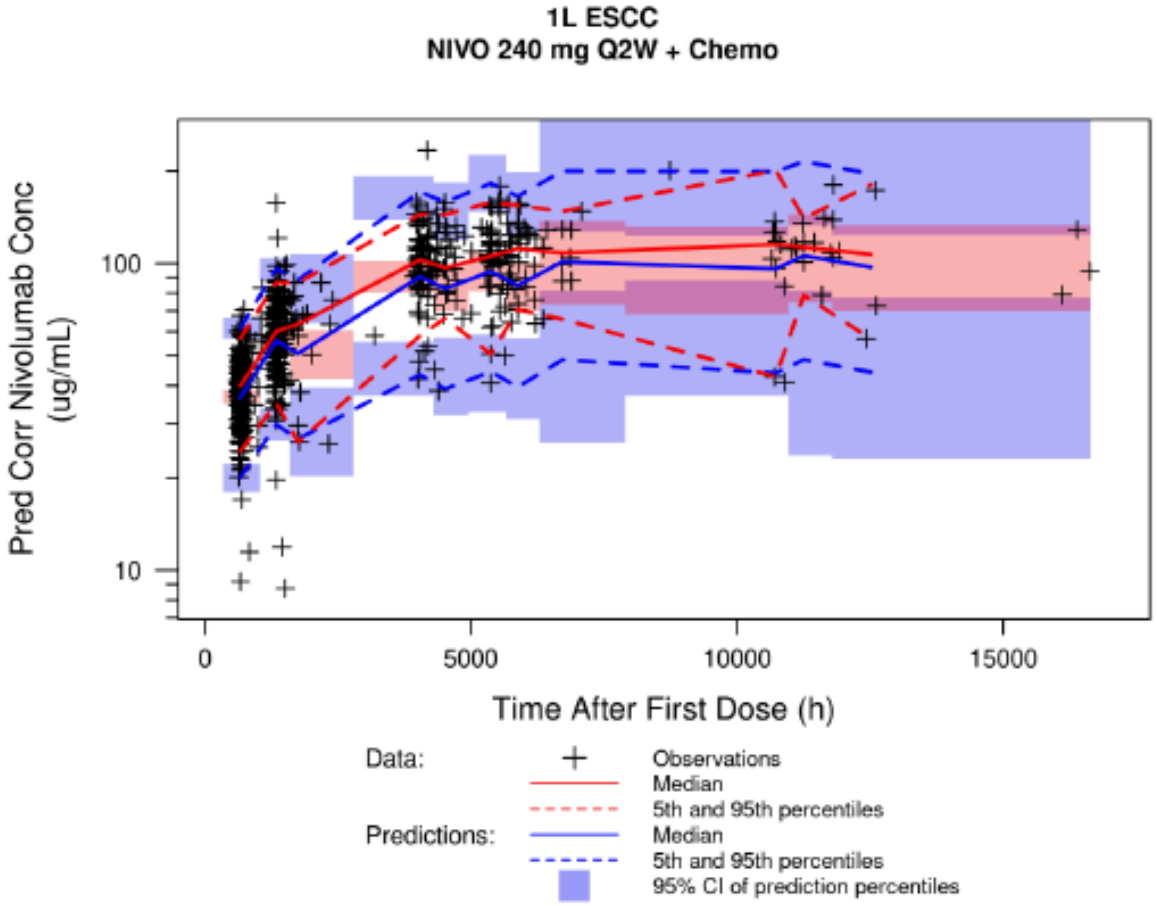


Figure 5.1.2-1: **Prediction-corrected Visual Predictive Check of Trough Concentrations (Log Scale) Versus Actual Time After First Dose for Data from the 1L ESCC Population by Treatment Using the Nivolumab Final Population Pharmacokinetic Model**



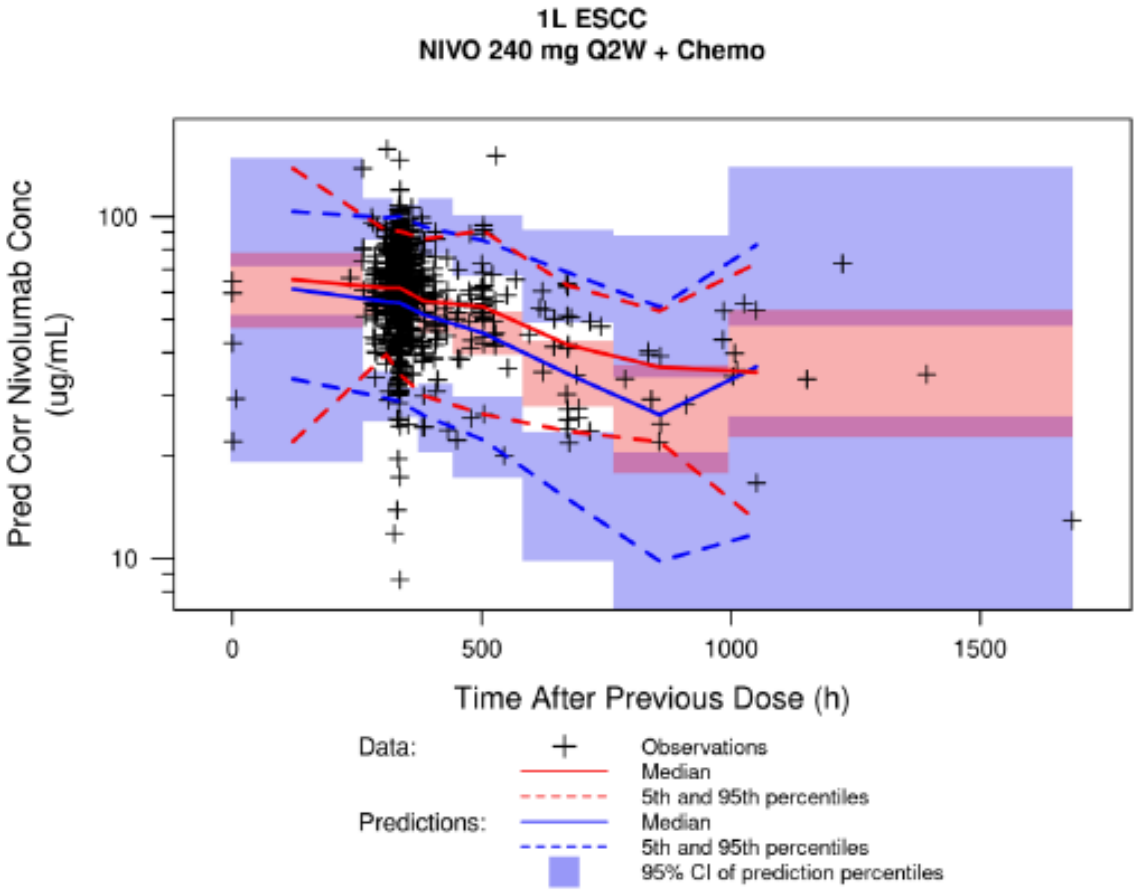
Abbreviations: 1L = first-line; Chemo = chemotherapy; CI = confidence interval; Conc = concentration; ESCC = esophageal squamous cell carcinoma; IPI = ipilimumab; NIVO = nivolumab; Pred Corr = prediction corrected; Q2W = every 2 weeks; Q6W = every 6 weeks.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-5-model-development.Rmd

Source: Analysis-Directory/d1pk-nivo/graphs/rmd-pnghi/nivo-s648-final-02-pcvpc-atafd-s648-trough-by-combo-001.png and nivo-s648-final-02-pcvpc-atafd-s648-trough-by-combo-002.png

Figure 5.1.2-2: **Prediction-corrected Visual Predictive Check of All Concentrations (Log Scale) Versus Actual Time After Previous Dose for Data from the 1L ESCC Population by Treatment Using the Nivolumab Final Population Pharmacokinetic Model**



Abbreviations: 1L = first-line; Chemo = chemotherapy; CI = confidence interval; Conc = concentration; ESCC = esophageal squamous cell carcinoma; IPI = ipilimumab; NIVO = nivolumab; Pred Corr = prediction corrected; Q2W = every 2 weeks; Q6W = every 6 weeks.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-5-model-development.Rmd

Source: Analysis-Directory/d1pk-nivo/graphs/rmd-pnghi/nivo-s648-final-02-pcvpc-s648-by-combo-001.png and nivo-s648-final-02-pcvpc-s648-by-combo-002.png

Exposure relevant for safety evaluation

Summary statistics of the individual PK parameter estimates obtained from the final PPK model for subjects with 1L OSCC in Study CA209648 (by treatment group), 2L NSCLC, 2L+ EC, adjuvant EC/GEJC, 1L NSCLC (by treatment group), 1L MESO, and ALL (all subjects in the PPK analysis) populations are provided in Table 5.1.3.1-1 and Figure 5.1.3.1-1.

Table 5.1.3.1-1: Summary Statistics (Geometric Mean [%CV]) of Individual Nivolumab Pharmacokinetic Parameter Estimates by Subject Population and Overall Population in the Population Pharmacokinetic Analysis (n = 3671)

Parameter	Geometric Mean (%CV)									
	Nivo Monotherapy				Nivo+Chemo		Nivo+Ipi			ALL (n=3671)
	2L NSCLC (n=539)	1L NSCLC (n=328)	2L+ EC (n=251)	Adjuvant EC/GEJC (n=494)	1L ESCC (n=286)	1L NSCLC (n=494)	1L ESCC (n=289)	1L NSCLC (n=484)	1L MESO (n=297)	
CL0 (mL/h)	11.6 (34.3)	12.1 (32.2)	9.21 (27.2)	10.2 (24.3)	9.03 (29.3)	10.4 (31.9)	10.8 (29.8)	12.7 (33.1)	15.5 (29.2)	11.3 (34.9)
CLss (mL/h)	7.34 (37.4)	7.77 (35.1)	5.92 (30.6)	6.03 (26.8)	5.75 (31.5)	6.57 (37.0)	6.99 (31.6)	8.04 (36.7)	8.72 (30.9)	7.08 (37.6)
Vss (L)	6.00 (27.9)	6.16 (22.3)	5.28 (19.1)	6.38 (20.2)	5.59 (18.3)	6.16 (22.0)	5.41 (18.7)	6.11 (23.4)	6.38 (23.1)	6.08 (24.2)
T1/2α,ss (h)	24.7 (26.6)	26.3 (17.6)	25.5 (14.1)	27.2 (12.6)	26.5 (12.4)	26.5 (15.3)	25.1 (14.6)	26.0 (19.1)	26.5 (19.4)	26.1 (18.8)
T1/2β,ss (days)	24.4 (33.6)	23.7 (32.1)	26.5 (24.2)	31.3 (19.0)	28.8 (24.7)	27.8 (27.6)	23.1 (26.5)	22.8 (33.5)	21.9 (31.7)	25.6 (32.3)

Note: n = 3671 is the sum of the 2L NSCLC, 2L+ EC, 1L ESCC, adjuvant EC/GEJC, 1L NSCLC, 1L MESO, and Other (not shown) populations comprising the ALL population (overall PPK analysis population).

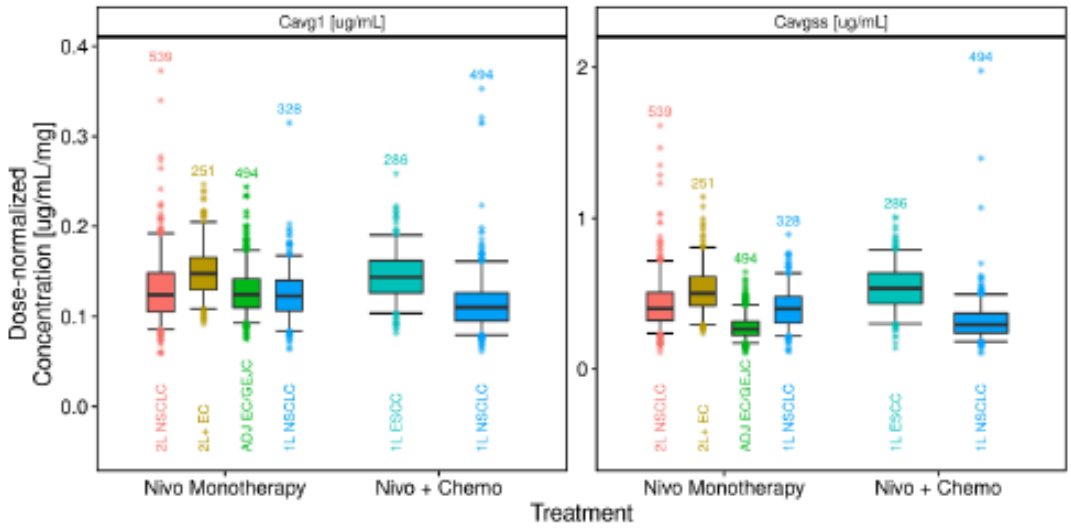
Abbreviations: 1L = first-line; 2L = second-line; Chemo = chemotherapy; CL0 = clearance at time 0; CLss = clearance at steady state; %CV = coefficient of variation expressed as a percentage; EC = esophageal cancer; ESCC = esophageal squamous cell carcinoma; GEJC = gastroesophageal junction cancer; IPI = ipilimumab; MESO = mesothelioma; n = number of subjects; NSCLC = non-small cell lung cancer; Nivo = nivolumab; T1/2α,ss = alpha half-life at steady state; T1/2β,ss = beta half-life at steady state; Vss = sum of volume of the central compartment and volume of the peripheral compartment.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

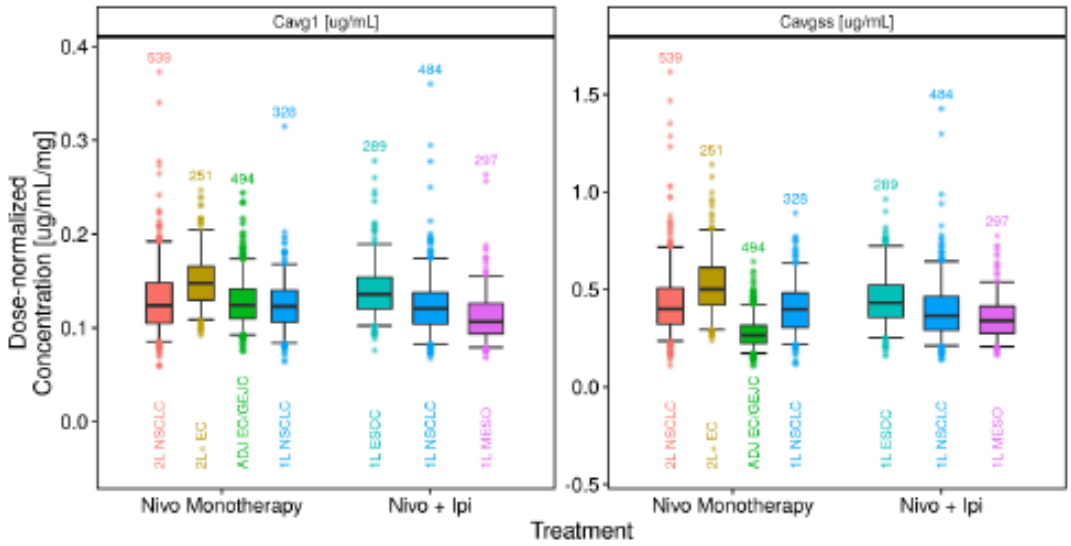
Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-5-model-application.Rmd

Source: Analysis-Directory/d1pk-nivo/tables/rmd-rtf/sumstat-pkparams-by-pop-combo-v01.rtf

Figure 5.1.3.1-1: Distributions of Dose-normalized Nivolumab Cavg1 and Cavgss by Subject Populations and by Treatment



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles. Asterisks show data points outside this range. The number of subjects is above each box. Two 1L NSCLC subjects with dose-normalized Nivolumab Cavg Steady-state > 2 in Nivo + Chemo group were excluded from plot for better visualization.



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles. Asterisks show data points outside this range. The number of subjects is above each box.

Abbreviations: 1L = first-line; 2L = second-line; Adj = adjuvant; Cavg = daily average nivolumab concentration; Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Chemo = chemotherapy; EC = esophageal cancer; EC/GEJC = esophageal cancer and gastroesophageal junction cancer; ESCC = esophageal squamous cell carcinoma; Ipi = ipilimumab; Meso = mesothelioma; Nivo = nivolumab; NSCLC = non-small cell lung cancer.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

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Source: Analysis-Directory/d1pk-nivo/graphs/rmd-pnghi/rpt-b-dncavg-by-popn-combo-v02.png and rpt-b-dncavg-by-popn-combo-v03.png

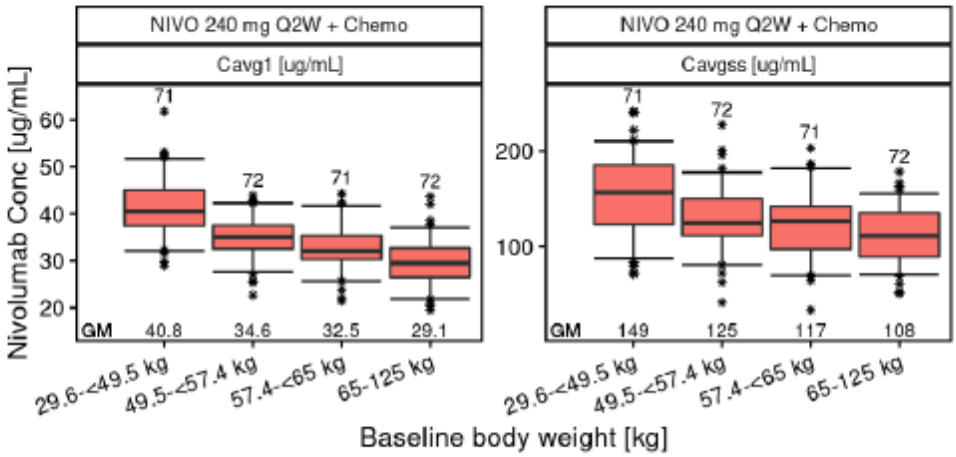
Special populations

Baseline Body weight on Nivolumab exposure

As presented,, nivolumab CL increased approximately 20% with an increase in BBWT from the median to 95th percentile value. The VC was higher with higher BBWT (approximately 28%, between the

median and 95th percentile values for BBWT). The impact of this effect on nivolumab exposure was evaluated in subjects with 1L OSCC.

Figure 5.1.3.2-1: Boxplots of Predicted Nivolumab Exposures (Cavg1 and Cavgss) by Body Weight Quartiles for Nivolumab 240 mg Q2W + Chemotherapy Q4W in Subjects with 1L ESCC



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles.
Asterisks show data points outside this range.
The number of subjects is above each box.

Abbreviations: 1L = first-line; Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Chemo = chemotherapy; Conc = concentration; ESCC = esophageal squamous cell carcinoma; GM = geometric mean; NIVO = nivolumab; Q2W = every 2 weeks; Q4W = every 4 weeks.

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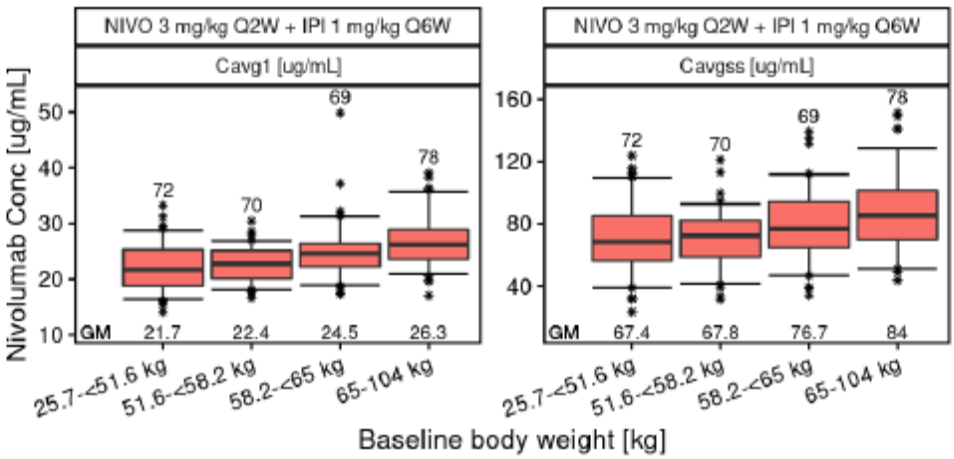
Source: Analysis-Directory/d1pk-nivo/graphs/rmd-pnglo/rpt-b-exp-by-WTQRT-cavg-NIVO240mgQ2WChemo-v01.png

Figure 5.1.3.2-2: Boxplots of Predicted Nivolumab Exposures (Cavg1 and Cavgss) by Body Weight Quartiles for Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W in Subjects with 1L ESCC



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles.
Asterisks show data points outside this range.
The number of subjects is above each box.

Abbreviations: 1L = first-line; Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Conc = concentration; ESCC = esophageal squamous cell carcinoma; GM = geometric mean; IPI = ipilimumab; NIVO = nivolumab; Q2W = every 2 weeks; Q6W = every 6 weeks.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

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Source:Analysis-Directory/d1pk-nivo/graphs/rmd-pnglo/rpt-b-exp-by-WTQRT-cavg-NIVO3mgkgQ2WIPI1mgkgQ6W-v01.png

Table 5.1.3.2-1: Predicted Exposures for the 5th/95th Percentiles of Body Weight for a Typical Subject and Percent Differences in Relation to the Median for Nivolumab 240 mg Q2W + Chemotherapy Q4W in Subjects with 1L ESCC

Exposure	P05 (41.5 kg)	Median (57.4 kg)	P95 (79.0 kg)	% Difference (P05-Median)	% Difference (P95-Median)
Cavg1	40.1	33.2	27.6	20.8	-16.9
Cmin1	27.1	22.7	19	19.4	-16.3
Cmax1	81.9	67	55	22.2	-17.9
Cavgss	141	120	103	17.5	-14.2
Cminss	115	98.5	85	16.8	-13.7
Cmaxss	196	165	140	18.8	-15.2

Abbreviations: 1L = first-line; Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Cmax1 = post dose 1 peak serum concentration; Cmaxss = peak serum concentration at steady state; Cmin1 = trough serum concentration after the first nivolumab dose; Cminss = trough serum concentration at steady state; ESCC = esophageal squamous cell carcinoma; P05 = 5th percentile; P95 = 95th percentile; Q2W = every 2 weeks; Q4W = every 4 weeks

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-5-model-application.Rmd

Source:Analysis-Directory/d1pk-nivo/tables/rmd-rtf/sumstat-pk-exp-ccov-typical-sub-by-tx-BBWT-NIVO240mgQ2WChemo-v01.rtf

Baseline Albumin Impact on Nivolumab Exposure

Table 5.1.3.3-2: Predicted Exposures for the 5th/95th Percentiles of Baseline Serum Albumin for a Typical Subject and Percent Differences in Relation to the Median for Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W in Subjects with 1L ESCC

Exposure	P05 (2.9 g/dL)	Median (4 g/dL)	P95 (4.6 g/dL)	% Difference (P05-Median)	% Difference (P95-Median)
Cavg1	21.9	24.2	25.1	-9.5	3.72
Cmin1	12.8	15.8	17.1	-19	8.23
Cmax1	50.6	50.6	50.6	0	0
Cavgss	61.1	80.5	90.8	-24.1	12.8
Cminss	45.1	64.1	74.2	-29.6	15.8
Cmaxss	95.7	115	125	-16.8	8.7

Abbreviations: 1L = first-line; Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Cmax1 = post dose 1 peak serum concentration; Cmaxss = peak serum concentration at steady state; Cmin1 = trough serum concentration after the first nivolumab dose; Cminss = trough serum concentration at steady state; ESCC = esophageal squamous cell carcinoma; P05 = 5th percentile; P95 = 95th percentile; Q2W = every 2 weeks; Q6W = every 6 weeks

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-5-model-application.Rmd

Source: Analysis-Directory/d1pk-nivo/tables/rmd-rtf/sumstat-pk-exp-ccov-typical-sub-by-tx-BALB-NIVO3mgkgQ2WIPI1mgkgQ6W-v01.rtf

Dose recommendations

Nivolumab

Nivolumab Exposures in Subjects with 1L OSCC When Administered as 240 mg Q2W or 480 mg Q4W in Combination with Chemotherapy

Nivolumab exposures were predicted for subjects with 1L OSCC in Study CA209648 following the nivolumab 240 mg Q2W or 480 mg Q4W in combination with chemotherapy. The predicted concentration-time profiles were used to calculate key summary measures of exposure.

The geometric mean (with 90% PI) nivolumab concentration-time profiles in subjects with 1L OSCC for the first 28 days and at steady state are presented for the 240 mg Q2W and 480 mg Q4W regimens (Figure 5.1.3.7-1). Although the nivolumab Cmax following the first dose was expected to be higher with 480 mg Q4W compared to 240 mg Q2W, the predicted Cmax following the first dose with 480 mg Q4W was still well below that achieved with 10 mg/kg Q3W + chemo, which was applied in study CA209012 and was considered to be safe and tolerable (Figure 5.1.3.7-2).

The Cavgss exposure at steady state was identical between the nivolumab 240 mg Q2W + chemo and nivolumab 480 mg Q4W + chemo dosing regimens. The Cminss and the Cmaxss of 480 mg Q4W + chemo were 17.7 % lower and 30.8% higher, respectively, as compared with the nivolumab 240 mg Q2W dosing regimen.

Table 5.1.3.7-1: Summary of Nivolumab Exposures (Geometric Mean) for Nivolumab 240 mg Q2W + Chemotherapy Q4W or Nivolumab 480 mg Q4W + Chemotherapy Q4W in Subjects with 1L ESCC in Study CA209648

Time	Summary Exposure (µg/mL)	Geometric Mean (%CV)		% Difference (G2-G1)[a]
		240 mg Q2W + Chemo (n=286)	480 mg Q4W + Chemo (n=286)	
Week 0-2	CmaxW2	69.6 (19.4)	139 (19.4)[b]	99.7
	CminW2	23.2 (24.6)	NA	NA
	CavgW2	34.0 (19.5)	NA	NA
Week 0-4	CmaxW4	93.0 (19.8)	139 (19.4)[b]	49.5
	CminW4	37.9 (27.3)	28.0 (34.6)	-26.1
	CavgW4	43.3 (20.8)	52.3 (21.8)	20.8
Steady State	Cmaxss	172 (26.3)	225 (23.6)	30.8
	Cminss	101 (37.0)	83.1 (43.1)	-17.7
	Cavgss	124 (31.4)	124 (31.4)	0

[a] Percent difference in geometric mean of 480 Q4W (G2) relative to 240 mg Q2W (G1).

[b] Equivalent.

Abbreviations: 1L = first-line; Cavgss = time-averaged serum concentration at steady state (2 weeks for Q2W and 4 weeks for Q4W); CavgW2 = average nivolumab concentration over the first dosing interval for Q2W (CavgW2 is equivalent to Cavg1 for Q2W; CavgW2 is not applicable for Q4W); CavgW4 = average nivolumab concentration over the first dosing interval for Q4W and the first 2 dosing intervals for Q2W (CavgW4 is equivalent to Cavg1 for Q4W; CavgW4 is the average nivolumab concentration after 2 doses for Q2W); Chemo = chemotherapy; Cmaxss = peak serum concentration at steady state; CmaxW2 = maximum nivolumab serum concentration after the first dose (CmaxW2 is equivalent to Cmax1 for Q2W and Q4W); CmaxW4 = maximum nivolumab concentration after the first dose for Q4W and after the second dose for Q2W (CmaxW4 is equivalent to Cmax1 for Q4W; CmaxW2 and CmaxW4 are equivalent for Q4W); Cminss = trough serum concentration at steady state; CminW2 = minimum nivolumab concentration after the first nivolumab dose for Q2W (CminW2 is equivalent to Cmin1 for Q2W; CminW2 is not applicable for Q4W); CminW4 = minimum nivolumab concentration after the first nivolumab dose for Q4W and after the second dose for Q2W (CminW4 is equivalent to Cmin1 for Q4W); %CV = coefficient of variation expressed as a percent; ESCC = esophageal squamous cell carcinoma; n = number of subjects; NA: not applicable; Q2W = every 2 weeks; Q4W = every 4 weeks.

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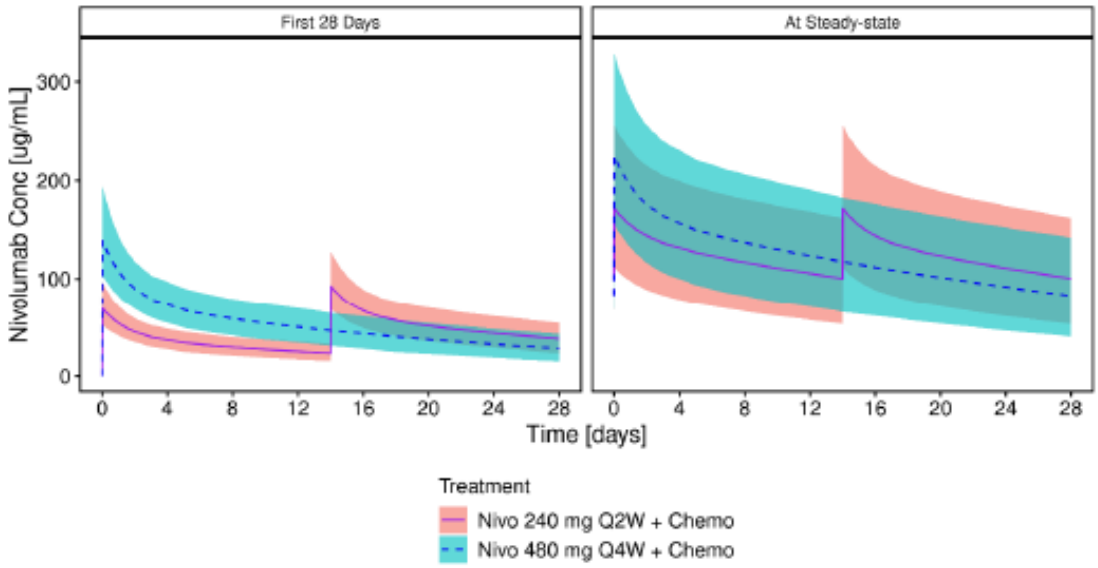
Source: Analysis-Directory/d1pk-nivo/tables/rmd-rtf/sumstat-pk-exp-by-tx-240-vs-480-nivo-chemo-v01.rtf

Figure 5.1.3.7-1: Predicted Geometric Mean (90% PI) Nivolumab Concentration-Time Profiles by Dosing Regimen (Nivolumab 240 mg Q2W + Chemotherapy Versus Nivolumab 480 mg Q4W + Chemotherapy) in Subjects with 1L ESCC



Treatment
Nivo 240 mg Q2W + Chemo
Nivo 480 mg Q4W + Chemo

Line represents geometric mean and shaded area represents 90% prediction interval

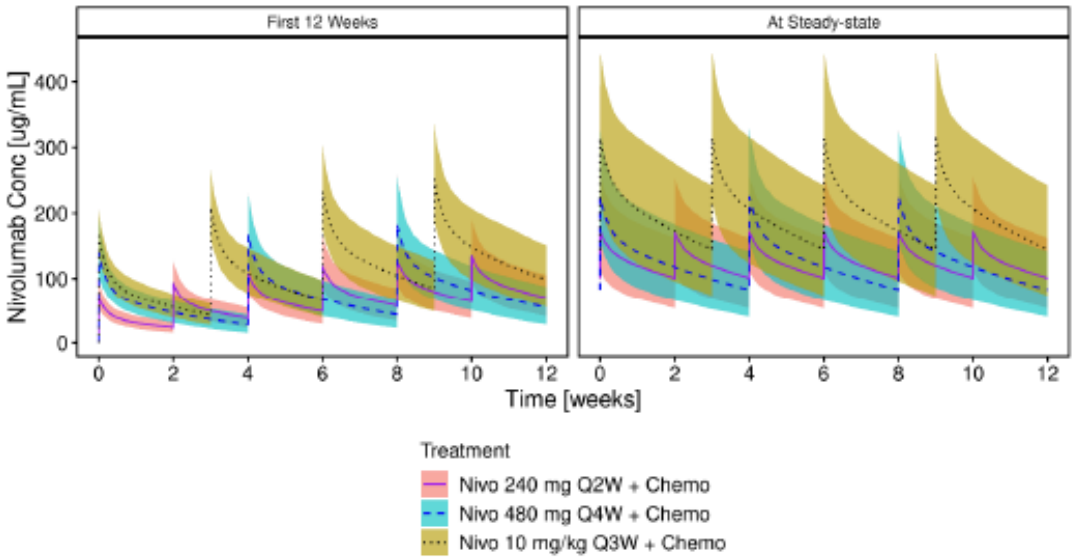
Abbreviations: 1L = first-line; Chemo = chemotherapy; Conc = concentration; ESCC = esophageal squamous cell carcinoma; Nivo = nivolumab; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Analysis-Directory: /global/pkms/data/CA/209/ec-11/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-11-escc-pmr-tfl-section-5-model-application.Rmd

Source:Analysis-Directory/d1pk-nivo/graphs/rmd-pnghi/1-cp-time-geomean-ci-240nivochem-480nivochemo-v01.png

Figure 5.1.3.7-2: Predicted Geometric Mean (90% PI) Nivolumab Concentration-Time Profiles by Dosing Regimens (Nivolumab 240 mg Q2W + Chemotherapy Versus Nivolumab 480 mg Q4W + Chemotherapy Versus Nivolumab 10 mg/kg Q3W + Chemotherapy) in Subjects with 1L ESCC



Line represents geometric mean and shaded area represents 90% prediction interval

Abbreviations: 1L = first-line; Chemo = chemotherapy; Conc = concentration; ESCC = esophageal squamous cell carcinoma; Nivo = nivolumab; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks.

Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-5-model-application.Rmd

Source: Analysis-Directory/d1pk-nivo/graphs/rmd-pnghi/1-cp-time-geomean-ci-240nivochem-480nivochemo-10nivochemo-v01.png

2.3.1. Pharmacodynamics

Mechanism of action

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that selectively binds to the programmed death-1 (PD-1) membrane receptor. The PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation.Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens and self-antigens.

2.3.2. PK/PD modelling

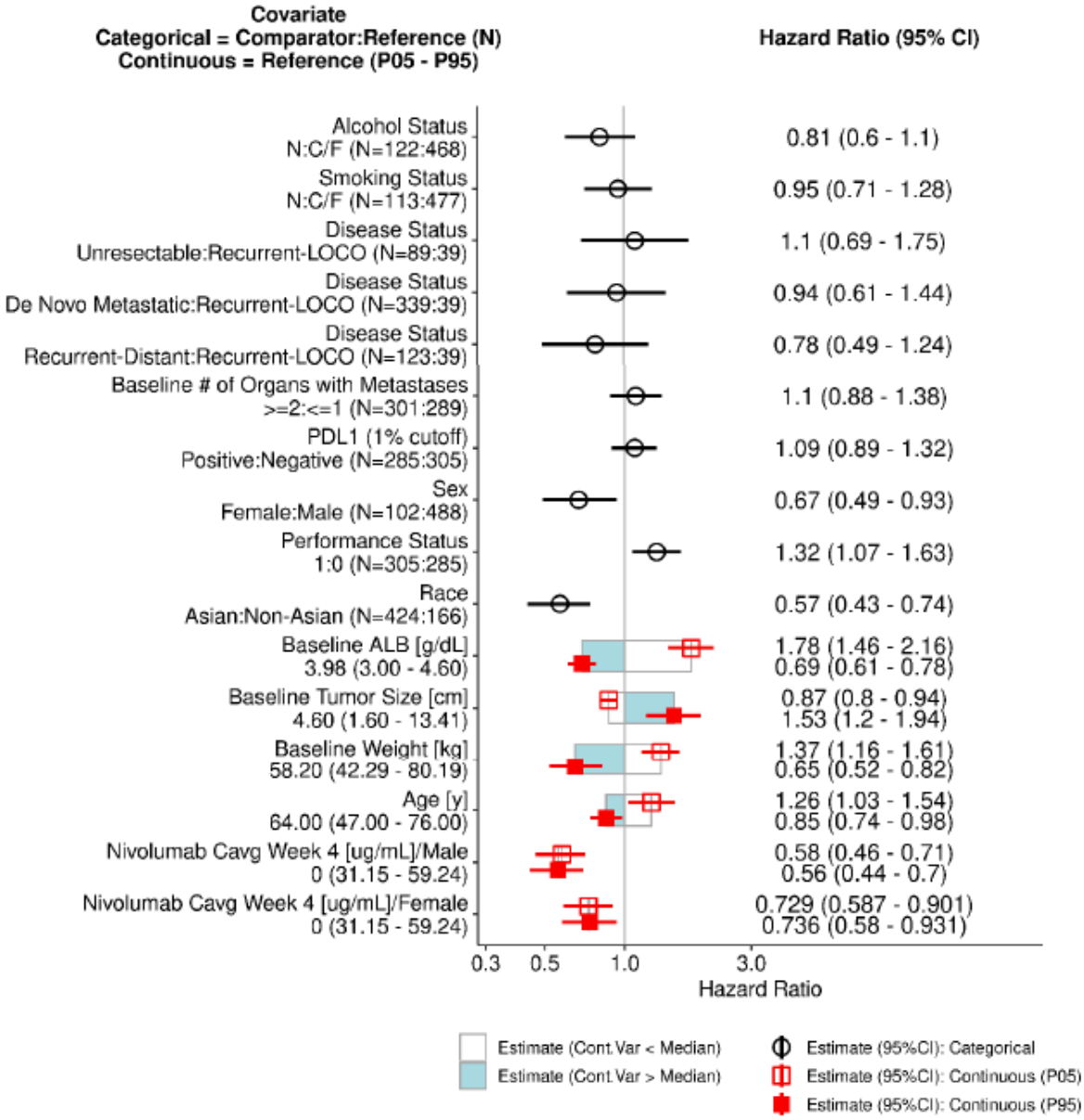
Exposure-efficacy

E-R Analysis of Efficacy for OS - Nivo+Chemo - Overall Study Population: Among the evaluated functional forms of exposure effect, the log-linear function of nivolumab CavgW4 (reference model) had the lowest BIC value. The interaction between nivolumab CavgW4 and sex was the only significant predictor of OS with a reduction in BIC of 0.94 and was included in the full model. No other significant covariates resulted in an interaction effect with nivolumab CavgW4 that decreased the BIC.

In the full model assessment, the relationship between nivolumab CavgW4 with OS was dependent on whether subjects with 1L OSCC were male or female. Males had a slightly lower OS HR than females at

the same nivolumab CavgW4. In male subjects, nivolumab CavgW4 exposures were associated with significantly (95% CI interval excluded 1) lower risk of death than the chemo alone (HR of 0.58 [95% CI: 0.46, 0.71] over chemo [CavgW4 = 0] at the 5th percentile of CavgW4 [CavgW4 = 31 µg/mL], and HR of 0.56 [95% CI: 0.44, 0.7] over chemo at the 95th percentile of CavgW4 [CavgW4 = 59 µg/mL]). In female subjects, nivolumab CavgW4 exposures were also associated with significantly (95% CI interval excluded 1) lower risk of death than the chemo alone (HR of 0.729 [95% CI: 0.587, 0.901] over chemo [CavgW4 = 0] at the 5th percentile of CavgW4 [CavgW4 = 31 µg/mL], and HR of 0.736 [95% CI: 0.58, 0.931] over chemo at the 95th percentile of CavgW4 [CavgW4 = 59 µg/mL]). The E-R relationship was relatively flat across the range of nivolumab CavgW4 in this study as evidenced by the limited range of HRs associated with the 5th and 95th percentiles of nivolumab CavgW4.

Figure 1: **Estimated Covariate Effects of the Exposure-Response of OS (Full Model) in Study CA209648 (Nivo+Chemo) - Overall Study Population**



Note: The effect of nivolumab Cavg Week 4 in males was based on the nivolumab Cavg effect alone. The effect of nivolumab Cavg Week 4 in females was based on the nivolumab Cavg effect plus the interaction between nivolumab Cavg and females.

Abbreviations: ALB = albumin; Cavg = average serum concentration at Week 4; C/F = current/former; Chemo = chemotherapy; CI = confidence interval; Cont. Var = continuous variable; LOCO = loco regional; N = number of subjects or never; Nivo = nivolumab; OS = overall survival; PDL1 = programmed death-ligand 1.

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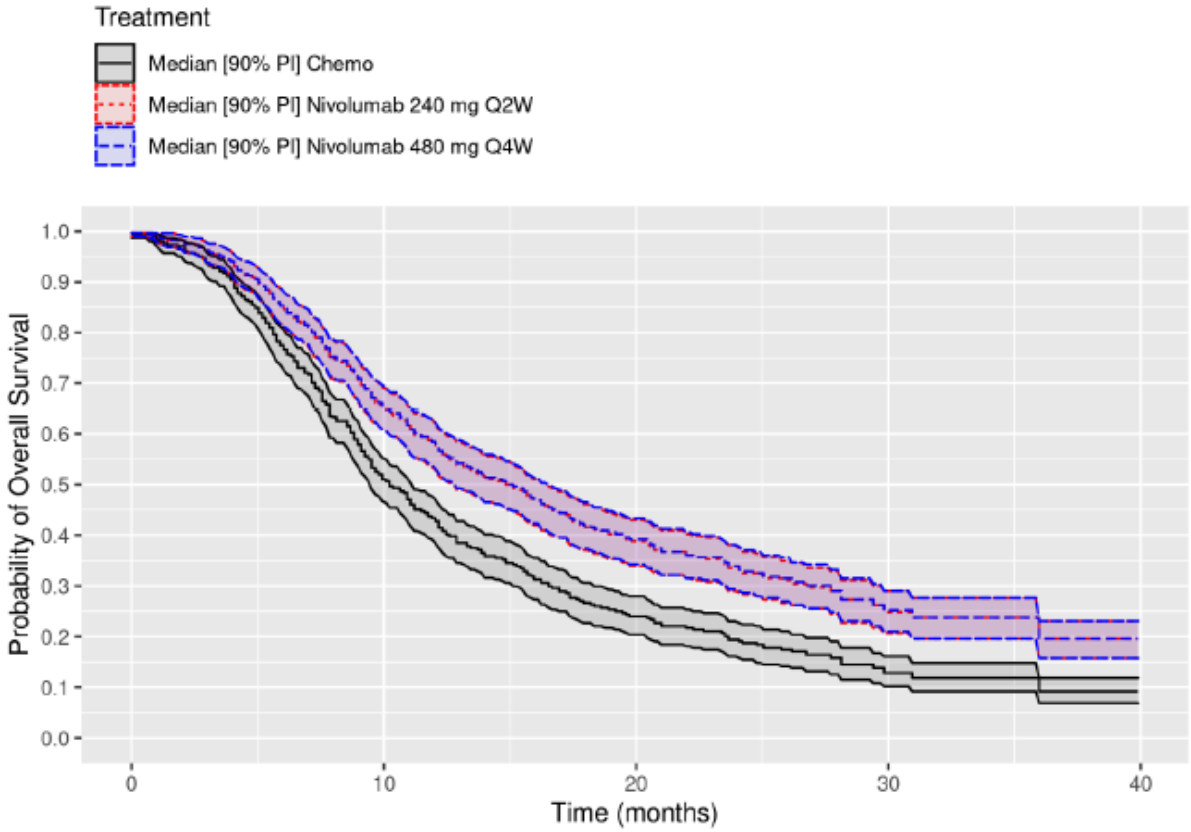
Figure 2: **Predicted Median [90% PI] Probability of OS Using Simulated CavgW4 from 2 Proposed Dosing Regimens (Nivo 240 mg Q2W or Nivo 480 mg Q4W+chemo) in Subjects with 1L ESCC in Study CA209648 - Overall Study Population**



Abbreviations: 1L = first-line; CavgW4 = average serum concentration at Week 4; Chemo = chemotherapy; ESCC = esophageal squamous cell carcinoma; OS = overall survival; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Analysis-Directory: /global/pkms/data/CA/209/ec-11/prd/cognigen/sd/final/

Program Source: Analysis-Directory/010063/d1pkpd-eff/R/os/er-os-alltreat-model-dev-code.Rmd

Source: Analysis-Directory/010063/d1pkpd-eff/graphs/R/os-alltreat/os-alltreat-model-app-km-nc-pi.png

E-R Analysis of Efficacy for OS - Nivo+Chemo - Tumour Cell PD-L1 Expression ≥ 1% Population: Among the evaluated functional forms of exposure effect, the log-linear function of nivolumab CavgW4 (reference model) had the lowest BIC value. Next, the interactions between nivolumab CavgW4 and significant covariates in the full model were assessed. None of the significant covariates resulted in an interaction effect with nivolumab CavgW4 that decreased the BIC.

The categorical variables that were identified as significant predictors (95% CI of effect did not include 1) on OS in the full model were PS and sex. The risk of death increased with PS (= 1) and decreased with female sex.

The continuous variables that were identified as significant predictors (95% CI of effect did not include 1) on OS in the full model were nivolumab CavgW4 and baseline ALB. Nivolumab CavgW4 exposures were associated with significantly lower (95% CI interval excluded 1) risk of death than chemo only (HR of 0.46 [95% CI: 0.34, 0.61] over chemo [CavgW4 = 0] at the 5th percentile of CavgW4 [CavgW4 = 31 µg/mL], and HR of 0.43 [95% CI: 0.32, 0.59] over chemo at the 95th percentile of CavgW4

[CavgW4 = 59 µg/mL]). The risk of death increased with lower baseline ALB (HR of 1.74 [95% CI: 1.37, 2.21] for 5th percentile of ALB relative to the median baseline ALB).

The 95% CI of the HRs for all the other predictor variables evaluated (eg, age, baseline weight, baseline tumour size, race, number of organs with metastases at baseline, disease status, smoking status, and alcohol use) included 1, indicating that these factors did not have statistically significant effects on OS.

The VPC plots indicate the model-predicted median (90% PI) was in good agreement with the observed KM of OS, indicating adequate model performance.

E-R Analysis of Efficacy for PFS - Nivo+Chemo - Tumour Cell PD-L1 Expression ≥ 1% Population: For the E-R PFS model, the log-linear function of nivolumab CavgW4 (reference model) had the lowest BIC value. Next, the interactions between nivolumab CavgW4 and significant covariates in the full model were assessed. None of the significant covariates resulted in an interaction effect with nivolumab CavgW4 that decreased the BIC.

The categorical variable that was identified as a significant predictor (95% CI of effect did not include 1) on PFS in the full model was PS. The risk of disease progression or death increased with PS (= 1).

The continuous variables identified as significant predictors (95% CI of effect did not include 1) on PFS in the full model were nivolumab CavgW4 and baseline ALB. Nivolumab CavgW4 exposures were associated with significantly (95% CI interval excluded 1) lower risk of disease progression or death than with chemo only (HR of 0.57 [95% CI: 0.43, 0.76] over chemo [CavgW4 = 0] at the 5th percentile of CavgW4 [CavgW4 = 31 µg/mL], and HR of 0.55 [95% CI: 0.4, 0.75] over chemo at the 95th percentile of CavgW4 [CavgW4 = 59 µg/mL]). The risk of disease progression or death increased with lower baseline ALB (a HR of 1.57 [95% CI: 1.21, 2.04] for 5th percentile of ALB relative to the median baseline ALB).

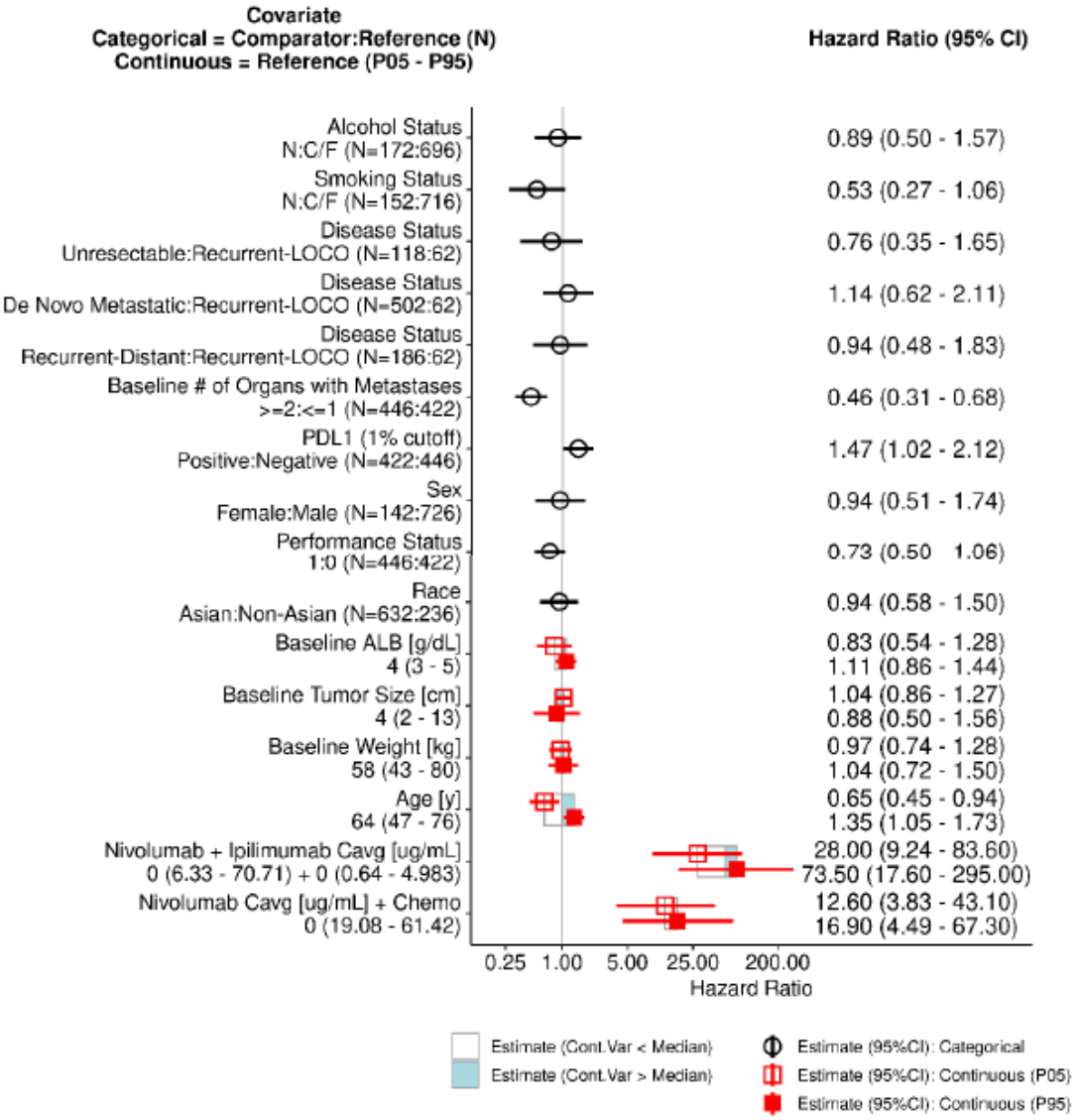
The 95% CI of the HRs for all the other predictor variables evaluated (eg, age, baseline weight, baseline tumour size, race, sex, number of organs with metastases at baseline, disease status, smoking status, and alcohol use) included 1, indicating that these factors did not have statistically significant effects on PFS.

The VPC plots indicate the model-predicted median (90% PI) was in good agreement with the observed KM of PFS, indicating adequate model performance.

Exposure-safety

E-R Analysis of Safety for Gr2+ IMAEs: For the E-R safety model, both linear and log-linear functional forms of daily exposure of nivolumab and ipilimumab were assessed for their effect on the risk of Gr2+ IMAEs in the full model. Among the evaluated functional forms of exposure effect, the log-linear function of nivolumab daily Cavg and ipilimumab daily Cavg had the lowest BIC value and was selected as the full model. An ipilimumab treatment effect was tested instead of the log-linear ipilimumab daily Cavg, but it did not lower the BIC by 2 points and therefore was not included in the Gr2+ IMAE full model. No interactions between nivolumab or ipilimumab daily Cavg and covariates were significant predictors of Gr2+ IMAEs that reduced the BIC, and therefore none were included in the full model.

Figure 5: **Estimated Covariate Effects of the Exposure-Response of Gr2+ IMAEs (Full Model) in Study CA209648 - All Treated Subjects**



Note: Time-varying daily Cavg was used in E-R Gr2+ IMAEs model development. The effects of exposure were calculated using the average concentration of the daily Cavg values from Day 1 to the day of event/censor. The hazard ratio of the effect of nivolumab plus ipilimumab Cavg was calculated as exp(0. 257•(LCAVGDN-reference median) + 0.167•(LCAVGDI-reference median)) where LCAVGDN/LCAVGDI are the 5th and 95th percentiles and references are the median of log nivolumab/ipilimumab daily Cavg based on the sum of nivolumab and ipilimumab effects.

Abbreviations: ALB = albumin; Cavg = averaged nivolumab daily Cavg from beginning of treatment to the day of event/censor; C/F = current/former; CI = confidence interval; Chemo = chemotherapy; Cont. Var = continuous variable; E-R = exposure-response; Gr2+ IMAEs = Grade ≥ 2 immune-mediated adverse events; LCAVGDN = log nivolumab daily Cavg; LCAVGI = log ipilimumab daily Cavg; LOCO = loco regional; N = number of subjects or never; PDL1 = programmed death-ligand 1.

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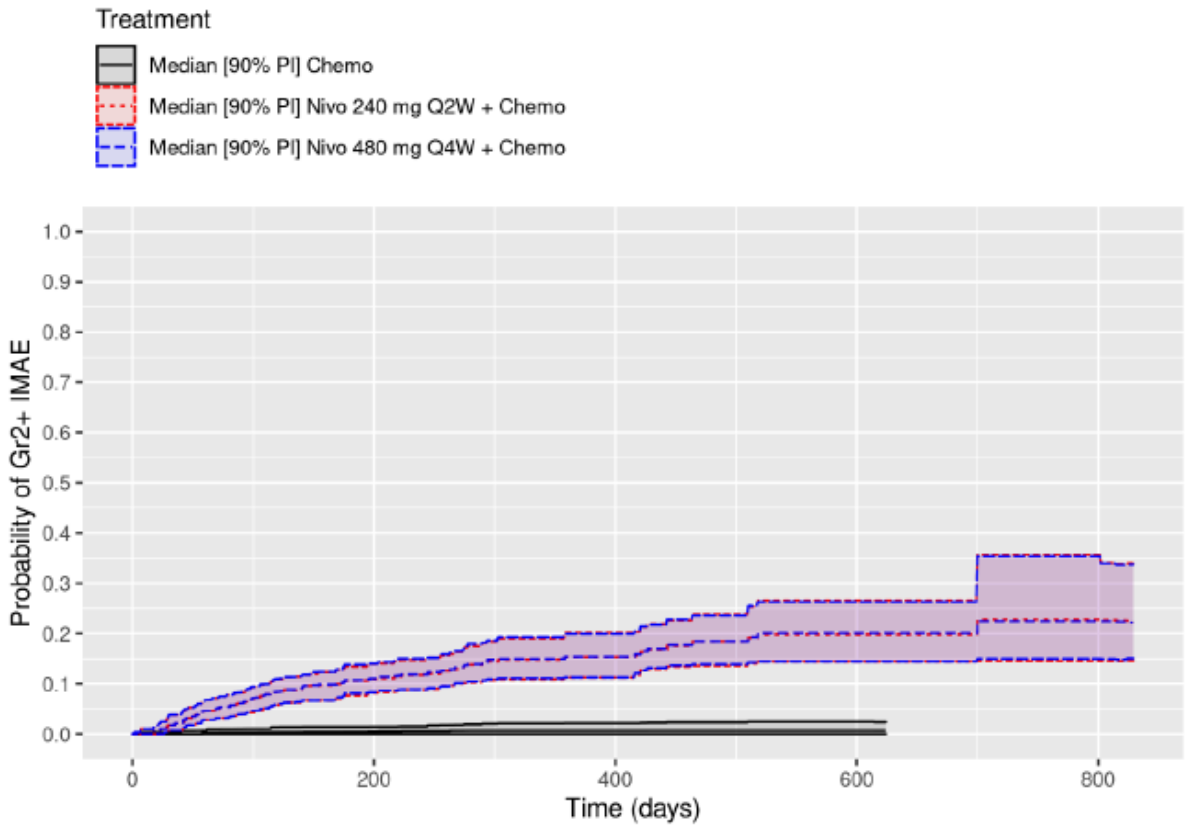
Figure 6: **Predicted Median [90% PI] Probability of Gr2+ IMAEs Using Simulated Nivolumab Cavg from 2 Proposed Dosing Regimens (Nivo 240 mg Q2W or Nivo 480 mg Q4W+Chemo) in Subjects with 1L ESCC for Study CA209648 - Overall Study Population**



Abbreviations: 1L = first-line; Cavg = average concentration; Chemo = chemotherapy; ESCC = esophageal squamous cell carcinoma; Gr2+ IMAEs = Grade ≥ 2 immune-mediated adverse events; Nivo = nivolumab; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Analysis-Directory: /global/pkms/data/CA/209/ec-11/prd/cognigen/sd/final/

Program Source: Analysis-Directory/010063/d1pkpd-saf/R/er-saf-model-dev.Rmd

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2.3.3. Discussion on clinical pharmacology

Population PK model

The Applicant has conducted a model-based approach by implementing the previously developed population PK models of nivolumab and ipilimumab in patients with oesophageal squamous cell carcinoma (OSCC). The modelling strategy is endorsed and the data analysis, exploratory assessment and data handling seems appropriate.

The population PK model of nivolumab is able to characterize the time-course profile based on the pcVPC and GOF plots of nivolumab in OSCC patients. The statistically significant covariate relationships were included and allowed to partially reduce the inter-individual variability.

The clinical impact of significant covariates on nivolumab exposure has been conducted, suggesting no clinically relevant changes in nivolumab exposure due to body weight, and clinically relevant differences on Cmin,ss and Cavg,ss in patients with very low (5th percentile) baseline albumin levels, which could partially explain the differences in the exposure-efficacy relationship.

Dosing regimens

The evaluation of alternative dosing schedules for nivolumab through a model-based approach is appreciated. Similar Cavg concentrations are predicted between 240 mg Q2W and 480 mg Q4W since linear mechanisms described the PK properties of nivolumab. However, a less frequent dosing schedule (Q4W) provides higher Cmax,ss and lower Cmin,ss exposure levels, which has not resulted in a higher incidence of safety concerns.

Exposure-efficacy analysis

The evaluation of the exposure-efficacy on OS and PFS endpoints using the overall study population and the stratified group of tumour cell PD-L1 expression population revealed the improved efficacy when nivolumab+chemo vs. chemo alone arms are selected, which is expected based on the additional indications of nivolumab already approved. The recommendation of nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy seems to be justified based on the OS and PFS in adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma.

Exposure-safety

The exposure-safety evaluation revealed a higher probability of Grade2+ IMAE (10-20%) in the nivolumab+chemo group compared to chemo group. The impact of a less frequent nivolumab dosing regimen (Q4W) is expected to have a minor impact in terms of safety concerns compared to (Q2W) since similar Caverage values are predicted.

2.3.4. Conclusions on clinical pharmacology

The clinical pharmacology properties of nivolumab+chemo groups were evaluated through the implementation of a previously developed population PK model of nivolumab, which has been adapted to patients with oesophageal squamous cell carcinoma. The pharmacokinetic and exposure-response characterization seems appropriate based on the evidence provided.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

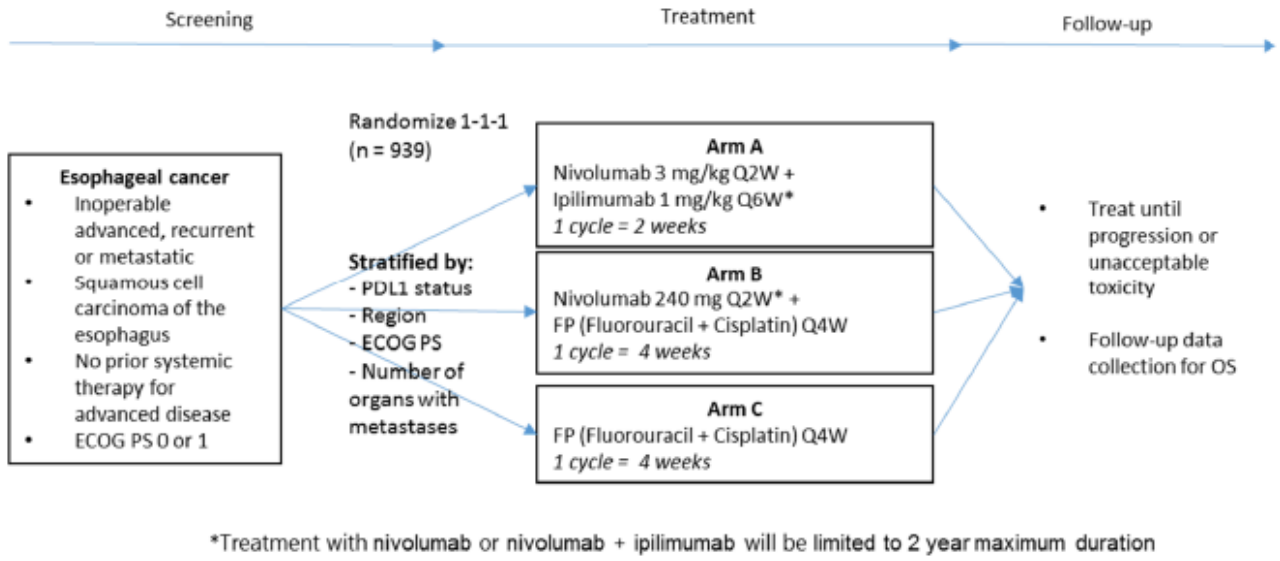
No dose-response studies were submitted as part of this application

2.4.2. Main study

Study CA209648: **A randomized Phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated oesophageal squamous cell carcinoma.**

Methods

Figure 1. CA209648 Study Design Schematic



This study will consist of 3 phases: screening, treatment, and follow-up. Subjects will be evaluated for disease progression every 6 weeks from the date of first dose (± 7 days) up to and including Week 48, and then every 12 weeks (± 7 days) thereafter, regardless of treatment schedule, until disease progression or the subject discontinues the study, whichever comes first.

Study participants

Key inclusion criteria

Subjects were required to be ≥ 18 years of age and have histologically confirmed **squamous cell carcinoma** or adenosquamous cell carcinoma (predominant squamous differentiation) of the oesophagus that was classified as **unresectable advanced, recurrent or metastatic** (per AJCC 7th edition). Disease must not have been amenable to curative approaches such as definitive chemoradiation and/or surgery, and **no prior systemic anticancer therapy** was allowed as primary therapy for advanced or metastatic disease. Prior adjuvant, neoadjuvant, or definitive, chemotherapy/ radiotherapy/ chemoradiotherapy for OSCC was permitted if given as part of curative intent regimen and completed before enrolment. A minimum 24-week recurrence-free period was required after completion of neoadjuvant or adjuvant chemotherapies or after completion of multimodal therapies for locally advanced disease.

In addition, all subjects were required to have:

- Baseline ECOG PS of ≤ 1.
- A least one measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria performed within 28 days prior to randomization.
- PD-L1 immunohistochemistry (IHC) testing, with evaluable results, performed by the central lab during the Screening period. Either 1 formalin-fixed paraffin-embedded (FFPE) tumour tissue block or 15 unstained tumour tissue slides, with an associated pathology report if available, were to be submitted for biomarker evaluation prior to study drug administration.
- In order to be randomized, subjects were required to have an evaluable tumour cell PD-L1 expression classification (≥ 1%, < 1%, or indeterminate) as determined by the central lab. Subjects with non-evaluable results will not be allowed to be randomized.

Key exclusion criteria

- Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before randomization.
- Prior malignancy requiring active treatment 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.
- Patients with any metastasis in the brain or meninx that is symptomatic or requires treatment. Patients may be randomized if the metastasis is asymptomatic and requires no treatment.
- Patients at high risks of bleeding or fistula due to apparent invasion of tumour to organs (the aorta or the trachea) adjacent to oesophageal lesions.
- Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.
- Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

Treatments

Eligible subjects were randomized to one of the following open label treatments (Arms A, B, and C):

- **Arm A** (nivo + ipi): nivolumab 3 mg/kg every 2 weeks (Q2W) intravenously (IV) + ipilimumab 1 mg/kg every 6 weeks (Q6W) IV.
- **Arm B** (nivo + chemo): nivolumab 240 mg Q2W IV + fluorouracil 800 mg/m2/day IV on Day 1 through Day 5 + cisplatin 80 mg/m2 IV on Day 1 of a 4-week cycle.
- **Arm C** (chemo): fluorouracil 800 mg/m2/day IV Day 1 through Day 5 + cisplatin 80 mg/m2 IV on Day 1 of a 4-week cycle.

Treatment with nivolumab or nivolumab with ipilimumab was to be given for up to 24 months in the absence of disease progression (unless treatment beyond progression was permitted) or unacceptable toxicity. No dose escalations or reductions of nivolumab and ipilimumab were allowed. Doses of nivolumab and/or ipilimumab could be interrupted, delayed, or discontinued depending on how well the subject tolerated the treatment. If a subject met the criteria for discontinuation of nivolumab but not for ipilimumab, both nivolumab and ipilimumab were to be discontinued. If discontinuation criteria were met for ipilimumab but not for nivolumab, treatment with nivolumab might be continued if ipilimumab was discontinued.

Treatment beyond initial, investigator-assessed RECIST 1.1-defined progression was permitted in the nivo + ipi or nivo + chemo arms if the subject had investigator-assessed clinical benefit and was tolerating treatment.

Fluorouracil + cisplatin chemotherapy was given as per the study dosing schedule until disease progression or unacceptable toxicity. Doses of fluorouracil and/or cisplatin could be interrupted, delayed, reduced, or discontinued depending on how well the subject tolerated the treatment.

Note that country-specific CA209648 Protocol Amendment 10 (27-Sep-2018) allowed for a 4-day continuous infusion of 1000 mg/m^2 fluorouracil as an alternative to a 5-day continuous infusion for subjects in Korea and Taiwan in the nivo +chemo arm or chemo arm. The total dose of fluorouracil per cycle remained 4000 mg/m^2.

Objectives

Primary objectives

- To compare the OS of nivolumab plus ipilimumab (Arm A) to fluorouracil plus cisplatin chemotherapy (Arm C) in subjects with PD-L1 expression ≥ 1%.
- To compare the OS of nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil plus cisplatin chemotherapy (Arm C) in subjects with PD-L1 expression ≥ 1%.
- To compare the PFS of nivolumab plus ipilimumab (Arm A) to fluorouracil and cisplatin combination (Arm C) as assessed by BICR in subjects with PD-L1 expression ≥ 1%.
- To compare the PFS of nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by BICR in subjects with PD-L1 expression ≥ 1%.

Secondary objectives

- To compare the OS of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) in all randomized subjects.
- To compare the PFS of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by BICR in all randomized subjects.
- To compare the objective response rate (ORR) of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by BICR in subjects with PD-L1 expression ≥ 1%.
- To compare the ORR of nivolumab plus ipilimumab (Arm A) and nivolumab combined with fluorouracil plus cisplatin (Arm B) to fluorouracil and cisplatin combination (Arm C) as assessed by BICR in all randomized subjects.

Outcomes/endpoints

Primary endpoint

Primary endpoints are overall survival (OS) and progression free survival (PFS) in subjects with PD-L1 expressing tumours.

OS is defined as the time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

PFS is defined as the time from randomization to the date of the first documented PD per BICR or death due to any cause. Subjects who die without a reported prior PD per BICR (and die without start of subsequent therapy) will be considered to have progressed on the date of death. Subjects who did not have documented PD per BICR per RECIST1.1 criteria and who did not die, will be censored at the date of the last evaluable tumour assessment on or prior to initiation of the subsequent anti-cancer therapy. Subjects who did not have any on-study tumour assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date. Subjects who started any subsequent anti-cancer therapy without a prior reported PD per BICR will be censored at the last tumour assessment on or prior to initiation of the subsequent anti-cancer therapy.

Secondary endpoints

- OS in All Randomized subjects.
- PFS (as assessed by BICR) in All Randomized subjects.
- Objective Response Rate (ORR) (as assessed by BICR) in subjects with PD-L1 expressing tumours and All Randomized subjects.

  It is defined as the number of subjects with a best overall response (BOR) of CR or PR divided by the number of randomized subjects in the population for each treatment group. BOR is defined as the best response designation as determined by BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1 as determined by BICR) or the date of subsequent anti-cancer therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination.

Exploratory endpoints

- PFS (as assessed by investigator) in subjects with PD-L1 expressing tumours and All Randomized subjects.
- ORR (as assessed by investigator) in subjects with PD-L1 expressing tumours and All Randomized subjects.
- Duration of Response (DOR) (as assessed by BICR and as assessed by investigator) is defined as the time between the date of first documented response (CR or PR) to the date of the first disease progression, per RECIST 1.1 or death due to any cause, whichever occurs first.
- PFS2/TSST in subjects with PD-L1 expressing tumours and all randomized subjects. PFS2/TSST is defined as the time from randomization to the date of investigator-defined documented second objective disease progression or start of second subsequent therapy or death due to any cause, whichever comes first.
- Patient-reported Outcomes (PRO).

Sample size

Sample size calculations assumed that the prevalence of subjects with tumour cell PD-L1 expression ≥ 1% was approximately 50%, and the proportion of subjects with (≥ 1%) or without (< 1% or indeterminate) PD-L1 tumour expression was monitored during enrolment.

The study sample size was based on the primary objectives, i.e., on the comparisons of the PFS/OS distributions of subjects with tumour cell PD-L1 expression ≥ 1% between those who were randomized to receive nivolumab plus ipilimumab and those randomized to receive chemotherapy, and between those who were randomized to receive nivolumab plus chemotherapy and those randomized to receive chemotherapy. For both experimental arms, the same OS distributions and the same PFS distributions were assumed. A piecewise mixture cure rate model was used for the design setup, with cure rates in the experimental arms of 15% for OS in tumour cell PD-L1 ≥ 1%, 10% for OS in tumour cell PD-L1 < 1%, and 0% for PFS per BICR. As a result, for each of the nivo + ipi (Arm A) vs. chemo (Arm C) and nivo + chemo (Arm B) vs. chemo (Arm C) comparisons:

- 250 PFS events in approximately 313 subjects with tumour cell PD-L1 expression ≥ 1% would provide approximately 90% power to detect an average hazard ratio (HR) of 0.62 with a Type I error of 1.5% (two-sided);
- 250 OS events in approximately 313 subjects with tumour cell PD-L1 expression ≥ 1% would provide approximately 90% power to detect an average HR of 0.6 with a Type I error of 1% (two-sided).

In case the significance level from the corresponding primary endpoint in subjects with tumour cell PD-L1 expression ≥ 1% was passed to the secondary endpoint in all randomized subjects:

- 512 PFS events in approximately 626 subjects (all comers) would provide approximately 90% power to detect an average HR of 0.72 with a Type I error of 1.5% (two-sided);
- 514 OS events in approximately 626 subjects (all comers) would provide approximately 94% power to detect an average HR of 0.68 with a Type I error of 1% (two-sided).

To have approximately 313 randomized subjects with tumour cell PD-L1 expression ≥ 1% for each comparison, approximately 470 subjects with tumour cell PD-L1 expression ≥ 1% needed to be randomized in a 1:1:1 ratio in the 3 arms. This translated to a total of approximately 939 subjects (with any PD-L1 result) to be randomized in a 1:1:1 ratio to the nivo + ipi (Arm A) or nivo + chemo (Arm B) or chemo (Arm C) arms. Assuming a piecewise constant accrual rate, it was estimated that these 939 subjects would be accrued within 29 months.

Randomisation

Eligible subjects were randomized in a 1:1:1 ratio to one of the treatments. At randomization, patients were stratified according to the following stratification factors:

- Tumour cell PD-L1 status: ≥ 1% vs. < 1% (including indeterminate)*
- Region: East Asia (Japan, Korea, Taiwan) vs. Rest of Asia (China, Hong Kong, Singapore) vs. Rest of World (RoW)
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 vs. 1)
- Number of organs with metastases (≤ 1 vs. ≥ 2)

*The proportions of subjects with or without tumour cell PD-L1 expression were monitored and reassessed as needed to ensure that the sample size of randomized subjects with tumour cell PD-L1 expression ≥ 1% was adequate for analysis (i.e. approximately 50% of all randomized).

Blinding (masking)

Not applicable as the trial was open-label.

Statistical methods

Populations for analyses

The following definitions of populations will be applicable for subjects whose tumours express PD-L1 and also for subjects regardless of PD-L1 expression.

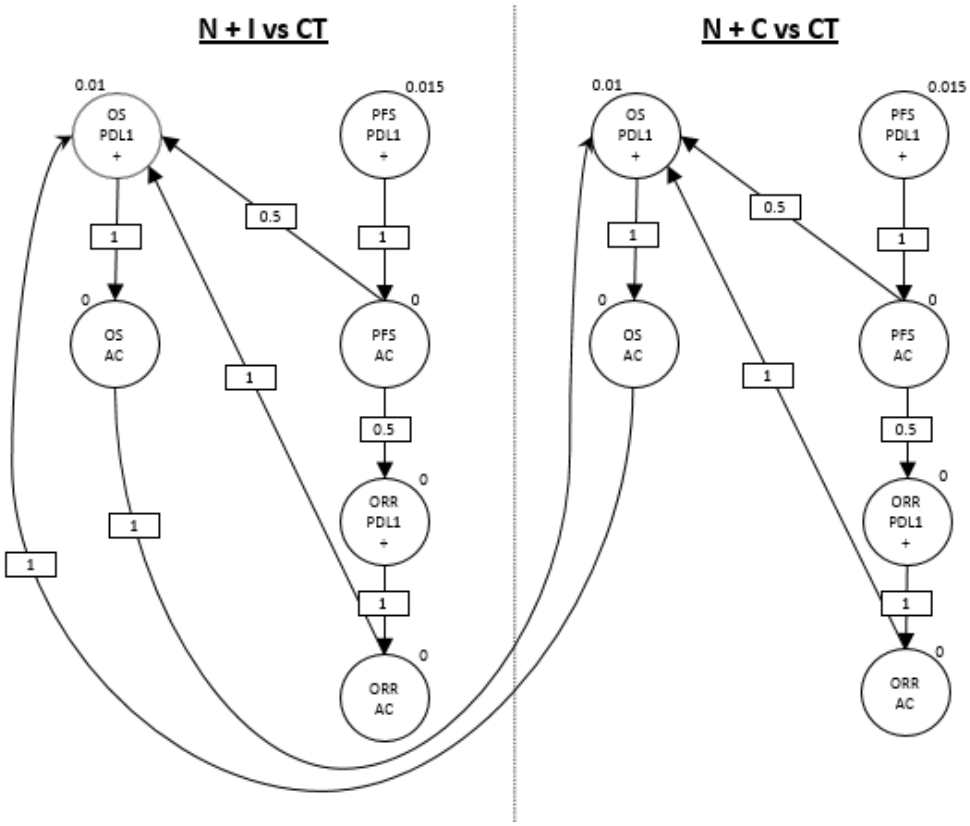
- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IRT
- All Randomized Subjects: All enrolled subjects who were randomized to any treatment arm in the study
- All Treated Subjects: All randomized subjects who received at least one dose of study drug during the study
- PK Subjects: All randomized subjects with available serum time-concentration data.
- Outcome Research subjects: All randomized subjects who have an assessment at screening/baseline and at least 1 follow-up assessment
- Immunogenicity subjects: All randomized subjects who have an assessment at screening/baseline and at least 1 follow-up assessment
- Biomarker subjects: All randomized subjects with available biomarker data.

Protection of Type I error

Family-wise Type I error will be protected in the strong sense across all primary and secondary endpoints. The p-values from sensitivity analyses for efficacy endpoints are for descriptive purpose only and not adjusted for multiplicity.

The primary and secondary endpoints were tested using the Bonferroni-based graphical approach by Maurer and Bretz (2013). Figure below presents a graphical display of the multiple testing procedure.

Figure 2. Graphical Representation of the Testing Strategy for the Primary and Secondary Endpoints



The planned test procedure was identical for the nivo + ipi (Arm A) vs. chemo (Arm C) and for the nivo + chemo (Arm B) vs. chemo (Arm C) comparisons and was conducted as follows.

At the time of the PFS final analysis, all 4 primary endpoints were tested, with the following initially allocated (endpoint-specific) 2-sided alpha levels:

- PFS in subjects with tumour cell PD-L1 expression ≥ 1%: 0.015 (2-sided)
- OS in subjects with tumour cell PD-L1 expression ≥ 1%: the overall initially allocated (endpoint-specific) alpha of 0.01 (2 sided) would be distributed over the IA and FA based on the actual number of deaths for each comparison at OS IA, using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

Alpha levels in this study are 2-sided. Upon availability of study data after database lock, the statistical testing procedure proceeded as follows.

Nivo + chemo vs. chemo:

- For PFS: since the primary endpoint of PFS in all randomized subjects with tumour cell PD-L1 expression ≥ 1% was significant at the 2-sided alpha level 0.015 (p-value: 0.0023), then the secondary endpoint of PFS in all randomized subjects was tested with the 2-sided alpha level 0.015 passed from the primary endpoint. Since the secondary endpoint of PFS was not significant at the 2-sided alpha level 0.015 (p-value: 0.0355), the subsequent secondary endpoints ORR in all randomized subjects with tumour cell PD-L1 expression ≥ 1% and in all randomized subjects were not formally tested and no alpha was passed from the secondary endpoint of PFS in all randomized subjects to the ORR secondary endpoints and OS primary endpoint.

– For OS: the observed number of OS events in all randomized subjects with tumour cell PD-L1 expression ≥ 1% at IA was 219 [87.6% of the target final number of 250 OS events]; with initial allocated overall alpha of 0.01, the significance level was 0.005 for OS IA in all randomized subjects with tumour cell PD-L1 expression ≥ 1% using O'Brien-Fleming alpha spending function. Since the primary endpoint of OS was significant at the IA 2-sided alpha level 0.005 (p-value<0.0001), then the secondary endpoint of OS in all randomized subjects was tested with the overall 2-sided alpha level of 0.01 passed from the primary endpoint of OS in all randomized subjects with tumour cell PD-L1 expression ≥ 1%. The observed number of OS events in all randomized subjects at IA was 441 [85.8% of the target final number of 514 OS events]. With the overall alpha of 0.01, the significance level was 0.009 for OS IA in all randomized subjects using Pocock alpha spending function. Since the secondary endpoint of OS was significant at the IA 2-sided alpha level 0.009 (p-value: 0.0021), the overall alpha of 0.01 was passed from the secondary OS endpoint in all randomized subjects for nivo + chemo vs. chemo to the primary OS endpoint for nivo + ipi vs. chemo.

Analysis of primary endpoints

OS and PFS as assessed by BICR in all subjects with tumour cell PD-L1 expression ≥ 1% were planned to be compared between nivo + ipi (Arm A) and chemo (Arm C), and between nivo + chemo (Arm B) and chemo (Arm C) using a two-sided log-rank test, stratified by the following stratification factors: ECOG performance status (0 vs. 1) and number of organs with metastases (≤ 1 vs. ≥ 2). Though the study randomization was stratified by region (East Asia vs Rest of Asia vs RoW), region was excluded from all stratified analyses due to small sample size in Rest of Asia.

For each comparison, the HR of PFS and OS with its associated two-sided 100(1-α)% confidence intervals (CIs) were estimated via a stratified Cox model with treatment arm as the only covariate in the model.

Median OS and PFS for each treatment arm were estimated and plotted using the Kaplan-Meier (KM) product-limit method. Median OS and PFS along with 95% CIs were constructed based on a log-log transformed CI for the survival function.

Per Revised Protocol 05, final PFS analysis could have had either an event-based trigger (ie, conducted when 136 events were observed among the subjects with tumour cell PD-L1 expression ≥ 1% in the chemo arm) or a time-based trigger (i.e., conducted when at least 12 months of minimum follow-up was reached). The trigger for the final PFS analysis based on the 01-Mar-2021 database lock was the time-based trigger of achieving a minimum follow-up of at least 12 months.

At the time of the final PFS analysis, a formal interim analysis for OS was planned to be conducted. Analyses of OS and PFS in all randomized subjects were planned to be carried out at the time of the primary analysis in all randomized subjects with tumour cell PD-L1 expression ≥ 1%. OS and PFS in all randomized subjects were to be tested only if significance level was passed on them. As the OS comparisons were statistically significant at the interim analysis, OS analyses (database lock: 01-Mar-2021) are considered final.

Sensitivity analyses for OS and PFS

Sensitivity analyses for both OS and PFS included the following:

- 2-sided, unstratified log-rank test using an unstratified Cox proportional hazards model with treatment as the single covariate.
- A multivariate adjusted, stratified Cox model was fitted to assess the treatment effect when adjusted for potential prognostic factors, including: age (< 65 vs. ≥ 65), sex (male vs. female),

race (Asian vs. non-Asian), weight (< 60 kg vs. ≥ 60 kg), disease status at current diagnosis (recurrent vs. metastatic vs. unresectable advanced), smoking status (current/former vs. never/unknown), and alcohol use (current/former vs. never/unknown).

- Max-combo analysis of OS and PFS per BICR when the KM curves indicated the HR was not constant over time, such as with a clear delayed separation.
- PFS analysis accounting for assessment on/after subsequent therapy. PFS will be defined similarly to the primary definition except that events (progression or death) and disease assessments that occurred on or after subsequent anti-cancer therapy will be considered (no time point truncation).

Two sensitivity analyses were not performed due to not meeting sample-size thresholds for analysis: analyses using stratification factors as obtained from the baseline CRF pages (instead of IRT) if > 10% of subjects with discordance, and analyses of subjects with no relevant deviation if > 10% of subjects with relevant protocol deviations.

Analysis of secondary endpoints

If any of the primary endpoints was significantly superior, the corresponding secondary endpoint of **OS** and **PFS** per BICR in all randomized subjects was compared using a two-sided log-rank test at the allocated significance level, stratified by: ECOG PS, number of organs with metastases, and tumour cell PD-L1 expression (≥ 1% vs < 1% or indeterminate)

For each comparison, the HR with its associated two-sided 95% CI (in case the given endpoint is formally tested, also with the 100[1-α]% CI) was estimated via a stratified Cox model with treatment arm as the only covariate in the model. OS and PFS for each treatment arm were estimated and plotted using the KM product-limit method. Median OS and PFS with associated two-sided 95% CI were constructed based on a log-log transformed CI for the survival function.

The same additional analyses were carried out for OS and PFS in all randomized subjects as for OS and PFS in all randomized subjects with tumour cell PD-L1 ≥ 1%.

ORR (as assessed by BICR) in subjects with PD-L1 expressing tumours and in all randomized subjects was to be tested only if significance level is passed on them.

ORR was computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in ORRs and corresponding 95% CI (in case the given endpoint is formally tested, also with the 100[1-α]% CI) were calculated using Cochran-Mantel-Haenszel (CMH) methodology and adjusted by the stratification factors. The stratified (source: IRT) odds ratios (Mantel-Haenszel estimator) between the treatments were provided along with the 95% CI (in case the given endpoint is formally tested, also with the 100[1-α]% CI).

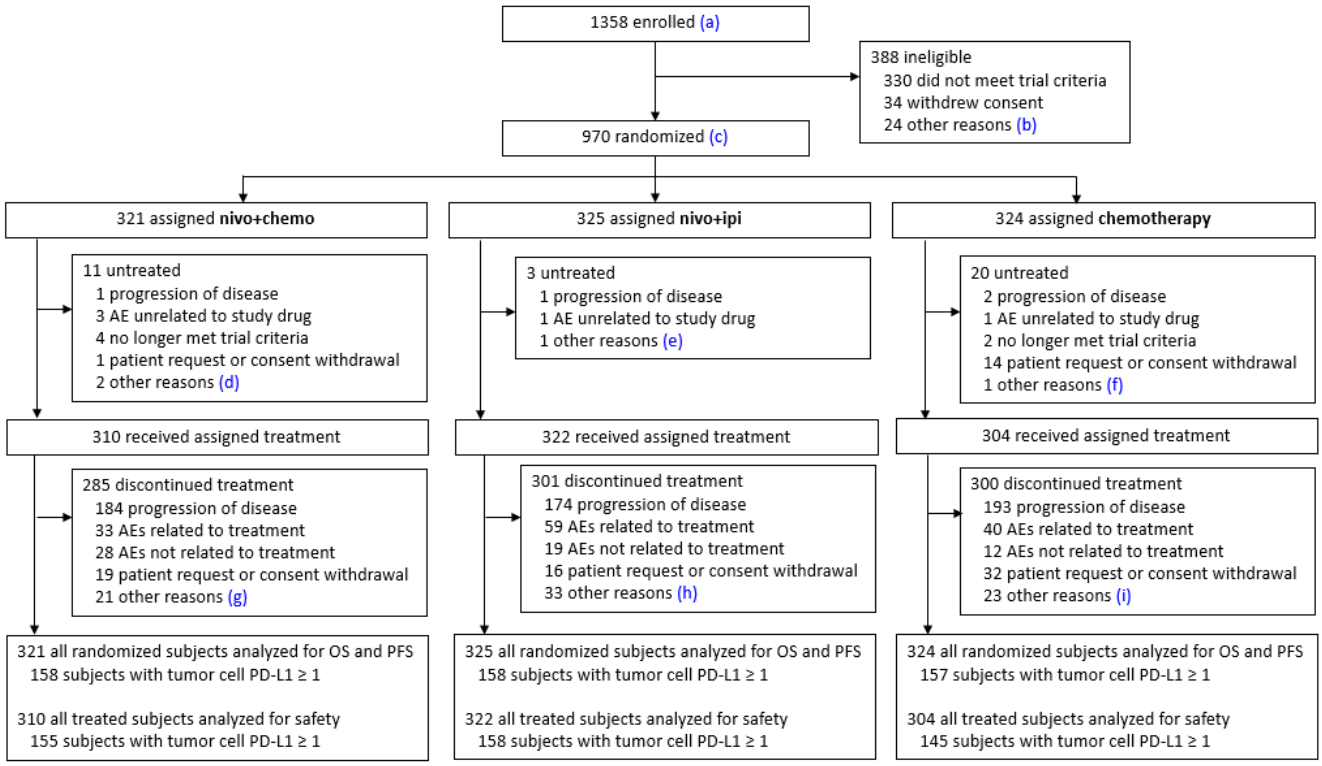
Analysis of PRO

An analysis of EQ-5D-3L and FACT-E (including FACT-G7 and ECS) data was performed in all randomized subjects with tumour cell PD-L1 ≥ 1% and all randomized subjects who had a PRO assessment at baseline (assessment on or prior to first dose on Day 1) and at least 1 subsequent assessment while on treatment. EQ-5D-3L and FACT-E data were summarized of each dimension/category by assessment time point and changes from baseline.

Results

Participant flow

Figure 3. Participant Flow Chart - All Randomized Subjects in the Nivo + Chemo, Nivo + Ipi, and Chemo Arms in CA209648 (01-Mar-2021 Database Lock)



(a) Enrolled patients included all concurrently randomized subjects to nivo + chemo, nivo + ipi, or chemo.
(b) Included death (n = 11), adverse events (n = 6), lost to follow-up (n = 1), poor/noncompliance (n = 1), and additional (other) reasons (n = 5: each 1 subject: subject no longer fit for trial/screen fail, Investigator's opinion, 'decided to participate in JCOG', acute lacunar cerebral infarction needed treatment, subject voluntarily discontinued).
(c) Relevant protocol deviations were noted in 5 (0.5%) subjects. This included 2 subjects in the nivo + chemo arm (1 subject at study entry without squamous cell carcinoma or adenosquamous cell carcinoma of the oesophagus [subject had sarcomatoid carcinoma of the oesophagus and was randomized but never treated], and 1 subject reported by the investigator to have received concurrent anti-cancer therapies, specifically botanical formulations and traditional medicines used for cancer treatment: Glycyrrhiza spp. root, Panax ginseng root, and taxus wallichiana. Its use by this subject was considered as a prohibited concomitant medication. However, this particular therapy is not considered as anti-cancer therapy by the Sponsor, and is, thus, not a prohibited concomitant medication for this study.) and 3 subjects in the chemo arm (1 subject without measurable disease at baseline, and 2 subjects who received concurrent anti-cancer therapies, specifically 1 subject received botanical formulations and traditional medicines used for cancer treatment: Astragalus spp. root, cantharidin, Eleutherococcus senticosus root with rhizome, and Panax ginseng root, and 1 subject received 'unspecified' herbal/traditional medicine).
(d) additional (other) reasons (n = 2: each 1 subject: worsening of PS, did not meet selection criteria)
(e) additional (other) reasons (n = 1: miscommunication over eligibility)
(f) additional (other) reasons (n = 1: renal function before administration)
(g) Included death (n = 3), maximum clinical benefit (n = 3), completion of treatment as per protocol (n = 8), and additional (other) reasons (n = 7: each 1 subject: 'visiting is difficult', only agreed to survey by phone or letter, 'patient unconscious, wife refuses follow-up', subject withdrew for safety, alternative therapy, 'subject dropped out due to violation', new treatment by radio-chemotherapy)
(h) Included death (n = 5), pregnancy (n = 1), maximum clinical benefit (n = 1), completion of treatment as per protocol (n = 13), not reported (n = 1), and additional (other) reasons (n = 12: Investigator's decision [n=4], and each 1 subject: loss of clinical performance, tubulointerstitial nephritis, hyperthyroidism and eating disorder, 'double cancer', delay more than 12 weeks due to subject refusal, internal bleeding, 'patient returned to Taitung for treatment', attend another trial')
(i) Included death (n = 4), maximum clinical benefit (n = 4), and additional (other) reasons (n = 15: Investigator's decision [n=3], Investigator's decision due to perception of no additional benefit to subject [n=3], Investigator's concern of clinical risk or toxicity to subject [n=2], worsened status of subject [n=2], and each 1 subject: 'CCR data met discontinuation', withdrawal of consent about visiting for exam, for the treatment of membranous nephropathy, 'independent central review judged PD', 'good response to chemotherapy',

In CA209648, 1358 subjects were enrolled, and 970 subjects were randomized; this includes 321

subjects in the nivo + chemo arm and 324 subjects in the chemo arm. A total of 936 subjects were treated; this includes 310 subjects in the nivo + chemo arm and 304 subjects in the chemo arm.

Table 1. End of Treatment Period Status Summary - All Enrolled, Randomized, and Treated Subjects

	Nivo+Ipi	Nivo+Chemo	Chemo
Enrolled = 1358 (all enrolled)			
Randomized[a]	325	321	324
Treated[b]	322 (99.1)	310 (96.6)	304 (93.8)
Not Treated	3	11	20
Reason for Not Being Treated, n (%)[b]			
Disease progression	1 (0.3)	1 (0.3)	2 (0.6)
Adverse event unrelated to study drug	1 (0.3)	3 (0.9)	1 (0.3)
Subject request to discontinue study treatment	0	0	2 (0.6)
Subject withdrew consent	0	1 (0.3)	12 (3.7)
Subject no longer meets study criteria	0	4 (1.2)	2 (0.6)
Other	1 (0.3)	2 (0.6)	1 (0.3)
Continuing in the Treatment Period, n (%)[c]	21 (6.5)	25 (8.1)	4 (1.3)
Not Continuing in the Treatment Period, n (%)[c]	301 (93.5)	285 (91.9)	300 (98.7)
Reason for Not Continuing in the Treatment Period, n (%)[c]			
Disease progression	174 (54.0)	184 (59.4)	193 (63.5)
Study drug toxicity	59 (18.3)	33 (10.6)	40 (13.2)
Death	5 (1.6)	3 (1.0)	4 (1.3)
Adverse event unrelated to study drug	19 (5.9)	28 (9.0)	12 (3.9)
Subject request to discontinue study treatment	13 (4.0)	15 (4.8)	20 (6.6)
Subject withdrew consent	3 (0.9)	4 (1.3)	12 (3.9)
Pregnancy	1 (0.3)	0	0
Maximum clinical benefit	1 (0.3)	3 (1.0)	4 (1.3)
Completed therapy as per protocol	13 (4.0)	8 (2.6)	0
Other	12 (3.7)	7 (2.3)	15 (4.9)
Not reported	1 (0.3)	0	0
Continuing in the Study, n (%)[c]	93 (28.9)	91 (29.4)	61 (20.1)
Not Continuing in the Study, n (%)[c]	229 (71.1)	219 (70.6)	243 (79.9)
Reason for Not Continuing in the Study , n (%)[c]			
Death	206 (64.0)	196 (63.2)	216 (71.1)
Subject withdrew consent	16 (5.0)	19 (6.1)	27 (8.9)
Lost to follow-up	2 (0.6)	1 (0.3)	0
Other	5 (1.6)	3 (1.0)	0

[a] Percentages based on subjects entering period.

[b] Percentages based on number of randomized subjects

[c] Percentages based on number of treated subjects

Abbreviations: Chemo - chemotherapy; CSR - clinical study report; Ipi - ipilimumab; Nivo - nivolumab; PD-L1 - programmed cell death protein ligand 1, ROW - rest of world

Recruitment

Enrolment in CA209648 study started on 29-June-2017 and was closed on 22-Nov-2019. The clinical cut-off occurred on 18-Jan-2021 (LPLV), clinical DBL occurred on 01-Mar-2021. The study is ongoing.

This study was conducted at 187 sites in 26 countries (Argentina, Australia, Austria, Brazil, Canada, Chile, China, Colombia, Czech Republic, Denmark, France, Hong Kong, Italy, Japan, Mexico, Peru, Poland, Republic of Korea, Romania, Russian Federation, Singapore, Spain, Taiwan, Turkey, United Kingdom [UK], and United States [US]). A total of 182 sites enrolled subjects (subjects were randomized at 175 sites).

Conduct of the study

Protocol amendments

The original protocol for this study was dated 01-Jun-2016. As of the 01-Mar-2021 DBL, there were a total of 5 global protocol revisions, with 1 global amendment; 12 country-specific revised protocols (5 in the UK, 7 in France) and 12 country-specific amendments to address local requirements; 2 global administrative letters, and 1 country-specific administrative letter.

Key global changes to the CA209648 protocol are explained as follows:

- Revised Protocol 01 incorporating Protocol Amendment 02 (dated 21-Dec-2016) changed CA209648 (originally planned as a Phase 2, 2-arm study of nivolumab plus ipilimumab vs. chemotherapy in oesophageal and gastric cancer) into a randomized global, Phase 3, 3-arm study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin compared with cisplatin and fluorouracil in subjects with inoperable advanced, recurrent or metastatic, previously untreated OSCC. The expansion of the oesophageal cohort into a 3-arm randomized Phase 3 study addressed a high unmet medical need in 1L OSCC. The gastric cohort was removed. This amendment applied to all sites. Note that enrolment to CA209648 was initiated after the approval and implementation of Amendment 02 (i.e., no subjects were enrolled prior to Amendment 02).
- Revised Protocol 05 (dated 29-Oct-2020) added another trigger for the interim analysis (Final PFS/Interim OS).

  Per Revised Protocol 01, the planned interim analysis (PFS final analysis and OS interim analysis) was to be triggered when 136 PFS events per BICR were observed among subjects expressing at least 1% tumour cell PD-L1 in the chemotherapy arm (Arm C). PFS event tracking was conducted by an independent external statistical group (AXIO), which supported statistical analyses and generated reports for review by an independent DMC. BMS remained blinded to the number of PFS events in Arm A and Arm B. Event tracking commenced in Jul-2020. PFS events were observed to be tracking at a much slower rate than projected per protocol. This was largely due to censoring due to the start of subsequent therapy or withdrawal of consent prior to progression, the extent of which was unforeseen when the Revised Protocol 01 was developed.

  The revised protocol allowed for the final PFS analysis to be triggered when 136 PFS events per BICR were observed among the subjects with tumour cell PD-L1 ≥ 1% in the chemotherapy arm, or when at least 12 months minimum follow-up (defined as the time from the date the last patient was randomized to the clinical cut-off date) was reached. In the eventuality that the target number of PFS events was not reached, the 12 months minimum follow-up ensured adequate follow-up for PFS in this patient population. As per original design, OS IA was to be

conducted at the same time as PFS FA, and the alpha allocation was to be calculated per the specified method.

Table 2. Summary of key global changes to Protocol CA209648

Document (Amendment) / Date	Summary of Key Global Changes	Planned Sample Size	Total No. of Subjects Randomized Prior to Protocol Revision or Amendment
Revised Protocol 01 (Amendment 02) / 21-Dec-2016	• CA209648 (originally planned as a Phase 2 study in esophageal and gastric cancer) was amended into a randomized global Phase 3 study of nivo + ipi or nivo + chemo compared with chemo (cisplatin and fluorouracil) in subjects with inoperable advanced, recurrent or metastatic, previously untreated OSCC. The expansion of the esophageal cohort into a 3-arm randomized Phase 3 study addresses a high unmet medical need in first line OSCC. The gastric cohort was removed.	939	0
Revised Protocol 02 / 25-Oct-2017	• Clarified terminology in description of study subjects, replacing "inoperable" with "unresectable" advanced, recurrent or metastatic esophageal squamous cell carcinoma to ensure consistency of terminology used across the study protocol. • Rationale for Arm B nivolumab dose updated to reflect current approval by FDA of nivolumab 240 mg Q2W for a variety of tumour types, and under review by other health authorities. • Clarified that an evaluable PD-L1 IHC test result by central lab would be required for randomization. • Other changes to align with the IB, simplify procedures, and provide clarifications.	939	17
Revised Protocol 03 / 02-Feb-2018	• Removed the procedures for the reinitiation of nivo ± ipi treatment after disease progression for up to 1 additional year. In addition, it added clarification to the treatment beyond progression procedures to limit treatment to a maximum duration of 24 months. There is minimal, if any, benefit derived from continuing IO treatment beyond 2 years in advanced tumours. Treatment beyond 2 years is no longer allowed in studies with nivolumab.	939	70
Revised Protocol 04 / 12-Sep-2018	• Restricted study entry to participants of previous nivolumab clinical studies where OS was listed as a primary or co-primary endpoint since participation in CA209648 could confound the interpretation of efficacy results in these studies. • Live /attenuated vaccines were prohibited to address any potential safety risks. • Inclusion criterion related to renal function assessment was expanded to allow consideration of measured creatinine clearance instead of calculated creatinine clearance per Cockcroft-Gault formula on the basis that measured creatinine clearance represents an accurate estimation of glomerular filtration rate. • Cisplatin infusion times longer than 120 minutes were allowed if deemed necessary by investigator per local standard of care/local label. • PFS2/TSST was added as an exploratory endpoint to help understand the relevance of meaningful improvements in PFS.	939	316

Document (Amendment) / Date	Summary of Key Global Changes	Planned Sample Size	Total No. of Subjects Randomized Prior to Protocol Revision or Amendment
	• Biomarker assessments section was revised to reflect current prioritizations in the biomarker analyses plan. • Program updates were added and internal inconsistencies were corrected.		
Revised Protocol 05 / 29-Oct-2020	• Added provision for triggering the planned IA when at least 12 months minimum follow-up is reached, in the eventuality that the planned 136 PFS events per BICR among subjects with tumour cell PD-L1 ≥1% in the chemotherapy arm was unlikely to be reached. If the target number of PFS events was not reached, the 12 months minimum follow-up ensured adequate follow-up for PFS in this patient population.	939	970

Protocol deviations

Important Protocol Deviations (IPDs), previously known as Significant Protocol Deviations (SPDs), are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

A total of 404 IPDs/SPDs were reported among all enrolled subjects.

Table 3. Summary of Important/Significant Protocol Deviations - All Enrolled Subjects

Protocol Deviation Category	Protocol Deviation	Not randomized	Randomized to Nivo + Chemo	Randomized to Nivo + Ipi	Randomized to Chemo	Total No. of IPDs
Overall Total of IPDs/SPDs		**6**	**151**	**115**	**132**	**404**
Discontinuation		**0**	**4**	**0**	**1**	**5**
	Dosing continued after discontinuation criteria met [a]	0	4	0	1	5
Inclusion/Exclusion Criteria		**0**	**1**	**2**	**4**	**7**
	Failure to meet inclusion criteria	0	1	2	3	6
	Subject met exclusion criteria	0	0	0	1	1
Informed Consent / Ethics (IEC/IRB)		**2**	**14**	**10**	**17**	**43**
	Implementation of protocol changes prior to IRB/IEC review or failure to implement IRB/IEC approved amendment	1	4	7	7	19
	Subject not re-consented in a timely manner	1	4	1	9	15
	Consent for treatment beyond progression not signed	0	4	1	1 [b]	6
	Deficiency in consent process	0	2	1	0	3
Prohibited Concomitant Medication		**0**	**3**	**3**	**5**	**11**
	Prohibited concomitant medication or concurrent therapy	0	3	3	5	11

Protocol Deviation Category	Protocol Deviation	Not randomized	Randomized to Nivo + Chemo	Randomized to Nivo + Ipi	Randomized to Chemo	Total No. of IPDs
Safety Reporting		**4**	**33**	**23**	**31**	**91**
	Failure to report SAE within the required window per protocol	4	33	23	31	91
Study Intervention (Study Treatment)		**0**	**26**	**11**	**19**	**56**
	Dose administration error	0	15	6	10	31
	Dose not delayed or reduced per protocol	0	9	0	4	13
	IRT stratification error	0	2	5	5	12
Trial Procedures		**0**	**70**	**66**	**55**	**191**
	Baseline procedures not performed per protocol	0	6	7	11	24
	Dosing visit schedule not maintained	0	22	18	4	44
	First dose of study treatment greater than 5 days after randomization	0	6	2	1	9
	Tumor tissue used for eligibility greater than maximum time prior to randomization	0	4	2	2	8
	Pregnancy testing not performed per protocol	0	0	2	3	5
	Required labs not performed prior to dosing	0	0	2	1	3
	Tumor assessment missed or performed out of window per protocol	0	32	33	33	98

Note that the grand total is the sum of all IPDs/SPDs, but not the total of all subjects with IPDs/SPDs, as one subject may have more than one deviation.

The window for tumor assessments were every 6 weeks (±7 days) from first dose up to and including Week 48, then every 12 weeks (±7 days) regardless of treatment schedule until disease progression (unless treatment beyond progression was permitted). The SAE reporting window was 24 hours.

[a] Treatment discontinuation criteria are listed in Section 4.5.5 of the CA209648 protocol.
[b] For Subject CA209648-xx-xxxx (chemo arm), as part of continued periodic, administrative review of PDs, it was discovered after the Erratum to the CA209648 Primary CSR was prepared that this occurrence did not meet criteria for an IPD. The subject was recorded as having progressed, and discontinued treatment 9 days later.

Relevant protocol deviations (RPDs) are IPDs that could affect the interpretability of key study results, are programmable deviations from clinical database, and are protocol-specific.

A total of 5 (0.5%) subjects reported with at least 1 RPD among all randomized subjects; the proportions of subjects with at least 1 RPD and the individual RPDs were as follows:

Nivo + chemo (2 subjects [0.6%]):

- 1 subject (0.3%) at study entry without squamous cell carcinoma or adenosquamous cell carcinoma of the oesophagus. This subject had sarcomatoid carcinoma of the esophagus and was randomized but never treated.
- 1 subject (0.3%) was reported by the investigator to have received concurrent anti-cancer therapies, specifically botanical formulations and traditional medicines used for cancer treatment: Glycyrrhiza spp. root, Panax ginseng root, and taxus wallichiana. Its use by this subject was considered as a prohibited concomitant medication. However, this particular therapy is not

considered as anti-cancer therapy by the Sponsor, and is, thus, not a prohibited concomitant medication for this study.

Nivo + ipi: 0 subjects

Chemo (3 subjects [0.9%]):

- 1 subject (0.3%) without measurable disease at baseline.
- 2 subjects (0.6%) who received concurrent anti-cancer therapies, specifically botanical formulations and traditional medicines used for cancer treatment: Astragalus spp. root, cantharidin, Eleutherococcus senticosus root with rhizome, and Panax ginseng root.

Table 4. Relevant Protocol Deviations Summary - All Randomized Subjects

	Number of Subjects (%)			
	Nivo + Ipi N = 325	Nivo + Chemo N = 321	Chemotherapy N = 324	Total N = 970
SUBJECTS WITH AT LEAST ONE DEVIATION	0	2 (0.6)	3 (0.9)	5 (0.5)
AT ENTRANCE				
SUBJECTS WITHOUT SQUAMOUS CELL CARCINOMA OR ADENOSQUAMOUS CELL CARCINOMA OF ESOPHAGUS	0	1 (0.3)	0	1 (0.1)
SUBJECTS WITH NO UNRESECTABLE ADVANCED, RECURRENT OR METASTATIC ESCC	0	1 (0.3)	0	1 (0.1)
SUBJECTS WHO HAVE RECEIVED PRIOR SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE	0	0	0	0
SUBJECT WITH BASELINE ECOG PERFORMANCE STATUS > 1	0	0	0	0
SUBJECTS WITHOUT ANY MEASURABLE DISEASE AT BASELINE	0	0	1 (0.3)	1 (0.1)
SUBJECTS WITHOUT ANY TUMOR CELL PD-L1 RESULT	0	0	0	0
ON-TREATMENT				
SUBJECTS RECEIVING CONCURRENT ANTI-CANCER THERAPY	0	1 (0.3)	2 (0.6)	3 (0.3)
SUBJECT TREATED DIFFERENTLY AS RANDOMIZED	0	0	0	0

Baseline data

Table 5. Key Demographic and Baseline Characteristics - All Randomized Subjects

	Nivo+Ipi N=325	Nivo+Chemo N=321	Chemo N=324	Total N=970
Age				
Mean (SD) (y)	62.2 (9.1)	63.1 (9.2)	63.3 (8.7)	62.9 (9.0)
Median (min, max) (y)	63.0 (28, 81)	64.0 (40, 90)	64.0 (26, 81)	64.0 (26, 90)
<65	185 (56.9)	167 (52.0)	166 (51.2)	518 (53.4)
≥65	140 (43.1)	154 (48.0)	158 (48.8)	452 (46.6)
≥65 - <75	116 (35.7)	123 (38.3)	129 (39.8)	368 (37.9)
≥75	24 (7.4)	31 (9.7)	29 (9.0)	84 (8.7)
Sex				
Male	269 (82.8)	253 (78.8)	275 (84.9)	797 (82.2)
Female	56 (17.2)	68 (21.2)	49 (15.1)	173 (17.8)
Race				
White	79 (24.3)	85 (26.5)	84 (25.9)	248 (25.6)
Black or African American	4 (1.2)	1 (0.3)	6 (1.9)	11 (1.1)
American Indian or Alaska Native	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.4)
Asian Indian	1 (0.3)	4 (1.2)	3 (0.9)	8 (0.8)
Chinese	71 (21.8)	74 (23.1)	70 (21.6)	215 (22.2)
Japanese	131 (40.3)	126 (39.3)	137 (42.3)	394 (40.6)
Asian Other	28 (8.6)	23 (7.2)	17 (5.2)	68 (7.0)
Other	10 (3.1)	6 (1.9)	6 (1.9)	22 (2.3)
IRT Stratification Factors:				
Tumour Cell PD-L1 Expression				
≥1%	158 (48.6)	158 (49.2)	157 (48.5)	473 (48.8)
<1% or indeterminate	167 (51.4)	163 (50.8)	167 (51.5)	497 (51.2)
Region				

	Nivo+Ipi N=325	Nivo+Chemo N=321	Chemo N=324	Total N=970
East Asia (Japan, Korea, Taiwan)	185 (56.9)	183 (57.0)	184 (56.8)	552 (56.9)
Rest of Asia (China, Hong Kong, Singapore)	44 (13.5)	42 (13.1)	42 (13.0)	128 (13.2)
Rest of World	96 (29.5)	96 (29.9)	98 (30.2)	290 (29.9)
ECOG PS				
0	151 (46.5)	150 (46.7)	154 (47.5)	455 (46.9)
1	174 (53.5)	171 (53.3)	170 (52.5)	515 (53.1)
Number of organs with metastases (BICR)				
≤1	160 (49.2)	158 (49.2)	158 (48.8)	476 (49.1)
≥2	165 (50.8)	163 (50.8)	166 (51.2)	494 (50.9)
Country by Geographic Region (per CRF)				
Asia	229 (70.5)	225 (70.1)	226 (69.8)	680 (70.1)
Non-Asia	96 (29.5)	96 (29.9)	98 (30.2)	290 (29.9)
Tumour Cell PD-L1 Expression (CRF), n/N (%)				
Tumour cell PD-L1 quantifiable at baseline	322/325 (99.1)	321/321 (100.0)	322/324 (99.4)	965/970 (99.5)
≥1%	158/322 (49.1)	158/321 (49.2)	156/322 (48.4)	472/965 (48.9)
<1%	164/322 (50.9)	163/321 (50.8)	166/322 (51.6)	493/965 (51.1)
≥5%	120/322 (37.3)	120/321 (37.4)	115/322 (35.7)	355/965 (36.8)
<5%	202/322 (62.7)	201/321 (62.6)	207/322 (64.3)	610/965 (63.2)
≥10%	103/322 (32.0)	102/321 (31.8)	97/322 (30.1)	302/965 (31.3)
<10%	219/322 (68.0)	219/321 (68.2)	225/322 (69.9)	663/965 (68.7)
Indeterminate	3/325 (0.9)	0	2/324 (0.6)	5/970 (0.5)
Weight (kg)				
Mean (SD)	58.819 (11.218)	58.014 (12.509)	60.140 (11.141)	58.994 (11.657)
Median (Min, Max)	58.000 (25.70, 103.80)	57.000 (29.60, 125.20)	58.900 (33.90, 105.20)	58.050 (25.70, 125.20)
Histology				
Squamous cell carcinoma	322 (99.1)	311 (96.9)	318 (98.1)	951 (98.0)
Adenosquamous cell carcinoma	3 (0.9)	9 (2.8)	6 (1.9)	18 (1.9)
Other	0	1 (0.3)	0	1 (0.1)
Disease status at current diagnosis				
De novo metastatic	196 (60.3)	184 (57.3)	187 (57.7)	567 (58.5)
Recurrent - distant	73 (22.5)	72 (22.4)	60 (18.5)	205 (21.1)
Recurrent - loco-regional	25 (7.7)	21 (6.5)	25 (7.7)	71 (7.3)
Unresectable advanced	31 (9.5)	44 (13.7)	52 (16.0)	127 (13.1)
Disease stage at initial diagnosis				
Stage I-III	115 (35.4)	114 (35.5)	117 (36.1)	346 (35.7)
Stage IV	208 (64.0)	206 (64.2)	206 (63.6)	620 (63.9)
Not reported	2 (0.6)	1 (0.3)	1 (0.3)	4 (0.4)
Location at initial diagnosis				
Upper thoracic	64 (19.7)	60 (18.7)	51 (15.7)	175 (18.0)
Middle thoracic	131 (40.3)	121 (37.7)	134 (41.4)	386 (39.8)
Lower thoracic	103 (31.7)	112 (34.9)	119 (36.7)	334 (34.4)
Gastroesophageal junction	25 (7.7)	28 (8.7)	18 (5.6)	71 (7.3)
Not reported	2 (0.6)	0	2 (0.6)	4 (0.4)
Smoking status				
Current/former	268 (82.5)	254 (79.1)	256 (79.0)	778 (80.2)
Never smoker	57 (17.5)	67 (20.9)	68 (21.0)	192 (19.8)
Alcohol use				
Current/former	260 (80.0)	246 (76.6)	250 (77.2)	756 (77.9)
Never	65 (20.0)	75 (23.4)	74 (22.8)	214 (22.1)
Time from Initial Disease Diagnosis to Randomization				

	Nivo+Ipi N=325	Nivo+Chemo N=321	Chemo N=324	Total N=970
< 6 months	224 (68.9)	227 (70.7)	240 (74.1)	691 (71.2)
6 months - < 1 year	19 (5.8)	25 (7.8)	18 (5.6)	62 (6.4)
1 - < 2 years	51 (15.7)	38 (11.8)	34 (10.5)	123 (12.7)
2 - < 3 years	15 (4.6)	14 (4.4)	15 (4.6)	44 (4.5)
3 - < 4 years	8 (2.5)	8 (2.5)	4 (1.2)	20 (2.1)
4 - < 5 years	4 (1.2)	6 (1.9)	6 (1.9)	16 (1.6)
≥ 5 years	3 (0.9)	3 (0.9)	7 (2.2)	13 (1.3)
Not reported	1 (0.3)	0	0	1 (0.1)

Tumour Cell PD-L1

Among all randomized subjects, 321 (100%), 322 (99.1%), and 322 (99.4%) of subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively, had quantifiable tumour cell PD-L1 expression at baseline. Among all randomized subjects with quantifiable tumour cell PD-L1 expression at baseline, tumour cell PD-L1 levels were well balanced across the nivo + chemo, nivo + ipi, and chemo arms.

The 5 (0.5%) subjects with indeterminate tumour cell PD-L1 expression among all randomized subjects were considered as having tumour cell PD-L1 < 1% for IRT-based stratification but were considered separately in subgroup analyses of efficacy and were not included in the safety subgroups analyses.

Table 6. Frequency of PD-L1 Tumour Cell Expression Status - All Randomized Subjects

Population PD-L1 Expression Category	Nivo + Ipi N = 325	Nivo + Chemo N = 321	Chemotherapy N = 324	Total N = 970
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE (N(%))	0	0	0	0
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	322 (99.1)	321 (100.0)	322 (99.4)	965 (99.5)
PD-L1 EXPRESSION (%)				
MEAN	14.9	13.9	13.7	14.2
MEDIAN	0.0	0.0	0.0	0.0
MIN , MAX	0 , 100	0 , 100	0 , 100	0 , 100
Q1 , Q3	0.0 , 20.0	0.0 , 20.0	0.0 , 10.0	0.0 , 15.0
STANDARD DEVIATION	26.1	24.5	25.1	25.2
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	158/322 (49.1)	158/321 (49.2)	156/322 (48.4)	472/965 (48.9)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	164/322 (50.9)	163/321 (50.8)	166/322 (51.6)	493/965 (51.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	120/322 (37.3)	120/321 (37.4)	115/322 (35.7)	355/965 (36.8)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	202/322 (62.7)	201/321 (62.6)	207/322 (64.3)	610/965 (63.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 10%	103/322 (32.0)	102/321 (31.8)	97/322 (30.1)	302/965 (31.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 10%	219/322 (68.0)	219/321 (68.2)	225/322 (69.9)	663/965 (68.7)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE (N(%))	3 (0.9)	0	2 (0.6)	5 (0.5)
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	0	0	0	0

Previous treatments

Among all randomized subjects, 23.3% received prior systemic anticancer therapy in the adjuvant, neo-adjuvant, or definitive chemotherapy/radiotherapy/chemoradiotherapy (CRT) treatment setting, with similar proportions of subjects observed across treatment arms. Prior surgery related to cancer or radiotherapy was reported in 29.7% and 19.9% of subjects, respectively, and similar proportions of subjects were observed across treatment arms.

Note that, due to a data entry error, 1 (0.4%) subject in the chemo arm was reported to have received prior treatment in the metastatic setting with vinorelbine; however, this subject received vinorelbine as subsequent therapy.

In subjects with prior systemic therapy, the time from prior systemic treatment in the adjuvant, neo-adjuvant, or definitive CRT treatment setting to randomization was similar across treatment arms, with

study treatment for most subjects starting 6 to < 12 months (39.6%) or ≥ 12 months (53.8%) after prior treatment.

Table 7. Prior Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)			
	Nivo + Ipi N = 325	Nivo + Chemo N = 321	Chemotherapy N = 324	Total N = 970
TYPE OF PRIOR SYSTEMIC THERAPY RECEIVED (A)				
ANY PRIOR SYSTEMIC THERAPY	81 (24.9)	72 (22.4)	73 (22.5)	226 (23.3)
NO PRIOR SYSTEMIC THERAPY	244 (75.1)	249 (77.6)	251 (77.5)	744 (76.7)
SETTING OF PRIOR SYSTEMIC THERAPY REGIMEN RECEIVED (A) (F)				
ADJUVANT THERAPY	17 (21.0)	10 (13.9)	12 (16.4)	39 (17.3)
METASTATIC THERAPY	0	0	1 (1.4)	1 (0.4)
NEO-ADJUVANT THERAPY	42 (51.9)	45 (62.5)	38 (52.1)	125 (55.3)
DEFINITIVE CRT THERAPY	24 (29.6)	18 (25.0)	26 (35.6)	68 (30.1)
TIME FROM COMPLETION OF PRIOR ADJUVANT/NEO-ADJUVANT/DEFINITIVE THERAPY TO TREATMENT (B)				
< 6 MONTHS	2 (2.5)	1 (1.4)	3 (4.2)	6 (2.7)
6 - < 12 MONTHS	31 (38.3)	30 (41.7)	28 (38.9)	89 (39.6)
>= 12 MONTHS	47 (58.0)	36 (50.0)	38 (52.8)	121 (53.8)
NOT REPORTED	1 (1.2)	5 (6.9)	3 (4.2)	9 (4.0)
PRIOR SURGERY RELATED TO CANCER				
YES	215 (66.2)	217 (67.6)	207 (63.9)	639 (65.9)
NO	110 (33.8)	104 (32.4)	117 (36.1)	331 (34.1)
TIME FROM PRIOR SURGERY (C)				
< 3 MONTHS	166 (77.2)	153 (70.5)	156 (75.4)	475 (74.3)
3 - <= 6 MONTHS	8 (3.7)	16 (7.4)	10 (4.8)	34 (5.3)
> 6 MONTHS	39 (18.1)	39 (18.0)	32 (15.5)	110 (17.2)
NOT REPORTED	2 (0.9)	9 (4.1)	9 (4.3)	20 (3.1)
TYPE OF SURGERY (C)				
BIOPSY	167 (77.7)	165 (76.0)	168 (81.2)	500 (78.2)
OTHER	100 (46.5)	102 (47.0)	86 (41.5)	288 (45.1)
PRIOR SURGERY RELATED TO CANCER (EXCLUDING BIOPSY)				
YES	100 (30.8)	102 (31.8)	86 (26.5)	288 (29.7)
NO	225 (69.2)	219 (68.2)	238 (73.5)	682 (70.3)
TIME FROM PRIOR SURGERY (EXCLUDING BIOPSY) (D)				
< 3 MONTHS	27 (27.0)	20 (19.6)	17 (19.8)	64 (22.2)
3 - <= 6 MONTHS	7 (7.0)	15 (14.7)	9 (10.5)	31 (10.8)
> 6 MONTHS	64 (64.0)	61 (59.8)	55 (64.0)	180 (62.5)
NOT REPORTED	2 (2.0)	6 (5.9)	5 (5.8)	13 (4.5)
TYPE OF SURGERY (EXCLUDING BIOPSY) (D)				
TOTAL	100	102	86	288
TRANSTHORACIC ESOPHAGECTOMY	21 (21.0)	31 (30.4)	22 (25.6)	74 (25.7)
TRANSHIATAL ESOPHAGECTOMY	2 (2.0)	2 (2.0)	1 (1.2)	5 (1.7)
THORACOABDOMINAL ESOPHAGECTOMY	26 (26.0)	18 (17.6)	14 (16.3)	58 (20.1)
MINIMALLY INVASIVE ESOPHAGECTOMY	9 (9.0)	11 (10.8)	8 (9.3)	28 (9.7)
LYMPHADENECTOMY	16 (16.0)	11 (10.8)	12 (14.0)	39 (13.5)
ENDOSCOPIC MUCOSAL RESECTION	2 (2.0)	1 (1.0)	3 (3.5)	6 (2.1)
ENDOSCOPIC SUBMUCOSAL DISSECTION	5 (5.0)	7 (6.9)	3 (3.5)	15 (5.2)
OTHER	46 (46.0)	41 (40.2)	40 (46.5)	127 (44.1)
PRIOR RADIOTHERAPY				
YES	74 (22.8)	60 (18.7)	59 (18.2)	193 (19.9)
NO	251 (77.2)	261 (81.3)	265 (81.8)	777 (80.1)
TIME FROM PRIOR RADIOTHERAPY (E)				
< 3 MONTHS	11 (14.9)	11 (18.3)	10 (16.9)	32 (16.6)
3 - <= 6 MONTHS	1 (1.4)	0	0	1 (0.5)
> 6 MONTHS	59 (79.7)	40 (66.7)	42 (71.2)	141 (73.1)
NOT REPORTED	3 (4.1)	9 (15.0)	7 (11.9)	19 (9.8)

(A) Some subjects may have been treated with more than 1 type of therapy.
(B) Percentages are based on subjects with prior adjuvant/neo-adjuvant/definitive therapy.
(C) Percentages are based on subjects with prior surgery related to cancer.
(D) Percentages are based on subjects with prior surgery related to cancer (excluding biopsy).
(E) Percentages are based on subjects with prior radiotherapy.
(F) Percentages are based on subjects with any prior systemic therapy.

Among all randomized subjects (N = 970), 226 (23.3%) subjects received anti-neoplastic agents, which were primarily cisplatin (16.2%) and/or fluorouracil (15.6%). These drugs were used at similar proportions across the treatment arms:

- Nivo + chemo arm: 15.3% received prior cisplatin and 16.8% received prior fluorouracil
- Nivo + ipi arm: 17.8% received prior cisplatin and 14.5% received prior fluorouracil
- Chemo arm: 15.4% received prior cisplatin and 15.4% received prior fluorouracil

No subject received immunotherapy prior to randomization.

Subsequent anti-cancer therapy

More subjects in the chemo arm (62.7%) compared with the nivo + chemo (50.8%) and nivo + ipi (51.7%) arms initiated any subsequent therapy. Proportions of all randomized subjects who received subsequent cancer therapy in the nivo + chemo, nivo + ipi, and chemo arms were as follows, respectively:

- Subsequent systemic therapy: 46.4%, 46.5%, and 55.9%.
- Subsequent anti-PD-(L)1 immunotherapy: 5.0%, 4.3%, and 15.7%

One subject in the nivo + ipi arm received ipilimumab in combination with nivolumab as subsequent therapy.

Table 8. Subsequent Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)		
	Nivo + Ipi N = 325	Nivo + Chemo N = 321	Chemotherapy N = 324
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	168 (51.7)	163 (50.8)	203 (62.7)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	75 (23.1)	70 (21.8)	91 (28.1)
RADIOTHERAPY FOR TREATMENT OF TUMORS (%)			
CURATIVE	5 (1.5)	9 (2.8)	8 (2.5)
PALLIATIVE	70 (21.5)	62 (19.3)	83 (25.6)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	4 (1.2)	9 (2.8)	9 (2.8)
SURGERY FOR TREATMENT OF TUMORS (%)			
TUMOR RESECTION CURATIVE	1 (0.3)	1 (0.3)	4 (1.2)
TUMOR RESECTION PALLIATIVE	3 (0.9)	8 (2.5)	4 (1.2)
OTHER	0	0	1 (0.3)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	151 (46.5)	149 (46.4)	181 (55.9)
ANTI-PD1	14 (4.3)	16 (5.0)	51 (15.7)
NIVOLUMAB	12 (3.7)	13 (4.0)	38 (11.7)
CAMRELIZUMAB	1 (0.3)	0	2 (0.6)
PEMBROLIZUMAB	1 (0.3)	2 (0.6)	6 (1.9)
BI 754091	0	0	1 (0.3)
SINTILIMAB	0	1 (0.3)	2 (0.6)
SUGEMALIMAB	0	0	1 (0.3)
TISLELIZUMAB	0	0	1 (0.3)
TORIPALIMAB	0	0	1 (0.3)
ANTI-CTLA4	1 (0.3)	0	0
IPILIMUMAB	1 (0.3)	0	0
OTHER SYSTEMIC ANTICANCER THERAPY	149 (45.8)	148 (46.1)	167 (51.5)
FLUOROURACIL	108 (33.2)	43 (13.4)	64 (19.8)
CISPLATIN	102 (31.4)	33 (10.3)	45 (13.9)
PACLITAXEL	51 (15.7)	75 (23.4)	85 (26.2)
DOCETAXEL	30 (9.2)	44 (13.7)	41 (12.7)
OXALIPLATIN	16 (4.9)	12 (3.7)	12 (3.7)
CARBOPLATIN	11 (3.4)	12 (3.7)	13 (4.0)
NEDAPLATIN	11 (3.4)	18 (5.6)	16 (4.9)
GIMERACIL;OTERACIL POTASSIUM;TEGAFUR	10 (3.1)	16 (5.0)	15 (4.6)
IRINOTECAN	9 (2.8)	3 (0.9)	10 (3.1)
CAPECITABINE	8 (2.5)	2 (0.6)	0
ASTRAGALUS PROPINQUUS ROOT;OXYMATRINE;PANAX GINSENG DRY EXTRACT	2 (0.6)	0	1 (0.3)
BEVACIZUMAB	2 (0.6)	0	1 (0.3)
GEMCITABINE HYDROCHLORIDE	2 (0.6)	4 (1.2)	1 (0.3)

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

Note: The complete table has not been included in the AR and only a summary of most frequent "other systemic anticancer therapy" has been kept.

Numbers analysed

Table 9. Analysis populations presented in CA209648

Population	Nivo+Ipi	Nivo+Chemo	Chemo	Total
Enrolled Subjects				1358
All Randomized Subjects	325	321	324	970
Tumor Cell PD-L1 ≥1%	158	158	157	473
Quantifiable Tumor Cell PD-L1	322	321	322	965
Quantifiable PD-L1 by CPS	297	305	304	906
All Treated Subjects	322	310	304	936

Abbreviations: Chemo - chemotherapy; CPS - combined positive score; CSR - clinical study report; Ipi - ipilimumab; Nivo - nivolumab; PD-L1 - programmed cell death protein ligand 1

Outcomes and estimation

The initial analyses of efficacy data were based on a clinical data cut-off of 18-Jan-2021 (LPLV) and a clinical database lock (DBL) of 01 Mar-2021. Minimum follow-up (date the last patient was randomized to the clinical cut-off date) for OS was 12.9 months for the comparison of nivo + chemo vs. chemo and 13.1 months for the comparison of nivo + ipi vs. chemo. Across arms, the median follow-up was 23.7 months (range: 12.9, 40.7 months).

During the procedure, updated efficacy data with a minimum follow-up of 20 months based on a DBL of 04-Oct-2021 were provided.

Data presented below are based on the initial DBL (01 Mar 2021) unless otherwise specified.

Table 10. Results of the statistical testing hierarchy for Study CA209648

		Nivo+Chemo vs Chemo			Nivo+Ipi vs Chemo		
Hierarchy	**Study Population**	**Significance Level Threshold (overall alpha for OS)**	**p-value**	**Met the Threshold?**	**Significance Level Threshold (overall alpha for OS)**	**p-value**	**Met the Threshold?**
Primary Endpoints:							
OS	All Randomized Subjects with Tumour Cell PD-L1 Expression ≥1%	0.005[a] (0.01)	<0.0001	Yes	0.014[c] (0.02[d])	0.0010	Yes
PFS per BICR	All Randomized Subjects with Tumour Cell PD-L1 Expression ≥1%	0.015	0.0023	Yes	0.015	0.8958	No
Secondary Endpoints:							
OS	All Randomized Subjects	0.009[b] (0.01)	0.0021	Yes	0.018[e] (0.02)	0.0110	Yes
PFS per BICR	All Randomized Subjects	0.015	0.0355	No	N.A.	N.A.	Not formally tested
ORR per BICR	All Randomized Subjects with Tumour Cell PD-L1 Expression ≥1%	N.A.	N.A.	Not formally tested	N.A.	N.A.	Not formally tested

		Nivo+Chemo vs Chemo			Nivo+Ipi vs Chemo		
Hierarchy	**Study Population**	**Significance Level Threshold (overall alpha for OS)**	**p-value**	**Met the Threshold?**	**Significance Level Threshold (overall alpha for OS)**	**p-value**	**Met the Threshold?**
ORR per BICR	All Randomized Subjects	N.A.	N.A.	Not formally tested	N.A.	N.A.	Not formally tested

[a] Based on O'Brien-Fleming alpha spending function with 87.6% (219/250) observed information fraction at interim.

[b] Based on Pocock alpha spending function with 85.8% (441/514) observed information fraction at interim.

[c] Based on O'Brien-Fleming alpha spending function with 90.8% (227/250) observed information fraction at interim.

[d] The overall alpha of 0.02 for OS is the sum of 1) an initial allocated overall alpha of 0.01 for OS in all randomized subjects with tumour cell PD-L1 expression ≥ 1% for nivo + ipi vs chemo and 2) 0.01 alpha passed from the secondary OS endpoint in all randomized subjects for nivo + chemo vs chemo.

[e] Based on Pocock alpha spending function with 87.2% (448/514) observed information fraction at interim.

Table 11. Summary of Key Efficacy Results - Nivolumab + Chemotherapy vs. Chemotherapy - All Randomized Subjects with Tumour Cell PD-L1 ≥1% and All Randomized Subjects

	All Randomized Subjects with Tumour Cell PD-L1 ≥1%		**All Randomized Subjects**	
Efficacy Parameter	**Nivo+Chemo N = 158**	**Chemo N = 157**	**Nivo+Chemo N= 321**	**Chemo N = 324**
OS	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	98 (62.0)	121 (77.1)	209 (65.1)	232 (71.6)
HR (alpha-adjusted CI)[a]	0.54 (99.5% CI: 0.37, 0.80)		0.74 (99.1% CI: 0.58, 0.96)	
HR (95% CI)[a]	0.54 (0.41, 0.71)		0.74 (0.61, 0.90)	
Stratified 2-sided log-rank test p-value[b]	< 0.0001		0.0021	
Median OS, mo (95% CI)[c]	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)	13.21 (11.14, 15.70)	10.71 (9.40, 11.93)
OS Rate (95% CI),[c] %				
At 6 mo.	82.77 (75.88, 87.84)	72.80 (64.83, 79.26)	80.41 (75.60, 84.38)	75.85 (70.65, 80.26)
At 12 mo.	57.99 (49.79, 65.32)	37.07 (29.22, 44.91)	53.53 (47.83, 58.90)	44.32 (38.63, 49.85)
PFS per BICR	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	117 (74.1)	100 (63.7)	235 (73.2)	210 (64.8)
HR (98.5% CI)[a]	0.65 (0.46, 0.92)		0.81 (0.64, 1.04)	
HR (95% CI)[a]	0.65 (0.49, 0.86)		0.81 (0.67, 0.99)	
Stratified 2-sided log-rank test p-value[b]	0.0023		0.0355	
Median PFS, mo. (95% CI)[c]	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)	5.82 (5.55, 7.00)	5.59 (4.27, 5.88)
PFS Rate (95% CI),[c] %				
At 6 mo.	54.79 (46.31, 62.50)	39.04 (30.07, 47.90)	49.44 (43.56, 55.04)	43.15 (36.96, 49.19)
At 12 mo.	25.41 (18.24, 33.19)	10.45 (4.71, 18.84)	23.62 (18.63, 28.95)	16.02 (11.02, 21.86)
ORR per BICR	**Secondary Endpoint**		**Secondary Endpoint**	
N Responders (ORR%)[d]	84 (53.2)	31 (19.7)	152 (47.4)	87 (26.9)
95% CI	(45.1, 61.1)	(13.8, 26.8)	(41.8, 53.0)	(22.1, 32.0)
Difference (95% CI)[e]	33.4 (23.5, 43.4)		20.6 (13.4, 27.7)	
CR, n (%)	26 (16.5)	8 (5.1)	43 (13.4)	20 (6.2)
DOR per BICR	**Exploratory Endpoint**		**Exploratory Endpoint**	
n Events/N Responders (%)	55/84 (65.5)	17/31 (54.8)	96/152 (63.2)	51/87 (58.6)

	All Randomized Subjects with Tumour Cell PD-L1 ≥1%		All Randomized Subjects	
Efficacy Parameter	**Nivo+Chemo N = 158**	**Chemo N = 157**	**Nivo+Chemo N= 321**	**Chemo N = 324**
Median, mo. (95% CI)[c]	8.38 (6.90, 12.35)	5.68 (4.40, 8.67)	8.18 (6.90, 9.69)	7.13 (5.65, 8.21)
Min, Max, mo.	1.4+, 34.6	1.4+, 31.8+	1.4+, 35.9+	1.4+, 31.8+
Proportion (95% CI)[c] with DOR of:				
≥6 mo.	0.66 (0.54, 0.76)	0.39 (0.19, 0.59)	0.64 (0.55, 0.71)	0.54 (0.41, 0.65)
≥12 mo.	0.40 (0.28, 0.51)	0.13 (0.02, 0.33)	0.39 (0.30, 0.47)	0.23 (0.13, 0.34)
PFS per Investigator	**Exploratory Endpoint**		**Exploratory Endpoint**	
Events, n (%)	121 (76.6)	122 (77.7)	247 (76.9)	249 (76.9)
HR (95% CI)[a]	0.53 (0.41, 0.69)		0.69 (0.58, 0.83)	
Median PFS, mo.(95% CI)[c]	6.93 (5.85, 8.18)	4.21 (3.06, 5.39)	6.24 (5.62, 6.93)	5.39 (4.21, 5.68)
PFS Rate (95% CI),[c] %				
At 6 mo.	57.69 (49.23, 65.26)	32.94 (24.95, 41.14)	51.49 (45.65, 57.01)	39.36 (33.52, 45.13)
At 12 mo.	27.91 (20.73, 35.51)	6.24 (2.65, 11.98)	23.69 (18.90, 28.81)	9.52 (6.14, 13.78)
PFS2/TSST per Investigator	**Exploratory Endpoint**		**Exploratory Endpoint**	
Events, n (%)	109 (69.0)	131 (83.4)	232 (72.3)	260 (80.2)
HR (95% CI)[a]	0.48 (0.37, 0.62)		0.64 (0.54, 0.77)	
Median PFS, mo.[c] (95% CI)[c]	12.52 (10.45, 14.82)	7.06 (6.54, 7.82)	11.04 (9.26, 12.52)	7.89 (7.13, 8.44)

[a] Stratified Cox proportional hazards model. HR is Nivo + Chemo over Chemo.

[b] Log-rank test stratified by ECOG PS (0 vs 1) and number of organs with metastases (≤1 vs ≥2) as recorded in IRT for All Randomized Subjects with Tumour Cell PD-L1 ≥1%, and stratified by ECOG PS, number of organs with metastases, and tumour cell PD-L1 expression (≥1% or <1% and indeterminate) as recorded in IRT for All Randomized Subjects.

[c] Based on Kaplan-Meier estimates.

[d] CR or PR per RECIST 1.1. CI based on the Clopper and Pearson method.

[e] Strata adjusted difference in objective response rate (Nivo+Chemo - Chemo) based on CMH method of weighting. Stratified by ECOG PS (0 vs 1) and number of organs with metastases (≤1 vs ≥2) as recorded in IRT for All Randomized Subjects with Tumour Cell PD-L1 ≥1%, and stratified by ECOG PS, number of organs with metastases, and tumour cell PD-L1 expression (≥1% or <1% and indeterminate) as recorded in IRT for All Randomized Subjects.

Symbol + indicates a censored value

Database lock: 01-Mar-2021. Minimum follow-up for OS was 12.9 months.

Primary endpoints

- ***Overall Survival*** *- All Randomized Subjects with Tumour Cell* ***PD-L1 ≥ 1%***

At DBL (01-Mar-2021), minimum follow-up for OS in all randomized subjects with tumour cell PD-L1 expression ≥ 1% was 12.9 months. In all randomized subjects with tumour cell PD-L1 ≥ 1%, a statistically significant improvement in OS was observed with nivo + chemo over chemo: HR = 0.54 (99.5% CI: 0.37, 0.80); stratified 2-sided log-rank test p-value < 0.0001. Median OS (95% CI) was longer in the nivo + chemo arm compared to the chemo arm: 15.44 (11.93, 19.52) vs 9.07 (7.69, 9.95) months, with non-overlapping CIs. OS rates (95% CI) were higher in the nivo + chemo arm vs chemo arm as follows:

- At 6 months: 82.77% (75.88, 87.84) vs 72.80% (64.83, 79.26)
- At 12 months: 57.99% (49.79, 65.32) vs 37.07% (29.22, 44.91)

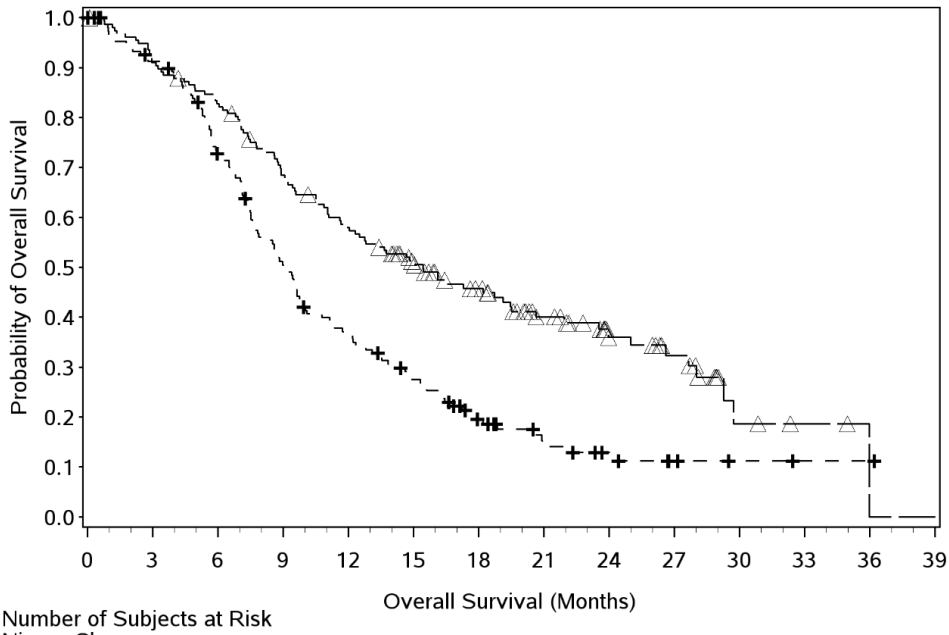
60 (38.0%) subjects in the nivo + chemo arm and 36 (22.9%) subjects in the chemo arm were censored for OS at DBL. Of the censored subjects, 10/60 (16.7%) and 0 subjects in the nivo + chemo and chemo arms, respectively, were continuing on-treatment and 38/60 (63.3%) and 19/36 (52.8%) subjects in the nivo + chemo and chemo arms, respectively, were in follow-up. The majority of subjects who were off study in the nivo + chemo (N = 12) and chemo (N = 17) arms, withdrew consent: 11/12 (91.7%) and 15/17 (88.2%), respectively.

Follow-up for OS was current for the majority of subjects: 92.4% of subjects in the nivo + chemo arm and 89.8% of subjects in the chemo arm either died or had a last known alive date on or after the clinical cut-off date (18-Jan-2021).

Results for the following **sensitivity analyses** were consistent with the primary OS analysis:

- Unstratified analysis with treatment as the single covariate: HR = 0.54 (99.5% CI: 0.37, 0.80); 2-sided unstratified log-rank test descriptive p-value < 0.0001.
- Max-combo analysis of OS data: HR = 0.51 (95% CI: 0.38, 0.67), descriptive p value < 0.0001.
- In a multivariate analysis of OS, the treatment effect of nivo + chemo vs chemo was consistent with the primary OS analysis: HR = 0.54, 95% CI: 0.41, 0.71; multivariate Cox model descriptive p value < 0.0001.

Figure 4. Kaplan-Meier Plot of Overall Survival - Nivolumab + Chemotherapy over Chemotherapy - All Randomized Subjects with Tumour Cell PD L1 ≥1%



Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs. ≥ 2) as recorded in IRT.

- ***Progression-free Survival*** *per BICR - All Randomized Subjects with Tumour Cell* ***PD-L1 ≥ 1%***

In all randomized subjects with tumour cell PD-L1 ≥ 1%, a statistically significant and clinically relevant improvement in PFS per BICR (primary definition [i.e., includes censoring for subsequent therapy]) was observed with nivo + chemo compared with chemo: HR = 0.65 (98.5% CI: 0.46, 0.92); stratified 2-sided log-rank test p-value = 0.0023. Median PFS per BICR (95% CI) was numerically longer in the nivo + chemo arm compared to the chemo arm: 6.93 (5.68, 8.34) vs 4.44 (2.89, 5.82) months. PFS rates (95% CI) were numerically higher in the nivo + chemo arm vs chemo arm, respectively, as follows:

- At 6 months: 54.79% (46.31, 62.50) vs 39.04% (30.07, 47.90)
- At 12 months: 25.41% (18.24, 33.19) vs 10.45% (4.71, 18.84)

41 (25.9%) subjects in the nivo + chemo arm and 57 (36.3%) subjects in the chemo arm were censored for PFS per BICR at DBL. The most common reason for censoring was receiving subsequent anti-cancer therapy: 21/41 (51.2%) subjects in the nivo + chemo arm and 42/57 (73.7%) subjects in the chemo arm. Of the subjects who were censored, 8/41 subjects in the nivo + chemo arm and 0 subjects in the chemo arm were still on treatment and 6/41 subjects in the nivo + chemo arm and 1/57 subjects in the chemo arm were in follow-up. All 4 of the subjects who were off study (3 in the nivo + chemo arm; 1 in the chemo arm), withdrew consent.

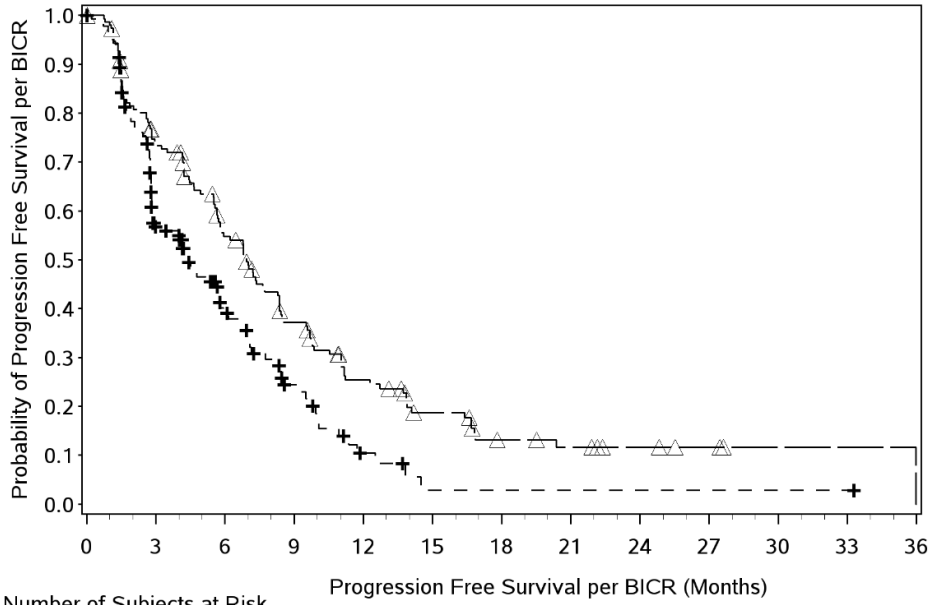
Follow-up for PFS was current for the majority of subjects: 84.8% of subjects in the nivo + chemo arm and 91.1% of subjects in the chemo arm either progressed, died, or had a last known alive date on or after the clinical cut-off date (18 Jan 2021).

Results for the following **sensitivity analyses** were consistent with the primary analysis of PFS by BICR:

- Unstratified analysis with treatment as the single covariate: HR = 0.64 (98.5% CI: 0.45, 0.90); unstratified log-rank test descriptive p-value = 0.0012.
- Max-combo analysis of PFS by BICR: HR = 0.64 (adjusted 95% CI: 0.49, 0.83), descriptive p value = 0.0086.
- In a multivariate analysis of PFS per BICR, the treatment effect of nivo + chemo vs chemo was consistent with the primary analysis: HR = 0.67, 95% CI: 0.50, 0.89; multivariate Cox model descriptive p-value = 0.0061.
- Analysis of PFS per BICR accounting for assessment on/after subsequent therapy was consistent with the primary PFS analysis: HR = 0.67 (98.5% CI: 0.49, 0.90), descriptive p-value = 0.0009.
- Analysis of PFS per BICR accounting for loss of follow-up was consistent with the primary PFS analysis: HR = 0.65 (98.5% CI: 0.46, 0.92).

The concordance between BICR and investigator assessments of PFS events (progressive disease or death) and censoring was 89.9% and 86.0% in the nivo + chemo and chemo arms, respectively.

Figure 5. Kaplan-Meier Plot of Progression Free Survival per BICR - Nivolumab + Chemotherapy vs Chemotherapy - All Randomized Subjects with Tumour Cell PD-L1 ≥1%



Number of Subjects at Risk

Nivo + Chemo	158	107	75	47	29	18	10	8	5	3	1	1	0
Chemotherapy	157	67	35	17	5	1	1	1	1	1	1	1	0

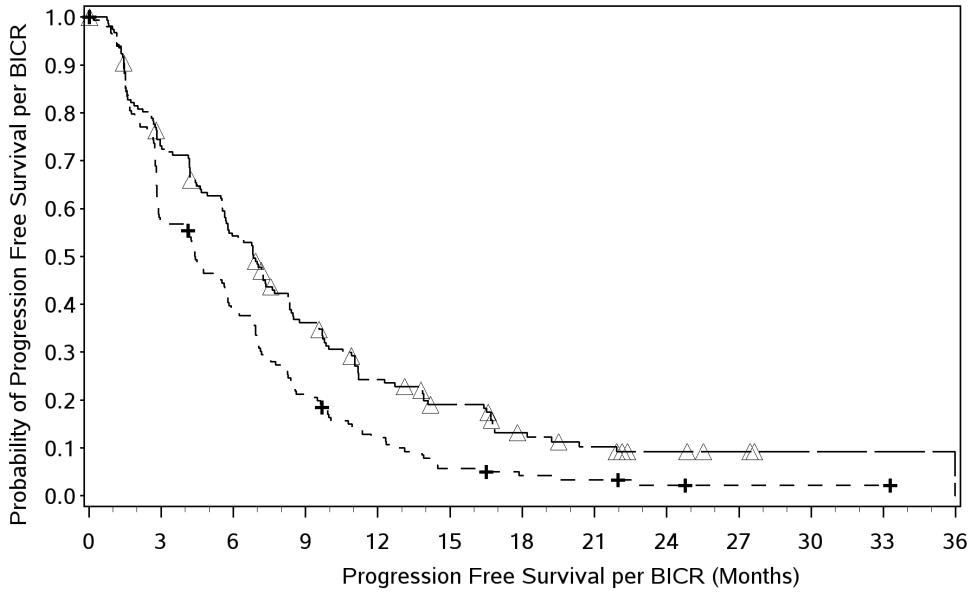
Nivo + Chemo (events : 117/158), median and 95% CI : 6.93 (5.68, 8.34)
Chemotherapy (events : 100/157), median and 95% CI : 4.44 (2.89, 5.82)
Nivo + Chemo vs Chemotherapy - hazard ratio (98.5% CI): 0.65 (0.46, 0.92)
Nivo + Chemo vs Chemotherapy - hazard ratio (95% CI): 0.65 (0.49, 0.86)
Stratified log-rank test p-value : 0.0023

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

Symbols represent censored observations.

Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs. ≥ 2) as recorded in IRT.

Figure 6. Kaplan-Meier Plot of Progression Free Survival per BICR - Nivolumab + Chemotherapy vs Chemotherapy - Analysis Accounting for Assessment on/after Subsequent Therapy - All Randomized Subjects with Tumour Cell PD-L1 ≥1%



Number of Subjects at Risk

Nivo + Chemo	158	113	83	53	34	24	14	10	5	3	1	1	0
Chemotherapy	157	85	57	31	17	8	5	4	2	1	1	1	0

Nivo + Chemo (events : 134/158), median and 95% CI : 6.83 (5.65, 7.72)
Chemotherapy (events : 142/157), median and 95% CI : 4.40 (2.92, 5.78)
Nivo + Chemo vs Chemotherapy - hazard ratio (98.5% CI): 0.67 (0.49, 0.90)
Nivo + Chemo vs Chemotherapy - hazard ratio (95% CI): 0.67 (0.52, 0.85)
Stratified log-rank test p-value : 0.0009

Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs. ≥ 2) as recorded in IRT.

Updated data (DBL 04 Oct 2021) – All randomised subjects with tumour cell PD-L1⩾ 1%

Table 12. Efficacy of Nivo + Chemo vs Chemo - All Randomized Subjects with Tumour Cell PD L1 ⩾ 1% in CA209648 (01-Mar-2021 and 04-Oct-2021 Database Locks)

	01-Mar-2021 DBL		04-Oct-2021 DBL[a]	
	Nivo + Chemo N = 158	**Chemo[b] N = 157**	**Nivo + Chemo N = 158**	**Chemo[b] N = 157**
Overall survival				
Events, n (%)	98 (62.0)	121 (77.1)	118 (74.7)	130 (82.8)
Hazard ratio (95% CI) [c]	0.54 (0.41, 0.71)		0.59 (0.46, 0.76)	
Median (95% CI),[d] months	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)	15.047 (11.926, 18.628)	9.068 (7.688, 10.021)

	01-Mar-2021 DBL		04-Oct-2021 DBL[a]	
	Nivo + Chemo N = 158	**Chemo[b] N = 157**	**Nivo + Chemo N = 158**	**Chemo[b] N = 157**
OS Rate (95% CI),[d] %				
At 6 months	82.77 (75.88, 87.84)	72.80 (64.83, 79.26)	82.24 (75.33, 87.38)	73.17 (65.27, 79.55)
At 12 months	57.99 (49.79, 65.32)	37.07 (29.22, 44.91)	57.62 (49.45, 64.95)	37.26 (29.45, 45.06)
At 18 months	-	-	45.01 (37.01, 52.67)	21.09 (14.85, 28.08)
Progression-free survival per BICR				
Events, n (%)	117 (74.1)	100 (63.7)	123 (77.8)	101 (64.3)
Hazard ratio (95% CI) [c]	0.65 (0.49, 0.86)		0.66 (0.50, 0.87)	
Median (95% CI),[d] months	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)	6.932 (5.684, 8.345)	4.435 (2.891, 5.815)
PFS Rate (95% CI),[d] %				
At 6 months	54.79 (46.31, 62.50)	39.04 (30.07, 47.90)	54.44 (45.98, 62.13)	39.58 (30.62, 48.39)
At 12 months	25.41 (18.24, 33.19)	10.45 (4.71, 18.84)	25.39 (18.27, 33.11)	10.30 (4.64, 18.59)
At 18 months	-	-	14.82 (9.18, 21.74)	2.75 (0.27, 11.28)
Objective response rate per BICR,[e] n (%)	84 (53.2)	31 (19.7)	84 (53.2)	31 (19.7)
(95% CI)[e]	(45.1, 61.1)	(13.8, 26.8)	(45.1, 61.1)	(13.8, 26.8)
Complete response	26 (16.5)	8 (5.1)	26 (16.5)	8 (5.1)
Partial response	58 (36.7)	23 (14.6)	58 (36.7)	23 (14.6)
Difference (95% CI),[f] %	33.4 (23.5, 43.4)		33.4 (23.5, 43.4)	
Duration of response per BICR				
Median (95% CI),[d] months	8.38 (6.90, 12.35)	5.68 (4.40, 8.67)	8.378 (6.899, 12.353)	5.684 (4.402, 8.674)
Min, Max,[g] months	1.4+, 34.6	1.4+, 31.8+	1.4+, 34.6	1.4+, 40.1+
Proportion (95% CI)[d] with DOR of:				
≥ 6 months	0.66 (0.54, 0.76)	0.39 (0.19, 0.59)	0.66 (0.54, 0.76)	0.39 (0.19, 0.59)
≥ 12 months	0.40 (0.28, 0.51)	0.13 (0.02, 0.33)	0.40 (0.29, 0.51)	0.13 (0.02, 0.33)

Minimum follow-up for 01-Mar-2021 DBL: 12.9 months. Minimum follow-up for 04-Oct-2021 DBL: 20 months.

[a] Descriptive analysis based on database lock of 04-Oct-2021.

[b] Fluorouracil and cisplatin.

[c] Stratified Cox Proportional hazards model. Hazard Ratio is Nivo + Chemo vs Chemo. Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT. Region is excluded from the stratified analysis due to small size in Rest of Asia.

[d] Based on Kaplan-Meier estimates.

[e] CR+PR, confidence interval based on the Clopper and Pearson method.

[f] Strata adjusted difference in objective response rate (Nivo + Chemo - Chemo) based on Cochran-Mantel-Haenszel (CMH) method of weighting. Stratified by ECOG Performance Status (0 vs 1), number of organs with metastases

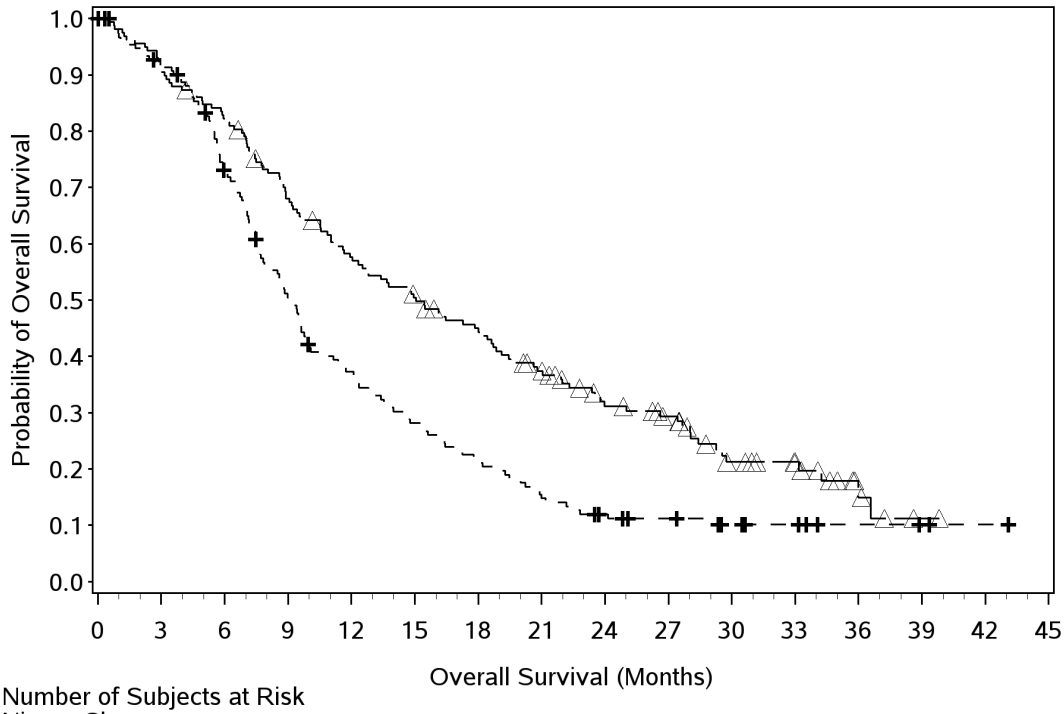
(<= 1 vs. >= 2) as recorded in IRT. Region is excluded from the stratified analysis due to small size in Rest of Asia.

[g] Symbol + indicates a censored value

Sources: Mar-2021 DBL: Table 7.1.1-1 and Table S.5.5.1.2 (ORR per BICR) in the CA209648 Primary CSR.

Oct-2021 DBL: Table S.5.22.2 (OS), Table S.5.23.2 (OS rate), Table S.5.22.6 (PFS per BICR), Table S.5.23.6 (PFS rate per BICR), Table S.5.5.6 (BOR), Table S.5.10.6 (DOR) in Appendix 5.1

Figure 7: Kaplan-Meier Plot of Overall Survival for Nivo + Chemo vs Chemo - All Randomized Subjects with Tumour Cell PD L1 ≥ 1% in CA209648 (04-Oct-2021 Database Lock)



Number of Subjects at Risk

Nivo + Chemo	158	143	129	105	88	76	66	52	38	32	19	15	5	1	0	0
Chemotherapy	157	137	107	73	53	40	30	21	15	12	8	6	3	2	1	0

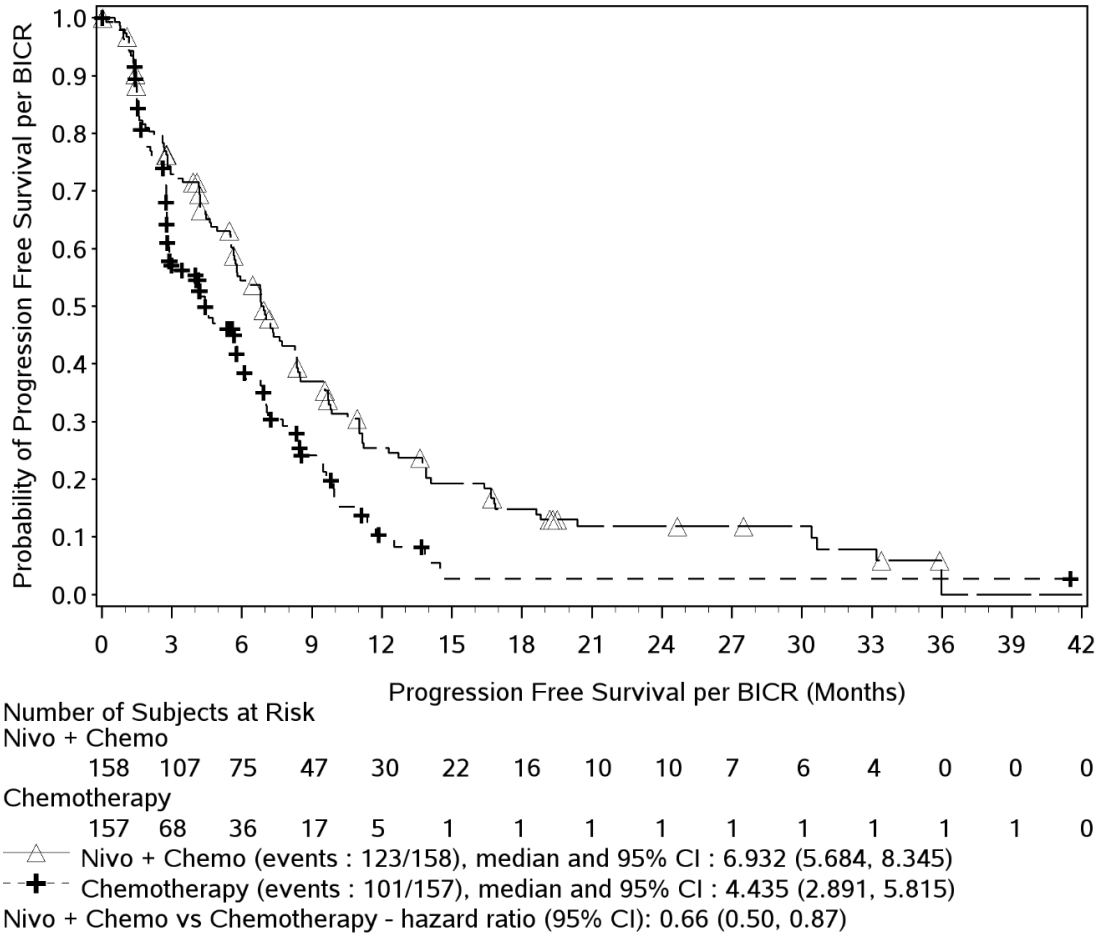
△ Nivo + Chemo (events : 118/158), median and 95% CI : 15.047 (11.926, 18.628)

+ Chemotherapy (events : 130/157), median and 95% CI : 9.068 (7.688, 10.021)

Nivo + Chemo vs Chemotherapy - hazard ratio (95% CI): 0.59 (0.46, 0.76)

Statistical model for hazard ratio: Stratified Cox proportional hazard model.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.
Region is excluded from the stratified analysis due to small size in rest of Asia.

Figure 8: Kaplan-Meier Plot of Progression-free Survival per BICR for Nivo + Chemo vs Chemo - All Randomized Subjects with Tumour Cell PD L1 ≥ 1% in CA209648 (04-Oct-2021 Database Lock)



Statistical model for hazard ratio: Stratified Cox proportional hazard model.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.
Region is excluded from the stratified analysis due to small size in rest of Asia.

Secondary endpoints

- ***Overall survival - All Randomized Subjects***

At DBL (01-Mar-2021), minimum follow-up for OS in all randomized subjects was 12.9 months (Table S.5.4.4). In all randomized subjects, a statistically significant and clinically relevant improvement in OS was observed with nivo + chemo compared with chemo: HR = 0.74 (99.1% CI: 0.58, 0.96); stratified 2-sided log-rank test p-value = 0.0021. Median OS (95% CI) was longer in the nivo + chemo arm compared with the chemo arm: 13.21 (11.14, 15.70) vs 10.71 (9.40, 11.93) months. The KM curves separated at 6 months favouring nivo + chemo over chemo, with increased separation over time. Landmark OS rates (95% CI) were higher with nivo + chemo vs. chemo, respectively, as follows:

- At 6 months: 80.41% (75.60, 84.38) vs 75.85% (70.65, 80.26)
- At 12 months: 53.53% (47.83, 58.90) vs 44.32% (38.63, 49.85)

112 (34.9%) subjects in the nivo + chemo arm and 92 (28.4%) subjects in the chemo arm were censored for OS at DBL. Of the censored subjects, 25/112 (22.3%) and 4/92 (4.3%) subjects in the nivo + chemo and chemo arms, respectively, were continuing on-treatment and 66/112 (58.9%) and 57/92 (62.0%) subjects in the nivo + chemo and chemo arms, respectively, were in follow-up. The majority of subjects

who were off study in the nivo + chemo (N = 21) and chemo (N = 31) arms, withdrew consent: 19/21 (90.5%) and 27/31 (87.1%), respectively.

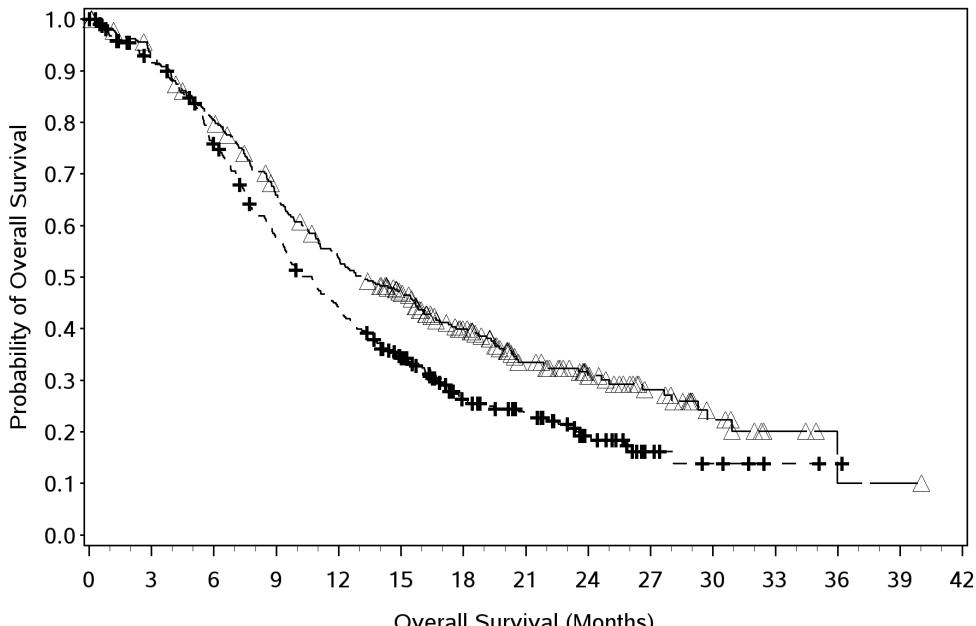
Follow-up for OS was current for the majority of randomized subjects: 93.5% of subjects in the nivo + chemo arm and 91.0% of subjects in the chemo arm either died or had a last known alive date on or after the clinical cut-off date (18-Jan-2021).

Results for the following **sensitivity analyses** were consistent with the primary OS analysis:

- Unstratified OS analysis with treatment as the single covariate: HR = 0.74 (99.1% CI: 0.58, 0.95); 2-sided unstratified log-rank test descriptive p-value = 0.0015.
- Max-combo analysis: HR = 0.72 (adjusted 95% CI: 0.59, 0.87), descriptive p-value < 0.0001.
- In a multivariate analysis of OS, the treatment effect of nivo + chemo vs chemo was consistent with the primary OS analysis: HR = 0.73 (95% CI: 0.61, 0.89); multivariate Cox model descriptive p-value = 0.0015.

50.8% and 62.7% of subjects in the nivo + chemo and chemo arms, respectively, received subsequent cancer therapy. In the nivo + chemo arm, 46.4% of subjects received subsequent systemic therapy: 5.0% received subsequent anti-PD-[L]1 therapy and 46.1% received subsequent other systemic anticancer therapy (chemotherapy agents being the most common types of subsequent therapies within this category). In the chemo arm, 55.9% of subjects received subsequent systemic therapy: 15.7% received subsequent anti-PD-[L]1 therapy and 51.5% received subsequent other systemic anticancer therapy (chemotherapy agents being the most common types of subsequent therapies within this category).

Figure 9. Kaplan-Meier Plot of Overall Survival - Nivolumab + Chemotherapy over Chemotherapy - All Randomized Subjects



Number of Subjects at Risk

Nivo + Chemo	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemotherapy	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

Nivo + Chemo (events : 209/321), median and 95% CI : 13.21 (11.14, 15.70)
Chemotherapy (events : 232/324), median and 95% CI : 10.71 (9.40, 11.93)
Nivo + Chemo vs Chemotherapy - hazard ratio (99.1% CI): 0.74 (0.58, 0.96)
Nivo + Chemo vs Chemotherapy - hazard ratio (95% CI): 0.74 (0.61, 0.90)
Stratified log-rank test p-value : 0.0021

Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs. ≥ 2) as recorded in IRT.

- ***Progression-free Survival - All Randomized Subjects***

In all randomized subjects, PFS per BICR (primary definition; i.e., includes censoring for subsequent therapy) results for nivo + chemo vs chemo did not meet the criteria for statistical significance: HR = 0.81 (98.5% CI: 0.64, 1.04); stratified 2-sided log-rank test p-value = 0.0355. Median PFS per BICR (95% CI) was: 5.82 (5.55, 7.00) vs 5.59 (4.27, 5.88) months in the nivo + chemo and chemo arms, respectively. PFS rates (95% CI) in the nivo + chemo vs chemo arms were as follows:

- At 6 months: 49.44% (43.56, 55.04) vs 43.15% (36.96, 49.19)
- At 12 months: 23.62% (18.63, 28.95) vs 16.02% (11.02, 21.86)

86 (26.8%) subjects in the nivo + chemo arm and 114 (35.2%) subjects in the chemo arm were censored for PFS per BICR at DBL. The most common reason for censoring was receiving subsequent anti-cancer therapy: 42/86 (48.8%) subjects in the nivo + chemo arm and 83/114 (72.8%) subjects in the chemo arm. Among the subjects who were censored for receiving subsequent anti-cancer therapy, 29/42 subjects in the nivo + chemo arm and 69/83 subjects in the chemo arm had a PFS event after subsequent anti-cancer therapy. Of the subjects who were censored, 19/86 subjects in the nivo + chemo arm and 2/114 subjects in the chemo arm were still on treatment and 13/86 subjects in the nivo + chemo arm and 3/114 subjects in the chemo arm were in follow-up. All 9 subjects who were off study (4 in the nivo + chemo arm; 5 in the chemo arm), withdrew consent.

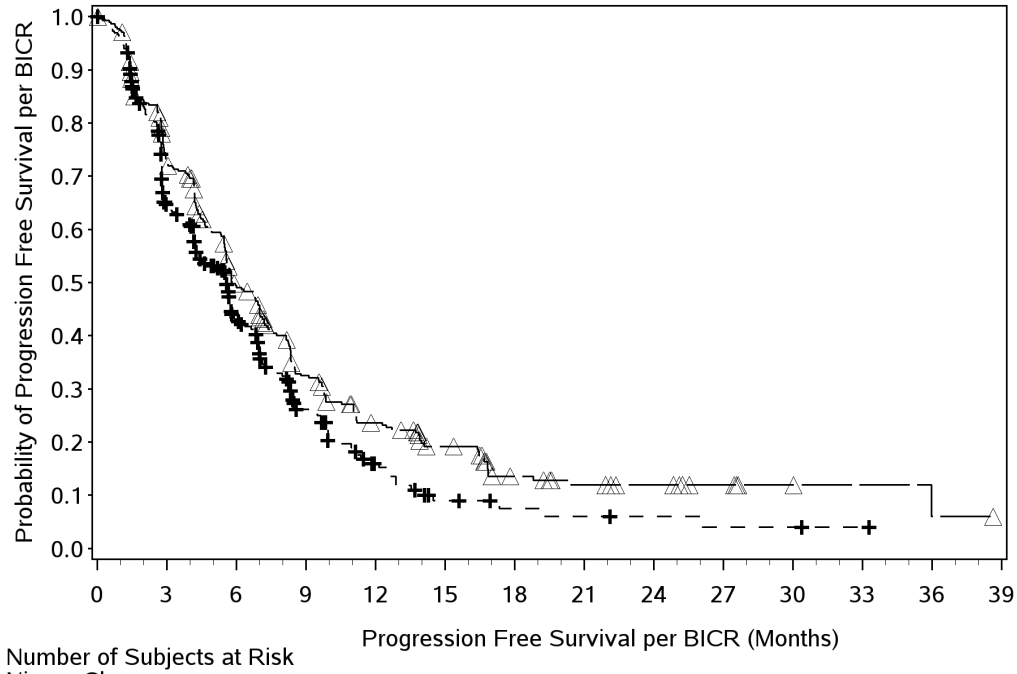
Follow-up for PFS was current for the majority of all randomized subjects: 83.8% of subjects in the nivo + chemo arm and 88.3% of subjects in the chemo arm either progressed, died, or had a last known alive date on or after the clinical cut-off date (18-Jan-2021).

Results for the following **sensitivity analyses** were consistent with the primary PFS analysis:

- Max-combo analysis when the proportionality assumption did not hold: HR = 0.79 (adjusted 95% CI: 0.66, 0.95), descriptive p-value = 0.0318.
- The post-hoc analysis comparing the RMST of PFS per BICR between nivo + chemo and chemo was performed when the proportionality assumption did not hold. PFS benefit was demonstrated with nivo + chemo vs. chemo, with a larger difference (95% CI) over time favoring nivo + chemo over chemo: 0.27 (-0.03, 0.58) at 6 months, 0.69 (0.04, 1.34) at 12 months, 1.59 (0.39, 2.80) at 24 months, 2.29 (0.63, 3.95) at 36 months.

In the sensitivity analysis of PFS per BICR accounting for assessment on/after subsequent therapy with nivo + chemo over chemo an improvement was observed: HR = 0.77 (98.5% CI: 0.62, 0.95); descriptive p value = 0.0024. Median PFS (95% CI) accounting for assessment on/after subsequent therapy was 6.01 (5.55, 7.03) months for nivo + chemo vs 5.55 (4.30, 5.78) months for chemo.

Figure 8. Kaplan-Meier Plot of Progression Free Survival per BICR - Nivolumab + Chemotherapy vs Chemotherapy - All Randomized Subjects



Number of Subjects at Risk

Nivo + Chemo	321	216	136	81	53	35	18	13	10	6	3	2	1	0
Chemotherapy	324	170	90	43	19	8	5	4	3	2	2	1	0	0

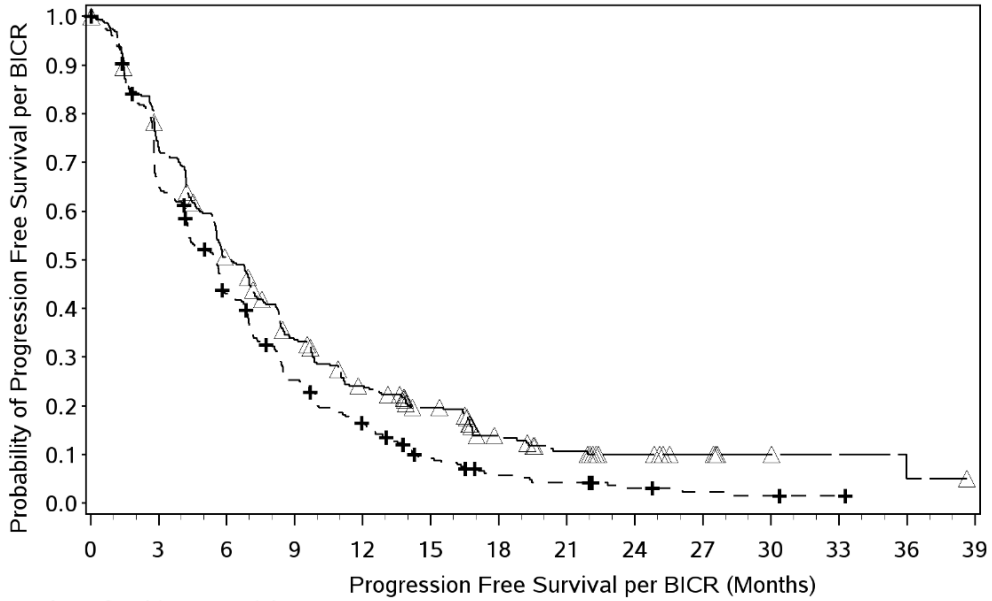
Nivo + Chemo (events : 235/321), median and 95% CI : 5.82 (5.55, 7.00)
Chemotherapy (events : 210/324), median and 95% CI : 5.59 (4.27, 5.88)
Nivo + Chemo vs Chemotherapy - hazard ratio (98.5% CI): 0.81 (0.64, 1.04)
Nivo + Chemo vs Chemotherapy - hazard ratio (95% CI): 0.81 (0.67, 0.99)
Stratified log-rank test p-value : 0.0355

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

Symbols represent censored observations.

Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs. ≥ 2), PD-L1 status (>= 1% vs. < 1% or indeterminate) as recorded in IRT.

Figure 9. Kaplan-Meier Plot of Progression Free Survival per BICR - Nivolumab + Chemotherapy over Chemotherapy - Analysis Accounting for Assessment on/after Subsequent Therapy - All Randomized Subjects



Number of Subjects at Risk

Nivo + Chemo	321	231	156	101	69	48	27	18	10	6	3	2	1	0
Chemotherapy	324	200	127	73	45	22	12	9	5	3	2	1	0	0

Nivo + Chemo (events : 269/321), median and 95% CI : 6.01 (5.55, 7.03)
Chemotherapy (events : 284/324), median and 95% CI : 5.55 (4.30, 5.78)
Nivo + Chemo vs Chemotherapy - hazard ratio (95% CI): 0.77 (0.65, 0.91)
Nivo + Chemo vs Chemotherapy - hazard ratio (98.5% CI): 0.77 (0.62, 0.95)
Stratified log-rank test p-value : 0.0024

Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs. ≥ 2) as recorded in IRT.

- ***Objective Response Rate*** *- All Randomized Subjects with Tumour Cell* ***PD-L1 ≥ 1%***

In all randomized subjects with tumour cell PD-L1 expression ≥ 1%, an improvement in BICR-assessed ORR (95% CI) was observed with nivo + chemo vs. chemo, with non-overlapping CIs: 53.2% (45.1, 61.1) vs 19.7% (13.8, 26.8). CRs were observed in 26 (16.5%) subjects in the nivo + chemo arm and 8 (5.1%) subjects in the chemo arm.

ORRs (95% CI) per investigator (exploratory endpoint) for nivo + chemo (56.3%; 48.2, 64.2) and chemo (22.9%; 16.6, 30.3) were comparable to those per BICR.

Table 13. Best Overall Response per BICR - Nivolumab + Chemotherapy over Chemotherapy - All Randomized Subjects with Tumour Cell PD L1 ≥1%

	Number of Subjects (%)	
	Nivo + Chemo N = 158	Chemotherapy N = 157
BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	26 (16.5)	8 (5.1)
PARTIAL RESPONSE (PR)	58 (36.7)	23 (14.6)
STABLE DISEASE (SD)	40 (25.3)	72 (45.9)

PROGRESSIVE DISEASE (PD)	22 (13.9)	24 (15.3)
UNABLE TO DETERMINE (UTD)	12 (7.6)	30 (19.1)
OBJECTIVE RESPONSE RATE (1)	84/158 (53.2%)	31/157 (19.7%)
(95% CI)	(45.1, 61.1)	(13.8, 26.8)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	33.4%	
(95% CI)	(23.5, 43.4)	
(99.25% CI)	N.A.	
ESTIMATE OF ODDS RATIO (3, 4)	4.84	
(95% CI)	(2.90, 8.08)	
(99.25% CI)	N.A.	
P-VALUE (5)	N.A.	

Per RECIST 1.1. (1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivo + Chemo - Chemo) based on Cochran-Mantel-Haenszel (CMH) method of weighting.
(3) Stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) as recorded in IRT.
(4) Strata adjusted odds ratio (Nivo + Chemo over Chemo) using Mantel-Haenszel method.
(5) Two-sided p-value from stratified CMH Test.

- ***Objective response rate - All Randomized Subjects***

In all randomized subjects, a numerical improvement in BICR-assessed ORR (95% CI) was observed with nivo + chemo vs. chemo, with non-overlapping CIs: 47.4% (41.8, 53.0) vs 26.9% (22.1, 32.0). CRs were observed in 43 (13.4%) subjects in the nivo + chemo arm vs 20 (6.2%) subjects in the chemo arm.

ORRs (95% CI) per investigator (exploratory endpoint) for nivo + chemo (48.9%; 43.3, 54.5) and chemo (28.7%; 23.8, 34.0) were comparable to those per BICR. For each treatment arm, cumulative response rates per BICR and per investigator were comparable.

Table 14: Best Overall Response per BICR - Nivolumab + Chemotherapy over Chemotherapy - All Randomized Subjects

	Number of Subjects (%)	
	Nivo + Chemo N = 321	Chemotherapy N = 324
BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	43 (13.4)	20 (6.2)
PARTIAL RESPONSE (PR)	109 (34.0)	67 (20.7)
STABLE DISEASE (SD)	103 (32.1)	148 (45.7)
PROGRESSIVE DISEASE (PD)	42 (13.1)	38 (11.7)
UNABLE TO DETERMINE (UTD)	24 (7.5)	51 (15.7)
OBJECTIVE RESPONSE RATE (1)	152/321 (47.4%)	87/324 (26.9%)
(95% CI)	(41.8, 53.0)	(22.1, 32.0)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	20.6%	
(95% CI)	(13.4, 27.7)	
(99.25% CI)	N.A.	
ESTIMATE OF ODDS RATIO (3, 4)	2.48	
(95% CI)	(1.78, 3.45)	
(99.25% CI)	N.A.	
P-VALUE (5)	N.A.	

Per RECIST 1.1. (1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) Strata adjusted difference in objective response rate (Nivo + Chemo - Chemo) based on Cochran-Mantel-Haenszel (CMH) method of weighting.
(3) Stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2), PD-L1 status (>= 1% vs. < 1% or indeterminate) as recorded in IRT.
(4) Strata adjusted odds ratio (Nivo + Chemo over Chemo) using Mantel-Haenszel method.
(5) Two-sided p-value from stratified CMH Test.

***Updated data (DBL 04 Oct 2021)* - All Randomized Subjects**

Table 15: Efficacy of Nivo + Chemo vs Chemo - All Randomized Subjects in CA209648 (01-Mar-2021 and 04 Oct-2021 Database Locks)

	01-Mar-2021 DBL		04-Oct-2021 DBL[a]	
	Nivo + Chemo N = 321	**Chemo[b] N = 324**	**Nivo + Chemo N = 321**	**Chemo[b] N = 324**
Overall survival				
Events, n (%)	209 (65.1)	232 (71.6)	239 (74.5)	250 (77.2)
Hazard ratio (95% CI)[c]	0.74 (0.61, 0.90)		0.77 (0.64, 0.92)	
Median (95% CI),[d] months	13.21 (11.14, 15.70)	10.71 (9.40, 11.93)	13.207 (11.105, 15.671)	10.710 (9.363, 11.926)
OS Rate (95% CI),[d] %				
At 6 months	80.41 (75.60, 84.38)	75.85 (70.65, 80.26)	80.16 (75.34, 84.14)	76.01 (70.83, 80.39)
At 12 months	53.53 (47.83, 58.90)	44.32 (38.63, 49.85)	53.37 (47.67, 58.73)	44.36 (38.69, 49.87)
At 18 months	-	-	40.16 (34.66, 45.58)	27.54 (22.61, 32.69)
Progression-free survival per BICR				
Events, n (%)	235 (73.2)	210 (64.8)	245 (76.3)	214 (66.0)
Hazard ratio (95% CI)[c]	0.81 (0.67, 0.99)		0.82 (0.67, 0.99)	
Median (95% CI),[d] months	5.82 (5.55, 7.00)	5.59 (4.27, 5.88)	5.815 (5.520, 6.998)	5.618 (4.271, 5.914)
PFS Rate (95% CI),[d] %				
At 6 months	49.44 (43.56, 55.04)	43.15 (36.96, 49.19)	49.28 (43.42, 54.87)	43.61 (37.43, 49.61)
At 12 months	23.62 (18.63, 28.95)	16.02 (11.02, 21.86)	23.60 (18.63, 28.91)	16.41 (11.39, 22.23)
At 18 months	-	-	15.16 (10.99, 19.96)	7.99 (4.18, 13.38)
Objective response rate per BICR,[e] n (%)	152 (47.4)	87 (26.9)	152 (47.4)	86 (26.5)
(95% CI)[e]	(41.8, 53.0)	(22.1, 32.0)	(41.8, 53.0)	(21.8, 31.7)
Complete response	43 (13.4)	20 (6.2)	44 (13.7)	20 (6.2)
Partial response	109 (34.0)	67 (20.7)	108 (33.6)	66 (20.4)
Difference (95% CI),[f] %	20.6 (13.4, 27.7)		20.9 (13.7, 28.0)	
Duration of response per BICR				
Median (95% CI),[d] months	8.18 (6.90, 9.69)	7.13 (5.65, 8.21)	8.181 (6.899, 9.692)	7.129 (5.651, 8.214)
Min, Max,[g] months	1.4+, 35.9+	1.4+, 31.8+	1.4+, 41.7+	1.4+, 40.1+

	01-Mar-2021 DBL		04-Oct-2021 DBL[a]	
	Nivo + Chemo N = 321	Chemo[b] N = 324	Nivo + Chemo N = 321	Chemo[b] N = 324
Proportion (95% CI)[d] with DOR of:				
≥ 6 months	0.64 (0.55, 0.71)	0.54 (0.41, 0.65)	0.64 (0.55, 0.71)	0.54 (0.41, 0.65)
≥ 12 months	0.39 (0.30, 0.47)	0.23 (0.13, 0.34)	0.39 (0.31, 0.48)	0.23 (0.13, 0.34)

Minimum follow-up for 01-Mar-2021 DBL: 12.9 months. Minimum follow-up for 04-Oct-2021 DBL: 20 months.

[a] Descriptive analysis based on database lock of 04-Oct-2021.

[b] Fluorouracil and cisplatin.

[c] Stratified Cox Proportional hazards model. Hazard Ratio is Nivo + Chemo vs Chemo. Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2), PD-L1 status (≥ 1% vs < 1% or indeterminate) as recorded in IRT. Region is excluded from the stratified analysis due to small size in Rest of Asia.

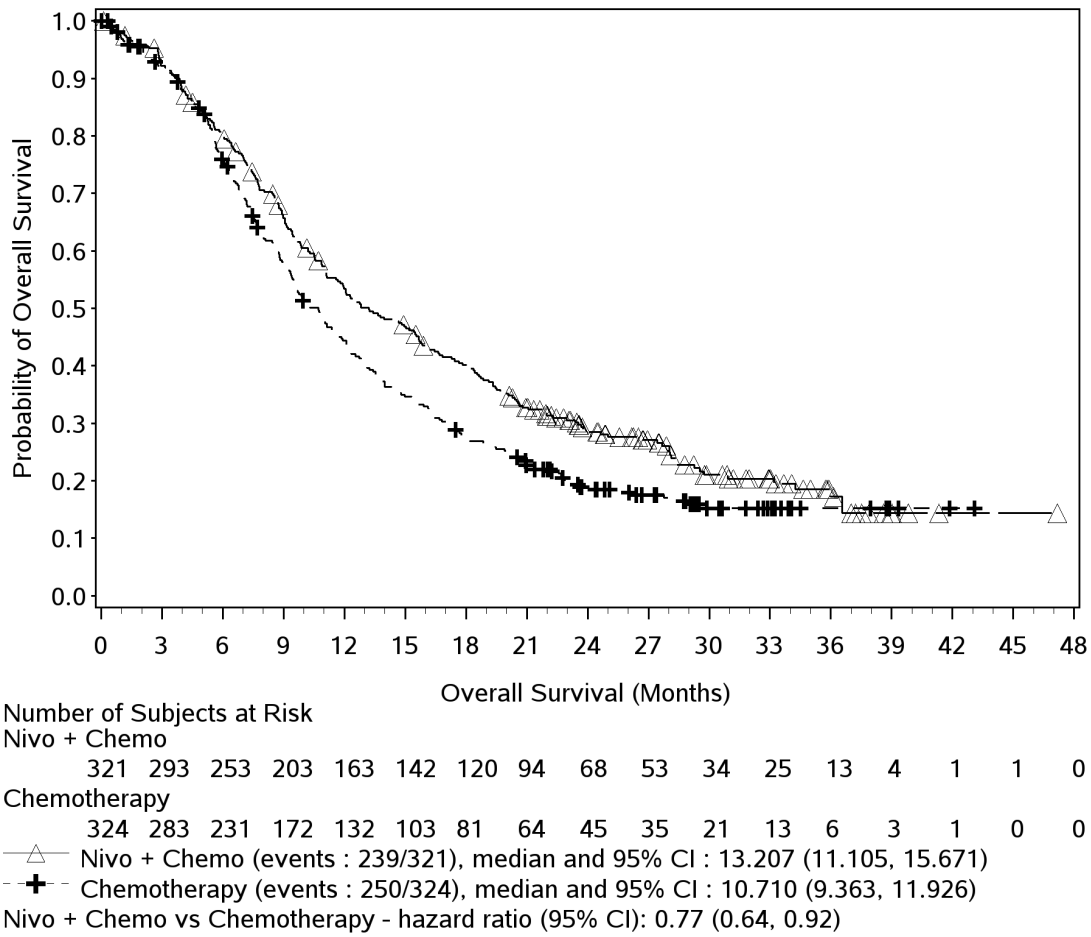
[d] Based on Kaplan-Meier estimates.

[e] CR+PR, confidence interval based on the Clopper and Pearson method.

[f] Strata adjusted difference in objective response rate (Nivo + Chemo - Chemo) based on Cochran-Mantel-Haenszel (CMH) method of weighting. Stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2) , PD-L1 status (≥ 1% vs < 1% or indeterminate) as recorded in IRT. Region is excluded from the stratified analysis due to small size in Rest of Asia.

[g] Symbol + indicates a censored value

Figure 12: Kaplan-Meier Plot of Overall Survival for Nivo + Chemo vs Chemo - All Randomized Subjects in CA209648 (04-Oct-2021 Database Lock)

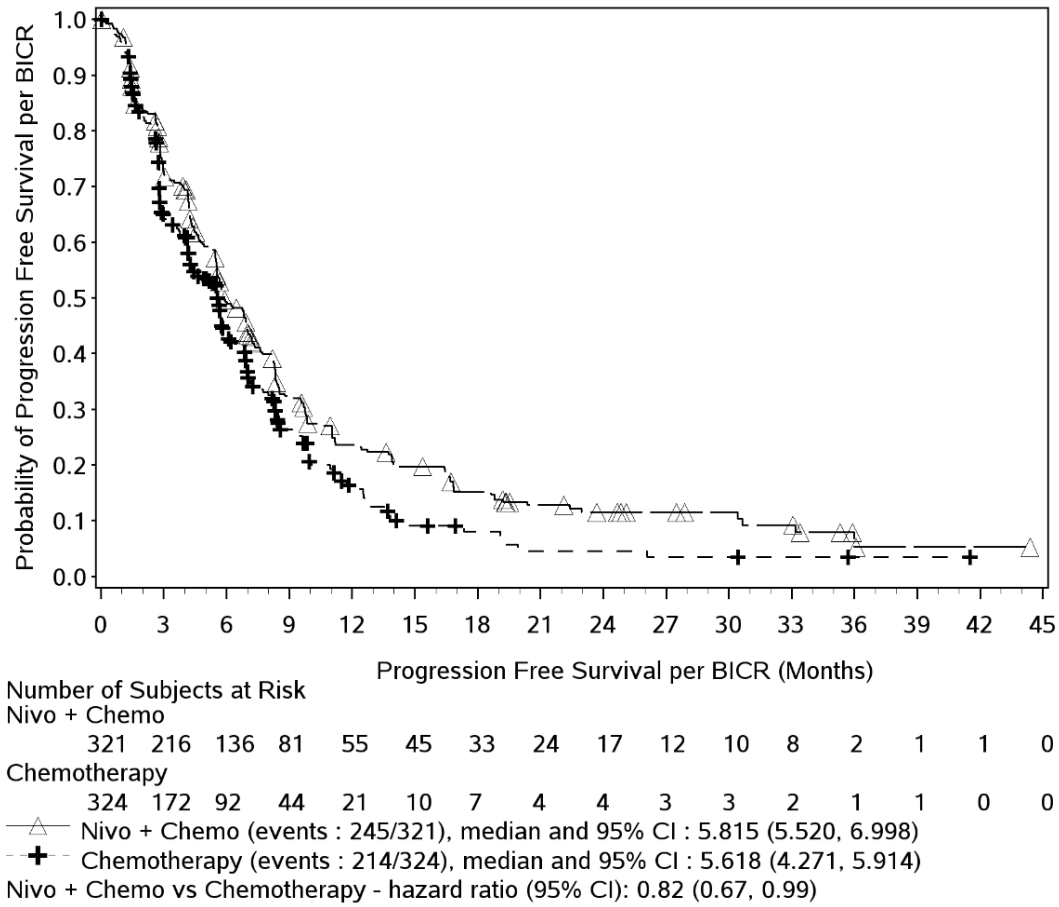


Statistical model for hazard ratio: Stratified Cox proportional hazard model.

Symbols represent censored observations.

Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2), PD-L1 status (>= 1% vs. < 1% or indeterminate) as recorded in IRT.
Region is excluded from the stratified analysis due to small size in rest of Asia.

Figure 13. Kaplan-Meier Plot of Progression-free Survival per BICR for Nivo + Chemo vs Chemo - All Randomized Subjects in CA209648 (04 Oct-2021 Database Lock)



Statistical model for hazard ratio: Stratified Cox proportional hazard model.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2), PD-L1 status (>= 1% vs. < 1% or indeterminate) as recorded in IRT.
Region is excluded from the stratified analysis due to small size in rest of Asia.

Exploratory endpoints

- ***PFS by Investigator in All Randomized Subjects***

An improvement in PFS per investigator with nivo+ chemo over chemo was observed: HR = 0.69 (95% CI: 0.58, 0.83); median PFS (95% CI) was 6.24 (5.62, 6.93) vs. 5.39 (4.21, 5.68) months.

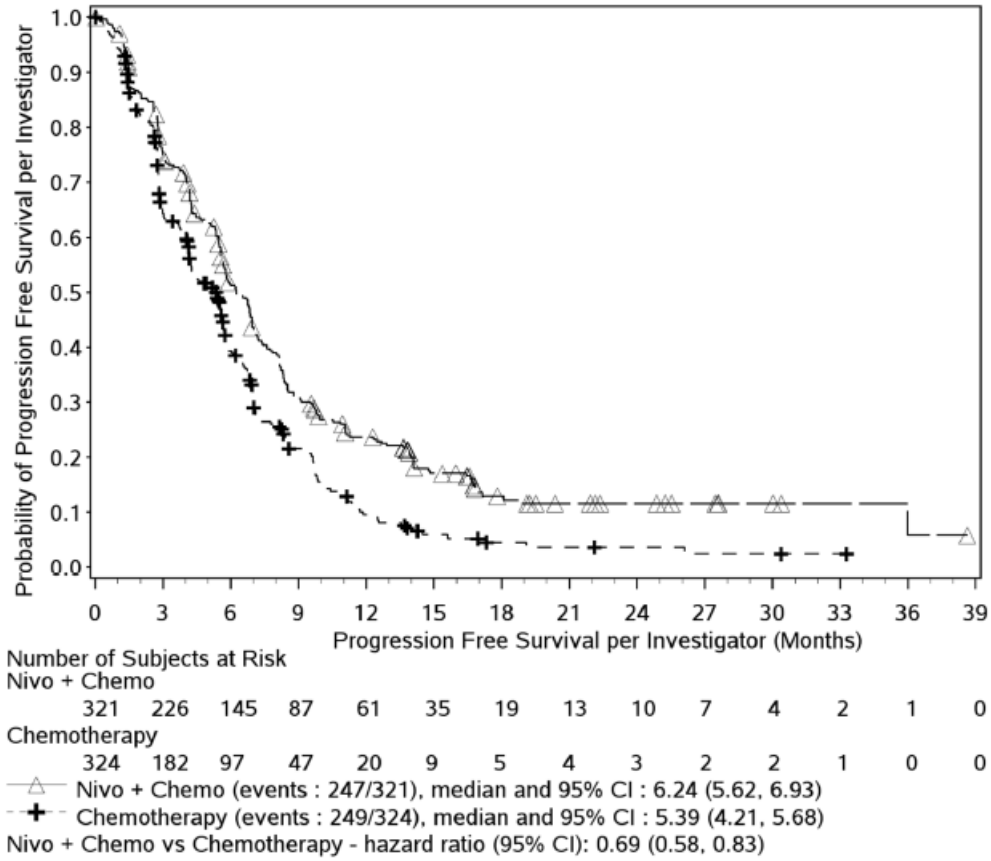
At DBL, 74 (23.1%) subjects in the nivo + chemo arm and 75 (23.1%) subjects in the chemo arm were censored for PFS per investigator. 25 (7.8%) subjects in the nivo + chemo arm and 40 (12.3%) subjects in the chemo arm were censored due to receiving subsequent anti-cancer therapy. Among the subjects censored for receiving subsequent anti-cancer therapy, 18/25 (72.0%) subjects in the nivo + chemo arm and 34/40 (85.0%) subjects in the chemo arm had a PFS event after subsequent anti-cancer therapy.

Compared with the analysis of PFS per investigator, the analysis of PFS per BICR (primary definition) resulted in the censoring of subjects who had progression per investigator and had started subsequent

therapy prior to progression event assessed by BICR. The higher number of subjects, who were censored due to receiving subsequent anti-cancer therapy in the analyses of PFS per BICR compared with the analyses of PFS per investigator may have influenced the results of the analysis of PFS per BICR (primary definition).

The concordance in assessment of PFS events (progressive disease or death) and censoring between the BICR and investigator was 90.0% and 84.3% in the nivo + chemo and chemo arms, respectively.

Figure 14. Kaplan-Meier Plot of Progression Free Survival per Investigator - Nivolumab + Chemotherapy over Chemotherapy - All Randomized Subjects



Statistical model for hazard ratio: Stratified Cox proportional hazard model.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs ≥ 2), and PD-L1 status (≥ 1% vs. < 1% or indeterminate) as recorded in IRT.

- ***Time to response and duration of Response - All Responders***

Among all responders in the nivo + chemo (N = 152) vs. chemo (N = 87) arms:

Median TTR (min, max) per BICR was similar in the nivo + chemo (1.51 [0.6, 6.8] months) and chemo (1.51 [1.1, 9.7] months) arms.

Median DOR per BICR (95% CI) was numerically longer with nivo + chemo vs. chemo: 8.18 (6.90, 9.69) vs. 7.13 (5.65, 8.21) months, respectively.

In the nivo + chemo and chemo arms, 64% vs. 54% had a DOR ≥ 6 months and 39% vs. 23% had a DOR ≥ 12 months.

- ***PFS2/TSST - All Randomized Subjects***

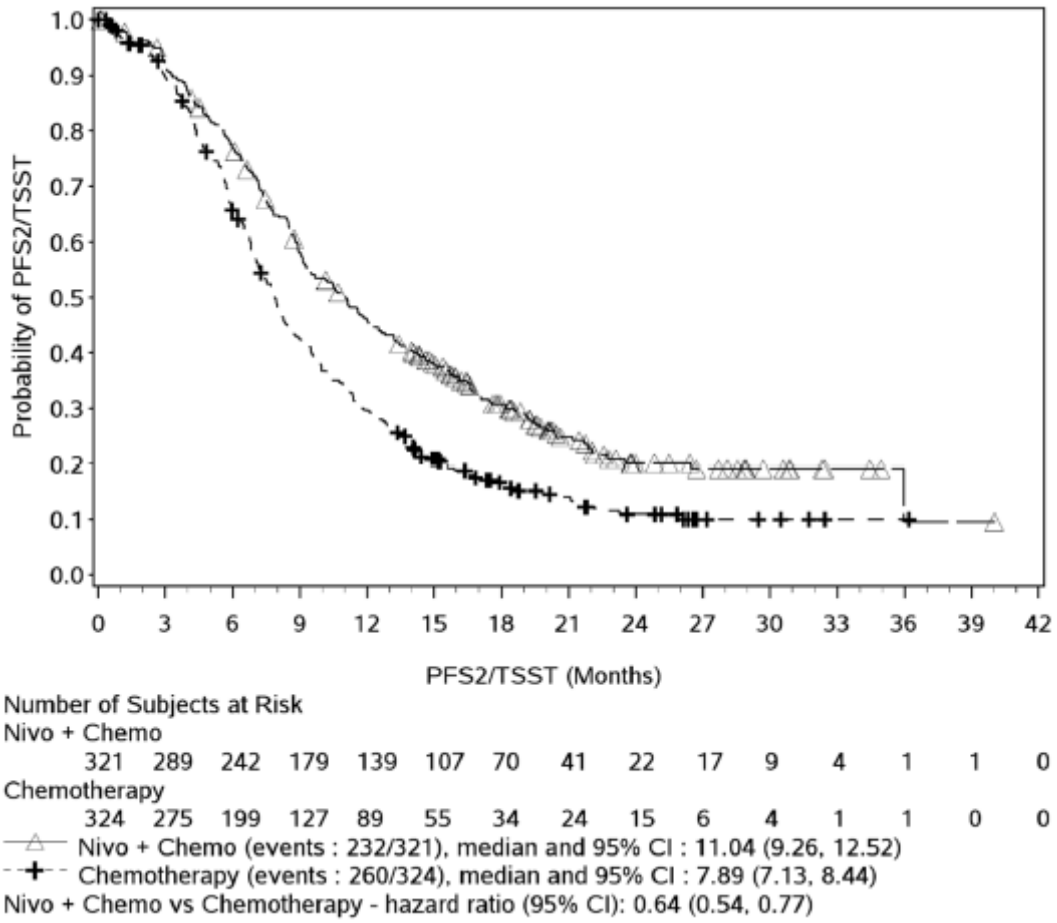
A numerical improvement in PFS2/TSST per investigator was observed with nivo + chemo compared to chemo in all randomized subjects:

Median PFS2/TSST (95% CI) per investigator was numerically longer with nivo + chemo vs. chemo: 11.04 (9.26, 12.52) vs. 7.89 (7.13, 8.44) months. The HR favoured nivo + chemo over chemo, with the upper bound of the 95% CI below 1: 0.64 (95% CI: 0.54, 0.77). The 12-month PFS2/TSST rates (95% CI) were 45.59% (39.97, 51.02) vs. 29.74% (24.67, 34.96), respectively.

50.8% vs. 62.7% of subjects, respectively, received subsequent cancer therapy.

Among subjects who did not receive any subsequent cancer therapy, 68 (21.2%) vs. 42 (13.0%) were censored, respectively. Among subjects who received at least 1 subsequent cancer therapy, 21 (6.5%) vs. 22 (6.8%) were censored, respectively.

Figure 105. Kaplan-Meier Plot of PFS on Next-line Therapy/ Time To Second Subsequent Therapy per Investigator - Nivolumab + Chemotherapy vs. Chemotherapy - All Randomized Subjects



Statistical model for hazard ratio and p-value: stratified Cox proportional hazard model and stratified log-rank test.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs ≥ 2) and tumor cell PD-L1 expression (≥ 1% or < 1% and indeterminate) as recorded in IRT.

Biomarker analysis

Efficacy by tumour cell PD-L1 expression

Table 16. Efficacy of nivolumab+chemotherapy vs. chemotherapy by baseline tumour cell PD-L1 levels – All Randomised subjects

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	Nivo+ Chemo N=163	Chemo N=166	Nivo+ Chemo N=158	Chemo N=156	Nivo+ Chemo N=201	Chemo N=207	Nivo+ Chemo N=120	Chemo N=115	Nivo+ Chemo N=219	Chemo N=225	Nivo+ Chemo N=102	Chemo N=97
OS												
HR (95% CI)[a]	0.98 (0.76, 1.28)		0.55 (0.42, 0.72)		0.82 (0.65, 1.04)		0.61 (0.45, 0.83)		0.79 (0.63, 0.99)		0.62 (0.44, 0.87)	
Events, n	111	111	98	120	131	146	78	85	143	161	66	70
Median OS, mo (95% CI)[b]	11.96 (9.86, 15.54)	12.16 (10.71, 14.00)	15.44 (11.93, 19.52)	9.20 (7.72, 10.02)	12.81 (10.87, 15.84)	11.14 (9.59, 12.88)	13.67 (10.55, 19.12)	9.49 (7.82, 11.37)	12.29 (10.87, 15.80)	10.84 (9.40, 12.35)	14.69 (11.04, 19.52)	9.49 (8.51, 12.19)
PFS per BICR												
HR (95% CI)[a,]	0.95 (0.73, 1.24)		0.64 (0.48, 0.84)		0.85 (0.67, 1.08)		0.68 (0.50, 0.93)		0.80 (0.63, 1.00)		0.77 (0.55, 1.09)	
Events, n	118	108	117	100	142	134	93	74	155	147	80	61
Median PFS, mo. (95% CI)[b]	5.55 (4.44, 6.93)	5.75 (5.39, 6.97)	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)	5.75 (5.45, 7.00)	5.68 (4.44, 6.90)	6.80 (5.52, 7.72)	4.40 (2.83, 5.91)	5.78 (5.45, 7.00)	5.65 (4.27, 6.37)	6.80 (4.47, 8.34)	4.50 (2.86, 6.93)
ORR per BICR (CR + PR)[c]												
ORR, % (95% CI)	41.7 (34.1, 49.7)	33.7 (26.6, 41.5)	53.2 (45.1, 61.1)	19.9 (13.9, 27.0)	44.8 (37.8, 51.9)	30.9 (24.7, 37.7)	51.7 (42.4, 60.9)	20.0 (13.1, 28.5)	46.1 (39.4, 53.0)	29.3 (23.5, 35.8)	50.0 (39.9, 60.1)	21.6 (13.9, 31.2)
Complete Response, n (%)	17 (10.4)	12 (7.2)	26 (16.5)	8 (5.1)	20 (10.0)	14 (6.8)	23 (19.2)	6 (5.2)	24 (11.0)	15 (6.7)	19 (18.6)	5 (5.2)
Partial Response, n (%)	51 (31.3)	44 (26.5)	58 (36.7)	23 (14.7)	70 (34.8)	50 (24.2)	39 (32.5)	17 14.8)	77 (35.2)	51 (22.7)	32 (31.4)	16 (16.5)
Stable Disease, n (%)	63 (38.7)	74 (44.6)	40 (25.3)	72 (46.2)	72 (35.8)	92 (44.4)	31 (25.8)	54 (47.0)	77 (35.2)	102 (45.3)	26 (25.5)	44 (45.4)
Progressive Disease, n (%)	20 (12.3)	14 (8.4)	22 (13.9)	24 15.4)	22 (10.9)	22 (10.6)	20 (16.7)	16 (13.9)	23 (10.5)	24 (10.7)	19 18.6)	14 (14.4)
Unable to Determine, n (%)	12 (7.4)	22 (13.3)	12 (7.6)	29 (18.6)	17 (8.5)	29 (14.0)	7 (5.8)	22 (19.1)	18 (8.2)	33 (14.7)	6 (5.9)	18 (18.6)

Tumor cell PD-L1 expression subgroups are based on CRF.

[a] Unstratified Cox proportional hazards model.

[b] Based on Kaplan-Meier estimates.

[c] In subjects with measurable disease. Confidence interval based on the Clopper and Pearson method.

Abbreviations: BICR - Blinded Independent Central Review; Chemo - chemotherapy; CI - confidence interval; CR - complete response; CRF - case report form; CSR - clinical study report; HR - hazard ratio; Nivo - nivolumab; ORR - objective response rate; OS - overall survival, PD-L1- programmed death ligand 1; PFS - progression-free survival; PR - partial response

Figure 116. Kaplan-Meier Plot of Overall Survival by Tumour Cell PD-L1 (All Randomised Patients)

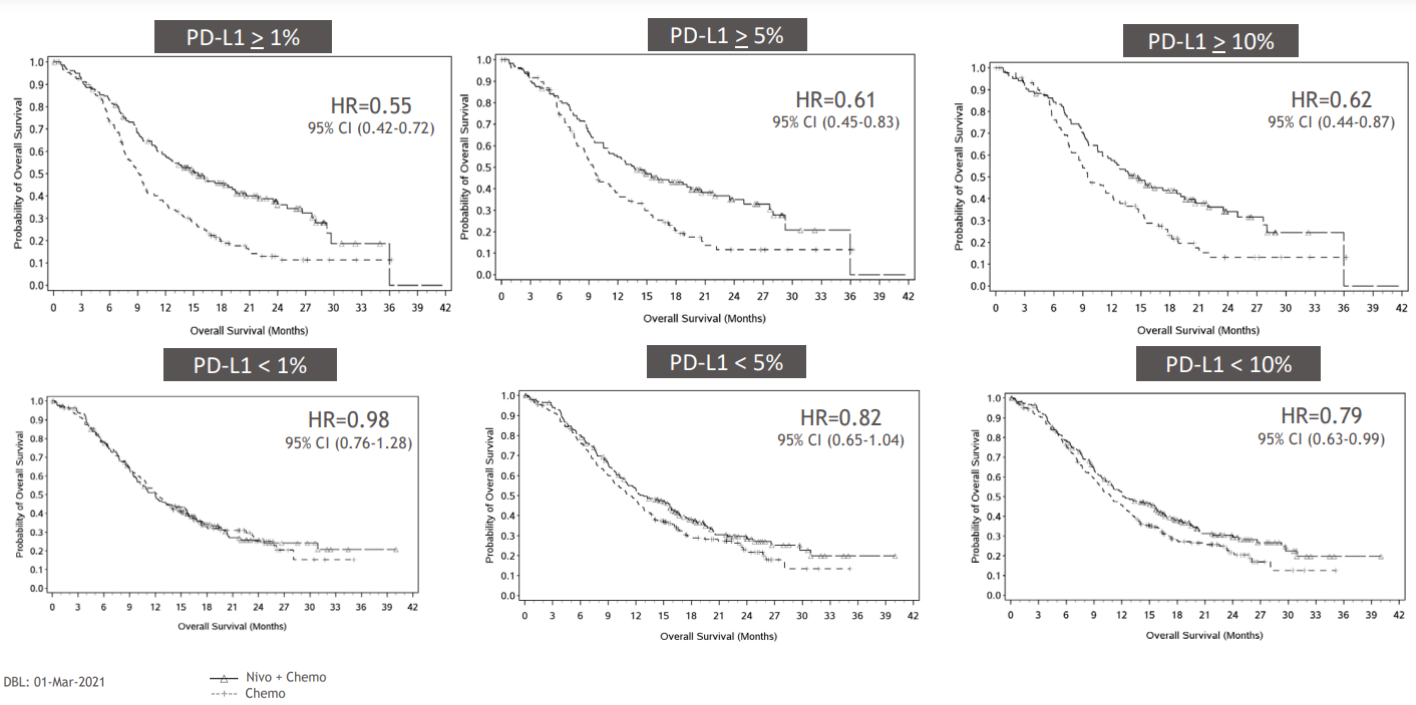
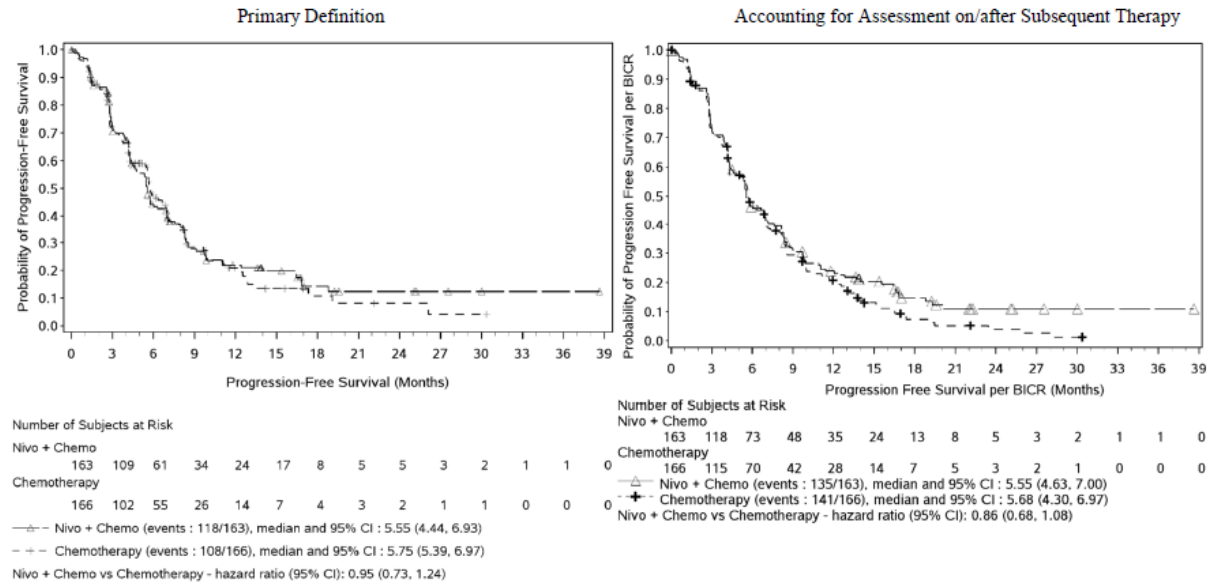


Figure 17. Kaplan-Meier Plot of Progression Free Survival per BICR - Nivolumab + Chemotherapy vs Chemotherapy - Subjects with Tumour Cell PD-L1 < 1%



Symbols represent censored observations. Unstratified Cox proportional hazard model. Biomarker result as recorded in CRF

PFS is the time from randomization to the date of the first documented PD per BICR or death due to any cause, whichever was earlier. Subjects who started any subsequent anti-cancer therapy without a prior reported PD per BICR were censored at the last tumor assessment on or prior to initiation of the subsequent anti-cancer therapy (PFS primary definition).

Table 17. The MAH fitted a Cox proportional hazards regression model with treatment, PD-L1 status, and treatment by PD-L1 status interaction for both OS and PFS. See results in the table below.

Predictive Relationship of PD-L1 Status for Efficacy Endpoints: Nivo + Chemo over Chemo
All PD-L1 Evaluable Subjects

PD-L1 Expression Cutoff: 1%	
PROGRESSION-FREE SURVIVAL PER BICR (1)	
HAZARD RATIO (95% CI): NIVO + CHEMO VS. CHEMOTHERAPY (PD-L1 NEGATIVE)	0.94 (0.72, 1.22)
HAZARD RATIO (95% CI): NIVO + CHEMO VS. CHEMOTHERAPY (PD-L1 POSITIVE)	0.65 (0.49, 0.85)
HAZARD RATIO (95% CI): PD-L1 POSITIVE VS. PD-L1 NEGATIVE (NIVO + CHEMO)	0.90 (0.70, 1.16)
HAZARD RATIO (95% CI): PD-L1 POSITIVE VS. PD-L1 NEGATIVE (CHEMOTHERAPY)	1.31 (1.00, 1.72)
INTERACTION P-VALUE	0.0503
OVERALL SURVIVAL (1)	
HAZARD RATIO (95% CI): NIVO + CHEMO VS. CHEMOTHERAPY (PD-L1 NEGATIVE)	0.97 (0.75, 1.27)
HAZARD RATIO (95% CI): NIVO + CHEMO VS. CHEMOTHERAPY (PD-L1 POSITIVE)	0.55 (0.42, 0.72)
HAZARD RATIO (95% CI): PD-L1 POSITIVE VS. PD-L1 NEGATIVE (NIVO + CHEMO)	0.80 (0.61, 1.05)
HAZARD RATIO (95% CI): PD-L1 POSITIVE VS. PD-L1 NEGATIVE (CHEMOTHERAPY)	1.42 (1.10, 1.84)
INTERACTION P-VALUE	0.0029

Although not powered to determine statistical significance, the descriptive p-values for the interactions between tumour cell PD-L1 status (≥ 1% and < 1%) and treatment were p=0.0503 for PFS per BICR and p=0.0029 for OS from the Cox proportional hazard model, indicating that there was as signal of interaction between treatment and baseline tumour cell PD-L1 status at the 1% cut-off for PFS per BICR and OS at a prespecified significance level of 0.2.

Updated efficacy data by tumour cell PD-L1 expression (DBL 04 Oct 2021)

Table 18. Overall Survival of Nivo + Chemo vs Chemotherapy by Baseline Tumour Cell PD-L1 Levels - All Randomized Subjects (01-Mar-2021 and 04-Oct-2021 Database Locks) - Exploratory Analysis

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	Nivo+ Chemo N=163	Chemo N=166	Nivo+ Chemo N=158	Chemo N=156	Nivo+ Chemo N=201	Chemo N=207	Nivo+ Chemo N=120	Chemo N=115	Nivo+ Chemo N=219	Chemo N=225	Nivo+ Chemo N=102	Chemo N=97
01-Mar-2021 DBL												
HR (95% CI)[a]	0.98 (0.76, 1.28)		0.55 (0.42, 0.72)		0.82 (0.65, 1.04)		0.61 (0.45, 0.83)		0.79 (0.63, 0.99)		0.62 (0.44, 0.87)	
Events, n	111	111	98	120	131	146	78	85	143	161	66	70
Median OS, mo (95% CI)[b]	11.96 (9.86, 15.54)	12.16 (10.71, 14.00)	15.44 (11.93, 19.52)	9.20 (7.72, 10.02)	12.81 (10.87, 15.84)	11.14 (9.59, 12.88)	13.67 (10.55, 19.12)	9.49 (7.82, 11.37)	12.29 (10.87, 15.80)	10.84 (9.40, 12.35)	14.69 (11.04, 19.52)	9.49 (8.51, 12.19)
04-Oct-2021 DBL												
HR (95% CI)[a]	1.01 (0.78, 1.30)		0.60 (0.47, 0.77)		0.86 (0.68, 1.07)		0.67 (0.50, 0.90)		0.83 (0.67, 1.03)		0.71 (0.51, 0.97)	
Events, n	121	120	118	129	147	158	92	91	161	174	78	75
Median OS, mo (95% CI)[b]	11.959 (9.856, 15.540)	12.156 (10.710, 13.996)	15.047 (11.926, 18.628)	9.199 (7.721, 10.021)	12.452 (10.875, 15.836)	11.039 (9.495, 12.879)	13.667 (10.546, 18.004)	9.495 (8.115, 11.368)	12.090 (10.579, 15.803)	10.842 (9.363, 12.353)	14.686 (11.039, 18.431)	9.626 (8.509, 12.189)

Minimum follow-up for 01-Mar-2021 DBL: 12.9 months. Minimum follow-up for 04-Oct-2021 DBL: 20 months.

[a] Unstratified Cox proportional hazards model.

[b] Based on Kaplan-Meier estimates.

HR is not computed for subset category with less than 10 subjects per treatment group. Biomarker result as recorded in CRF.

Figure 18: Kaplan-Meier Plot of Overall Survival for Nivo + Chemo vs Chemo - All Randomized Subjects (by Tumour Cell PD-L1 Expression) in CA209648 (04-Oct-2021 Database Lock) - Exploratory Analysis

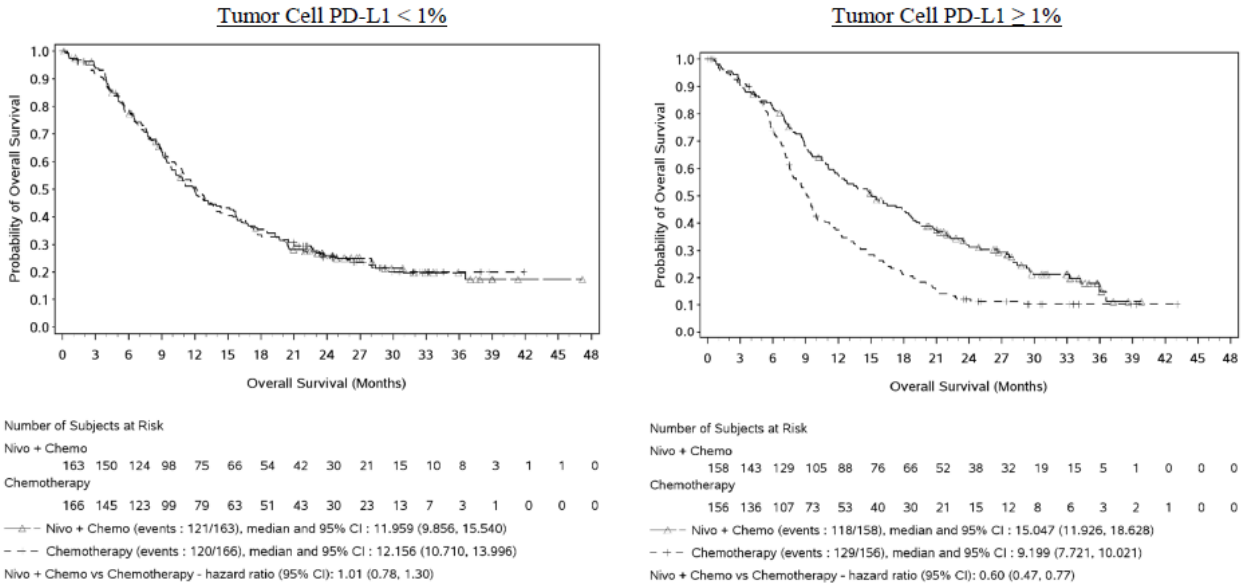


Table 19: Progression-free Survival per BICR of Nivo + Chemo vs Chemotherapy by Baseline Tumor Cell PD-L1 Levels - All Randomized Subjects (01-Mar-2021 and 04-Oct-2021 Database Locks) - Exploratory Analysis

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	Nivo+ Chemo N=163	Chemo N=166	Nivo+ Chemo N=158	Chemo N=156	Nivo+ Chemo N=201	Chemo N=207	Nivo+ Chemo N=120	Chemo N=115	Nivo+ Chemo N=219	Chemo N=225	Nivo+ Chemo N=102	Chemo N=97
01-Mar-2021 DBL												
HR (95% CI)[a]	0.95 (0.73, 1.24)		0.64 (0.48, 0.84)		0.85 (0.67, 1.08)		0.68 (0.50, 0.93)		0.80 (0.63, 1.00)		0.77 (0.55, 1.09)	
Events, n	118	108	117	100	142	134	93	74	155	147	80	61
Median PFS, mo. (95% CI)[b]	5.55 (4.44, 6.93)	5.75 (5.39, 6.97)	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)	5.75 (5.45, 7.00)	5.68 (4.44, 6.90)	6.80 (5.52, 7.72)	4.40 (2.83, 5.91)	5.78 (5.45, 7.00)	5.65 (4.27, 6.37)	6.80 (4.47, 8.34)	4.50 (2.86, 6.93)
04-Oct-2021 DBL												
HR (95% CI)[a]	0.94 (0.73, 1.22)		0.66 (0.50, 0.86)		0.85 (0.67, 1.08)		0.70 (0.51, 0.96)		0.80 (0.64, 1.00)		0.80 (0.57, 1.12)	
Events, n	122	111	123	101	148	138	97	74	162	151	83	61
Median PFS, mo. (95% CI)[b]	5.552 (4.435, 6.932)	5.749 (5.487, 6.998)	6.932 (5.684, 8.345)	4.435 (2.891, 5.815)	5.749 (5.454, 6.998)	5.717 (4.435, 6.899)	6.801 (5.520, 7.721)	4.402 (2.825, 5.914)	5.749 (5.454, 6.998)	5.684 (4.304, 6.374)	6.801 (4.468, 8.345)	4.501 (2.858, 6.932)

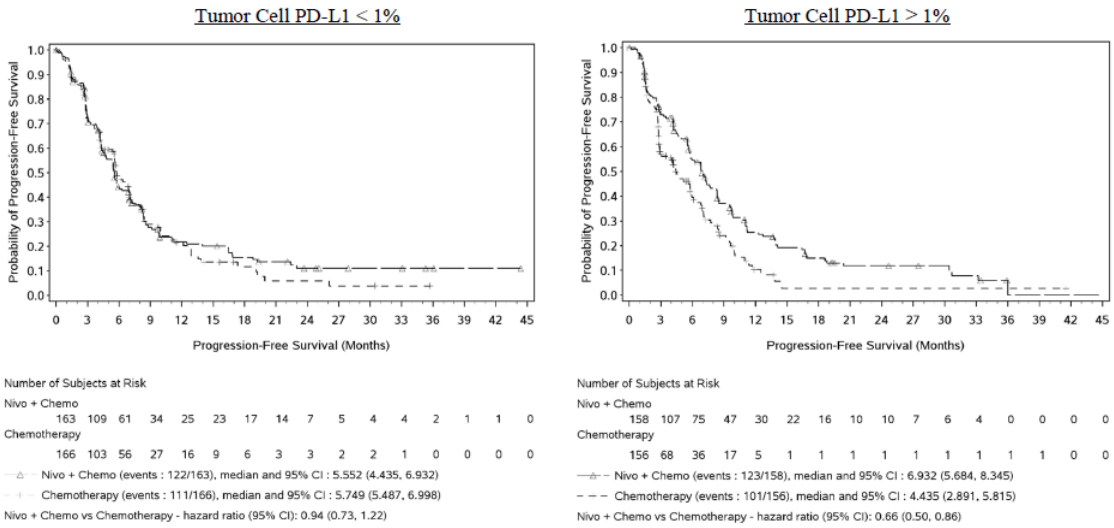
Minimum follow-up for 01-Mar-2021 DBL: 12.9 months. Minimum follow-up for 04-Oct-2021 DBL: 20 months.

[a] Unstratified Cox proportional hazards model.

[b] Based on Kaplan-Meier estimates.

HR is not computed for subset category with less than 10 subjects per treatment group. Biomarker result as recorded in CRF.

Figure 19: Kaplan-Meier Plot of Progression-free Survival (per BICR) for Nivo + Chemo vs Chemo - All Randomized Subjects (by Tumor Cell PD-L1 Expression) in CA209648 (04-Oct-2021 Database Lock) - Exploratory Analysis



Efficacy in PD-L1 by CPS subgroups

Table 20. Frequency of PD-L1 by CPS Status - All Randomized Subjects

Population PD-L1 Expression Category	Nivo + Ipi N = 325	Nivo + Chemo N = 321	Chemotherapy N = 324	Total N = 970
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE (N(%))	2 (0.6)	3 (0.9)	0	5 (0.5)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	297 (91.4)	305 (95.0)	304 (93.8)	906 (93.4)
PD-L1 EXPRESSION (%)				
MEAN	20.0	18.5	19.0	19.2
MEDIAN	6.0	7.0	8.0	7.0
MIN , MAX	0 , 100	0 , 100	0 , 100	0 , 100
Q1 , Q3	3.0 , 20.0	3.0 , 20.0	3.0 , 20.0	3.0 , 20.0
STANDARD DEVIATION	28.6	26.6	25.1	26.8
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1	266/297 (89.6)	278/305 (91.1)	280/304 (92.1)	824/906 (90.9)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1	31/297 (10.4)	27/305 (8.9)	24/304 (7.9)	82/906 (9.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5	191/297 (64.3)	208/305 (68.2)	213/304 (70.1)	612/906 (67.5)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5	106/297 (35.7)	97/305 (31.8)	91/304 (29.9)	294/906 (32.5)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 10	126/297 (42.4)	135/305 (44.3)	145/304 (47.7)	406/906 (44.8)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 10	171/297 (57.6)	170/305 (55.7)	159/304 (52.3)	500/906 (55.2)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE (N(%))	4 (1.2)	4 (1.2)	3 (0.9)	11 (1.1)
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	22 (6.8)	9 (2.8)	17 (5.2)	48 (4.9)

Biomarker result as recorded in CRF

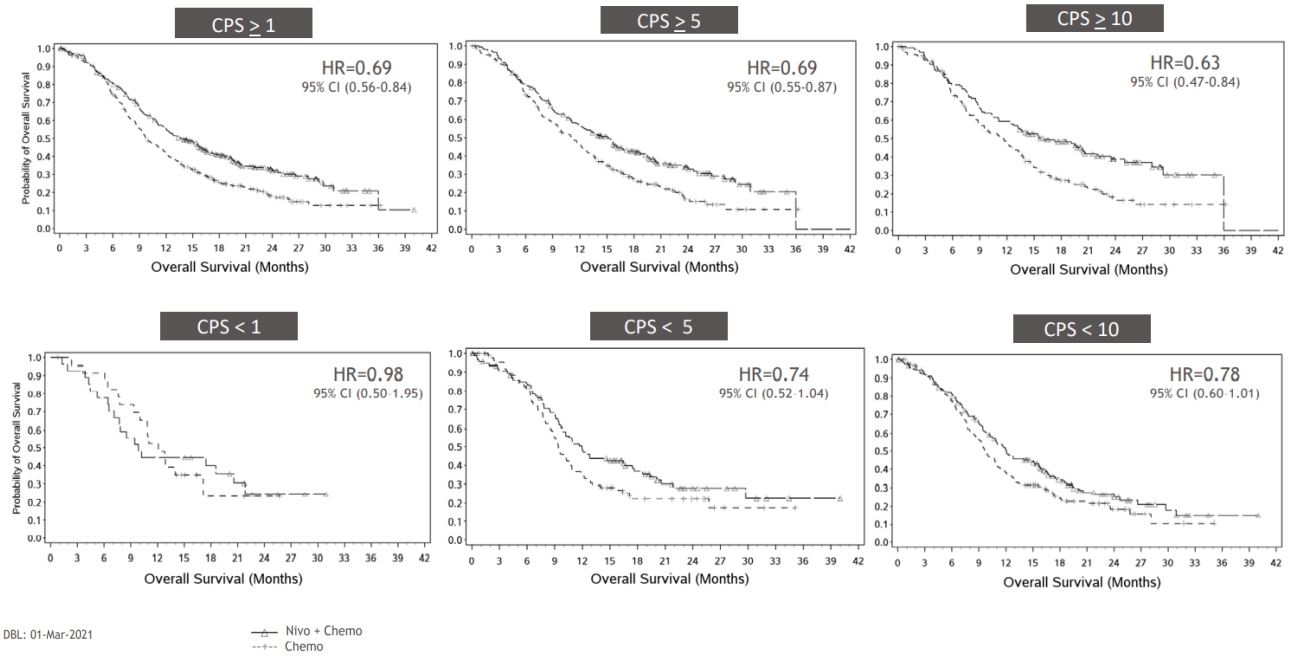
Table 21. Efficacy of Nivolumab + Chemotherapy vs Chemotherapy by Baseline PD-L1 CPS - All Randomized Subjects

	CPS < 1		CPS ≥ 1		CPS < 5		CPS ≥ 5		CPS < 10		CPS ≥ 10	
	Nivo+ Chemo N=27	Chemo N=24	Nivo+ Chemo N=278	Chemo N=280	Nivo+ Chemo N=97	Chemo N=91	Nivo+ Chemo N=208	Chemo N=213	Nivo+ Chemo N=170	Chemo N=159	Nivo+ Chemo N=135	Chemo N=145
OS												
HR (95% CI)[a]	0.98 (0.50, 1.95)		0.69 (0.56, 0.84)		0.74 (0.52, 1.04)		0.69 (0.55, 0.87)		0.78 (0.60, 1.01)		0.63 (0.47, 0.84)	
Events, n	19	16	177	205	62	66	134	155	115	118	81	103
Median OS, mo (95% CI)[b]	9.86 (6.54, 20.57)	12.09 (9.33, 17.12)	13.77 (11.96, 16.13)	9.76 (8.84, 11.63)	11.96 (9.69, 16.62)	9.40 (8.44, 10.84)	15.18 (12.06, 17.28)	11.14 (9.20, 12.55)	12.06 (10.51, 15.67)	9.69 (8.61, 10.97)	16.13 (12.32, 21.91)	11.63 (8.84, 13.54)
PFS per BICR (primary definition)												
HR (95% CI)[a,]	0.79 (0.39, 1.60)		0.78 (0.64, 0.95)		0.74 (0.51, 1.06)		0.79 (0.63, 1.00)		0.81 (0.62, 1.06)		0.74 (0.56, 0.98)	
Events, n	21	14	201	184	66	56	156	142	121	99	101	99
Median PFS, mo. (95% CI)[b]	6.31 (3.98, 9.86)	5.68 (2.86, 11.24)	5.78 (5.49, 7.03)	5.55 (4.24, 5.91)	5.75 (4.57, 7.13)	4.27 (3.22, 5.88)	6.80 (5.45, 7.33)	5.62 (4.27, 6.90)	5.55 (4.76, 6.31)	4.76 (4.17, 5.75)	7.03 (5.55, 8.34)	5.78 (4.24, 7.06)

[a] Unstratified Cox proportional hazards model.

[b] Based on Kaplan-Meier estimates.

Figure 20. Subgroup Analyses of OS by PD-L1 CPS Cut-offs



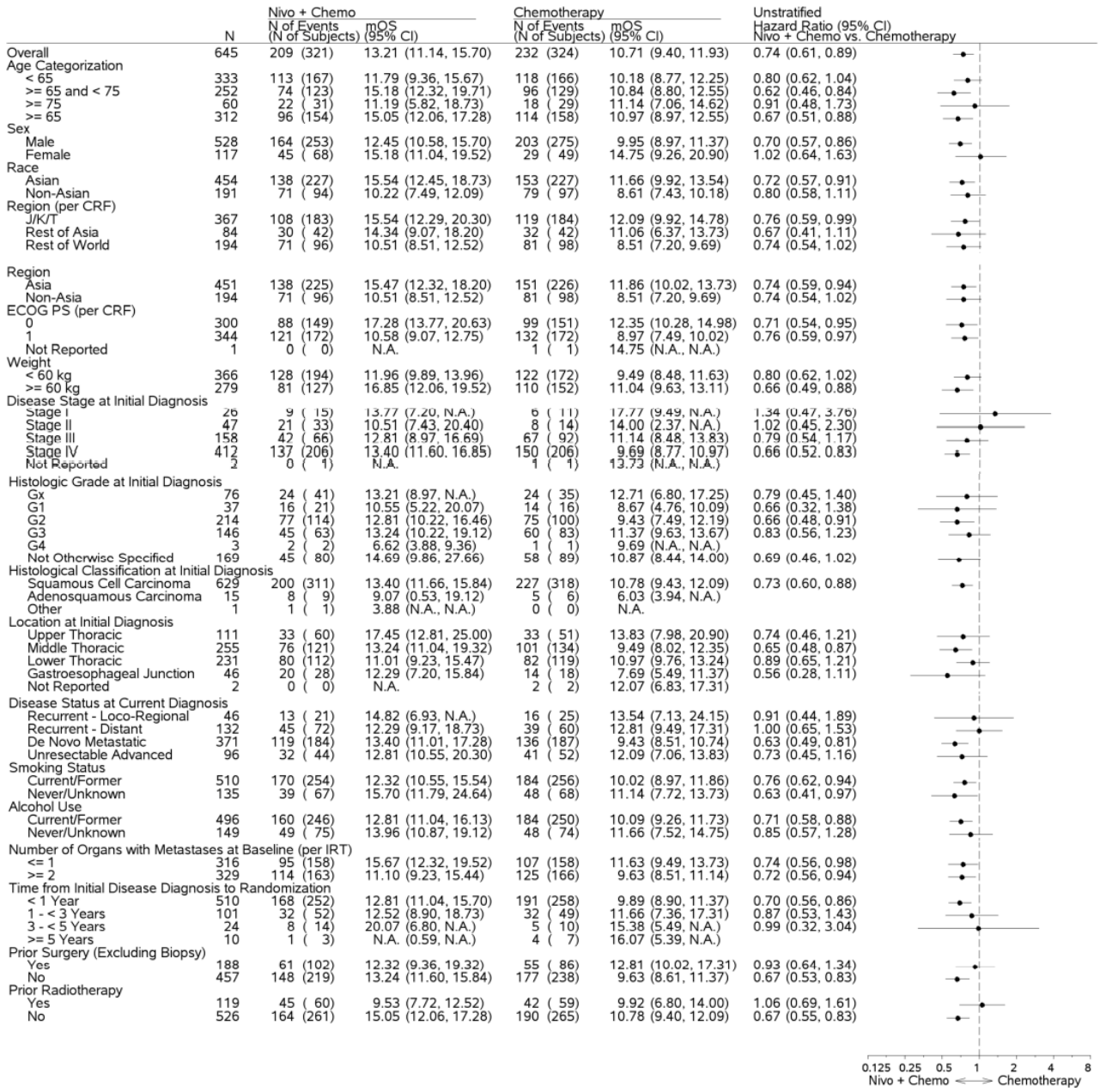
Ancillary analyses

Subgroup analyses

In a subgroup analysis of all randomized subjects, OS HRs (95% CIs) for most subgroups favoured nivo + chemo over chemo (i.e., point estimate of HR < 1). Point estimates of the OS HRs were ≥ 1.0 for 5 subgroups: stage I disease at initial diagnosis (N = 26), stage II disease at initial diagnosis (N = 47), female subjects (N = 117), recurrent - distant disease status at current diagnosis (ie, at study entry) (N = 132), subjects who received prior radiotherapy (N = 119).

According to the MAH, a review of the baseline demographic and disease characteristics did not identify any apparent differences that would explain the observed treatment effect. For some of the subgroups listed above, sample sizes and event counts were relatively small, and the CIs were wide (encompassing 1); thus, the interpretation of these results is limited.

Figure 21. Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - Nivolumab + Chemotherapy vs. Chemotherapy - **All Randomized Subjects**



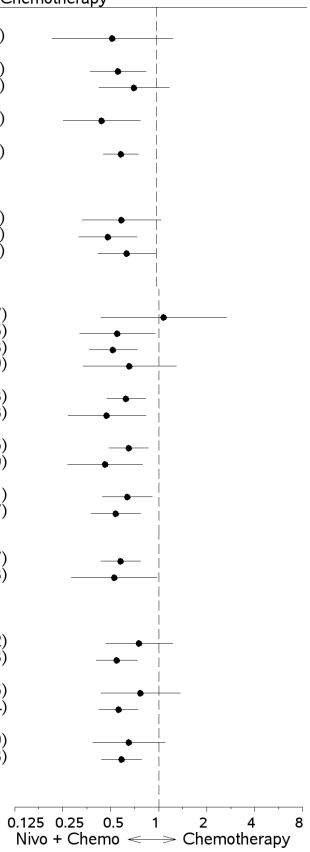
	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemotherapy N of Events (N of Subjects)	Chemotherapy mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemotherapy
Overall	645	209 (321)	13.21 (11.14, 15.70)	232 (324)	10.71 (9.40, 11.93)	0.74 (0.61, 0.89)
Age Categorization						
< 65	333	113 (167)	11.79 (9.36, 15.67)	118 (166)	10.18 (8.77, 12.25)	0.80 (0.62, 1.04)
>= 65 and < 75	252	74 (123)	15.18 (12.32, 19.71)	96 (129)	10.84 (8.80, 12.55)	0.62 (0.46, 0.84)
>= 75	60	22 (31)	11.19 (5.82, 18.73)	18 (29)	11.14 (7.06, 14.62)	0.91 (0.48, 1.73)
>= 65	312	96 (154)	15.05 (12.06, 17.28)	114 (158)	10.97 (8.97, 12.55)	0.67 (0.51, 0.88)
Sex						
Male	528	164 (253)	12.45 (10.58, 15.70)	203 (275)	9.95 (8.97, 11.37)	0.70 (0.57, 0.86)
Female	117	45 (68)	15.18 (11.04, 19.52)	29 (49)	14.75 (9.26, 20.90)	1.02 (0.64, 1.63)
Race						
Asian	454	138 (227)	15.54 (12.45, 18.73)	153 (227)	11.66 (9.92, 13.54)	0.72 (0.57, 0.91)
Non-Asian	191	71 (94)	10.22 (7.49, 12.09)	79 (97)	8.61 (7.43, 10.18)	0.80 (0.58, 1.11)
Region (per CRF)						
J/K/T	367	108 (183)	15.54 (12.29, 20.30)	119 (184)	12.09 (9.92, 14.78)	0.76 (0.59, 0.99)
Rest of Asia	84	30 (42)	14.34 (9.07, 18.20)	32 (42)	11.06 (6.37, 13.73)	0.67 (0.41, 1.11)
Rest of World	194	71 (96)	10.51 (8.51, 12.52)	81 (98)	8.51 (7.20, 9.69)	0.74 (0.54, 1.02)
Region						
Asia	451	138 (225)	15.47 (12.32, 18.20)	151 (226)	11.86 (10.02, 13.73)	0.74 (0.59, 0.94)
Non-Asia	194	71 (96)	10.51 (8.51, 12.52)	81 (98)	8.51 (7.20, 9.69)	0.74 (0.54, 1.02)
ECOG PS (per CRF)						
0	300	88 (149)	17.28 (13.77, 20.63)	99 (151)	12.35 (10.28, 14.98)	0.71 (0.54, 0.95)
1	344	121 (172)	10.58 (9.07, 12.75)	132 (172)	8.97 (7.49, 10.02)	0.76 (0.59, 0.97)
Not Reported	1	0 (0)	N.A.	1 (1)	14.75 (N.A., N.A.)	
Weight						
< 60 kg	366	128 (194)	11.96 (9.89, 13.96)	122 (172)	9.49 (8.48, 11.63)	0.80 (0.62, 1.02)
>= 60 kg	279	81 (127)	16.85 (12.06, 19.52)	110 (152)	11.04 (9.63, 13.11)	0.66 (0.49, 0.88)
Disease Stage at Initial Diagnosis						
Stage I	26	9 (15)	13.77 (7.20, N.A.)	6 (11)	17.77 (9.49, N.A.)	1.34 (0.47, 3.76)
Stage II	47	21 (33)	10.51 (7.43, 20.40)	8 (14)	14.00 (2.37, N.A.)	1.02 (0.45, 2.30)
Stage III	158	42 (66)	12.81 (8.97, 16.69)	67 (92)	11.14 (8.48, 13.83)	0.79 (0.54, 1.17)
Stage IV	412	137 (206)	13.40 (11.60, 16.85)	150 (206)	9.69 (8.77, 10.97)	0.66 (0.52, 0.83)
Not Reported	2	0 (1)	N.A.	1 (1)	13.73 (N.A., N.A.)	
Histologic Grade at Initial Diagnosis						
Gx	76	24 (41)	13.21 (8.97, N.A.)	24 (35)	12.71 (6.80, 17.25)	0.79 (0.45, 1.40)
G1	37	16 (21)	10.55 (5.22, 20.07)	14 (16)	8.67 (4.76, 10.09)	0.66 (0.32, 1.38)
G2	214	77 (114)	12.81 (10.22, 16.46)	75 (100)	9.43 (7.49, 12.19)	0.66 (0.48, 0.91)
G3	146	45 (63)	13.24 (10.22, 19.12)	60 (83)	11.37 (9.63, 13.67)	0.83 (0.56, 1.23)
G4	3	2 (2)	6.62 (3.88, 9.36)	1 (1)	9.69 (N.A., N.A.)	
Not Otherwise Specified	169	45 (80)	14.69 (9.86, 27.66)	58 (89)	10.87 (8.44, 14.00)	0.69 (0.46, 1.02)
Histological Classification at Initial Diagnosis						
Squamous Cell Carcinoma	629	200 (311)	13.40 (11.66, 15.84)	227 (318)	10.78 (9.43, 12.09)	0.73 (0.60, 0.88)
Adenosquamous Carcinoma	15	8 (9)	9.07 (0.53, 19.12)	5 (6)	6.03 (3.94, N.A.)	
Other	1	1 (1)	3.88 (N.A., N.A.)	0 (0)	N.A.	
Location at Initial Diagnosis						
Upper Thoracic	111	33 (60)	17.45 (12.81, 25.00)	33 (51)	13.83 (7.98, 20.90)	0.74 (0.46, 1.21)
Middle Thoracic	255	76 (121)	13.24 (11.04, 19.32)	101 (134)	9.49 (8.02, 12.35)	0.65 (0.48, 0.87)
Lower Thoracic	231	80 (112)	11.01 (9.23, 15.47)	82 (119)	10.97 (9.76, 13.24)	0.89 (0.65, 1.21)
Gastroesophageal Junction	46	20 (28)	12.29 (7.20, 15.84)	14 (18)	7.69 (5.49, 11.37)	0.56 (0.28, 1.11)
Not Reported	2	0 (0)	N.A.	2 (2)	12.07 (6.83, 17.31)	
Disease Status at Current Diagnosis						
Recurrent - Loco-Regional	46	13 (21)	14.82 (6.93, N.A.)	16 (25)	13.54 (7.13, 24.15)	0.91 (0.44, 1.89)
Recurrent - Distant	132	45 (72)	12.29 (9.17, 18.73)	39 (60)	12.81 (9.49, 17.31)	1.00 (0.65, 1.53)
De Novo Metastatic	371	119 (184)	13.40 (11.01, 17.28)	136 (187)	9.43 (8.51, 10.74)	0.63 (0.49, 0.81)
Unresectable Advanced	96	32 (44)	12.81 (10.55, 20.30)	41 (52)	12.09 (7.06, 13.83)	0.73 (0.45, 1.16)
Smoking Status						
Current/Former	510	170 (254)	12.32 (10.55, 15.54)	184 (256)	10.02 (8.97, 11.86)	0.76 (0.62, 0.94)
Never/Unknown	135	39 (67)	15.70 (11.79, 24.64)	48 (68)	11.14 (7.72, 13.73)	0.63 (0.41, 0.97)
Alcohol Use						
Current/Former	496	160 (246)	12.81 (11.04, 16.13)	184 (250)	10.09 (9.26, 11.73)	0.71 (0.58, 0.88)
Never/Unknown	149	49 (75)	13.96 (10.87, 19.12)	48 (74)	11.66 (7.52, 14.75)	0.85 (0.57, 1.28)
Number of Organs with Metastases at Baseline (per IRT)						
<= 1	316	95 (158)	15.67 (12.32, 19.52)	107 (158)	11.63 (9.49, 13.73)	0.74 (0.56, 0.98)
>= 2	329	114 (163)	11.10 (9.23, 15.44)	125 (166)	9.63 (8.51, 11.14)	0.72 (0.56, 0.94)
Time from Initial Disease Diagnosis to Randomization						
< 1 Year	510	168 (252)	12.81 (11.04, 15.70)	191 (258)	9.89 (8.90, 11.37)	0.70 (0.56, 0.86)
1 - < 3 Years	101	32 (52)	12.52 (8.90, 18.73)	32 (49)	11.66 (7.36, 17.31)	0.87 (0.53, 1.43)
3 - < 5 Years	24	8 (14)	20.07 (6.80, N.A.)	5 (10)	15.38 (5.49, N.A.)	0.99 (0.32, 3.04)
>= 5 Years	10	1 (3)	N.A. (0.59, N.A.)	4 (7)	16.07 (5.39, N.A.)	
Prior Surgery (Excluding Biopsy)						
Yes	188	61 (102)	12.32 (9.36, 19.32)	55 (86)	12.81 (10.02, 17.31)	0.93 (0.64, 1.34)
No	457	148 (219)	13.24 (11.60, 15.84)	177 (238)	9.63 (8.61, 11.37)	0.67 (0.53, 0.83)
Prior Radiotherapy						
Yes	119	45 (60)	9.53 (7.72, 12.52)	42 (59)	9.92 (6.80, 14.00)	1.06 (0.69, 1.61)
No	526	164 (261)	15.05 (12.06, 17.28)	190 (265)	10.78 (9.40, 12.09)	0.67 (0.55, 0.83)

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

Updated data (DBL 04 Oct 2021)

Figure 22. Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets - Nivo + Chemo over Chemo - All Randomized **PD-L≥1 Expressing** Subjects

	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemotherapy N of Events (N of Subjects)	Chemotherapy mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemotherapy
Histologic Grade at Initial Diagnosis						
Gx	29	9 (15)	18.431 (3.483, N.A.)	12 (14)	7.622 (5.618, 17.248)	0.53 (0.22, 1.27)
G1	18	8 (10)	8.345 (1.150, 18.201)	7 (8)	9.117 (4.764, 10.086)	
G2	118	51 (62)	15.441 (11.663, 18.727)	47 (56)	8.575 (6.505, 12.813)	0.58 (0.39, 0.86)
G3	74	28 (34)	15.047 (10.513, 21.914)	32 (40)	10.021 (8.608, 14.784)	0.73 (0.44, 1.21)
G4	0	0 (0)	N.A.	0 (0)	N.A.	
Not Otherwise Specified	76	22 (37)	18.858 (8.575, 27.663)	32 (39)	7.819 (6.275, 12.090)	0.46 (0.26, 0.80)
Histological Classification at Initial Diagnosis						
Squamous Cell Carcinoma	311	116 (156)	15.047 (11.926, 18.628)	128 (155)	9.199 (7.721, 10.021)	0.60 (0.47, 0.77)
Adenosquamous Carcinoma	4	2 (2)	12.255 (5.388, 19.121)	2 (2)	4.731 (3.943, 5.520)	
Other	0	0 (0)	N.A.	0 (0)	N.A.	
Location at Initial Diagnosis						
Upper Thoracic	66	26 (37)	18.201 (12.813, 29.536)	24 (29)	9.396 (7.064, 17.873)	0.61 (0.34, 1.07)
Middle Thoracic	113	42 (55)	15.441 (9.528, 21.060)	48 (58)	8.575 (6.801, 9.955)	0.50 (0.33, 0.76)
Lower Thoracic	113	39 (52)	14.686 (8.903, 20.797)	51 (61)	9.495 (7.064, 11.729)	0.65 (0.43, 1.00)
Gastroesophageal Junction	23	11 (14)	12.287 (5.881, 18.004)	7 (9)	9.626 (5.684, 12.813)	
Disease Status at Current Diagnosis						
Recurrent - Loco-Regional	27	10 (13)	14.817 (6.801, 33.183)	9 (14)	14.752 (5.947, N.A.)	1.08 (0.43, 2.67)
Recurrent - Distant	67	29 (40)	13.766 (8.903, 21.060)	25 (27)	9.495 (7.359, 12.813)	0.55 (0.32, 0.95)
De Novo Metastatic	175	65 (86)	16.131 (11.663, 20.632)	73 (89)	8.608 (7.458, 9.626)	0.52 (0.37, 0.73)
Unresectable Advanced	46	14 (19)	15.474 (8.608, 28.025)	23 (27)	12.090 (5.290, 14.784)	0.66 (0.33, 1.29)
Smoking Status						
Current/Former	244	96 (125)	13.405 (10.513, 18.431)	98 (119)	8.838 (7.589, 9.758)	0.62 (0.47, 0.83)
Never/Unknown	71	22 (33)	23.392 (12.747, 28.419)	32 (38)	9.955 (7.064, 13.832)	0.47 (0.27, 0.83)
Alcohol Use						
Current/Former	240	91 (117)	13.766 (10.546, 18.431)	102 (123)	9.068 (7.721, 10.021)	0.65 (0.49, 0.86)
Never/Unknown	75	27 (41)	16.131 (11.039, 28.419)	28 (34)	9.429 (6.111, 13.405)	0.46 (0.27, 0.79)
Number of Organs with Metastases at Baseline (per IRT)						
<= 1	160	57 (81)	18.201 (12.057, 23.524)	62 (79)	9.495 (7.129, 12.222)	0.64 (0.44, 0.91)
>= 2	155	61 (77)	13.766 (9.166, 18.004)	68 (78)	8.608 (7.524, 9.922)	0.54 (0.38, 0.77)
Time from Initial Disease Diagnosis to Randomization						
< 1 Year	242	89 (116)	14.949 (11.039, 18.628)	106 (126)	8.838 (7.524, 9.955)	0.58 (0.43, 0.77)
1 - < 3 Years	54	22 (32)	16.131 (10.513, 29.536)	19 (22)	8.969 (5.947, 14.752)	0.53 (0.28, 0.98)
3 - < 5 Years	13	6 (9)	13.766 (5.815, N.A.)	2 (4)	N.A. (8.115, N.A.)	
>= 5 Years	6	1 (1)	20.797 (N.A., N.A.)	3 (5)	16.066 (5.388, N.A.)	
Prior Surgery (Excluding Biopsy)						
Yes	86	35 (48)	13.766 (8.739, 20.797)	32 (38)	9.495 (7.359, 13.996)	0.75 (0.47, 1.22)
No	229	83 (110)	15.474 (11.926, 19.450)	98 (119)	8.805 (7.491, 9.922)	0.54 (0.40, 0.73)
Prior Radiotherapy						
Yes	58	25 (30)	10.021 (6.801, 16.131)	23 (28)	7.524 (5.947, 9.922)	0.77 (0.43, 1.36)
No	257	93 (128)	16.460 (12.747, 19.515)	107 (129)	9.429 (7.819, 11.368)	0.56 (0.42, 0.74)
Prior Systemic Therapy						
Yes	73	28 (39)	16.131 (9.528, 21.060)	29 (34)	10.021 (7.819, 14.752)	0.65 (0.39, 1.10)
No	242	90 (119)	14.686 (11.039, 19.121)	101 (123)	8.608 (7.425, 9.922)	0.58 (0.44, 0.78)



Additional analyses

A post-hoc analysis comparing the RMST of OS between nivo + chemo and chemo was performed when the proportionality assumption did not hold. A survival benefit was demonstrated with nivo + chemo vs. chemo, with a larger difference (95% CI) over time favouring nivo + chemo over chemo: 0.07 (-0.13, 0.26) at 6 months, 0.55 (0, 1.10) at 12 months, 1.93 (0.68, 3.19) at 24 months, 3.02 (1.06, 4.98) at 36 months.

Table 22. Restricted Mean Survival Time, Overall Survival: Nivo + Chemo over Chemo - All Randomized Subjects

	Nivo + Chemo N = 321	Chemotherapy N = 324	
	RMST (95% CI)	RMST (95% CI)	Difference (95% CI)
6 MONTHS	5.51 (5.38, 5.65)	5.45 (5.30, 5.59)	0.07 (-0.13, 0.26)
12 MONTHS	9.50 (9.12, 9.88)	8.95 (8.56, 9.35)	0.55 (0.00, 1.10)
24 MONTHS	14.36 (13.46, 15.27)	12.43 (11.56, 13.29)	1.93 (0.68, 3.19)
36 MONTHS	17.25 (15.81, 18.70)	14.23 (12.90, 15.57)	3.02 (1.06, 4.98)
36.2 MONTHS (A)	17.27 (15.82, 18.72)	14.26 (12.92, 15.60)	3.01 (1.04, 4.99)

RMST = Restricted Mean Survival Time
Based on trapezoidal integration of the area under the Kaplan-Meier estimated curve until restricted time point.
The difference of RMST is Nivo + Chemo over Chemo.
(A) The minimum of the longest survival time in each treatment arm, regardless of censoring.

Table 23. Restricted Mean Survival Time, Progression Free Survival per BICR: Nivo + Chemo over Chemo - All Randomized Subjects

	Nivo + Chemo N = 321	Chemotherapy N = 324	
	RMST (95% CI)	RMST (95% CI)	Difference (95% CI)
6 MONTHS	4.60 (4.39, 4.80)	4.32 (4.10, 4.54)	0.27 (-0.03, 0.58)
12 MONTHS	6.67 (6.21, 7.12)	5.98 (5.51, 6.45)	0.69 (0.04, 1.34)
24 MONTHS	8.55 (7.69, 9.42)	6.96 (6.13, 7.79)	1.59 (0.39, 2.80)
33.3 MONTHS (A)	9.66 (8.43, 10.89)	7.37 (6.26, 8.48)	2.29 (0.63, 3.95)
36 MONTHS	N.A.	N.A.	N.A.

RMST = Restricted Mean Survival Time
Based on trapezoidal integration of the area under the Kaplan-Meier estimated curve until restricted time point.
The difference of RMST is Nivo + Chemo over Chemo.
(A) The minimum of the longest survival time in each treatment arm, regardless of censoring.

Summary of main study

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

Table 1. Summary of Efficacy for trial CA209648

Title: A Randomized Phase 3 Study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated oesophageal squamous cell carcinoma		
Study identifier	CA209648	
Design	Phase 3, randomized, study of nivolumab plus ipilimumab (nivo + ipi) or nivolumab in combination with fluorouracil plus cisplatin (nivo + chemo) versus fluorouracil plus cisplatin (chemo) as first line-therapy in unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	From 29 Jun 2017 (FPFV) to 18 Jan 2021 (LPLV) not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Arm A (nivo+ipi)	Nivolumab 3 mg/kg IV Q2W Ipilimumab 1 mg/kg IV Q6W Until progression, unacceptable toxicity, withdrawal of consent, or completion of 24 months of treatment, whichever occurred first. N=325
	Arm B (nivo+chemo)	Nivolumab 240 mg IV Q2W Fluorouracil 800 mg/m2/day IV Days 1-5 Cisplatin 80 mg/m2 IV Day 1, of a 4-week cycle Treatment continued until progression, unacceptable toxicity, or withdrawal of consent, whichever occurred first. Nivolumab treatment was given for up to 24 months. N=321

	Arm C (chemo)		Fluorouracil 800 mg/m2/day IV Days 1-5 Cisplatin 80 mg/m2 IV Day 1, of a 4-week cycle Chemotherapy will be given until disease progression, unacceptable toxicity or other reasons specified in the protocol. N= 324
Endpoints and definitions	Primary endpoint	Overall survival (OS), in subjects with PD-L1≥1%	Time from randomisation until death from any cause.
	Primary endpoint	Progression free survival (PFS), in subjects with PD-L1≥1%	Time from randomization to the date of the first documented PD per BICR or death due to any cause, whichever was earlier.
	Secondary endpoint	OS in all randomised subjects	See definition above
	Secondary endpoint	PFS in all randomised subjects	See definition above
	Secondary endpoint	Objective response rates (ORR) in subjects with PD-L1≥1% and all randomised subjects	Percentage of patients whose best overall response is either confirmed complete or partial response as assessed by BICR per RECIST 1.1
Database lock	01 Mar 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Nivo+Chemo	Chemo
	Number of subjects	321 All randomised 158 PD-L1≥1%	324 All randomised 157 PD-L1≥1%
	OS (**PD-L1⩾1**%) (median, months)	15.44	9.07
	95% CI	11.93, 19.52	7.69, 9.95
	PFS (**PD-L1≥1**%) (median, months)	6.93	4.44
	95% CI	5.68, 8.34	2.89, 5.82

	OS (**all randomised**) (median, months)	13.21	10.71
	95% CI	11.14, 15.70	9.40, 11.93
	PFS (**all randomised**) (median, months)	5.82	5.59
	95% CI	5.55, 7.00	4.27, 5.88
	ORR (PD-L1≥1%) (%)	53.2	19.7
	95% CI	45.1, 61.1	13.8, 26.8
	ORR (All randomised) (%)	47.4	26.9
	95% CI	41.8, 53.0	22.1, 32.0
Effect estimate per comparison	Primary endpoint **OS (PD-L1≥1%)**	Comparison groups	Nivo+Chemo vs Chemo
		Hazard ratio (HR)	0.54
		99.5% CI	0.37, 0.80
		p value (stratified 2-sided)	<0.0001
	Primary endpoint **PFS (PD-L1≥1%)**	Comparison groups	Nivo+Chemo vs Chemo
		Hazard ratio (HR)	0.65
		98.5% CI	0.46, 0.92
		p value (stratified 2-sided)	0.0023
	Secondary endpoint **OS (all randomised)**	Comparison groups	Nivo+Chemo vs Chemo
		Hazard ratio (HR)	0.74
		99.1% CI	0.58, 0.96
		p value (stratified 2-sided)	0.0021
	Secondary endpoint **PFS (all randomised)**	Comparison groups	Nivo+Chemo vs Chemo
		Hazard ratio (HR)	0.81
		98.5% CI	0.64, 1.04
		p value (stratified 2-sided)	0.0355
	Secondary endpoint **ORR (PD-L1≥1%)**	Comparison groups	Nivo+Chemo vs Chemo
		Difference	33.4
		95% CI	23.5, 43.4
		P-value	Not applicable
	Secondary endpoint **ORR (all randomised)**	Comparison groups	Nivo+Chemo vs Chemo
		Difference	20.6
		95% CI	13.4, 27.7
		P-value	Not applicable
Notes			

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

Not applicable

Clinical studies in special populations

Table 24: Summary of Subject Disposition by Age Category - All Randomized Subjects - By Treatment Arm and Total for Study CA209648

	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**	**Total**	**Nivo + Ipi**	**Nivo + Chemo**	**Chemo**	**Total**	**Nivo + Ipi**	**Nivo + Chemo**	**Chemo**	**Total**
Controlled Trials	116/325 (35.7)	123/321 (38.3)	129/324 (39.8)	368/970 (37.9)	24/325 (7.4)	28/321 (8.7)	29/324 (9.0)	81/970 (8.4)	0/325	3/321 (0.9)	0/324	3/970 (0.3)
Non Controlled trials	Not applicable				Not applicable				Not applicable			

Source: Table S.3.2.1.2 (all randomized subjects) in the CA209648 Primary CSR.[1]

Supportive study(ies)

Not applicable

2.4.3. Discussion on clinical efficacy

This is an application for an extension of the indication for Opdivo (nivolumab) in combination with chemotherapy for the first-line treatment of adult patients with advanced or metastatic oesophageal squamous cell carcinoma (OSCC).

An application has been submitted in parallel for a new indication for nivolumab in combination with ipilimumab for the same target population (EMEA/H/C/3985/II/WS/2113).

Design and conduct of clinical studies

This application is based on the results of **study CA209648**, a randomised, open-label, phase 3 study of nivolumab+ipilimumab or nivolumab in combination with chemotherapy (fluorouracil plus cisplatin) versus chemotherapy (fluorouracil plus cisplatin) in patients with recurrent or metastatic previously untreated OSCC. Overall, the study design can be considered adequate to support a marketing authorisation in the claimed indication.

The study was open-label. However, considering the primary endpoints were overall survival (OS) and progression free survival (PFS) as assessed by blinded independent central review (BICR), this is considered acceptable.

Patient population

Overall, inclusion and exclusion criteria are considered acceptable. Patients with an advanced disease of squamous cell histology, who were treatment-naïve and had a good performance status (ECOG 0 or 1) were enrolled in the study. Patients with brain or meninx metastasis were only allowed to enter the study if asymptomatic and not requiring treatment. This population can be considered representative of a patient population for which chemotherapy is considered the SoC.

Patients were included in the study regardless of tumour cell PD-L1 expression. However, tumour tissue was required for PD-L1 expression determination by a central lab. Patients with non-evaluable results were not allowed to enter the study.

Treatments

Nivolumab was used at a dose of 240 mg Q2W, which is the dose currently approved for nivolumab (monotherapy) in the treatment of OSCC in the second line setting and in several other indications. In study CA209648, nivolumab was administered in combination with chemotherapy consisting of fluorouracil (5-FU) and cisplatin.

With regards to the comparator (5-FU+cisplatin), it is considered adequate since this is one of the regimens recommended in the current guidelines for the treatment of advanced oesophageal cancer. In the NCCN guideline a combination of fluoropyrimidine (either 5-FU or capecitabine) and cisplatin or

oxaliplatin are the preferred recommended regimens[1]. Use of oxaliplatin is also preferred over cisplatin due to lower toxicity. According to the ESMO guideline the value of palliative chemotherapy is less clear for OSCC than for oesophageal adenocarcinoma, although reference to cisplatin combinations is made[2].

The recommended regimen in the CA209648 study was 5-FU 800 mg/m^2 IV for 5 days (days 1 to 5) plus cisplatin 80 mg/m^2 IV on day 1, cycled every 4 weeks. As stated by the MAH, the 5-FU+cisplatin regimen varies among countries. Current NCCN guidelines recommends 5-FU (750 - 1000 mg/m² on Days 1 - 4) plus cisplatin (75 - 100 mg/m² on Day 1) every 4 weeks. According to the MAH, the proposed regimen in this study is the most commonly used in Japan and it is also used in the US and Europe. The proposed regimen is considered acceptable.

Further, the proposed posology for nivolumab in the PI when combined with chemotherapy is 240 mg Q2W or 480 mg Q4W. The justification for this additional posology is mainly based on pharmacology data (see PK/PD section).

According to the protocol, treatment beyond radiological confirmed progression was allowed if the subject had investigator-assessed clinical benefit and was tolerating treatment. Considering the population of patients with tumour cell PD-L1≥1%, there were 39 patients in the nivo+chemo arm who were treated beyond progression, with a median treatment duration of 1.28 months (range: 0.1, 16.8). According to the MAH, among patients treated beyond progression there were patients with confirmed disease progression and patients for whom disease progression was doubtful and that required further confirmation. The MAH was requested to provide separate numbers of the patients that received treatment beyond unequivocal progression and those who received treatment while awaiting confirmation/rejection of progression, but these data were not available. Treatment beyond progression was not allowed in the chemo arm, however, investigators could continue study therapy while awaiting the RECIST 1.1 assessment. There were 13 patients in the chemo arm with PD-L1≥1% that received treatment beyond progression with a median treatment duration of 0.23 months (range: 0.1 , 4.3). Bearing in mind that the number of patients with a long duration of treatment beyond progression was low it is considered unlikely this may have impacted the (OS) results and therefore no changes in the SmPC are deemed necessary.

Endpoints

The dual primary endpoints of the study were OS and PFS (as assessed by BICR per RECIST 1.1 criteria) in patients with PD-L1≥1%. Secondary endpoints included OS and PFS in all randomised subjects and ORR (both in PD-L1≥1% and the overall population, by BICR). Duration of response, PFS and ORR according to investigator assessment, PFS2/TSST and PROs were exploratory endpoints. The choice of the primary and secondary endpoints is considered appropriate.

Sample size

The operating characteristics concerning the sample size calculation are clearly described. The MAH has assumed the same distributions for OS and PFS and a piecewise mixture cure rate model was applied for the current design. Overall, the proposal for the sample size is acceptable and meets regulatory requirements.

Statistical analysis

The MAH has designed a graphical testing strategy to control the type I error through different endpoints and in particular, the primary endpoints and a number of secondary endpoints were tested

[1]NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric junction cancers. Version 4.2021.
[2] Lordick F, Mariette C, Haustermans K et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 27 (Supplement 5): v50–v57, 2016

using the Bonferroni-based graphical approach by Maurer and Bretz (2013). Overall, the strategy is considered acceptable.

Regarding the analysis of OS, the MAH planned to perform an interim analysis (IA) for OS at the time the PFS final analysis was triggered. The decision was foreseen when 136 PFS events were observed among the population selected for the primary analysis in the chemo arm. The tracking was conducted by an independent external statistical group (AXIO). In the revised protocol v05, the MAH decided to add an additional criterion to trigger the PFS final analysis (and OS interim analysis), a 12-month minimum follow-up, since the collection of PFS events were slow.

Concerning the primary analyses, the MAH considered the hypothetical strategy, and censored the intercurrent events which deals with the administration of subsequent therapy and withdrawal of consent. Sensitivity analysis considering intercurrent events as events were consistent with the primary analyses.

Study conduct

The study was originally designed as a Phase 2 study of nivolumab monotherapy (Arm A) and in combination with ipilimumab (Arm B) in subjects with advanced or metastatic previously treated gastric, GEJ or previously untreated oesophageal cancer. With amendment 2, the study was modified into a randomized Phase 3 study with three treatment arms including only patients with squamous oesophageal cancer. At the time of this amendment no patients had been randomised.

Afterwards several further changes were performed although it is not considered that these changes could have impacted the results. Of importance, with revision 5 (dated 29 Oct 2020) a time-based trigger for the IA (final PFS/IA OS) was added. Five patients had relevant protocol deviations (2 subjects in the nivo+chemo arm and 3 subjects in the chemo arm). One subject in the nivo+chemo arm had sarcomatoid carcinoma of the oesophagus, although this patient was not treated; a second patient in the chemo arm, entered the study without measurable disease at baseline; and there were 3 patients that received concurrent traditional medicines used for cancer treatment (botanical formulations). Taking into account the low number of patients with protocol deviations and considering cases were almost comparable between treatment arms, no impact on the results is expected.

The MAH has provided information on important protocol deviations (IPDs), which according to the MAH reflect protocol deviations that may significantly impact completeness, accuracy and/or reliability of the study data. A total of 404 IPDs were reported among all enrolled subjects (151 in the nivo+chemo arm, 115 in the nivo+ipi arm, 132 in the chemo arm and 6 in patients who were not randomised). After a review of the reported IPDs, it is not considered that these could have impacted the results.

Efficacy data and additional analyses

Baseline characteristics

The median age of patients included in the study was 64 (range: 26, 90) years. There were 84 (8.7%) patients who were 75 years or older. Demographics and other baseline characteristics were overall well balanced between treatment arms.

With regards to prior treatment, 23% of patients had received prior systemic therapy in the neoadjuvant (55%) or adjuvant (17%) setting, or definitive CRT therapy (30%). Prior radiotherapy was received by around 20% of patients.

In the chemo arm 55.9% received subsequent systemic therapy, compared with 46.4% in the nivo+chemo arm. In the chemo group, a higher number of patients received anti-PD-(L)1 therapy (15.7% vs. 5%), mainly nivolumab.

Efficacy outcomes

The efficacy data initially provided were based on a clinical data cut-off of 18 Jan 2021 and a clinical DBL of 1 Mar 2021, with a median follow-up of 23.7 months (range: 12.9, 40.7). The submission is based on results of the final analysis of PFS and an IA of OS, which is now considered the final analysis.

The study met its primary objective. Nivo+chemo demonstrated a statistically significant improvement in OS (HR 0.54; 99.5% CI: 0.37, 0.80) and PFS by BICR (HR 0.65; 98.5% CI: 0.46, 0.92) over chemotherapy alone in patients with PD-L1≥1%. ORR in patients with PD-L1≥1% (secondary endpoint) was also higher in the nivo+chemo arm (53.2% vs. 19.7%).

In the all-randomised patient population, with 65.1% events in the nivo+chemo and 71.6% in the chemo arms (i.e. 85.8% of the target final number of OS events), a statistically significant benefit in OS for nivo+chemo over chemo was observed (HR 0.74; 99.1% CI: 0.58, 0.96). Median OS was of 13.21 months vs. 10.71 months, respectively. The benefit is observed after approximately 6 months, when OS KM curves separated. Sensitivity analyses were consistent with the primary analysis.

OS (and PFS) in the all-randomised patients was assessed as a secondary endpoint, thus, results in the intended target population are based on secondary endpoints. However, since a hierarchical testing strategy was used, type I error control is warranted and therefore these results can be considered interpretable.

Regarding PFS, no statistically significant differences were observed between nivo+chemo vs. chemo in the all-randomised patient population (HR 0.81; 98.5% CI: 0.64, 1.04). Median PFS was 5.82 months in the nivo+chemo arm and 5.59 months in the chemo arm. Several sensitivity analyses were consistent with the primary analysis. However, PFS (per BICR) accounting for assessment on/after subsequent therapy (i.e. secondary definition, considering events and disease assessments that occurred on or after subsequent anti-cancer), which is EMA preferred, showed an improvement in favour of the combination (HR 0.77; 98.5% CI: 0.62, 0.95). In fact, PFS analysis by the investigator (exploratory endpoint) also showed results in favour of the nivo+chemo arm (HR 0.69; 95% CI: 0.58, 0.83). According to the MAH differences between the BICR and investigator assessment, may be explained by differences in the number of censored patients due to receiving subsequent anti-cancer therapy (42 vs. 25 in the nivo+chemo arm and 83 vs. 40 in the chemo arm, BICR and investigator, respectively).

ORR (per BICR) was also higher in the nivo+chemo arm compared with the chemo arm (47.4% vs. 26.9%, respectively). ORR by the investigator was consistent. Median TTR was quite similar between treatment arms and DoR was slightly higher in the nivo+chemo arm (8.18 vs. 7.13 months). Since statistical significance was not reached for PFS in the all-randomised population, as per the hierarchical testing strategy ORR was not formally tested (neither in the primary efficacy population; i.e. PD-L1≥1%, nor in the all-randomised patients).

PFS2/TSST (exploratory endpoint) also favoured the experimental arm (HR 0.64; 95% CI: 0.54, 0.77).

PROs were assessed using the EQ-5D-3L VAS and Utility Index and FACT-E. According to the information provided, survey completion was of more than 90% at baseline and more than 80% at most subsequent treatment assessments. However, taking into account the open-label design of the study and the exploratory nature of this endpoint, no firm conclusions can be drawn in this regard.

During the procedure updated efficacy data (DBL 04 Oct 2021) with a minimum follow-up of 20 months were provided. Overall, results were consistent with the primary analysis. An improvement was observed with nivo+chemo over chemo in OS, PFS and ORR in both the primary efficacy population (i.e. patients with tumour cell PD-L1≥1%) and all randomised patients.

Subgroup analyses

Overall, OS subgroup analysis favoured the nivo+chemo arm (HR<1). However, no apparent benefit was observed with the addition of nivolumab in female patients (n=117; HR 1.02; 95% CI: 0.64, 1.63) and in patients who had received prior radiotherapy (n=119; HR 1.06; 95% CI: 0.69, 1.61). It is in any case acknowledged that sample size of these subgroups is relatively small and CIs overlap. According to the MAH, a review of the baseline demographic and disease characteristics did not identify any apparent differences that would explain the observed results in terms of treatment effect. Further, regarding female subgroup, the MAH states that chemo arm in the female subgroup performed better than the overall population (median OS: 14.75 months vs. 10.71 months, respectively). The MAH also argued that there were some imbalances in prognostic factors between both treatment arms. Besides, in the subgroup of female patients with PD-L1≥1%, a favourable effect was observed (HR 0.49; 95%CI: 0.25, 0.97) while not in patients with PD-L1<1%, although these subgroups are even smaller, thus results should be interpreted with caution.

An indication in a broad population (i.e. regardless of PD-L1 expression) was initially requested. However, there was an apparent lack of benefit in the subgroup of patients with PD-L1 <1% in OS (HR 0.98; 95% CI: 0.76, 1.28) and PFS (HR 0.95; 95% CI: 0.73, 1.24) and OS KM curves overlapped. The ORR was slightly higher in the nivo+chemo arm (41.7% vs. 33.7%). Consistent results were observed in the updated analysis submitted during the procedure (DBL 04 Oct 2021) which still showed an apparent lack of benefit with nivo+chemo over chemo in OS (HR 1.01; 95% CI: 0.78, 1.30) and PFS (HR 0.94; 95% CI: 0.73, 1.22). When considering a cut-off of 5%, while statistical significance was not reached in OS (HR 0.82; 95% CI: 0.65, 1.04) a slight separation in KM curves is observed, which appears more marked after 12 months. The MAH argues that a benefit of the combination over chemotherapy alone may be expected based on the higher ORR and longer DoR, with a DoR rate at 12 months of 38% (95% CI: 25, 50) in the nivo+chemo arm vs. 27% (95% CI: 14, 41) in the chemo arm, which may translate into a differential benefit with longer follow-up. However, since this is an add-on treatment this unclear benefit should be weighed against the (potential) added toxicity with the addition of nivolumab to the chemotherapy regimen. Bearing in mind the above results, the indication was restricted to the patient population with tumour cell PD-L1 expression ≥1%.

Additional exploratory biomarker analyses are planned for study CA209648, such as MSI, TMB, genetic alterations of select genes an inflammatory gene signature. The MAH is requested to provide results of these analyses once available (see proposed post authorisation measure REC).

The finally agreed indication is as follows (***text added***):

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma ***with tumour cell PD-L1 expression ≥ 1%****.*

A broad indication covering combination of nivolumab with fluoropyrimidine and platinum-based chemotherapy can be accepted.

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical efficacy

Not applicable

2.4.4. Conclusions on the clinical efficacy

In study CA209648, in adult patients with advanced or metastatic OSCC, treatment with nivolumab in combination with chemotherapy (5-FU+cisplatin) demonstrated a statistically significant clinically relevant improvement in OS and PFS compared with chemotherapy (5-FU+cisplatin) alone in the patient population with tumour cell PD-L1expression ≥1%.

The following measure is considered necessary to address issues related to efficacy:

Additional exploratory biomarker analyses are planned for study CA209648, such as MSI, TMB, genetic alterations of select genes an inflammatory gene signature. The MAH is requested to provide results of these analyses once available (REC).

2.5. Clinical safety

Safety assessment is based on All Treated Population (N=936) in study CA209648. In particular, safety data from 310 subjects treated with 1L nivo + chemo (nivo 240 mg Q2W + chemo [5-FU + cisplatin] Q4W) from treatment arm B and 304 subjects treated with chemo from arm C were used to characterize the safety profile of this combination regimen application in subjects with advanced or metastatic OSCC.

This is a phase 3, global, randomised, open-label study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin vs. fluorouracil plus cisplatin in patients with unresectable advanced, recurrent or metastatic previously untreated oesophageal squamous cell carcinoma. Randomization was stratified by tumour cell PD-L1 expression, region, ECOG PS and number of organs with metastases.

Patients in the Nivo + Chemo arm were to receive nivolumab 240 mg as a 30-min IV infusion Q2W, fluorouracil 800 mg/m^2/day as a continuous IV infusion on Days 1-5 Q4W and cisplatin 80 mg/m^2 as a 30-120-minute IV infusion (or longer if in accordance with local standard of care/local label) on Day 1 Q4W. Patients in the Chemo arm received the same above described chemotherapy scheme.

CA209648 study was conducted at 175 sites in 26 countries. The clinical cutoff occurred on 18-Jan-2021 and DBL occurred on 01-Mar-2021 for the CA209648 Primary CSR. Updated safety data were later provided based on a 04-Oct-2021 DBL. A summary of these results is included after the initial assessment.

Patient exposure

With the DBL of 01-Mar-2021, 936 subjects were treated: 310 with nivo + chemo, 322 with nivo + ipi and 304 with chemo. At the time of DBL, study treatment was discontinued in 91.9%, 93.5%, and 98.7% of the subjects treated with nivo + chemo, nivo + ipi and chemo, respectively. The reasons for not continuing on study treatment are displayed in Table 1.

Table 1. End of Treatment Period Status Summary – All Enrolled, Randomized, and Treated Subjects from CA209648

Status (%)	Nivo + Ipi	Nivo + Chemo	Chemotherapy	Total
ENROLLED				1358 (100.0)
RANDOMIZED (a)	325	321	324	970 (71.4)
NOT RANDOMIZED (a)				388 (28.6)
REASON FOR NOT RANDOMIZED				
DEATH				11 (0.8)
ADVERSE EVENT				6 (0.4)
SUBJECT WITHDREW CONSENT				34 (2.5)
LOST TO FOLLOW-UP				1 (0.1)
POOR/NON-COMPLIANCE				1 (0.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA				330 (24.3)
OTHER				5 (0.4)
TREATED (b)	322 (99.1)	310 (96.6)	304 (93.8)	936 (96.5)
NOT TREATED	3 (0.9)	11 (3.4)	20 (6.2)	34 (3.5)
REASON FOR NOT TREATED				
DISEASE PROGRESSION	1 (0.3)	1 (0.3)	2 (0.6)	4 (0.4)
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (0.3)	3 (0.9)	1 (0.3)	5 (0.5)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	0	2 (0.6)	2 (0.2)
SUBJECT WITHDREW CONSENT	0	1 (0.3)	12 (3.7)	13 (1.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	4 (1.2)	2 (0.6)	6 (0.6)
OTHER	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.4)
CONTINUING IN THE TREATMENT PERIOD (c)	21 (6.5)	25 (8.1)	4 (1.3)	50 (5.3)
NOT CONTINUING IN THE TREATMENT PERIOD	301 (93.5)	285 (91.9)	300 (98.7)	886 (94.7)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD				
DISEASE PROGRESSION	174 (54.0)	184 (59.4)	193 (63.5)	551 (58.9)
STUDY DRUG TOXICITY	59 (18.3)	33 (10.6)	40 (13.2)	132 (14.1)
DEATH	5 (1.6)	3 (1.0)	4 (1.3)	12 (1.3)
ADVERSE EVENT UNRELATED TO STUDY DRUG	19 (5.9)	28 (9.0)	12 (3.9)	59 (6.3)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	13 (4.0)	15 (4.8)	20 (6.6)	48 (5.1)
SUBJECT WITHDREW CONSENT	3 (0.9)	4 (1.3)	12 (3.9)	19 (2.0)
PREGNANCY	1 (0.3)	0	0	1 (0.1)
MAXIMUM CLINICAL BENEFIT	1 (0.3)	3 (1.0)	4 (1.3)	8 (0.9)
COMPLETED TREATMENT AS PER PROTOCOL	13 (4.0)	8 (2.6)	0	21 (2.2)
OTHER	12 (3.7)	7 (2.3)	15 (4.9)	34 (3.6)
NOT REPORTED	1 (0.3)	0	0	1 (0.1)
CONTINUING IN THE STUDY (c)	93 (28.9)	91 (29.4)	61 (20.1)	245 (26.2)
NOT CONTINUING IN THE STUDY	229 (71.1)	219 (70.6)	243 (79.9)	691 (73.8)
REASON FOR NOT CONTINUING IN THE STUDY				
DEATH	206 (64.0)	196 (63.2)	216 (71.1)	618 (66.0)
SUBJECT WITHDREW CONSENT	16 (5.0)	19 (6.1)	27 (8.9)	62 (6.6)
LOST TO FOLLOW-UP	2 (0.6)	1 (0.3)	0	3 (0.3)
OTHER	5 (1.6)	3 (1.0)	0	8 (0.9)

(a) Percentages based on subjects entering period.
(b) Percentages based on number of randomized subjects
(c) Percentages based on number of treated subjects

The primary reason for not continuing in the treatment period was disease progression: 59.4% subjects in the nivo + chemo arm, 54% in the nivo + ipi arm and 63.5% in the chemo arm. Study drug toxicity was reported as the reason for not continuing in the treatment period for the 10.6% of subjects in the nivo + chemo arm, 18.3% in the nivo + ipi arm and 13.2% in the chemo arm.

Among all treated subjects, the median durations of study therapy were 5.68 (0.1-30.6) months in the nivo + chemo arm, 2.79 (0-24.0) months in the nivo + ipi arm, and 3.35 (0-19.0) months in the chemo arm. The proportions of subjects with durations of therapy of >9 months were numerically higher in the nivo + chemo (28.4%) and nivo + ipi (20.5%) arms vs the chemo arm (9.2%).

Median duration of study treatment was longer in the nivo + chemo arm vs the chemo arm, both overall and for individual chemotherapy components. In the nivo + chemo arm, chemotherapy was administered for a numerically higher median number of cycles, but with reduced relative dose intensity compared with the chemo arm.

The median (min - max) number of doses of each therapy per arm were:

- Nivo + chemo arm (N = 310):
    - 12.0 (1 - 54) doses of nivolumab
    - 5.0 (1 - 24) doses of cisplatin
    - 6.0 (1 - 31) doses of fluorouracil
- Nivo + ipi arm (N = 322):

    - 6.0 (1 - 52) doses of nivolumab
    - 3.0 (1 - 18) doses of ipilimumab
- Chemo arm:
    - 4.0 (1 - 17) doses of cisplatin (N = 304)
    - 4.0 (1 - 21) doses of fluorouracil (N = 302)

The proportions of subjects who received ≥90% of the planned relative dose intensity of each therapy were as follows by arm:

- Nivo + chemo arm (N = 310):
    - 67.4% for nivolumab
    - 55.5% for cisplatin
    - 58.4% for fluorouracil
- Nivo + ipi arm (N = 322):
    - 76.1% for nivolumab
    - 87.0% for ipilimumab
- Chemo arm:
    - 68.1% for cisplatin (N = 304)
    - 76.2% for fluorouracil (N = 302)

The numbers of doses and cumulative dose per therapy are summarized in Table 2.

Table 2. Summary of Study Treatment Duration, Cumulative Dose, and Relative Dose Intensity – All Treated Subjects

	Nivo + Ipi N = 322	Nivo + Chemo N = 310	Chemotherapy N = 304
DURATION OF THERAPY (MONTHS)			
MEAN (MIN, MAX)	5.47 (0.0, 24.0)	7.43 (0.1, 30.6)	4.11 (0.0, 19.5)
MEDIAN	2.79	5.68	3.35
> 3 MONTHS (%)	154 (47.8)	224 (72.3)	165 (54.3)
> 6 MONTHS (%)	90 (28.0)	148 (47.7)	65 (21.4)
> 9 MONTHS (%)	66 (20.5)	88 (28.4)	28 (9.2)
> 12 MONTHS (%)	49 (15.2)	62 (20.0)	10 (3.3)

	Nivolumab N = 322	Ipilimumab N = 322	Nivolumab N = 310	Cisplatin N = 310	Fluorouracil N = 310	Cisplatin N = 304	Fluorouracil N = 302
DURATION OF THERAPY (MONTHS)							
MEAN	5.47	4.88	7.31	4.24	5.89	3.52	4.13
(SD)	(6.41)	(6.41)	(6.11)	(3.06)	(5.16)	(2.98)	(3.49)
MEDIAN	2.79	2.76	5.62	4.04	4.80	2.91	3.35
(MIN - MAX)	(0.0 - 24.0)	(0.0 - 24.0)	(0.0 - 24.7)	(0.0 - 21.3)	(0.1 - 30.6)	(0.0 - 16.9)	(0.1 - 19.5)
NUMBER OF DOSES RECEIVED							
MEAN	11.8	4.3	15.4	5.1	6.6	4.5	5.0
(SD)	(12.9)	(4.3)	(12.5)	(3.1)	(5.2)	(2.9)	(3.5)
MEDIAN	6.0	3.0	12.0	5.0	6.0	4.0	4.0
(MIN - MAX)	(1 - 52)	(1 - 18)	(1 - 54)	(1 - 24)	(1 - 31)	(1 - 17)	(1 - 21)
CUMULATIVE DOSE (1)							
MEAN	35.40	4.26	3685.59	370.36	24929.68	339.41	19391.17
(SD)	(38.16)	(4.28)	(2989.49)	(213.53)	(20012.03)	(216.58)	(13750.25)
MEDIAN	18.86	2.88	2880.00	322.39	20203.17	317.74	16123.79
(MIN - MAX)	(2.9 - 155.0)	(0.9 - 18.1)	(240.0 - 12960.0)	(23.7 - 1093.1)	(828.4 - 120876.0)	(73.3 - 1348.7)	(1206.7 - 84236.6)
RELATIVE DOSE INTENSITY (%)							
>= 110%	2 (0.6)	3 (0.9)	0	1 (0.3)	0	1 (0.3)	0
90% TO < 110%	243 (75.5)	277 (86.0)	209 (67.4)	171 (55.2)	181 (58.4)	206 (67.8)	230 (76.2)
70% TO < 90%	64 (19.9)	38 (11.8)	87 (28.1)	79 (25.5)	93 (30.0)	71 (23.4)	62 (20.5)
50% TO < 70%	10 (3.1)	4 (1.2)	13 (4.2)	51 (16.5)	32 (10.3)	24 (7.9)	7 (2.3)
< 50%	3 (0.9)	0	1 (0.3)	8 (2.6)	4 (1.3)	2 (0.7)	3 (1.0)

(1) Dose units: Nivo+Ipi arm: Nivo and Ipi in mg/kg; Nivo+Chemo and Chemo arms: Nivo in mg, Fluorouracil and Cisplatin in mg/m^2.
Source: Table S.4.1.2 (Cumulative Dose and Relative Dose Intensity Summary), Table S.4.61.2 (Duration of Study Therapy Summary)

Adverse events

The overall safety summary focuses on the comparison of the nivo + chemo and nivo + ipi arms with the chemo arm, which is the most relevant comparison in assessing benefit and risk of nivo + chemo and nivo + ipi combination therapies.

Table 3. Summary of Safety - All Treated Subjects

	No. of Subjects (%)					
Safety Parameter	**Nivo+Ipi (N=322)**		**Nivo+Chemo (N=310)**		**Chemo (N=304)**	
Deaths	215 (66.8)		200 (64.5)		224 (73.7)	
Primary Reason for Death						
Disease	176 (54.7)		168 (54.2)		204 (67.1)	
Study Drug Toxicity	5 (1.6)		5 (1.6)		4 (1.3)	
Unknown	12 (3.7)		10 (3.2)		8 (2.6)	
Other	22 (6.8)		17 (5.5)		8 (2.6)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	214 (66.5)	146 (45.3)	180 (58.1)	132 (42.6)	128 (42.1)	96 (31.6)
Drug-related SAEs	103 (32.0)	73 (22.7)	74 (23.9)	57 (18.4)	49 (16.1)	38 (12.5)
All-causality AEs leading to DC	81 (25.2)	54 (16.8)	126 (40.6)	51 (16.5)	77 (25.3)	28 (9.2)
Drug-Related AEs leading to DC	57 (17.7)	41 (12.7)	106 (34.2)	29 (9.4)	59 (19.4)	14 (4.6)
All-causality AE	316 (98.1)	192 (59.6)	308 (99.4)	216 (69.7)	301 (99.0)	165 (54.3)
Drug-related AEs	256 (79.5)	102 (31.7)	297 (95.8)	147 (47.4)	275 (90.5)	108 (35.5)
≥ 15% Drug-related AEs in Any Treatment						
Rash	55 (17.1)	7 (2.2)	24 (7.7)	1 (0.3)	5 (1.6)	0
Diarrhoea	32 (9.9)	2 (0.6)	60 (19.4)	3 (1.0)	46 (15.1)	6 (2.0)
Fatigue	29 (9.0)	4 (1.2)	61 (19.7)	7 (2.3)	50 (16.4)	11 (3.6)
Nausea	26 (8.1)	1 (0.3)	182 (58.7)	11 (3.5)	158 (52.0)	8 (2.6)

Safety Parameter	No. of Subjects (%)					
	Nivo+Ipi (N=322)		Nivo+Chemo (N=310)		Chemo (N=304)	
Decreased appetite	19 (5.9)	5 (1.6)	132 (42.6)	13 (4.2)	130 (42.8)	9 (3.0)
Vomiting	18 (5.6)	4 (1.2)	56 (18.1)	7 (2.3)	49 (16.1)	9 (3.0)
Stomatitis	14 (4.3)	0	98 (31.6)	20 (6.5)	71 (23.4)	5 (1.6)
Anaemia	12 (3.7)	2 (0.6)	93 (30.0)	30 (9.7)	67 (22.0)	17 (5.6)
Malaise	12 (3.7)	0	50 (16.1)	1 (0.3)	45 (14.8)	0
Constipation	7 (2.2)	1 (0.3)	59 (19.0)	2 (0.6)	66 (21.7)	1 (0.3)
Neutrophil count decreased	2 (0.6)	0	65 (21.0)	25 (8.1)	52 (17.1)	24 (7.9)
Hiccups	2 (0.6)	0	42 (13.5)	0	53 (17.4)	0
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality Select AEs by Category						
Endocrine	92 (28.6)	19 (5.9)	40 (12.9)	5 (1.6)	5 (1.6)	0
Gastrointestinal	78 (24.2)	10 (3.1)	94 (30.3)	12 (3.9)	62 (20.4)	7 (2.3)
Hepatic	67 (20.8)	24 (7.5)	55 (17.7)	11 (3.5)	22 (7.2)	6 (2.0)
Pulmonary	32 (9.9)	11 (3.4)	22 (7.1)	3 (1.0)	6 (2.0)	1 (0.3)
Renal	17 (5.3)	3 (0.9)	81 (26.1)	12 (3.9)	63 (20.7)	5 (1.6)
Skin	137 (42.5)	13 (4.0)	82 (26.5)	2 (0.6)	37 (12.2)	0
Hypersensitivity/Infusion Reactions	14 (4.3)	0	8 (2.6)	1 (0.3)	1 (0.3)	0
Drug-Related Select AEs by Category						
Endocrine	88 (27.3)	19 (5.9)	36 (11.6)	4 (1.3)	1 (0.3)	0
Gastrointestinal	38 (11.8)	5 (1.6)	64 (20.6)	7 (2.3)	47 (15.5)	7 (2.3)
Hepatic	42 (13.0)	14 (4.3)	32 (10.3)	7 (2.3)	12 (3.9)	2 (0.7)
Pulmonary	26 (8.1)	9 (2.8)	18 (5.8)	2 (0.6)	2 (0.7)	0
Renal	8 (2.5)	2 (0.6)	74 (23.9)	7 (2.3)	57 (18.8)	5 (1.6)
Skin	110 (34.2)	13 (4.0)	54 (17.4)	1 (0.3)	11 (3.6)	0
Hypersensitivity/Infusion Reactions	9 (2.8)	0	6 (1.9)	0	1 (0.3)	0
All-causality IMAEs within 100 d of last dose treated with IMM by Category						
Diarrhea/Colitis	11 (3.4)	4 (1.2)	6 (1.9)	4 (1.3)	0	0
Hepatitis	13 (4.0)	9 (2.8)	2 (0.6)	1 (0.3)	0	0
Pneumonitis	12 (3.7)	7 (2.2)	10 (3.2)	2 (0.6)	0	0
Nephritis/Renal Dysfunction	4 (1.2)	2 (0.6)	3 (1.0)	3 (1.0)	0	0
Rash	44 (13.7)	8 (2.5)	16 (5.2)	1 (0.3)	2 (0.7)	1 (0.3)
Hypersensitivity/Infusion Reactions	1 (0.3)	0	0	0	0	0
All-causality Endocrine IMAEs within 100 d of last dose by Category						
Adrenal Insufficiency	18 (5.6)	7 (2.2)	5 (1.6)	1 (0.3)	0	0
Hypophysitis	21 (6.5)	10 (3.1)	2 (0.6)	1 (0.3)	0	0
Hypothyroidism/Thyroiditis	50 (15.5)	1 (0.3)	19 (6.1)	0	0	0
Diabetes Mellitus	5 (1.6)	2 (0.6)	3 (1.0)	3 (1.0)	0	0
Hyperthyroidism	19 (5.9)	2 (0.6)	7 (2.3)	0	1 (0.3)	0
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality OESIs within 100 d of last dose with/without IMM by Category						
Pancreatitis	5 (1.6)	4 (1.2)	0	0	0	0
Encephalitis	3 (0.9)	3 (0.9)	0	0	0	0
Myositis/Rhabdomyolysis	2 (0.6)	0	2 (0.6)	1 (0.3)	0	0
Myasthenic Syndrome	0	0	0	0	0	0
Demyelination	0	0	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0	0	0
Uveitis	2 (0.6)	1 (0.3)	2 (0.6)	0	0	0
Myocarditis	2 (0.6)	0	0	0	0	0
Graft Versus Host Disease	0	0	0	0	0	0

MedDRA version 23.1 CTCAE version 4.0.
All events are within 30 days of the last dose of study drug, unless otherwise indicated (eg, any time for deaths, 100 days for IMAEs and OESIs).

Source: Table S.6.15.2 (deaths), Table S.6.3.1.2.3 (All-causality SAEs) , Table S.6.3.1.2.4 (Drug-related SAEs), Table S.6.4.2.2.2 (All-causality AEs leading to DC), Table S.6.4.2.2 (Drug-Related AEs leading to DC), Table S.6.1.31.2.2 (All-causality AEs), Table S.6.1.32.1 (Drug-related AEs), Table S.6.5.1.3.1 (non-endocrine all-causality select AEs), Table S.6.5.1.3.2 (non-endocrine drug-related select AEs), Table S.6.5.1.3.1.3 (Endocrine all-causality select AEs) Table S.6.5.1.3.1.4 (endocrine drug-related select AEs), Table S.6.2.02.4 (non-endocrine IMAEs), Table S.6.2.02.1 (endocrine IMAEs), Table S.6.5.3.3.1 (OESIs)

Updated Safety Results of Nivo + Chemo vs Chemo in CA209648 (04 Oct 2021 DBL)

Table 4: Updated Safety Results of Nivo + Chemo vs Chemo - All Treated Subjects in CA209648 (04-Oct-2021 Database Lock)

	No. of Subjects (%)			
Safety Parameter	**Nivo+Chemo N = 310**		**Chemo N = 304**	
Deaths (%)	229 (73.9)		242 (79.6)	
Primary Reason for Death				
Disease	193 (62.3)		222 (73.0)	
Study Drug Toxicity	5 (1.6)		5 (1.6)[a]	
Unknown	13 (4.2)		6 (2.0)	
Other	18 (5.8)[b]		9 (3.0)[c]	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	186 (60.0)	145 (46.8)	130 (42.8)	100 (32.9)
Drug-related SAEs	74 (23.9)	58 (18.7)	49 (16.1)	40 (13.2)
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality AEs leading to DC	130 (41.9)	56 (18.1)	81 (26.6)	33 (10.9)
Drug-Related AEs leading to DC	106 (34.2)	30 (9.7)	63 (20.7)	18 (5.9)
All-causality AE	308 (99.4)	226 (72.9)	301 (99.0)	170 (55.9)
Drug-related AEs	297 (95.8)	151 (48.7)	275 (90.5)	110 (36.2)
≥15% Drug-related AEs in Any Treatment Arm				
Nausea	183 (59.0)	11 (3.5)	158 (52.0)	8 (2.6)
Decreased appetite	132 (42.6)	13 (4.2)	130 (42.8)	9 (3.0)
Stomatitis	99 (31.9)	20 (6.5)	71 (23.4)	5 (1.6)
Anaemia	93 (30.0)	30 (9.7)	67 (22.0)	17 (5.6)
Neutrophil count decreased	65 (21.0)	25 (8.1)	52 (17.1)	24 (7.9)
Fatigue	61 (19.7)	7 (2.3)	50 (16.4)	11 (3.6)
Diarrhoea	59 (19.0)	3 (1.0)	46 (15.1)	6 (2.0)
Constipation	59 (19.0)	2 (0.6)	66 (21.7)	1 (0.3)
Vomiting	56 (18.1)	7 (2.3)	49 (16.1)	9 (3.0)
Malaise	51 (16.5)	0	45 (14.8)	0
Hiccups	42 (13.5)	0	53 (17.4)	0
All-causality Select AEs by Category				
Endocrine	42 (13.5)	6 (1.9)	5 (1.6)	0
Gastrointestinal	95 (30.6)	13 (4.2)	62 (20.4)	7 (2.3)
Hepatic	55 (17.7)	12 (3.9)	22 (7.2)	5 (1.6)
Pulmonary	23 (7.4)	3 (1.0)	6 (2.0)	2 (0.7)
Renal	81 (26.1)	13 (4.2)	63 (20.7)	5 (1.6)
Skin	83 (26.8)	2 (0.6)	38 (12.5)	0
Hypersensitivity/Infusion Reactions	9 (2.9)	1 (0.3)	1 (0.3)	0
Drug-Related Select AEs by Category				
Endocrine	38 (12.3)	5 (1.6)	1 (0.3)	0
Gastrointestinal	63 (20.3)	7 (2.3)	47 (15.5)	7 (2.3)
Hepatic	32 (10.3)	7 (2.3)	12 (3.9)	2 (0.7)
Pulmonary	19 (6.1)	2 (0.6)	1 (0.3)	0
Renal	73 (23.5)	8 (2.6)	57 (18.8)	5 (1.6)
Skin	54 (17.4)	1 (0.3)	12 (3.9)	0
Hypersensitivity/Infusion Reactions	6 (1.9)	0	1 (0.3)	0

Table 4: Updated Safety Results of Nivo + Chemo vs Chemo - All Treated Subjects in CA209648 (04-Oct-2021 Database Lock)

	No. of Subjects (%)			
Safety Parameter	**Nivo+Chemo N = 310**		**Chemo N = 304**	
All-causality IMAEs within 100 d of last dose treated with IMM by Category				
Diarrhea/Colitis	7 (2.3)	5 (1.6)	0	0
Hepatitis	2 (0.6)	1 (0.3)	0	0
Pneumonitis	14 (4.5)	3 (1.0)	0	0
Nephritis/Renal Dysfunction	4 (1.3)	4 (1.3)	0	0
Rash	16 (5.2)	1 (0.3)	3 (1.0)	1 (0.3)
Hypersensitivity/Infusion Reactions	1 (0.3)	0	0	0
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality Endocrine IMAEs within 100 d of last dose by Category				
Adrenal Insufficiency	6 (1.9)	2 (0.6)	0	0
Hypophysitis	2 (0.6)	1 (0.3)	0	0
Hypothyroidism/Thyroiditis	20 (6.5)	0	0	0
Diabetes Mellitus	3 (1.0)	3 (1.0)	0	0
Hyperthyroidism	7 (2.3)	0	1 (0.3)	0
All-causality OESIs within 100 d of last dose with/without IMM by Category				
Pancreatitis	0	0	0	0
Encephalitis	0	0	0	0
Myositis/Rhabdomyolysis	2 (0.6)	1 (0.3)	0	0
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0
Uveitis	2 (0.6)	0	0	0
Myocarditis	0	0	0	0
Graft Versus Host Disease	0	0	0	0

[a] In the chemo arm, the cause of death for one subject was updated from "Unknown" at the 01-Mar-2021 DBL to "Study Drug Toxicity" as of the 04-Oct-2021 DBL. See Appendix 1.2.1 for details of changes in cause of death between the two DBLs.

[b] In the nivo + chemo arm, one subject with "Other" cause of death was randomized to the nivo + chemo arm but never treated with study drug. There were 4 additional "Other" deaths as of the 04-Oct-2021 DBL, 3 new "Other" deaths after the 01-Mar-2021 DBL, and one subject had the cause of death updated from "Disease" at the 01-Mar-2021 DBL to "Other" as of the 04-Oct-2021 DBL. See Appendix 1.2.1 for further details.

[c] In the chemo arm, there was one additional "Other" death after the 01-Mar-2021 DBL. See Appendix 1.2.1 for further details.

MedDRA version 24.0, CTCAE version 4.0.

All events are within 30 days of the last dose of study drug, unless otherwise indicated (eg, any time for deaths, 100 days for IMAEs and OESIs).

Sources: Table S.6.15.2 (deaths), Appendix S.1.E.1 (death listing), Appendix 1.2.1 (changes in cause of death), Table S.6.3.1.2.3 (all-causality SAEs), Table S.6.3.1.2.4 (drug-related SAEs), Table S.6.4.2.3 (all-causality AEs leading to DC), Table S.6.4.2.4 (drug-related AEs leading to DC), Table S.6.1.31.1.2 (all-causality AEs), Table S.6.1.32.2 (drug-related AEs), Table S.6.5.1.3.3 (non-endocrine all-causality select AEs), Table S.6.5.1.3.4 (non-endocrine drug-related select AEs), Table S.6.5.1.3.2.3 (endocrine all-causality select AEs) Table S.6.5.1.3.2.4 (endocrine drug-related select AEs), Table S.6.2.02.4 (non-endocrine IMAEs), Table S.6.2.02.1 (endocrine IMAEs), and Table S.6.5.3.3.2 (OESIs) in Appendix 1.2

Adverse Events (regardless of causality)

Any-grade AEs were reported in 308 (99.4%), 316 (98.1%), and 301 (99.0%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively (Table 3). The most frequently reported (>20%) all-causality AEs of any grade per arm were:

- Nivo + chemo arm: nausea (65.2%), decreased appetite (51.3%), anaemia (45.8%), constipation (44.2%), stomatitis (32.6%), diarrhoea (29.4%), fatigue (25.8%), vomiting (22.6%), and neutrophil count decreased (22.3%)
- Nivo + ipi arm: nausea and pyrexia (22.4% each); diarrhoea and anaemia (22.0% each); rash (21.7%); constipation (20.5%); and neoplasms (20.2%)
- Chemo arm: nausea (55.9%), decreased appetite (49.7%), constipation (43.1%), anaemia (31.9%), stomatitis (24.0%), and hiccups (20.7%)

Grade 3-4 AEs were reported in 216 (69.7%), 192 (59.6%), and 165 (54.3%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively. All-causality Grade 3-4 AEs reported in > 5% of subjects in each treatment arm included the following:

- Nivo + chemo arm: anaemia (16.1%), neutrophil count decreased (9.0%), dysphagia (7.4%), decreased appetite (6.8%), stomatitis (6.5%), malignant neoplasm progression (5.5%), and pneumonia (5.2%)
- Nivo + ipi arm: pneumonia (6.8%), malignant neoplasm progression (6.5%), anaemia (6.2%), and dysphagia (5.3%)
- Chemo arm: anaemia (9.9%), neutrophil count decreased (8.6%), and decreased appetite (5.9%)

Drug-related Adverse Events

Any grade drug-related AEs in the 3 treatment arms consisted mainly of events in the SOCs as follows:

- Nivo + chemo arm: gastrointestinal disorders (79.4%), metabolism and nutritional disorders (54.8%), and Investigations (49.0%)
- Nivo + ipi arm: skin and subcutaneous tissue disorders (36.6%), gastrointestinal disorders (28.6%), and endocrine disorders (25.8%)
- Chemo arm: gastrointestinal disorders (74.0%), metabolism and nutritional disorders (51.6%), and general disorders and administration site conditions (46.1%)

Drug-related any-grade AEs were reported in 297 (95.8%), 256 (79.5%), and 275 (90.5%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively. The most frequently reported drug-related AEs of any grade were:

- Nivo + chemo arm: nausea (58.7%), decreased appetite (42.6%), and stomatitis (31.6%)
- Nivo + ipi arm: rash (17.1%), and pruritus and hypothyroidism (13.4% each)
- Chemo arm: nausea (52.0%), decreased appetite (42.8%), and stomatitis (23.4%)

Grade 3-4 drug-related AEs were reported in 147 (47.4%), 102 (31.7%), and 108 (35.5%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively. The most commonly reported drug-related Grade 3-4 AEs included:

- Nivo + chemo arm: anaemia (9.7%), neutrophil count decreased (8.1%), and stomatitis (6.5%)
- Nivo + ipi arm: hyponatraemia (2.5%); and rash, adrenal insufficiency, pneumonitis, alanine aminotransferase increased, and hepatic function abnormal (2.2% each)
- Chemo arm: neutrophil count decreased (7.9%), anaemia (5.6%), and fatigue (3.6%)

Table 5. Adverse Events by Worst CTC Grade in ≥10% of All Treated Subjects from CA209648

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 322			Nivo + Chemo N = 310			Chemotherapy N = 304		
	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	316 (98.1)	192 (59.6)	31 (9.6)	308 (99.4)	216 (69.7)	23 (7.4)	301 (99.0)	165 (54.3)	14 (4.6)
Gastrointestinal disorders	219 (68.0)	52 (16.1)	2 (0.6)	283 (91.3)	91 (29.4)	0	266 (87.5)	64 (21.1)	1 (0.3)
Nausea	72 (22.4)	2 (0.6)	0	202 (65.2)	13 (4.2)	0	170 (55.9)	8 (2.6)	0
Diarrhoea	71 (22.0)	6 (1.9)	0	91 (29.4)	9 (2.9)	0	60 (19.7)	6 (2.0)	0
Constipation	66 (20.5)	1 (0.3)	0	137 (44.2)	3 (1.0)	0	131 (43.1)	3 (1.0)	0
Vomiting	47 (14.6)	5 (1.6)	0	70 (22.6)	7 (2.3)	0	58 (19.1)	9 (3.0)	0
Dysphagia	38 (11.8)	17 (5.3)	0	44 (14.2)	23 (7.4)	0	35 (11.5)	15 (4.9)	0
Stomatitis	26 (8.1)	2 (0.6)	0	101 (32.6)	20 (6.5)	0	73 (24.0)	5 (1.6)	0
General disorders and administration site conditions	160 (49.7)	13 (4.0)	4 (1.2)	219 (70.6)	25 (8.1)	4 (1.3)	193 (63.5)	23 (7.6)	3 (1.0)
Pyrexia	72 (22.4)	3 (0.9)	0	58 (18.7)	1 (0.3)	0	35 (11.5)	1 (0.3)	0
Fatigue	48 (14.9)	4 (1.2)	0	80 (25.8)	7 (2.3)	0	58 (19.1)	12 (3.9)	0
Malaise	22 (6.8)	0	0	56 (18.1)	1 (0.3)	0	52 (17.1)	0	0
Oedema peripheral	22 (6.8)	0	0	41 (13.2)	0	0	24 (7.9)	0	0
Mucosal inflammation	5 (1.6)	0	0	36 (11.6)	9 (2.9)	0	30 (9.9)	4 (1.3)	0
Metabolism and nutrition disorders	158 (49.1)	62 (19.3)	0	233 (75.2)	88 (28.4)	0	204 (67.1)	47 (15.5)	0
Decreased appetite	56 (17.4)	13 (4.0)	0	159 (51.3)	21 (6.8)	0	151 (49.7)	18 (5.9)	0
Hyponatraemia	28 (8.7)	14 (4.3)	0	54 (17.4)	26 (8.4)	0	30 (9.9)	12 (3.9)	0
Hypokalaemia	26 (8.1)	10 (3.1)	0	45 (14.5)	21 (6.8)	0	27 (8.9)	11 (3.6)	0
Skin and subcutaneous tissue disorders	154 (47.8)	14 (4.3)	0	123 (39.7)	3 (1.0)	0	81 (26.6)	0	0
Rash	70 (21.7)	7 (2.2)	0	36 (11.6)	1 (0.3)	0	16 (5.3)	0	0
Pruritus	56 (17.4)	3 (0.9)	0	34 (11.0)	0	0	11 (3.6)	0	0
Alopecia	4 (1.2)	0	0	32 (10.3)	0	0	32 (10.5)	0	0
Investigations	137 (42.5)	40 (12.4)	0	190 (61.3)	59 (19.0)	0	156 (51.3)	49 (16.1)	0
Aspartate aminotransferase increased	40 (12.4)	7 (2.2)	0	27 (8.7)	4 (1.3)	0	10 (3.3)	2 (0.7)	0
Weight decreased	39 (12.1)	6 (1.9)	0	38 (12.3)	2 (0.6)	0	33 (10.9)	3 (1.0)	0
Alanine	37 (11.5)	8 (2.5)	0	25 (8.1)	4 (1.3)	0	11 (3.6)	1 (0.3)	0
Blood creatinine increased	12 (3.7)	0	0	42 (13.5)	2 (0.6)	0	37 (12.2)	1 (0.3)	0
Platelet count decreased	9 (2.8)	2 (0.6)	0	45 (14.5)	5 (1.6)	0	34 (11.2)	5 (1.6)	0
Neutrophil count decreased	3 (0.9)	1 (0.3)	0	69 (22.3)	28 (9.0)	0	54 (17.8)	26 (8.6)	0
Respiratory, thoracic and mediastinal disorders	125 (38.8)	28 (8.7)	4 (1.2)	154 (49.7)	32 (10.3)	0	130 (42.8)	16 (5.3)	1 (0.3)
Cough	36 (11.2)	1 (0.3)	0	40 (12.9)	0	0	29 (9.5)	1 (0.3)	0
Hiccups	8 (2.5)	1 (0.3)	0	53 (17.1)	0	0	63 (20.7)	0	0
Infections and infestations	118 (36.6)	47 (14.6)	2 (0.6)	117 (37.7)	32 (10.3)	4 (1.3)	80 (26.3)	18 (5.9)	3 (1.0)
Pneumonia	43 (13.4)	22 (6.8)	2 (0.6)	40 (12.9)	16 (5.2)	2 (0.6)	29 (9.5)	7 (2.3)	1 (0.3)
Blood and lymphatic system disorders	86 (26.7)	27 (8.4)	0	169 (54.5)	67 (21.6)	0	115 (37.8)	42 (13.8)	0
Anaemia	71 (22.0)	20 (6.2)	0	142 (45.8)	50 (16.1)	0	97 (31.9)	30 (9.9)	0
Neutropenia	2 (0.6)	1 (0.3)	0	32 (10.3)	13 (4.2)	0	21 (6.9)	7 (2.3)	0
Endocrine disorders	85 (26.4)	19 (5.9)	0	32 (10.3)	3 (1.0)	0	3 (1.0)	1 (0.3)	0
Hypothyroidism	45 (14.0)	0	0	20 (6.5)	0	0	1 (0.3)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	65 (20.2)	27 (8.4)	18 (5.6)	50 (16.1)	23 (7.4)	7 (2.3)	48 (15.8)	14 (4.6)	6 (2.0)
Malignant neoplasm progression	41 (12.7)	21 (6.5)	18 (5.6)	25 (8.1)	17 (5.5)	7 (2.3)	16 (5.3)	9 (3.0)	5 (1.6)
Psychiatric disorders	44 (13.7)	1 (0.3)	0	63 (20.3)	1 (0.3)	1 (0.3)	40 (13.2)	3 (1.0)	0
Insomnia	26 (8.1)	0	0	50 (16.1)	0	0	29 (9.5)	1 (0.3)	0

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 322			Nivo + Chemo N = 310			Chemotherapy N = 304		
	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	256 (79.5)	102 (31.7)	2 (0.6)	297 (95.8)	147 (47.4)	1 (0.3)	275 (90.5)	108 (35.5)	3 (1.0)
Skin and subcutaneous tissue disorders	118 (36.6)	14 (4.3)	0	85 (27.4)	1 (0.3)	0	51 (16.8)	0	0
Rash	55 (17.1)	7 (2.2)	0	24 (7.7)	1 (0.3)	0	5 (1.6)	0	0
Pruritus	43 (13.4)	3 (0.9)	0	23 (7.4)	0	0	2 (0.7)	0	0
Alopecia	2 (0.6)	0	0	31 (10.0)	0	0	32 (10.5)	0	0
Gastrointestinal disorders	92 (28.6)	15 (4.7)	0	246 (79.4)	49 (15.8)	0	225 (74.0)	30 (9.9)	0
Diarrhoea	32 (9.9)	2 (0.6)	0	60 (19.4)	3 (1.0)	0	46 (15.1)	6 (2.0)	0
Nausea	26 (8.1)	1 (0.3)	0	182 (58.7)	11 (3.5)	0	158 (52.0)	8 (2.6)	0
Vomiting	18 (5.6)	4 (1.2)	0	56 (18.1)	7 (2.3)	0	49 (16.1)	9 (3.0)	0
Stomatitis	14 (4.3)	0	0	98 (31.6)	20 (6.5)	0	71 (23.4)	5 (1.6)	0
Constipation	7 (2.2)	1 (0.3)	0	59 (19.0)	2 (0.6)	0	66 (21.7)	1 (0.3)	0
Endocrine disorders	83 (25.8)	19 (5.9)	0	30 (9.7)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
Hypothyroidism	43 (13.4)	0	0	18 (5.8)	0	0	0	0	0
General disorders and administration site conditions	71 (22.0)	7 (2.2)	0	151 (48.7)	17 (5.5)	0	140 (46.1)	16 (5.3)	1 (0.3)
Fatigue	29 (9.0)	4 (1.2)	0	61 (19.7)	7 (2.3)	0	50 (16.4)	11 (3.6)	0
Malaise	12 (3.7)	0	0	50 (16.1)	1 (0.3)	0	45 (14.8)	0	0
Mucosal inflammation	4 (1.2)	0	0	33 (10.6)	8 (2.6)	0	26 (8.6)	4 (1.3)	0
Investigations	67 (20.8)	19 (5.9)	0	152 (49.0)	44 (14.2)	0	130 (42.8)	38 (12.5)	0
Platelet count decreased	6 (1.9)	0	0	36 (11.6)	3 (1.0)	0	32 (10.5)	5 (1.6)	0
Blood creatinine increased	5 (1.6)	0	0	39 (12.6)	1 (0.3)	0	32 (10.5)	1 (0.3)	0
White blood cell count decreased	3 (0.9)	0	0	43 (13.9)	11 (3.5)	0	28 (9.2)	6 (2.0)	0
Neutrophil count decreased	2 (0.6)	0	0	65 (21.0)	25 (8.1)	0	52 (17.1)	24 (7.9)	0
Metabolism and nutrition disorders	47 (14.6)	20 (6.2)	0	170 (54.8)	45 (14.5)	0	157 (51.6)	23 (7.6)	0
Decreased appetite	19 (5.9)	5 (1.6)	0	132 (42.6)	13 (4.2)	0	130 (42.8)	9 (3.0)	0
Respiratory, thoracic and mediastinal disorders	39 (12.1)	11 (3.4)	1 (0.3)	71 (22.9)	3 (1.0)	0	69 (22.7)	4 (1.3)	1 (0.3)
Hiccups	2 (0.6)	0	0	42 (13.5)	0	0	53 (17.4)	0	0
Blood and lymphatic system disorders	23 (7.1)	3 (0.9)	0	124 (40.0)	44 (14.2)	0	84 (27.6)	28 (9.2)	0
Anaemia	12 (3.7)	2 (0.6)	0	93 (30.0)	30 (9.7)	0	67 (22.0)	17 (5.6)	0

MedDRA Version: 23.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.1.32.1

Exposure-adjusted Adverse Events Rates

The exposure-adjusted AE incidence rates (per 100 person-year [P-Y]) were 2516.4 with the nivo + chemo arm, 1809.5 with the nivo + ipi arm and 3019.5 with the chemo arm. Per SOC, the higher exposure-adjusted AE incidence rates were within the SOC of gastrointestinal disorders (648.8/100 P-Y with the nivo + chemo arm, 341.7 with the nivo + ipi arm and 878.7 with the chemo arm), investigations (366.9 with the nivo + chemo arm, 219.9 with the nivo + ipi arm and 377.9 with the chemo arm), metabolism and nutrition disorders (307.1 with the nivo + chemo arm, 197.6 with the nivo + ipi arm and 411.6 with the chemo arm), and general disorders and administration site conditions (290.8 with the nivo + chemo arm, 182.9 with the nivo + ipi arm and 357.6 with the chemo arm. Nausea was the most frequently reported PT for nivo + chemo (204.9/100 P-Y) and chemo treatment (286.4/100 P-Y).

When the drug-related AE occurrences were exposure-adjusted, drug-related AE incidence rates (per 100 P-Y) were 1420.4 with nivo + chemo vs 1893.5 with chemo treatment. In the nivo + chemo and chemo arms, the most frequently reported exposure adjusted drug-related AEs were within the SOC of gastrointestinal disorders (432.7/100 P-Y and 625.2/100 P-Y, respectively) with nausea as the most frequently reported PT (182.0/100 P-Y and 266.0/100 P-Y, respectively).

Serious adverse event/deaths/other significant events

Serious Adverse Events

Between the nivo + chemo and chemo arms, the overall proportion of subjects with all-causality SAEs were numerically higher in the nivo + chemo arm vs the chemo arm. The proportions of subjects with drug-related SAEs were comparable overall and by SOC between the treatment arms.

All-causality any-grade SAEs were reported in 180 (58.1%), 214 (66.5%), and 128 (42.1%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively (Table 6). The most frequently reported all-causality SAEs of any grade were:

- Nivo + chemo: malignant neoplasm progression (7.7%), pneumonia (7.1%), dysphagia (5.8%)
- Nivo + ipi: malignant neoplasm progression (12.4%), pneumonia (7.5%), and pneumonitis and pyrexia (3.7% each)
- Chemo: malignant neoplasm progression (4.9%), dysphagia and pneumonia (3.6% each), oesophageal stenosis (3.3%)

Drug-related any-grade SAEs were reported in 74 (23.9%), 103 (32.0%), and 49 (16.1%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively (Table 6). The most frequently reported drug-related SAEs of any grade were:

- Nivo + chemo: acute kidney injury (1.9%); colitis, pneumonia, and stomatitis (1.6% each); febrile neutropenia, pneumonitis, vomiting, hyponatraemia, and deceased appetite (1.3% each)
- Nivo + ipi: pneumonitis (3.7%), hepatic function abnormal (2.5%), adrenal insufficiency (2.2%)
- Chemo: vomiting (3.0%), and pulmonary embolism, diarrhoea, nausea, hyponatraemia, dehydration, atrial fibrillation, and acute kidney injury (1.0% each)

SAEs due to COVID-19 occurred in 1 subject in the nivo + chemo arm with Grade 5 COVID-19 pneumonia.

Table 6. Serious Adverse Events reported in ≥3% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 322			Nivo + Chemo N = 310			Chemotherapy N = 304		
	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	214 (66.5)	146 (45.3)	31 (9.6)	180 (58.1)	132 (42.6)	23 (7.4)	128 (42.1)	96 (31.6)	14 (4.6)
Gastrointestinal disorders	51 (15.8)	38 (11.8)	2 (0.6)	59 (19.0)	51 (16.5)	0	48 (15.8)	41 (13.5)	1 (0.3)
Dysphagia	11 (3.4)	11 (3.4)	0	18 (5.8)	17 (5.5)	0	11 (3.6)	9 (3.0)	0
Oesophageal stenosis	3 (0.9)	3 (0.9)	0	7 (2.3)	7 (2.3)	0	10 (3.3)	8 (2.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	46 (14.3)	24 (7.5)	18 (5.6)	32 (10.3)	21 (6.8)	7 (2.3)	21 (6.9)	13 (4.3)	6 (2.0)
Malignant neoplasm progression	40 (12.4)	21 (6.5)	18 (5.6)	24 (7.7)	17 (5.5)	7 (2.3)	15 (4.9)	9 (3.0)	5 (1.6)
Infections and infestations	43 (13.4)	32 (9.9)	2 (0.6)	39 (12.6)	27 (8.7)	4 (1.3)	24 (7.9)	17 (5.6)	3 (1.0)
Pneumonia	24 (7.5)	17 (5.3)	2 (0.6)	22 (7.1)	15 (4.8)	2 (0.6)	11 (3.6)	7 (2.3)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	41 (12.7)	25 (7.8)	4 (1.2)	31 (10.0)	26 (8.4)	0	18 (5.9)	14 (4.6)	1 (0.3)
Pneumonitis	12 (3.7)	7 (2.2)	0	4 (1.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Pneumonia aspiration	10 (3.1)	7 (2.2)	1 (0.3)	5 (1.6)	5 (1.6)	0	5 (1.6)	4 (1.3)	0
General disorders and administration site conditions	28 (8.7)	7 (2.2)	4 (1.2)	21 (6.8)	10 (3.2)	4 (1.3)	13 (4.3)	4 (1.3)	3 (1.0)
Pyrexia	12 (3.7)	2 (0.6)	0	6 (1.9)	0	0	4 (1.3)	1 (0.3)	0

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 322			Nivo + Chemo N = 310			Chemotherapy N = 304		
	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	103 (32.0)	73 (22.7)	2 (0.6)	74 (23.9)	57 (18.4)	1 (0.3)	49 (16.1)	38 (12.5)	3 (1.0)
Endocrine disorders	22 (6.8)	17 (5.3)	0	6 (1.9)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
Adrenal insufficiency	7 (2.2)	6 (1.9)	0	2 (0.6)	1 (0.3)	0	0	0	0
Hypophysitis	6 (1.9)	5 (1.6)	0	0	0	0	0	0	0
Hypopituitarism	5 (1.6)	4 (1.2)	0	1 (0.3)	1 (0.3)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	20 (6.2)	11 (3.4)	1 (0.3)	6 (1.9)	3 (1.0)	0	5 (1.6)	4 (1.3)	1 (0.3)
Pneumonitis	12 (3.7)	7 (2.2)	0	4 (1.3)	1 (0.3)	0	0	0	0
Interstitial lung disease	5 (1.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0	0	0	0
Pulmonary embolism	1 (0.3)	0	1 (0.3)	0	0	0	3 (1.0)	3 (1.0)	0
Gastrointestinal disorders	17 (5.3)	13 (4.0)	0	24 (7.7)	19 (6.1)	0	17 (5.6)	15 (4.9)	0
Colitis	4 (1.2)	2 (0.6)	0	5 (1.6)	4 (1.3)	0	0	0	0
Vomiting	3 (0.9)	3 (0.9)	0	4 (1.3)	3 (1.0)	0	9 (3.0)	9 (3.0)	0
Diarrhoea	1 (0.3)	1 (0.3)	0	3 (1.0)	2 (0.6)	0	3 (1.0)	2 (0.7)	0
Nausea	1 (0.3)	1 (0.3)	0	3 (1.0)	3 (1.0)	0	3 (1.0)	2 (0.7)	0
Stomatitis	0	0	0	5 (1.6)	4 (1.3)	0	0	0	0
Metabolism and nutrition disorders	14 (4.3)	13 (4.0)	0	14 (4.5)	13 (4.2)	0	11 (3.6)	7 (2.3)	0
Hyponatraemia	5 (1.6)	5 (1.6)	0	4 (1.3)	4 (1.3)	0	3 (1.0)	3 (1.0)	0
Decreased appetite	2 (0.6)	2 (0.6)	0	4 (1.3)	2 (0.6)	0	2 (0.7)	0	0
Dehydration	2 (0.6)	2 (0.6)	0	2 (0.6)	2 (0.6)	0	3 (1.0)	2 (0.7)	0
Hepatobiliary disorders	13 (4.0)	12 (3.7)	0	1 (0.3)	1 (0.3)	0	0	0	0
Hepatic function abnormal	8 (2.5)	7 (2.2)	0	1 (0.3)	1 (0.3)	0	0	0	0
General disorders and administration site conditions	7 (2.2)	3 (0.9)	0	8 (2.6)	5 (1.6)	0	3 (1.0)	0	1 (0.3)
Pyrexia	5 (1.6)	1 (0.3)	0	2 (0.6)	0	0	1 (0.3)	0	0
Fatigue	1 (0.3)	1 (0.3)	0	3 (1.0)	3 (1.0)	0	0	0	0
Infections and infestations	6 (1.9)	4 (1.2)	0	10 (3.2)	7 (2.3)	1 (0.3)	4 (1.3)	3 (1.0)	1 (0.3)
Pneumonia	0	0	0	5 (1.6)	4 (1.3)	1 (0.3)	1 (0.3)	1 (0.3)	0
Blood and lymphatic system disorders	1 (0.3)	0	0	9 (2.9)	9 (2.9)	0	5 (1.6)	5 (1.6)	0
Anaemia	0	0	0	3 (1.0)	3 (1.0)	0	2 (0.7)	2 (0.7)	0
Febrile neutropenia	0	0	0	4 (1.3)	4 (1.3)	0	2 (0.7)	2 (0.7)	0
Cardiac disorders	1 (0.3)	0	0	0	0	0	5 (1.6)	5 (1.6)	0
Atrial fibrillation	0	0	0	0	0	0	3 (1.0)	2 (0.7)	0
Renal and urinary disorders	1 (0.3)	1 (0.3)	0	8 (2.6)	5 (1.6)	0	5 (1.6)	3 (1.0)	0
Acute kidney injury	1 (0.3)	1 (0.3)	0	6 (1.9)	4 (1.3)	0	3 (1.0)	2 (0.7)	0

MedDRA Version: 23.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.3.1.2.4

Table 7. Drug-related Serious Adverse Events Reported in ≥1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 322			Nivo + Chemo N = 310			Chemotherapy N = 304		
	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	103 (32.0)	73 (22.7)	2 (0.6)	74 (23.9)	57 (18.4)	1 (0.3)	49 (16.1)	38 (12.5)	3 (1.0)
Endocrine disorders	22 (6.8)	17 (5.3)	0	6 (1.9)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
Adrenal insufficiency	7 (2.2)	6 (1.9)	0	2 (0.6)	1 (0.3)	0	0	0	0
Hypophysitis	6 (1.9)	5 (1.6)	0	0	0	0	0	0	0
Hypopituitarism	5 (1.6)	4 (1.2)	0	1 (0.3)	1 (0.3)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	20 (6.2)	11 (3.4)	1 (0.3)	6 (1.9)	3 (1.0)	0	5 (1.6)	4 (1.3)	1 (0.3)
Pneumonitis	12 (3.7)	7 (2.2)	0	4 (1.3)	1 (0.3)	0	0	0	0
Interstitial lung disease	5 (1.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0	0	0	0
Pulmonary embolism	1 (0.3)	0	1 (0.3)	0	0	0	3 (1.0)	3 (1.0)	0
Gastrointestinal disorders	17 (5.3)	13 (4.0)	0	24 (7.7)	19 (6.1)	0	17 (5.6)	15 (4.9)	0
Colitis	4 (1.2)	2 (0.6)	0	5 (1.6)	4 (1.3)	0	0	0	0
Vomiting	3 (0.9)	3 (0.9)	0	4 (1.3)	3 (1.0)	0	9 (3.0)	9 (3.0)	0
Diarrhoea	1 (0.3)	1 (0.3)	0	3 (1.0)	2 (0.6)	0	3 (1.0)	2 (0.7)	0
Nausea	1 (0.3)	1 (0.3)	0	3 (1.0)	3 (1.0)	0	3 (1.0)	2 (0.7)	0
Stomatitis	0	0	0	5 (1.6)	4 (1.3)	0	0	0	0
Metabolism and nutrition disorders	14 (4.3)	13 (4.0)	0	14 (4.5)	13 (4.2)	0	11 (3.6)	7 (2.3)	0
Hyponatraemia	5 (1.6)	5 (1.6)	0	4 (1.3)	4 (1.3)	0	3 (1.0)	3 (1.0)	0
Decreased appetite	2 (0.6)	2 (0.6)	0	4 (1.3)	2 (0.6)	0	2 (0.7)	0	0
Dehydration	2 (0.6)	2 (0.6)	0	2 (0.6)	2 (0.6)	0	3 (1.0)	2 (0.7)	0
Hepatobiliary disorders	13 (4.0)	12 (3.7)	0	1 (0.3)	1 (0.3)	0	0	0	0
Hepatic function abnormal	8 (2.5)	7 (2.2)	0	1 (0.3)	1 (0.3)	0	0	0	0
General disorders and administration site conditions	7 (2.2)	3 (0.9)	0	8 (2.6)	5 (1.6)	0	3 (1.0)	0	1 (0.3)
Pyrexia	5 (1.6)	1 (0.3)	0	2 (0.6)	0	0	1 (0.3)	0	0
Fatigue	1 (0.3)	1 (0.3)	0	3 (1.0)	3 (1.0)	0	0	0	0
Infections and infestations	6 (1.9)	4 (1.2)	0	10 (3.2)	7 (2.3)	1 (0.3)	4 (1.3)	3 (1.0)	1 (0.3)
Pneumonia	0	0	0	5 (1.6)	4 (1.3)	1 (0.3)	1 (0.3)	1 (0.3)	0
Blood and lymphatic system disorders	1 (0.3)	0	0	9 (2.9)	9 (2.9)	0	5 (1.6)	5 (1.6)	0
Anaemia	0	0	0	3 (1.0)	3 (1.0)	0	2 (0.7)	2 (0.7)	0
Febrile neutropenia	0	0	0	4 (1.3)	4 (1.3)	0	2 (0.7)	2 (0.7)	0
Cardiac disorders	1 (0.3)	0	0	0	0	0	5 (1.6)	5 (1.6)	0
Atrial fibrillation	0	0	0	0	0	0	3 (1.0)	2 (0.7)	0
Renal and urinary disorders	1 (0.3)	1 (0.3)	0	8 (2.6)	5 (1.6)	0	5 (1.6)	3 (1.0)	0
Acute kidney injury	1 (0.3)	1 (0.3)	0	6 (1.9)	4 (1.3)	0	3 (1.0)	2 (0.7)	0

MedDRA Version: 23.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.3.1.2.4

Deaths

As of the 01-Mar-2021 DBL, the proportions of treated subjects in the nivo + chemo and nivo + ipi arms who died were numerically lower than the chemo arm. Disease progression was the most common cause of death in all 3 arms (Table 8).

Note that only events that led to death within 24 hours were to be documented as Grade 5. Events leading to death >24 hours after onset were to be reported with the worst grade before death. All deaths were required to be reported as an SAE.

Table 8. Death Summary – All Treated Subjects

	Nivo + Ipi N = 322	Nivo + Chemo N = 310	Chemotherapy N = 304	Total N = 936
NUMBER OF SUBJECTS WHO DIED (%)	215 (66.8)	200 (64.5)	224 (73.7)	639 (68.3)
PRIMARY REASON FOR DEATH (%)				
DISEASE	176 (54.7)	168 (54.2)	204 (67.1)	548 (58.5)
STUDY DRUG TOXICITY	5 (1.6)	5 (1.6)	4 (1.3)	14 (1.5)
UNKNOWN	12 (3.7)	10 (3.2)	8 (2.6)	30 (3.2)
OTHER	22 (6.8)	17 (5.5)	8 (2.6)	47 (5.0)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	45 (14.0)	29 (9.4)	20 (6.6)	94 (10.0)
PRIMARY REASON FOR DEATH (%)				
DISEASE	28 (8.7)	15 (4.8)	11 (3.6)	54 (5.8)
STUDY DRUG TOXICITY	4 (1.2)	2 (0.6)	3 (1.0)	9 (1.0)
UNKNOWN	3 (0.9)	4 (1.3)	3 (1.0)	10 (1.1)
OTHER	10 (3.1)	8 (2.6)	3 (1.0)	21 (2.2)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	87 (27.0)	78 (25.2)	70 (23.0)	235 (25.1)
PRIMARY REASON FOR DEATH (%)				
DISEASE	60 (18.6)	55 (17.7)	57 (18.8)	172 (18.4)
STUDY DRUG TOXICITY	5 (1.6)	4 (1.3)	4 (1.3)	13 (1.4)
UNKNOWN	5 (1.6)	4 (1.3)	4 (1.3)	13 (1.4)
OTHER	17 (5.3)	15 (4.8)	5 (1.6)	37 (4.0)

Source: Table S.6.15.2

Deaths Attributed to Study Drug Toxicity

Death attributed to study drug toxicity by the investigator was reported as follows:

- Nivo + chemo arm: 5 subjects (1.6%) due to SAEs with reported relationships to study drug:
    - pneumonitis (2 subjects, both reported as related to nivo only)
    - pneumatosis intestinalis (1 subject, reported as related to nivo and chemo)
    - pneumonia (1 subject, reported as related to chemo only)
    - acute kidney injury (1 subject, reported as related to chemo only)
- Nivo + ipi arm: 5 subjects (1.6%), due to the following SAEs reported related to nivo and ipi:
    - pneumonitis (2 subjects)
    - interstitial lung disease (1 subject)
    - pulmonary embolism (1 subject)
    - acute respiratory distress syndrome (1 subject). Note that, while this death was attributed to study drug toxicity and linked to the term of acute respiratory distress

syndrome, the causality of this fatal SAE was reported on the AE CRF as not related to study therapy by the investigator.

- Chemo arm: 4 subjects (1.3%), due to SAEs reported related to chemo of septic shock, sepsis, acute kidney injury, and pneumonia in 1 subject each.

Drugs Attributed to Other Reasons

The death module of eCRF lists 4 options as primary cause of death:

1. Disease
2. Study drug toxicity
3. Unknown
4. Other

Typically, investigators select option "Other" to indicate a primary cause of death that is commonly an outcome of the adverse event due to complications of advanced malignant disease or unrelated conditions.

Deaths attributed to reason reported as "other" occurred in 17 (5.5%), 22 (6.8%), and 8 (2.6%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively. A review of these deaths was performed by the MAH which showed some consistency between the three treatment arms. Some of them were compatible with complications of advanced esophageal cancer or they were considered as fatal outcomes of unrelated adverse events. However, there were 3 subjects in the nivo + ipi arm and 2 subjects in the chemo arm with a reported drug-related AE with a fatal outcome listed in this group. The most commonly reported cause of death in this list was pneumonia.

Select Adverse Events

To characterize AEs of special clinical interest that are potentially associated with the use of nivolumab and nivolumab in combination with ipilimumab, the MAH identified select AEs based on the following 4 guiding principles:

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

Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, select AEs include endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash. Multiple event terms that may describe each of these were grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select AE categories, respectively.

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

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

- Nivo + chemo arm: renal (23.9%), gastrointestinal (20.6%), and skin (17.4%)
- Chemo arm: renal (18.8%), gastrointestinal (15.5%), and hepatic (3.9%)

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

- Nivo + chemo arm: diarrhoea (19.4%), blood creatinine increased (12.6%), and acute kidney injury (2.6%)
- Chemo arm: diarrhoea (15.1%), blood creatinine increased (10.5%), and acute kidney injury (3.3%)

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

- Nivo + chemo arm: acute kidney injury (1.9%), colitis (1.6%), and pneumonitis (1.3%)
- Chemo arm: acute kidney injury and diarrhoea (1.0% each), and renal failure (0.7%)

At the time of DBL, with the exception of the endocrine category, the majority of subjects' drug-related select AEs had resolved in the nivo + chemo arm (ranging from 56.8% to 100% across categories). The median time to resolution of drug-related select AEs ranged from 0.14 to 17.14 weeks in the nivo + chemo arm. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy (table 9).

Table 9. Onset, Management, and Resolution of Drug-Related Select AEs - All Subjects Treated with Nivolumab + Chemotherapy (N=310) from CA209648

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AEs	Median Time to Onset of Drug-related Select AEs (range), wks	% Treated Subj. with Drug-related Select AEs 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[c,d] (range[e]), wks	% Subj. with Drug-related Select AEs that Resolved[c,d]
Endocrine	11.6 / 1.3	13.00 (5.0-100.00)	0.6	22.2 / 2.8	N.E. (4.1-125.6+)	28.6
Gastrointestinal	20.6 / 2.3	5.07 (0.3-53.1)	1.9	10.9 / 7.8	1.50 (0.1-65.9+)	90.6
Hepatic	10.3 / 2.3	7.86 (0.3-84.1)	1.0	6.3 / 3.1	2.43 (0.4-24.0+)	90.3
Pulmonary	5.8 / 0.6	32.21 (5.0-85.1)	3.2	50.0 / 27.8	12.14 (1.0-39.9)	66.7
Renal	23.9 / 2.3	10.14 (0.7-60.7)	8.7	6.8 / 5.4	17.14 (0.4-128.1+)	56.8

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AEs	Median Time to Onset of Drug-related Select AEs (range), wks	% Treated Subj. with Drug-related Select AEs 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[c,d] (range[e]), wks	% Subj. with Drug-related Select AEs that Resolved[c,d]
Skin	17.4 / 0.3	5.93 (0.1-61.1)	0	42.6 / 1.9	7.07 (0.1-157.0+)	75.9
Hypersensitivity/ Infusion Reaction	1.9 / 0	2.21 (0.1-18.6)	0.3	33.3 / 16.7	0.14 (0.1-0.3)	100.0

MedDRA Version: 23.1. CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.

[a] Denominator is based on the number of subjects who experienced the event. High dose: dose ≥ 40 mg prednisone or equivalent.

[b] From Kaplan-Meier estimation.

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

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

[e] Symbol + indicates a censored value.

Source: refer to Table 8.5.1-1 of CA209648 Primary CSR

Immune-mediated Adverse Events

IMAE analyses included diarrhoea/colitis, hepatitis, pneumonitis, nephritis, renal dysfunction, rash, hypersensitivity/infusion reactions and endocrine events, regardless of causality, occurring within 100 days of the last dose (ie, with extended follow-up). These analyses were limited to subjects who received IMM for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these events were identified by the investigator as IMAEs with no clear alternate etiology, or with an immune-mediated component.

The total number of subjects with all-causality any grade IMAEs in the nivo + chemo and chemo arms were 57 (18.4%) and 3 (1.0%), respectively. Overall, the majority of IMAEs were Grade 1-2. The most frequently reported IMAEs by category were as follows in each treatment arm:

- Nivo + chemo arm (any Grade): hypothyroidism/thyroiditis (6.1%), rash (5.2%), pneumonitis (3.2%), hyperthyroidism (2.3%), and diarrhea/colitis (1.9%)
    - Proportion of subjects with Grade 3-4 IMAEs, by category: diarrhea/colitis (1.3%); nephritis/renal dysfunction and diabetes mellitus (1.0% each); and pneumonitis (0.6%). No subjects were reported with hypersensitivity IMAEs.
- Chemo arm (any Grade): rash (0.7%)
    - Proportion of subjects with Grade 3-4 IMAEs, by category: rash (0.3%)

Across IMAE categories, the majority of events were manageable using established management algorithms, with resolution occurring when IMMs (mostly systemic corticosteroids) were administered (table 10). Some subjects' endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

Re-challenge information was also summarized for subjects who continued to receive nivo + chemo treatment after the onset of an IMAE. Subjects who were rechallenged were subjects with study therapy re-initiated on or after symptom improvement/resolution. A positive re-challenge/recurrence was defined as any occurrence of new event(s) or worsening of any severity grade IMAE on or after study therapy re-initiation.

Table 10: Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - All Subjects Treated with Nivolumab + Chemotherapy (N=310) from CA209648

IMAE Category	% Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration of IMM (range), wks	% Subj. with Resolution of IMAE[b,c,d]	Median[e] Time to Resolution (range[f]), wks	% Subj. with Recurrence after Reinitiation[g] (n/N)
Pneumonitis	3.2 / 0.6	32.36 (5.7-85.1)	2.3 / 0.6	100 / 60.0	12.50 (0.9-20.0)	70.0	18.71 (2.9-25.1)	0 (0/0)
Diarrhea/Colitis	1.9 / 1.3	11.43 (0.7-12.9)	1.0 / 0.6	100 / 83.3	11.64 (0.1-56.0)	83.3	10.14 (0.9-33.6)	100 (1/1)
Hepatitis	0.6 / 0.3	14.43 (7.7-21.1)	0.3 / 0.3	100 / 50.0	2.93 (2.7-3.1)	100	3.00 (1.4-4.6)	0 (0/1)
Nephritis/Renal Dysfunction	1.0 / 1.0	2.14 (0.9-14.0)	0.6 / 0	100 / 100	3.29 (1.4-5.9)	66.7	4.71 (1.6-4.7)	0 (0/0)
Rash	5.2 / 0.3	10.57 (1.0-73.0)	0 / 1.0	100 / 6.3	25.64 (0.9-120.6)	62.5	29.71 (2.3-N.A.)	100 (1/1)
Adrenal Insufficiency	1.6 / 0.3	37.57 (25.1-60.3)	0.3 / 1.0	80.0 / 0	61.36 (23.4-75.1)	0	N.A.	0 (0/1)
Hypophysitis	0.6 / 0.3	62.57 (25.1-100.0)	0 / 0.6	100 / 0	39.71 (2.0-77.4)	0	N.A. (24.1+-78.4+)	0 (0/0)
Hypothyroidism/ Thyroiditis	6.1 / 0	16.71 (6.0-69.3)	0 / 2.3	0 / 0	N.A.	10.5	N.A. (6.1-125.6+)	33.3 (1/3)
Hyperthyroidism	2.3/ 0	6.71 (6.0-54.6)	0 / 1.0	14.3 / 14.3	1.86 (1.9-1.9)	71.4	4.29 (3.0-76.1+)	0 (0/2)
Diabetes Mellitus	1.0 / 1.0	20.29 (16.4-60.1)	0.3 / 0.3	0 / 0	N.A.	0	N.A. (36.0+-105.6+)	0 (0/1)

MedDRA Version: 23.1. CTC Version 4.0. Includes events reported between first dose and 100 days after last dose of study therapy.

[a] Denominator is based on the number of subjects who experienced the event. High dose: dose ≥ 40 mg prednisone or equivalent.

[b] Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis.

[c] Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved.
[d] For each subject, the longest duration of immune-mediated AEs where immune modulation is considered.
[e] From Kaplan-Meier estimation.
[f] Symbol + indicates a censored value.
[g] Percentages of subjects with recurrence are based on subjects who were re-challenged. A positive re-challenge/recurrence is defined as any occurrence of new event(s) or worsening of any severity grade IMAE on or after study therapy re-initiation. Subjects who were rechallenged are subjects with study therapy re-initiated on or after symptom improvement/resolution.

Source: refer to Table 8.5.2-1 of CA209648 Primary CSR

Other Events of Special Interest

OESIs do not fulfill all criteria to qualify as IMAEs but may require immunosupression as part of their management.

Among all treated subjects, OESIs (regardless of causality or IMM treatment, with extended follow-up) were infrequent, and most events resolved by the time of DBL (table 11):

- Nivo + chemo arm: OESIs were reported in 4 subjects (6 events), of which 4 events resolved. 2 of these events were resolved with IMMs.
- Nivo + ipi arm: OESIs were reported in 14 subjects (23 events), of which 19 events resolved. 11 of these events were resolved with IMMs.
- Chemo arm: no OESIs were reported.

Table 11. Treatment, Onset, and Resolution Information for Other Events of Special Interest – All Treated Subjects

OESI Category Grade, Relationship to Study Therapy, PT	Immune-modulating Medication	Onset Date (Study Day)	Duration of Event (Days)	Resolution (Yes/No)
Nivolumab + Chemotherapy				
Uveitis				
Grade 2 drug-related AE uveitis	betamethasone sodium phosphate	21-Feb-2020 (172)	32	Y
Grade 2 drug-related AE uveitis	betamethasone sodium phosphate	06-Aug-2019 (672)	ongoing	N
Rhabdomyolysis				
Grade 3 SAE rhabdomyolysis	none	08-Dec-2019 (115)	16	Y
Grade 1 AE rhabdomyolysis	none	23-Dec-2019 (130)	110	Y
Myositis				
Grade 2 SAE myositis	thalidomide, methylprednisolone	06-Sep-2019 (28)	55	Y
Grade 1 AE myositis	thalidomide, methylprednisolone	30-Oct-2019 (82)	ongoing	N
Nivolumab + Ipilimumab				
Pancreatitis				
Grade 3 drug-related SAE pancreatitis	prednisolone	08-Feb-2016 (16)	45	Y
Grade 3 SAE pancreatitis	none	29-Sep-2020 (649)	14	Y
Grade 4 drug-related AE acute pancreatitis	methylprednisolone	11-Aug-2020 (330)	2	Y
Grade 3 drug-related AE acute pancreatitis	prednisone	13-Aug-2020 (332)	70	Y
Grade 2 drug-related SAE pancreatitis	methylprednisolone, prednisone	03-Feb-2020 (56)	3	Y
Grade 3 drug-related SAE pancreatitis	prednisolone	04-Mar-2020 (169)	13	Y
Myocarditis				
Grade 1 drug-related AE myocarditis	prednisone	15-Jan-2019 (161)	ongoing	N
Grade 1 drug-related AE myocarditis	none	24-May-2018 (28)	39	Y

OESI Category Grade, Relationship to Study Therapy, PT	Immune-modulating Medication	Onset Date (Study Day)	Duration of Event (Days)	Resolution (Yes/No)
Nivolumab + Ipilimumab				
Uveitis				
Grade 4 drug-related AE uveitis	methylprednisolone, prednisone	03-Aug-2020 (244)	5	Y
Grade 3 drug-related AE uveitis	prednisone	08-Aug-2020 (249)	13	Y
Grade 2 drug-related AE uveitis	prednisone	21-Aug-2020 (262)	ongoing	N
Grade 2 drug-related SAE Vogt-Koyanagi-Harada disease	prednisolone	15-Mar-2019 (18)	11	Y
Grade 1 drug-related AE Vogt-Koyanagi-Harada disease	prednisolone	26-Mar-2019 (29)	ongoing	N
Encephalitis				
Grade 4 drug-related SAE encephalitis	methylprednisolone	01-Sep-2018 (73)	44	Y
Grade 2 drug-related SAE encephalitis	none	17-Jan-2018 (114)	9	Y
Grade 3 drug-related SAE encephalitis	none	26-Jan-2018 (123)	3	Y
Grade 4 drug-related SAE encephalitis	prednisolone	29-Jan-2018 (126)	99	Y
Grade 4 drug-related SAE immune-mediated encephalopathy	none	07-Dec-2018 (203)	245	Y
Myositis				
Grade 1 drug-related AE myositis	none	21-May-2018 (33)	10	Y
Grade 2 drug-related SAE myositis	prednisolone, methylprednisolone	31-May-2018 (43)	19	Y
Grade 1 drug-related AE myositis	prednisolone	18-Jun-2018 (61)	ongoing	N
Grade 2 drug-related AE myositis	none	24-May-2018 (28)	2	Y
Grade 1 drug-related AE myositis	none	26-May-2018 (30)	37	Y

All events are within 100 days of the last dose of study drug.
* Event assessed as not related
# No safety narrative available for Subject CA209648-xxx-xxx as the events of myocarditis and myositis were reported as non-serious AEs.
Source: refer to Table 8.5.3-1 of CA209648 Primary CSR

Laboratory findings

Laboratory abnormalities (hematology, liver tests, kidney function tests, and electrolytes) were primarily Grade 1-2 in severity and reflected the known laboratory abnormalities associated with the different treatment regimens.

Laboratory test results for all treated subjects are summarized by worst CTC Grade (Grade 1-4 and Grade 3-4) for laboratory parameters that worsened relative to baseline in Table 11 (30-day follow-up, SI units):

Table 12. Summary of On-Treatment Worst CTC Grade (Grade 1-4 and Grade 3-4) Laboratory Parameters that Worsened Relative to Baseline – 30 Days Follow Up – SI Units – All Treated Subjects

	Number of Subjects (%)								
	Nivo + Ipi			Nivo + Chemo			Chemotherapy		
Lab Test Description	N(A)	Grade 1-4	Grade 3-4	N(A)	Grade 1-4	Grade 3-4	N(A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	307	160 (52.1)	20 (6.5)	304	246 (80.9)	65 (21.4)	283	186 (65.7)	39 (13.8)
PLATELET COUNT	307	36 (11.7)	3 (1.0)	304	132 (43.4)	10 (3.3)	283	83 (29.3)	8 (2.8)
LEUKOCYTES	308	27 (8.8)	4 (1.3)	305	163 (53.4)	33 (10.8)	282	110 (39.0)	15 (5.3)
LYMPHOCYTES (ABSOLUTE)	308	155 (50.3)	39 (12.7)	305	205 (67.2)	71 (23.3)	282	124 (44.0)	23 (8.2)
ABSOLUTE NEUTROPHIL COUNT	308	41 (13.3)	4 (1.3)	305	187 (61.3)	54 (17.7)	282	135 (47.9)	38 (13.5)
ALKALINE PHOSPHATASE	305	96 (31.5)	10 (3.3)	305	78 (25.6)	4 (1.3)	278	43 (15.5)	0
ASPARTATE AMINOTRANSFERASE	306	120 (39.2)	17 (5.6)	305	70 (23.0)	10 (3.3)	280	31 (11.1)	4 (1.4)
ALANINE AMINOTRANSFERASE	306	102 (33.3)	18 (5.9)	305	70 (23.0)	7 (2.3)	281	23 (8.2)	2 (0.7)
BILIRUBIN, TOTAL	305	32 (10.5)	2 (0.7)	305	19 (6.2)	1 (0.3)	280	10 (3.6)	0
CREATININE	305	47 (15.4)	2 (0.7)	304	125 (41.1)	7 (2.3)	283	86 (30.4)	2 (0.7)
HYPERNATREMIA	305	13 (4.3)	2 (0.7)	304	27 (8.9)	2 (0.7)	281	15 (5.3)	1 (0.4)
HYPONATREMIA	305	141 (46.2)	36 (11.8)	304	157 (51.6)	45 (14.8)	281	114 (40.6)	25 (8.9)
HYPERKALEMIA	305	68 (22.3)	5 (1.6)	305	103 (33.8)	7 (2.3)	281	66 (23.5)	2 (0.7)
HYPOKALEMIA	305	62 (20.3)	16 (5.2)	305	88 (28.9)	29 (9.5)	281	48 (17.1)	17 (6.0)
HYPERCALCEMIA	298	45 (15.1)	6 (2.0)	304	36 (11.8)	9 (3.0)	274	23 (8.4)	1 (0.4)
HYPOCALCEMIA	298	97 (32.6)	0	304	138 (45.4)	9 (3.0)	274	63 (23.0)	2 (0.7)
HYPERMAGNESEMIA	59	5 (8.5)	1 (1.7)	60	5 (8.3)	0	56	1 (1.8)	0
HYPOMAGNESEMIA	59	11 (18.6)	0	60	22 (36.7)	1 (1.7)	56	15 (26.8)	1 (1.8)
HYPERGLYCEMIA	138	59 (42.8)	6 (4.3)	143	49 (34.3)	0	118	42 (35.6)	1 (0.8)
HYPOGLYCEMIA	243	38 (15.6)	3 (1.2)	246	44 (17.9)	1 (0.4)	213	15 (7.0)	0

Toxicity Scale: CTC version 4.0.

Includes laboratory results reported between first dose and last dose of 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 GI.8a-USPI.2.2

Hematology

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

- Nivo + chemo arm: decreased lymphocytes (23.3%), decreased hemoglobin (21.4%), decreased absolute neutrophil count (17.7%), and decreased leukocytes (10.8%)
- Nivo + ipi arm: decreased lymphocytes (12.7%), and decreased hemoglobin (6.5%)
- Chemo arm: decreased hemoglobin (13.8%), decreased absolute neutrophil count (13.5%), decreased lymphocytes (8.2%), and decreased leukocytes (5.3%)

Serum Chemistry

Liver Tests

During the treatment period, abnormalities (increases) in hepatic parameters (alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and total bilirubin) were primarily Grade 1-2 in each treatment arm. Grade 3-4 hepatic abnormalities that worsened from baseline occurred at higher frequencies in the nivo + ipi arm, though the overall frequencies were <6% of subjects across the treatment arms:

- Nivo + chemo arm: ALP (1.3%), AST (3.3%), ALT (2.3%), total bilirubin (0.3%)
- Nivo + ipi arm: ALP (3.3%), AST (5.6%), ALT (5.9%), total bilirubin (0.7%)
- Chemo arm: AST (1.4%), ALT (0.7%)

Concurrent ALT or AST >3×ULN with total bilirubin >2×ULN within 1 day and within 30 days, based on laboratory results reported after the first dose and within 30 days of last dose of study therapy, was reported in 2/305 (0.7%), 3/306 (1.0%), and 0 subjects with test results in the nivo + chemo, nivo + ipi, and chemo arms, respectively (table 13).

Table 13. On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) – All Treated Subjects

Abnormality (%)	Nivo + Ipi N = 322	Nivo + Chemo N = 310	Chemotherapy N = 304	Total N = 936
	N = 306	N = 305	N = 282	N = 893
ALT OR AST > 3XULN	40 (13.1)	22 (7.2)	7 (2.5)	69 (7.7)
ALT OR AST > 5XULN	22 (7.2)	12 (3.9)	5 (1.8)	39 (4.4)
ALT OR AST > 10XULN	5 (1.6)	3 (1.0)	0	8 (0.9)
ALT OR AST > 20XULN	2 (0.7)	1 (0.3)	0	3 (0.3)
	N = 306	N = 305	N = 281	N = 892
TOTAL BILIRUBIN > 2XULN	7 (2.3)	3 (1.0)	1 (0.4)	11 (1.2)
	N = 305	N = 305	N = 280	N = 890
ALP > 1.5XULN	69 (22.6)	48 (15.7)	29 (10.4)	146 (16.4)
	N = 306	N = 305	N = 280	N = 891
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN ONE DAY	3 (1.0)	4 (1.3)	0	7 (0.8)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	3 (1.0)	4 (1.3)	0	7 (0.8)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	3 (1.0)	2 (0.7)	0	5 (0.6)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	3 (1.0)	2 (0.7)	0	5 (0.6)

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

Kidney Function Tests

Most subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period. The abnormalities in creatinine (increases from baseline) were primarily reported as Grade 1 or 2, with Grade 3-4 creatinine (increased) (SI units) reported in 7 (2.3%), 2 (0.7%), and 2 (0.7%) subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively.

Thyroid Function Tests

The majority of all treated subjects in each treatment arm had normal TSH levels at baseline and throughout the treatment period. TSH (SI units) increases (>ULN) from baseline (≤ULN) were reported in 60 (20.5%), 61 (22.8%), and 9 (7.6%) of subjects in the nivo + chemo, nivo + ipi, and chemo treatment arms, respectively (Table 13). Decreases (<LLN) from baseline (≤LLN) were reported in 35 (12.0%), 61 (22.8%), and 12 (10.2%) of subjects in the nivo + chemo, nivo + ipi, and chemo treatment arms, respectively.

Table 14. Summary of Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All Treated Subjects with at Least One On-Treatment TSH Measurement

Abnormality (%)	Nivo + Ipi N = 267	Nivo + Chemo N = 292	Chemotherapy N = 118	Total N = 677
TSH > ULN	83 (31.1)	84 (28.8)	21 (17.8)	188 (27.8)
TSH > ULN				
WITH TSH <= ULN AT BASELINE	61 (22.8)	60 (20.5)	9 (7.6)	130 (19.2)
TSH > ULN				
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	48 (18.0)	45 (15.4)	7 (5.9)	100 (14.8)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	23 (8.6)	29 (9.9)	11 (9.3)	63 (9.3)
WITH FT3/FT4 TEST MISSING (A) (B)	12 (4.5)	10 (3.4)	3 (2.5)	25 (3.7)
TSH < LLN	74 (27.7)	40 (13.7)	15 (12.7)	129 (19.1)
TSH < LLN				
WITH TSH >= LLN AT BASELINE	61 (22.8)	35 (12.0)	12 (10.2)	108 (16.0)
TSH < LLN				
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	36 (13.5)	19 (6.5)	3 (2.5)	58 (8.6)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	28 (10.5)	14 (4.8)	10 (8.5)	52 (7.7)
WITH FT3/FT4 TEST MISSING (A) (B)	10 (3.7)	7 (2.4)	2 (1.7)	19 (2.8)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) Within a 2-week window after the abnormal TSH test date.
(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.
Source: Table S.7.6.2.1

Electrolytes

Most subjects had normal electrolyte levels during the treatment reporting period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. The following Grade 3-4 abnormalities (SI) in electrolytes from baseline were reported in ≥5% of treated subjects with on-treatment laboratory results:

- Nivo + chemo arm: hyponatremia (14.8%) and hypokalemia (9.5%)
- Nivo + ipi arm: hyponatremia (11.8%) and hypokalemia (5.2%)
- Chemo arm: hyponatremia (8.9%) and hypokalemia (6.0%)

Safety in special populations

In the nivo + chemo vs chemo arms, frequencies of subjects with all-causality (Table 15) and drug-related AEs (Table 16) in the subgroups of sex, age category, race, and region were comparable overall to the proportions of subjects with AEs reported for the overall study populations by arm.

Sex

Frequencies of all-causality AEs and drug-related AEs overall were comparable by sex in each treatment arm, with the exception of a numerically higher frequency of all-causality AEs reported for females (69.1%) vs males (57.7%) in the nivo + ipi arm.

Race

Frequencies of subjects with all-causality AEs and drug-related AEs were comparable between Asians and non-Asians in each treatment arm.

Age Category

Frequencies of all-causality and drug-related AEs were comparable by age category (<65, ≥65 - <75, ≥75 - <85, ≥65, ≥75, and ≥85 years) within each treatment arm, with the exception of numerically higher proportions of chemo-treated subjects with all-causality and drug-related Grade 3-4 AEs, respectively, in the ≥65 (61.1% and 44.3%) vs <65 (47.7% and 27.1%) categories.

Interpretation of safety data from the ≥75 (N=29) and ≥85 (N=3) age categories is limited by small sample sizes. The frequencies of AEs for subgroups of age <65 (N=164), 65 to 74 (N=117), and 75 to

84 years (N=26) were similar to the frequencies reported for the overall population (N=310), with these exceptions:

- The 75-84 years subgroup had higher frequency of SAEs (65.4%), fatal events (26.9%), hospitalization/prolongation (61.5%), accident and injuries (19.2%), and cardiac disorders (11.5%) compared to the overall population (58.1%, 11.9%, 54.8%, 9.0%, and 5.2%, respectively), and lower frequency of psychiatric disorders (11.5%) compared to overall population (20.3%).

Region

Frequencies of all-causality and drug-related Grade 3-4 AEs were numerically lower among subjects from Rest of Asia compared to East Asia and Rest of World within treatment arms:

- Frequencies of all-causality and drug-related Grade 3-4 AEs, respectively, in nivo +chemo arm: Rest of Asia (N = 42; 54.8% and 33.3%), East Asia (N = 178; 74.2% and 49.4%), and Rest of World (N = 90; 67.8% and 50.0%)
- Frequencies of all-causality and drug-related Grade 3-4 AEs, respectively, in nivo +ipi arm: Rest of Asia (N = 44; 50.0% and 27.3%), East Asia (N = 184; 60.9% and 30.4%), and Rest of World (N = 94; 61.7% and 36.2%)

Table 15. Summary of All-causality Adverse Events by Worst CTC Grade and by Demographic Subgroup – All Treated Subjects

	No. of Subjects (%)											
	Nivo + Ipi				Nivo + Chemo				Chemo			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	322	316 (98.1)	192 (59.6)	31 (9.6)	310	308 (99.4)	216 (69.7)	23 (7.4)	304	301 (99.0)	165 (54.3)	14 (4.6)
Sex												
Female	55	55 (100.0)	38 (69.1)	4 (7.3)	66	65 (98.5)	47 (71.2)	3 (4.5)	44	44 (100.0)	26 (59.1)	2 (4.5)
Male	267	261 (97.8)	154 (57.7)	27 (10.1)	244	243 (99.6)	169 (69.3)	20 (8.2)	260	257 (98.8)	139 (53.5)	12 (4.6)
Age Category												
<65	182	180 (98.9)	113 (62.1)	12 (6.6)	164	163 (99.4)	113 (68.9)	9 (5.5)	155	153 (98.7)	74 (47.7)	9 (5.8)
≥65-<75	116	112 (96.6)	64 (55.2)	18 (15.5)	117	116 (99.1)	83 (70.9)	9 (7.7)	125	125 (100.0)	74 (59.2)	3 (2.4)
≥75-<85	24	24 (100.0)	15 (62.5)	1 (4.2)	26	26 (100.0)	18 (69.2)	5 (19.2)	24	23 (95.8)	17 (70.8)	2 (8.3)
≥65	140	136 (97.1)	79 (56.4)	19 (13.6)	146	145 (99.3)	103 (70.5)	14 (9.6)	149	148 (99.3)	91 (61.1)	5 (3.4)
≥75	24	24 (100.0)	15 (62.5)	1 (4.2)	29	29 (100.0)	20 (69.0)	5 (17.2)	24	23 (95.8)	17 (70.8)	2 (8.3)
≥85	0	N.A.	N.A.	N.A.	3	3 (100.0)	2 (66.7)	0	0	N.A.	N.A.	N.A.
Race												
Asian	230	226 (98.3)	136 (59.1)	16 (7.0)	222	222 (100.0)	157 (70.7)	12 (5.4)	214	212 (99.1)	115 (53.7)	7 (3.3)
Non-Asian	92	90 (97.8)	56 (60.9)	15 (16.3)	88	86 (97.7)	59 (67.0)	11 (12.5)	90	89 (98.9)	50 (55.6)	7 (7.8)
Region												
East Asia	184	180 (97.8)	112 (60.9)	12 (6.5)	178	178 (100.0)	132 (74.2)	11 (6.2)	176	175 (99.4)	94 (53.4)	2 (1.1)
Rest of Asia	44	44 (100.0)	22 (50.0)	4 (9.1)	42	42 (100.0)	23 (54.8)	1 (2.4)	37	36 (97.3)	19 (51.4)	5 (13.5)
RoW	94	92 (97.9)	58 (61.7)	15 (16.0)	90	88 (97.8)	61 (67.8)	11 (12.2)	91	90 (98.9)	52 (57.1)	7 (7.7)

Note: East Asia consists of Japan, Korea, and Taiwan. Rest of Asia consists of China and Hong Kong.
Source: Table S.6.1.31.2.2 (AEs), Table S.6.1.5.1 (AEs by Sex), Table S.6.1.5.3 (AEs by Age), Table S.6.1.5.2 (AEs by Race), Table S.6.1.5.4 (AEs by Region)

Table 16. Summary of Drug-related Adverse Events by Worst CTC Grade and by Demographic Subgroup – All Treated Subjects

	No. of Subjects (%)											
	Nivo + Ipi				Nivo + Chemo				Chemo			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	322	256 (79.5)	102 (31.7)	2 (0.6)	310	297 (95.8)	147 (47.4)	1 (0.3)	304	275 (90.5)	108 (35.5)	3 (1.0)
Sex												
Female	55	49 (89.1)	20 (36.4)	0	66	64 (97.0)	35 (53.0)	0	44	39 (88.6)	16 (36.4)	0
Male	267	207 (77.5)	82 (30.7)	2 (0.7)	244	233 (95.5)	112 (45.9)	1 (0.4)	260	236 (90.8)	92 (35.4)	3 (1.2)
Age Category												
< 65	182	145 (79.7)	52 (28.6)	1 (0.5)	164	156 (95.1)	73 (44.5)	1 (0.6)	155	141 (91.0)	42 (27.1)	3 (1.9)
≥ 65 - < 75	116	91 (78.4)	40 (34.5)	1 (0.9))	117	112 (95.7)	59 (50.4)	0	125	114 (91.2)	56 (44.8)	0
≥ 75 - < 85	24	20 (83.3)	10 (41.7)	0	26	26 (100.0)	13 (50.0)	0	24	20 (83.3)	10 (41.7)	0
≥ 65	140	111 (79.3)	50 (35.7)	1 (0.7)	146	141 (96.6)	74 (50.7)	0	149	134 (89.9)	66 (44.3)	0
≥ 75	24	20 (83.3)	10 (41.7)	0	29	29 (100.0)	15 (51.7)	0	24	20 (83.3)	10 (41.7)	0
≥ 85	0	0	0	0	3	3 (100.0)	2 (66.7)	0	0	0	0	0
Race												
Asian	230	185 (80.4)	69 (30.0)	1 (0.4)	222	215 (96.8)	104 (46.8)	0	214	198 (92.5)	72 (33.6)	2 (0.9)
Non-Asian	92	71 (77.2)	33 (35.9)	1 (1.1)	88	82 (93.2)	43 (48.9)	1 (1.1)	90	77 (85.6)	36 (40.0)	1 (1.1)
Region												
East Asia	184	144 (78.3)	56 (30.4)	1 (0.5)	178	175 (98.3)	88 (49.4)	0	176	163 (92.6)	58 (33.0)	1 (0.6)
Rest of Asia	44	39 (88.6)	12 (27.3)	0	42	38 (90.5)	14 (33.3)	0	37	34 (91.9)	12 (32.4)	1 (2.7)
RoW	94	73 (77.7)	34 (36.2)	1 (1.1)	90	84 (93.3)	45 (50.0)	1 (1.1)	91	78 (85.7)	38 (41.8)	1 (1.1)

Note: East Asia consists of Japan, Korea, and Taiwan. Rest of Asia consists of China and Hong Kong.

Source: Table S.6.1.32.1 (drug-related AEs), Table S.6.1.5.1.1 (drug-related AEs by sex), Table S.6.1.5.1.3 (drug-related AEs by age), Table S.6.1.5.1.2 (drug-related AEs by race), Table S.6.1.5.1.4 (drug-related AEs by region)

Immunogenicity

Nivolumab + Chemotherapy

Of the 276 nivolumab ADA-evaluable subjects in the nivo + chemo arm, 15 (5.4%) subjects were nivolumab ADA-positive at baseline, and 12 (4.3%) subjects were nivolumab ADA-positive after start of treatment (Table 17).

- No subjects were considered persistent positive, and 3 (1.1%) subjects were NAb positive.
- The highest titer value observed among nivolumab ADA-positive subjects was 32, which occurred in 2 subjects. All other titers were low, ranging from 1 to 16.

Table 17. Anti-Drug Antibody Assessments Summary - All Nivolumab + Ipilimumab or Nivolumab + Chemotherapy Treated Subjects with Baseline and at Least One Post-Baseline Assessment

	Nivolumab + Ipilimumab		Nivolumab + Chemotherapy
Subject ADA Status (%)	Nivolumab ADA N = 281	Ipilimumab ADA N = 282	Nivolumab ADA N = 276
BASELINE ADA POSITIVE	19 (6.8)	6 (2.1)	15 (5.4)
ADA POSITIVE	68 (24.2)	17 (6.0)	12 (4.3)
PERSISTENT POSITIVE (PP)	1 (0.4)	1 (0.4)	0
NOT PP - LAST SAMPLE POSITIVE	27 (9.6)	6 (2.1)	4 (1.4)
OTHER POSITIVE	40 (14.2)	10 (3.5)	8 (2.9)

NEUTRALIZING POSITIVE	6 (2.1)	1 (0.4)	3 (1.1)
ADA NEGATIVE	213 (75.8)	265 (94.0)	264 (95.7)

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

Effect of Immunogenicity on Efficacy

Based on assessment of the presence of ADAs and NAbs vs BOR per BICR, some subjects positive for nivolumab ADAs and NAbs continued treatment with clinical benefit, and there was no apparent trend showing an effect of positive ADA or neutralizing ADA on the efficacy of nivo + chemo.

Among the 12 nivolumab ADA-positive subjects, 4 had CR/PR per BICR. The ADA titers among the 12 subjects with nivolumab ADAs ranged from 1 to 32. Though these results are based on a small sample size and should be interpreted with caution, these results are consistent with the ORR observed among all randomized subjects in the nivo + chemo arm (47.4%), which included subjects negative for ADA.

The incidence of positive nivolumab NAbs was low. Each of the 3 subjects with nivolumab neutralizing ADAs (Table 17) had a BOR per BICR of SD, and titers ranged from 1 to 32.

Effect of Immunogenicity on Safety

In the nivo + chemo arm, the incidence of nivolumab ADA was low, and an effect of ADA on the safety of nivo + chemo treatment was not observed (Table 17). Among the nivo + chemo-treated subjects evaluable and positive for nivolumab ADA, no subject had hypersensitivity/infusion-related reaction select AEs, compared with 8/264 subjects (3.0%) in the nivolumab ADA-negative subgroup (Table 18). Thus, for nivo + chemo treatment, the presence of nivolumab ADA did not appear to be associated with the occurrence of these events.

Table 18. Select AEs of Hypersensitivity/Infusion Reaction by ADA Status – All Treated Subjects with ADA Positive or ADA Negative – Nivolumab + Ipilimumab and Nivolumab + Chemotherapy Arms

	Nivolumab + Ipilimumab			
Preferred Term (%)	Nivolumab ADA Positive N = 68	Nivolumab ADA Negative N = 213	Ipilimumab ADA Positive N = 17	Ipilimumab ADA Negative N = 265
TOTAL SUBJECTS WITH AN EVENT	4 (5.9)	8 (3.8)	2 (11.8)	10 (3.8)
Anaphylactic shock	0	0	0	0
Bronchospasm	0	1 (0.5)	0	1 (0.4)
Hypersensitivity	2 (2.9)	2 (0.9)	1 (5.9)	3 (1.1)
Infusion related reaction	2 (2.9)	5 (2.3)	1 (5.9)	6 (2.3)

	Nivolumab + Chemotherapy	
Preferred Term (%)	Nivolumab ADA Positive N = 12	Nivolumab ADA Negative N = 264

TOTAL SUBJECTS WITH AN EVENT	0	8 (3.0)
Anaphylactic shock	0	1 (0.4)
Bronchospasm	0	0
Hypersensitivity	0	3 (1.1)
Infusion related reaction	0	4 (1.5)

MedDRA Version: 23.1
CTC Version 4.0
Includes events between first dose and within the last dose of therapy + 100 days
Source: Table S.7.11.1

Discontinuation due to adverse events

AEs leading to discontinuation of study therapy were defined as events when 1 or more study drugs of a multidrug regimen were discontinued, even if the subject remained on treatment or in follow-up.

The overall proportion of subjects with all-causality AEs leading to discontinuation was numerically higher in the nivo + chemo arm vs the chemo arm (40.6% vs 25.3%). The proportion of subjects with drug-related AEs leading to discontinuation was higher in the nivo + chemo arm vs the chemo arm (34.2% vs 19.4%) (Table 19).

All-causality any-grade AEs leading to discontinuation of any component of study therapy were reported in 126 (40.6%), 81 (25.2%), and 77 (25.3%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively (Table 19). The most frequently reported all-causality AEs leading to discontinuation of study therapy of any grade were:

- Nivo + chemo arm: blood creatinine increased (3.5%); pneumonitis, peripheral sensory neuropathy, and chronic kidney disease (2.6% each); and malignant neoplasm progression and creatinine renal clearance decreased (2.3% each)
- Nivo + ipi arm: pneumonitis (2.8%); malignant neoplasm progression (2.2%); and hepatic function abnormal, adrenal insufficiency, and aspartate aminotransferase increased (1.6% each)
- Chemo arm: blood creatinine increased (3.6%); malignant neoplasm progression and renal impairment (2.3% each); peripheral sensory neuropathy (2.0%); and creatinine renal clearance decreased (1.3%)

All-causality Grade 3-4 AEs leading to discontinuation of study therapy were reported in 51 (16.5%), 54 (16.8%), and 28 (9.2%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively.

Drug-related any-grade AEs leading to discontinuation of any component of study therapy were reported in 106 (34.2%), 57 (17.7%), and 59 (19.4%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively (Table 20). The most frequently reported drug-related AEs leading to discontinuation of study therapy of any grade were:

- Nivo + chemo arm: blood creatinine increased (3.5%); peripheral sensory neuropathy, pneumonitis and chronic kidney disease (2.6% each); creatinine renal clearance decreased (2.3%); and fatigue (1.9%)
- Nivo + ipi arm: pneumonitis (2.5%); and adrenal insufficiency and hepatic function abnormal (1.6% each)

- Chemo arm: blood creatinine increased (3.6%), renal impairment (2.3%), peripheral sensory neuropathy (2.0%), and creatinine renal clearance decreased (1.3%)

Drug-related Grade 3-4 AEs leading to discontinuation were reported in 29 (9.4%), 41 (12.7%), and 14 (4.6%) treated subjects in the nivo + chemo, nivo + ipi, and chemo arms, respectively.

Table 19. Adverse Events Leading to Discontinuation in ≥1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 322			Nivo + Chemo N = 310			Chemotherapy N = 304		
	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	81 (25.2)	54 (16.8)	2 (0.6)	126 (40.6)	51 (16.5)	1 (0.3)	77 (25.3)	28 (9.2)	2 (0.7)
Respiratory, thoracic and mediastinal disorders	17 (5.3)	6 (1.9)	1 (0.3)	12 (3.9)	5 (1.6)	0	5 (1.6)	4 (1.3)	1 (0.3)
Pneumonitis	9 (2.8)	3 (0.9)	0	8 (2.6)	1 (0.3)	0	0	0	0
Hepatobiliary disorders	11 (3.4)	10 (3.1)	0	2 (0.6)	2 (0.6)	0	0	0	0
Hepatic function abnormal	5 (1.6)	4 (1.2)	0	1 (0.3)	1 (0.3)	0	0	0	0
Endocrine disorders	10 (3.1)	8 (2.5)	0	1 (0.3)	0	0	0	0	0
Adrenal insufficiency	5 (1.6)	5 (1.6)	0	1 (0.3)	0	0	0	0	0
Gastrointestinal disorders	10 (3.1)	8 (2.5)	0	17 (5.5)	7 (2.3)	0	6 (2.0)	5 (1.6)	0
Colitis	3 (0.9)	2 (0.6)	0	4 (1.3)	4 (1.3)	0	0	0	0
Nausea	0	0	0	3 (1.0)	0	0	0	0	0
Oesophageal stenosis	0	0	0	1 (0.3)	1 (0.3)	0	3 (1.0)	2 (0.7)	0
Stomatitis	0	0	0	3 (1.0)	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (2.8)	7 (2.2)	0	7 (2.3)	7 (2.3)	0	9 (3.0)	6 (2.0)	1 (0.3)
Malignant neoplasm progression	7 (2.2)	6 (1.9)	0	7 (2.3)	7 (2.3)	0	7 (2.3)	4 (1.3)	1 (0.3)
Investigations	8 (2.5)	6 (1.9)	0	27 (8.7)	6 (1.9)	0	18 (5.9)	1 (0.3)	0
Aspartate aminotransferase increased	5 (1.6)	3 (0.9)	0	2 (0.6)	1 (0.3)	0	0	0	0
Alanine aminotransferase increased	4 (1.2)	3 (0.9)	0	1 (0.3)	1 (0.3)	0	0	0	0
Blood creatinine increased	0	0	0	11 (3.5)	0	0	11 (3.6)	0	0
Creatinine renal clearance decreased	0	0	0	7 (2.3)	0	0	4 (1.3)	0	0

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 322			Nivo + Chemo N = 310			Chemotherapy N = 304		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Infections and infestations	4 (1.2)	2 (0.6)	1 (0.3)	9 (2.9)	9 (2.9)	0	2 (0.7)	1 (0.3)	0
Pneumonia	2 (0.6)	1 (0.3)	1 (0.3)	6 (1.9)	6 (1.9)	0	0	0	0
Metabolism and nutrition disorders	6 (1.9)	6 (1.9)	0	11 (3.5)	6 (1.9)	0	3 (1.0)	2 (0.7)	0
Decreased appetite	1 (0.3)	1 (0.3)	0	5 (1.6)	0	0	1 (0.3)	0	0
Blood and lymphatic system disorders	2 (0.6)	0	0	5 (1.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Anaemia	1 (0.3)	0	0	3 (1.0)	1 (0.3)	0	0	0	0
Renal and urinary disorders	2 (0.6)	0	0	24 (7.7)	4 (1.3)	0	16 (5.3)	2 (0.7)	0
Acute kidney injury	1 (0.3)	0	0	5 (1.6)	3 (1.0)	0	2 (0.7)	0	0
Chronic kidney disease	0	0	0	8 (2.6)	0	0	3 (1.0)	0	0
Renal failure	0	0	0	4 (1.3)	1 (0.3)	0	3 (1.0)	1 (0.3)	0
Renal impairment	0	0	0	5 (1.6)	0	0	7 (2.3)	0	0
General disorders and administration site conditions	1 (0.3)	1 (0.3)	0	19 (6.1)	4 (1.3)	0	4 (1.3)	1 (0.3)	0
Pyrexia	0	0	0	3 (1.0)	0	0	0	0	0
Nervous system disorders	1 (0.3)	0	0	21 (6.8)	4 (1.3)	0	13 (4.3)	4 (1.3)	0
Neuropathy peripheral	0	0	0	5 (1.6)	1 (0.3)	0	3 (1.0)	0	0
Peripheral sensory neuropathy	0	0	0	8 (2.6)	1 (0.3)	0	6 (2.0)	1 (0.3)	0

MedDRA Version: 23.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.4.2.2.2

Table 20. Drug-Related Adverse Events Leading to Discontinuation in ≥1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + Ipi N = 322			Nivo + Chemo N = 310			Chemotherapy N = 304		
	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	57 (17.7)	41 (12.7)	0	106 (34.2)	29 (9.4)	0	59 (19.4)	14 (4.6)	0
Respiratory, thoracic and mediastinal disorders	11 (3.4)	4 (1.2)	0	10 (3.2)	3 (1.0)	0	0	0	0
Pneumonitis	8 (2.5)	3 (0.9)	0	8 (2.6)	1 (0.3)	0	0	0	0
Endocrine disorders	10 (3.1)	8 (2.5)	0	1 (0.3)	0	0	0	0	0
Adrenal insufficiency	5 (1.6)	5 (1.6)	0	1 (0.3)	0	0	0	0	0
Hepatobiliary disorders	10 (3.1)	9 (2.8)	0	1 (0.3)	1 (0.3)	0	0	0	0
Hepatic function abnormal	5 (1.6)	4 (1.2)	0	1 (0.3)	1 (0.3)	0	0	0	0
Gastrointestinal disorders	8 (2.5)	7 (2.2)	0	15 (4.8)	5 (1.6)	0	3 (1.0)	3 (1.0)	0
Colitis	3 (0.9)	2 (0.6)	0	4 (1.3)	4 (1.3)	0	0	0	0
Nausea	0	0	0	3 (1.0)	0	0	0	0	0
Stomatitis	0	0	0	3 (1.0)	0	0	0	0	0
Metabolism and nutrition disorders	6 (1.9)	6 (1.9)	0	11 (3.5)	6 (1.9)	0	3 (1.0)	2 (0.7)	0
Hyponatraemia	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0	0	0	0
Decreased appetite	1 (0.3)	1 (0.3)	0	5 (1.6)	0	0	1 (0.3)	0	0
Investigations	5 (1.6)	5 (1.6)	0	27 (8.7)	6 (1.9)	0	18 (5.9)	1 (0.3)	0
Blood creatinine increased	0	0	0	11 (3.5)	0	0	11 (3.6)	0	0
Creatinine renal clearance decreased	0	0	0	7 (2.3)	0	0	4 (1.3)	0	0
Renal and urinary disorders	2 (0.6)	0	0	24 (7.7)	4 (1.3)	0	16 (5.3)	2 (0.7)	0
Acute kidney injury	1 (0.3)	0	0	5 (1.6)	3 (1.0)	0	2 (0.7)	0	0
Chronic kidney disease	0	0	0	8 (2.6)	0	0	3 (1.0)	0	0
Nephropathy toxic	0	0	0	0	0	0	1 (0.3)	1 (0.3)	0
Renal failure	0	0	0	4 (1.3)	1 (0.3)	0	3 (1.0)	1 (0.3)	0
Renal impairment	0	0	0	5 (1.6)	0	0	7 (2.3)	0	0
Blood and lymphatic system disorders	1 (0.3)	0	0	5 (1.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Anaemia	0	0	0	3 (1.0)	1 (0.3)	0	0	0	0
Nervous system disorders	1 (0.3)	0	0	19 (6.1)	3 (1.0)	0	12 (3.9)	3 (1.0)	0
Neuropathy peripheral	0	0	0	5 (1.6)	1 (0.3)	0	3 (1.0)	0	0
Peripheral sensory	0	0	0	8 (2.6)	1 (0.3)	0	6 (2.0)	1 (0.3)	0
General disorders and administration site conditions	0	0	0	16 (5.2)	2 (0.6)	0	3 (1.0)	0	0
Fatigue	0	0	0	6 (1.9)	1 (0.3)	0	0	0	0

MedDRA Version: 23.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.4.2.2

Safety in All Treated Subjects with Tumour Cell PD-L1 ≥1%

The safety profiles of nivo + chemo, nivo + ipi and chemo among all treated subjects with tumour cell PD-L1 expression ≥1% were comparable to those for all treated subjects (Table 21).

Table 21: Summary of Safety - All Treated Subjects with Tumour Cell PD-L1 ≥ 1%

	No. of Subjects (%)		
Safety Parameter	**Nivo + Ipi (N=158)**	**Nivo + Chemo (N=155)**	**Chemo (N=145)**
Deaths	106 (67.1)	96 (61.9)	116 (80.0)
Primary Reason for Death			
Disease	87 (55.1)	79 (51.0)	104 (71.7)

Table 21: Summary of Safety - All Treated Subjects with Tumour Cell PD-L1 ≥ 1%

	No. of Subjects (%)					
Safety Parameter	**Nivo + Ipi (N=158)**		**Nivo + Chemo (N=155)**		**Chemo (N=145)**	
Study Drug Toxicity	1 (0.6)		5 (3.2)		1 (0.7)	
Unknown	7 (4.4)		5 (3.2)		7 (4.8)	
Other	11 (7.0)		7 (4.5)		4 (2.8)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	104 (65.8)	74 (46.8)	87 (56.1)	65 (41.9)	67 (46.2)	47 (32.4)
Drug-related SAEs	49 (31.0)	36 (22.8)	40 (25.8)	32 (20.6)	24 (16.6)	18 (12.4)
All-causality AEs leading to DC	45 (28.5)	30 (19.0)	69 (44.5)	28 (18.1)	35 (24.1)	14 (9.7)
Drug-Related AEs leading to DC	35 (22.2)	25 (15.8)	60 (38.7)	18 (11.6)	27 (18.6)	6 (4.1)
All-causality AE	155 (98.1)	96 (60.8)	155 (100.0)	109 (70.3)	144 (99.3)	85 (58.6)
Drug-related AEs	128 (81.0)	49 (31.0)	149 (96.1)	77 (49.7)	133 (91.7)	60 (41.4)
≥15% of Subjects in any Treatment Arm						
Rash	31 (19.6)	2 (1.3)	13 (8.4)	0	2 (1.4)	0
Pruritus	25 (15.8)	1 (0.6)	13 (8.4)	0	0	0
Diarrhoea	17 (10.8)	1 (0.6)	36 (23.2)	3 (1.9)	18 (12.4)	2 (1.4)
Nausea	11 (7.0)	1 (0.6)	91 (58.7)	4 (2.6)	78 (53.8)	5 (3.4)
Stomatitis	9 (5.7)	0	52 (33.5)	10 (6.5)	32 (22.1)	4 (2.8)
Vomiting	9 (5.7)	3 (1.9)	25 (16.1)	2 (1.3)	23 (15.9)	7 (4.8)
Constipation	3 (1.9)	1 (0.6)	20 (12.9)	1 (0.6)	35 (24.1)	1 (0.7)
Neutrophil count decreased	1 (0.6)	0	28 (18.1)	13 (8.4)	19 (13.1)	9 (6.2)
Fatigue	14 (8.9)	3 (1.9)	27 (17.4)	3 (1.9)	21 (14.5)	4 (2.8)
Malaise	9 (5.7)	0	23 (14.8)	0	23 (15.9)	0
Decreased appetite	9 (5.7)	2 (1.3)	70 (45.2)	7 (4.5)	66 (45.5)	4 (2.8)
Hiccups	2 (1.3)	0	19 (12.3)	0	27 (18.6)	0
Anaemia	3 (1.9)	1 (0.6)	45 (29.0)	10 (6.5)	33 (22.8)	12 (8.3)
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality Select AEs by Category						
Gastrointestinal	39 (24.7)	6 (3.8)	52 (33.5)	8 (5.2)	23 (15.9)	2 (1.4)
Hepatic	39 (24.7)	12 (7.6)	29 (18.7)	6 (3.9)	10 (6.9)	2 (1.4)

Table 21: Summary of Safety - All Treated Subjects with Tumour Cell PD-L1 ≥ 1%

	No. of Subjects (%)					
Safety Parameter	**Nivo + Ipi (N=158)**		**Nivo + Chemo (N=155)**		**Chemo (N=145)**	
Pulmonary	13 (8.2)	5 (3.2)	11 (7.1)	1 (0.6)	3 (2.1)	1 (0.7)
Renal	9 (5.7)	2 (1.3)	39 (25.2)	5 (3.2)	34 (23.4)	2 (1.4)
Skin	71 (44.9)	5 (3.2)	45 (29.0)	1 (0.6)	14 (9.7)	0
Hypersensitivity/Infusion Reactions	10 (6.3)	0	3 (1.9)	0	1 (0.7)	0
Drug-Related Select AEs by Category						
Gastrointestinal	18 (11.4)	3 (1.9)	39 (25.2)	7 (4.5)	18 (12.4)	2 (1.4)
Hepatic	25 (15.8)	8 (5.1)	19 (12.3)	4 (2.6)	7 (4.8)	1 (0.7)
Pulmonary	11 (7.0)	4 (2.5)	11 (7.1)	1 (0.6)	1 (0.7)	0
Renal	7 (4.4)	2 (1.3)	36 (23.2)	5 (3.2)	32 (22.1)	2 (1.4)
Skin	57 (36.1)	5 (3.2)	29 (18.7)	0	4 (2.8)	0
Hypersensitivity/Infusion Reactions	8 (5.1)	0	2 (1.3)	0	1 (0.7)	0
All-causality IMAEs within 100 d of last dose treated with IMM by Category						
Diarrhea/Colitis	6 (3.8)	3 (1.9)	6 (3.9)	4 (2.6)	0	0
Hepatitis	7 (4.4)	4 (2.5)	2 (1.3)	1 (0.6)	0	0
Pneumonitis	7 (4.4)	5 (3.2)	7 (4.5)	2 (1.3)	0	0
Nephritis/Renal Dysfunction	4 (2.5)	2 (1.3)	2 (1.3)	2 (1.3)	0	0
Rash	25 (15.8)	5 (3.2)	10 (6.5)	0	2 (1.4)	1 (0.7)
Hypersensitivity/Infusion Reactions	0	0	0	0	0	0
All-causality Endocrine IMAEs within 100 d of last dose by Category						
Adrenal Insufficiency	12 (7.6)	5 (3.2)	1 (0.6)	0	0	0
Hypophysitis	13 (8.2)	5 (3.2)	1 (0.6)	1 (0.6)	0	0
Hypothyroidism/Thyroiditis	27 (17.1)	0	11 (7.1)	0	0	0
Diabetes Mellitus	3 (1.9)	2 (1.3)	1 (0.6)	1 (0.6)	0	0
Hyperthyroidism	12 (7.6)	2 (1.3)	2 (1.3)	0	1 (0.7)	0

Table 21: Summary of Safety - All Treated Subjects with Tumour Cell PD-L1 ≥ 1%

	No. of Subjects (%)					
Safety Parameter	**Nivo + Ipi (N=158)**		**Nivo + Chemo (N=155)**		**Chemo (N=145)**	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality OESIs within 100 d of last dose with/without IMM by Category						
Pancreatitis	3 (1.9)	3 (1.9)	0	0	0	0
Encephalitis	0	0	0	0	0	0
Myositis/Rhabdomyolysis	0	0	1 (0.6)	0	0	0
Myasthenic Syndrome	0	0	0	0	0	0
Demyelination	0	0	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0	0	0
Uveitis	2 (1.3)	1 (0.6)	1 (0.6)	0	0	0
Myocarditis	1 (0.6)	0	0	0	0	0
Graft Versus Host Disease	0	0	0	0	0	0

MedDRA version 23.1 CTCAE version 4.0.

All events are within 30 days of the last dose of study drug, unless otherwise indicated (eg, any time for deaths, 100 days for IMAEs and OESIs).

Source: Table S.6.15.1 (deaths), Table S.6.3.1.2.1 (All-causality SAEs), Table S.6.3.1.2.2 (Drug-related SAEs), Table S.6.4.2.2.1 (All-causality AEs leading to DC). Table S.6.4.2.1 (Drug-Related AEs leading to DC), Table S.6.1.31.2.1 (All-causality AEs), Table S.6.1.32.1.1 (Drug-related AEs), Table S.6.5.1.3.2.1 (select AEs), Table S.6.5.1.3.2.2 (related select AEs), Table S.6.2.02.1.1 (endocrine IMAEs), Table S.6.2.02.1.2 (non-endocrine IMAEs), Table S.6.5.3.3.1.1 (OESIs)

Safety to Support the Product Information (PI)

The MAH proposes to pool nivo + chemo safety data from study CA209648 in 1L OSCC with study CA209649 in 1L GC/GEJ/OAC to support Section 4.8 of the SmPC. In both CA209648 and CA209649 studies nivolumab was combined with a platinum and fluoropyrimidine-based chemotherapy, i.e. cisplatin plus 5-fluorouracil in study CA209648 and FOLFOX (leucovorin plus fluorouracil plus oxaliplatin) or XELOX (capecitabine plus oxaliplatin) in study CA209649. This is also aligned with the proposed broad indication for OSCC that covers the combination of nivolumab with platinum and fluoropyrimidine-based chemotherapy.

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. Integrate all-causality AEs data from CA209648 with nivolumab 240 mg Q2W + fluorouracil /cisplatin Q4W in 1L OSCC and CA209649 with nivolumab 240 mg + FOLFOX (fluorouracil + leucovorin + oxaliplatin) Q2W or nivolumab 360 mg + XELOX (capecitabine + oxaliplatin) Q3W in 1L GC/GEJ/OAC.
2. Programmatically remap MedDRA PTs representing the same or similar clinical conditions for the integrated AE data and generate summary tables.
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.

The presentation of ADRs in section 4.8 of the current approved OPDIVO SmPC displays 2 columns in Table 8, one for nivolumab in combination with chemotherapy in GC/GEJ/OAC, one for nivolumab in combination with ipilimumab and chemotherapy in NSCLC.

With the current proposal, the first column in the ADR Table 8 is updated with pooled data from 1L treatment of OSCC (n = 310 of treated patients from CA209648) and 1L treatment of GC/GEJ/OAC (n=782 of treated patients from CA209649) for nivolumab in combination with chemotherapy. The intended dose regimen and/or schedule of administration for OSCC was similar to the approved regimen for GC/GEJ/OAC. The patient population with tumour cell PD-L1 ≥1% from CA209648 presented with a similar safety profile, and a qualitative statement was added in Section 4.8 of the OPDIVO SmPC. As explained above, for labelling purposes, some MedDRA PTs were remapped for the purposes of generating summary tables to support Section 4.8 of the SmPC pooling PTs representing the same or similar clinical conditions.

For the proposed OPDIVO SmPC, selection of specific ADRs (Table 8 in Section 4.8 of the SmPC) was based on clinical relevance as determined by the BMS medical reviewer and a review of all-causality AEs was conducted for CA209648 and the integrated safety data from CA209648 and CA209649 to ensure that appropriate MedDRA PTs are represented in the proposed Table of ADRs. The list of PTs included in the proposed Table of ADRs in Section 4.8 of the SmPC reflects the ADRs that were observed with nivolumab in combination with chemotherapy in CA209648 and its aim is to provide concise, relevant information, enabling HCPs to make appropriate decisions regarding patient treatment and management based on information regarding the frequency and nature of the ADRs that may occur in patients in clinical practice. Frequency of ADR is presented based on all-causality AEs, in line with the above mentioned guidelines recommendations.

To calculate the frequencies of laboratory ADR, BMS used the laboratory abnormality change from baseline tables (with 30 days of follow-up). The denominator used to compute frequency is the number of subjects for whom laboratory data were available, as opposed to all treated subjects. Hence, there is variability in the denominator for each individual laboratory abnormality and the respective reported frequency.

Presentation of Clinically Relevant Adverse Reactions

In the updated ADR table in Section 4.8 of the nivolumab SmPC, adverse reactions are presented by system organ class and by frequency grouping (e.g. common, uncommon, rare, or very rare). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Text on the proposed dosage and administration of nivolumab (OPDIVO) in combination with chemotherapy is provided in Section 4.2 of the nivolumab SmPC. Detailed guidelines for the management of immune-related adverse reactions are provided in Section 4.4 of the nivolumab SmPC.

In this application, no amendments or changes in the management of adverse reactions are proposed based on the data from CA209648.

2.5.1. Discussion on clinical safety

In the phase 3 CA209648 study supporting this application, 936 subjects were treated with nivo + chemo (N=310), nivo + ipi (N=322) or chemo (N=304). Patients in the nivo + chemo arm were to receive nivolumab 240 mg as a 30-min IV infusion Q2W, fluorouracil 800 mg/m2/day as a continuous

IV infusion on Days 1-5 Q4W and cisplatin 80 mg/m2 as a 30-120-minute IV infusion on Day 1 Q4W. The median number of nivolumab doses received by subjects in the nivo + chemo arm was 12 (1-54). The median number of chemotherapy doses received was around 6 (1-31) for 5-Fu and 5 (1-24) for cisplatin in the nivo+chemo arm, while in the chemotherapy arm the median number of cycles was lower (4 for each component), partly due to higher rate of disease progression (59.4% vs. 63.5%) and higher number of discontinuations due to study drug toxicity (10.6% vs. 13.2%). Of note, both arms received the same chemotherapy regimen but with a different dose intensity. The proportion of patients who received ≥90% of the planned relative dose intensity was higher for the chemo arm: in the nivo + chemo arm, this was 55.5% for cisplatin and 58.4% for fluorouracil while in the chemo arm these figures were 68.1% for cisplatin and 76.2% for fluorouracil, suggesting that the expected increased toxicity when adding nivolumab to chemotherapy could be managed with dose reductions for the cytotoxic components. Of note, all three components needed to be delayed when criteria for nivolumab delay were met, which could have influenced the reported lower relative dose intensity for the nivo + chemo arm. Updated safety data was later provided based on a 04-Oct-2021 DBL and a summary of these results has been included after the initial assessment. The overall safety profile remained consistent with that previously reported in the primary analysis.

The most frequently reported AEs (>20%) in the nivo + chemo arm were nausea (65.2%), decreased appetite (51.3%), anaemia (45.8%), constipation (44.2%), stomatitis (32.6%), diarrhoea (29.4%), nausea (29.4%), fatigue (25.8%), vomiting (22.6%), and neutrophil count decreased (22.3%) while, in the chemo arm, they were nausea (55.9%), decreased appetite (49.7%), constipation (43.1%), anaemia (31.9%), stomatitis (24.0%), and hiccups (20.7%). Grade 3-4 AEs were reported by 69.7% of subjects in the nivo + chemo arm and 54.3% in the chemo arm. The most common (>5%) Grade 3-4 AEs were anaemia (16.1%), neutrophil count decreased (9.0%), dysphagia (7.4%), decreased appetite (6.8%), stomatitis (6.5%), malignant neoplasm progression (5.5%), and pneumonia (5.2%) in the nivo + chemo arm and anaemia (9.9%), neutrophil count decreased (8.6%), and decreased appetite (5.9%) in the chemo arm. Regarding treatment-related AEs, any-grade treatment-related AEs were reported by the 95.8% of subjects in the nivo + chemo arm and 90.5% subjects in the chemo arm, being the most commonly reported: nausea (58.7%), decreased appetite (42.6%), and stomatitis (31.6%) in the nivo + chemo arm and nausea (52.0%), decreased appetite (42.8%), and stomatitis (23.4%) in the chemo arm. When considering only Grade 3-4 AEs, these were reported in the 47.4% of subjects in the nivo + chemo arm and the 35.5% subjects from the chemo arm, being the most common: anaemia (9.7%), neutrophil count decreased (8.1%), and stomatitis (6.5%) in the nivo + chemo arm, and neutrophil count decreased (7.9%), anaemia (5.6%), and fatigue (3.6%) in the chemo arm.

The frequencies of SAEs were higher in the nivo + chemo arm compared with the chemo arm but with similar PTs. SAEs were reported in 58.1% and 42.1% of subjects from the nivo + chemo and the chemo arm respectively. The most frequently reported were malignant neoplasm progression (7.7%), pneumonia (7.1%), dysphagia (5.8%) in the nivo + chemo arm, and malignant neoplasm progression (4.9%), dysphagia and pneumonia (3.6% each), oesophageal stenosis (3.3%) in the chemo treatment arm.

Up to the data cut-off (DCO), the number of patients who died was numerically lower in the nivo + chemo arm compared with the chemo arm (64.5% vs. 73.7%). The primary reason for death was mainly disease progression. Deaths attributable to study drug toxicity were 5 (1.6%) in the nivo + chemo arm and 4 (1.3%) in the chemo treatment arm. According to the investigator, two of these deaths were caused by nivolumab: two pneumonitis cases and one case of pneumatosis intestinalis, the latter related to both nivolumab and chemo treatment. There was also one reported death in the nivo + chemo arm due to pneumonia, considered related to chemo by the investigator, although pneumonia is an identified nivolumab drug reaction so its relation cannot be excluded. Up to the latest

DBL (4 Oct 2021), 73.9% of subjects in the nivo + chemo arm and 79.6% of subjects in the chemo arm had died. The main reasons of death were consistent with those previously reported.

AESI for nivolumab are classified into Select Adverse Events, IMAEs and OESIs. The most frequently reported drug-related select AE categories were renal (23.9%), gastrointestinal (20.6%), and skin (17.4%) in the nivo + chemo arm, and renal (18.8%), gastrointestinal (15.5%), and hepatic (3.9%) in the chemo arm. By PT, the most common select AE was diarrhoea in both cases. As seen with other nivolumab therapeutic indications, endocrine AEs tend to have the lowest rate resolved events (28.6% of subjects), followed by renal (56.8%) and pulmonary (66.7%) in the nivo + chemo treatment arm. As expected, incidence of IMAEs was higher in the nivo + chemo arm compared with the chemo arm where rash (0.7%) was the only reported event of this type. In the nivo + chemo arm, 18.4% of subjects reported any IMAE being the most common: hypothyroidism/thyroiditis (6.1%), rash (5.2%), pneumonitis (3.2%), hyperthyroidism (2.3%), and diarrhoea/colitis (1.9%). 1.3% of subjects reported Grade 3-4 diarrhoea/colitis, renal dysfunction and diabetes mellitus and 0.6% Grade 3-4 pneumonitis IMAEs. OESIs, events that do not fulfil all criteria to be considered IMAEs but which may require immunosuppression for their management, were reported by 4 subjects. These events were Grade 2 uveitis, Grade 1-3 rhabdomyolysis and Grade 1-2 myositis. All of them were considered resolved except for one Grade 2 event of uveitis and Grade 1 myositis. Of note, the two events of myositis were managed with thalidomide, in addition to methylprednisolone, based on the investigator's clinical experience. Although myositis is an identified risk with nivolumab treatment.

Focusing on laboratory abnormalities (up to 30 days after last treatment dose), reported incidences for these events were higher in the nivo + chemo arm compared with the chemo arm. The highest differences between both treatment arms were reported for haemoglobin (80.9% vs. 65.7%), platelet count (43.4% vs. 29.3%) and lymphocytes (67.2% vs. 44%), and those differences were also observed for Grade 3-4 abnormalities. Higher frequency of worsening parameters was found for nivo + chemo compared to chemo treatment arm, for all four items but more remarkable for ALT and AST. Liver test abnormalities that were considered clinically relevant by the investigator were reported as an adverse event (AE) or serious adverse event (SAE) but these terms have a broader meaning, as they may reflect clinical concepts rather than individual laboratory abnormalities, such as hepatitis. Concurrent ALT or AST >3×ULN with total bilirubin >2×ULN after the first dose and within 30 days of last dose of study therapy was reported in 2/305 (0.7%) in the nivo + chemo arm and 0 subjects, with test results, in the chemo arm. The most common thyroid function test abnormality was TSH increase (>ULN) which was reported by the 20.5% and the 7.6% of subjects from the nivo + chemo and the chemo arm, respectively. Electrolytes alterations were also higher in the chemo + nivo arm compared with the chemo arm, for example, incidence of any-Grade hyponatremia in the nivo + chemo arm was 51.6% and in the chemo arm it was of 40.6% of subjects while for Grade 3-4 hyponatremia, it was reported by 14.8% of subjects in the nivo + chemo arm and 8.9% in the chemo treatment arm. Hypocalcaemia was reported by 45.4% and 23% subjects in the nivo + chemo arm and the chemo arm, respectively; although Grade 3-4 events of hypocalcaemia were very limited. A similar pattern was observed for hypomagnesaemia. Discussion about the relation between these abnormalities and the high rate of diarrhoea and colitis reported with nivolumab has been included in previous submissions and, although very limited number of these results have clinical relevance, their relation cannot be excluded. A review of PTs that could be linked to vital sign-related AEs was performed. Overall, reported incidences of these events were comparable between both treatment arms with no relevant differences. One case of Grade 5 arrhythmia was observed in the nivo + chemo arm.

Considering safety in special populations, reported AEs were, in general, comparable between treatment arms. Overall, all-causality AEs and drug-related AEs (by SOC and PT) presented higher incidences in females but a thorough comparison between male and female subjects for both treatment arms did not show any particular trend. Frequencies of all-causality and drug-related AEs

were also comparable between different age groups. Data for ≥75 is limited due to the small sample size (32 subjects in the nivo + chemo arm and 24 in the chemo arm) and no data is available for ≥85 as only 3 subjects were included in the nivo + chemo arm.

The proportion of subjects with drug-related AEs leading to discontinuation of 1 or more study drug in multidrug regimen was substantially higher in the nivo + chemo arm vs. the chemo arm (34.2% vs. 19.4%). The most frequently reported drug-related AEs leading to discontinuation of study therapy were blood creatinine increased (3.5%), peripheral sensory neuropathy, pneumonitis and chronic kidney disease (2.6% each), creatinine renal clearance decreased (2.3%), and fatigue (1.9%) in the nivo + chemo arm; and blood creatinine increased (3.6%), malignant neoplasm progression and renal impairment (2.3% each), peripheral sensory neuropathy (2.0%), and creatinine renal clearance decreased (1.3%) in the chemo arm. As seen, reasons for discontinuation were comparable between arms, except for pneumonitis. Drug-related Grade 3-4 AEs leading to discontinuation were reported in 29 (9.4%) subjects from the nivo + chemo arm and 14 (4.6%) subjects in the chemo treatment arm.

Safety data analyses have also been submitted for the All Treated Subjects with Tumour Cell PD-L1 ≥1% population. Overall, no major differences were reported between these subjects and the All Treated population.

Regarding data to support safety information included in section 4.8 of the SmPC, the MAH proposes to pool nivo + chemo safety data from study CA209648 in 1L OSCC with study CA209649 in 1L GC/GEJ/OAC (approved by procedure EMEA/H/C/003985/II/096). This is justifiable considering that in both CA209648 and CA209649 studies nivolumab was combined with a platinum and fluoropyrimidine-based chemotherapy regimen, i.e. cisplatin plus 5-fluorouracil in CA209648, and FOLFOX (leucovorin plus fluorouracil plus oxaliplatin) or XELOX (capecitabine plus oxaliplatin) in CA209649. A comparison between identified ADRs from the pooled safety data and the individual studies has been performed and the MAH's approach is considered acceptable.

2.5.2. Conclusions on clinical safety

The addition of nivolumab to platinum-based chemotherapy for the first-line treatment of patients with unresectable advanced, recurrent or metastatic OSCC results in a worse safety profile which combines the already known toxicities for both nivolumab and the standard chemotherapy scheme for this setting.

Although higher incidences of AEs have been found for the combination in almost all categories, the toxicity profile of this combination could still be considered manageable, as some of the most common events overlap and no major differences have been identified between both arms.

However, particular attention must be drawn to nivolumab-related IMAEs as its occurrence could be somehow disguised by other chemotherapy-related toxicities.

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 26.2 with this application.

The PRAC considered that the risk management plan version 26.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 26.2 with the following content:

Safety concerns

Summary of Safety Concerns

Important identified risks	Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Complications of allogeneic HSCT following nivolumab therapy in cHL Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis,	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024

Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s
		solid organ transplant rejection, and VKH), and infusion reactions		
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCT Ongoing	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

Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8 Additional risk minimization measures: Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

2.7. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reason:

The inclusion of the new proposed indication for Opdivo (i.e. in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma) does not have

a relevant impact on the PIL and therefore it is agreed with the MAH that there is no need to conduct additional consultation with target patients groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH is seeking an extension of the indication for Opdivo in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

3.1.1. Disease or condition

Oesophageal cancer (OC) is the eighth-most common cancer and the sixth-most common cause of death worldwide, with an estimated 604,100 new cases (3.1% of all cancers) and 544,076 cancer deaths (5.5% of all cancer deaths)[3]. In the UE, oesophageal cancer is the 19th most common cancer, although variability between countries is high. There are two distinct histologic types of OC: squamous cell carcinoma (SCC) and adenocarcinoma (AC). Globally, OSCC is the most common histological subtype, however while the incidence of OSCC has decreased in many regions, a marked increase in the incidence of OAC has been observed in Europe, North America, and Australia during the past four decades[4].

The main risk factors for OSCC are smoking and alcohol consumption.

3.1.2. Available therapies and unmet medical need

For patients with advanced and recurrent OC and a good performance status (PS) palliative chemotherapy is commonly used, particularly for patients with AC. In OSCC, the value of palliative chemotherapy is less proved and best supportive care (BSC) or palliative monotherapy can also be considered[5]. Among the regimens used in the first-line setting, a combination of fluoropyrimidine (either 5-FU or capecitabine) and cisplatin or oxaliplatin are the preferred recommended regimens[6]. Use of oxaliplatin is also preferred over cisplatin due to lower toxicity.

Recent findings from the KEYNOTE 590 study showed that immune checkpoint inhibitor pembrolizumab in combination with chemotherapy in the first line (1L) setting was superior to chemotherapy for overall survival (OS) and progression free survival (PFS) in patients with locally advanced/unresectable or metastatic OAC, OSCC (73% of the study population), or GEJ adenocarcinoma. Based on these study findings, pembrolizumab (in combination with platinum- and fluoropyrimidine-based chemotherapy) has been approved in the EU for the 1L treatment of patients with locally advanced unresectable or metastatic oesophageal carcinoma (including OSCC) whose tumours express PD-L1 with a CPS ≥ 10. (Keytruda II/97).

3.1.3. Main clinical studies

The evidence in support of the claimed indication is based on results from the **study CA209648**. The study CA209648 is a Phase 3, randomised, multicentre, open-label study of nivolumab plus ipilimumab

[3] GLOBOCAN 2020 (accessed October 2021)
[4] Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet. 2017 Nov 25;390(10110):2383 2396.
[5] Lordick F, Mariette C, Haustermans K et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 27 (Supplement 5): v50–v57, 2016
[6] NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric junction cancers. Version 4.2021.

or nivolumab in combination with chemotherapy (fluorouracil plus cisplatin) versus chemotherapy (fluorouracil plus cisplatin) in subjects with unresectable advanced, recurrent or metastatic previously untreated OSCC.

The primary endpoints were OS and PFS, as assessed by BICR per RECIST 1.1 criteria, in patients with PD-L1≥1%. Secondary endpoints included OS and PFS in all randomised subjects and ORR (both in PD-L1≥1% and the overall population, by BICR). A hierarchical testing strategy was used for the primary and secondary endpoints.

A total of 970 patients were randomised (325 in the nivo+ipi arm, 321 in the nivo+chemo arm and 324 in the chemo arm). Results presented below are based on the comparison of nivo+chemo vs. chemo at the time of the primary analysis (DBL: 1 March 2021).

3.2. Favourable effects

Primary endpoints (**PD-L1≥1%**) (n=315)

OS results (event rate 62% nivo+chemo vs. 77.1% chemo) showed a statistically significant improvement in favour of the nivo+chemo arm over chemo arm (HR 0.54; 99.5% CI: 0.37, 0.80). Median OS was of 15.44 (95% CI: 11.93, 19.52) months in the nivo+chemo group and 9.07 (95% CI: 7.69, 9.95) months in the chemo group.

PFS results (event rate 74.1% nivo+chemo vs. 63.7% chemo) were also statistically significant in favour of the nivo+chemo arm (HR 0.65; 98.5% CI: 0.46, 0.92). Median PFS was 6.93 (95% CI: 5.68, 8.34) months and 4.44 (95% CI: 2.89, 5.82) months, in the nivo+chemo and chemo groups, respectively.

Secondary endpoints

OS in the **all-randomised patients** (event rate of 65.1% in the nivo+chemo arm and 71.6% in the chemo arm), showed a statistically significant benefit of nivo+chemo over chemo (HR 0.74; 99.1% CI: 0.58, 0.96). Median OS was of 13.21 (95% CI: 11.14, 15.70) months and 10.71 (95% CI: 9.40, 11.93) months in the experimental and control arm, respectively.

Results in terms of **PFS** (by BICR) in the **all-randomised patients** did not reach statistical significance (HR 0.81; 98.5% CI: 0.64, 1.04). Median PFS was 5.82 (95%CI: 5.55, 7.00) months in the nivo+chemo arm versus 5.59 (95% CI: 4.27, 5.88) months in the chemo arm.

The **ORR** (by BICR) was higher in the nivo+chemo arm compared with the chemo arm in patients with PD-L1≥1 (53.2% vs. 19.7%) and in the all-randomised patients (47.7% vs. 26.9%).

Updated efficacy data were provided during the procedure with a DBL of 04 Oct 2021 and a minimum follow-up of 20 months. Results were consistent with those reported in the primary analysis.

3.3. Uncertainties and limitations about favourable effects

The combination of nivo+chemo demonstrated a statistically significant improvement in OS in the all-randomised patient population. However, this effect appeared to be driven mostly by patients with tumour cell PD-L1≥1%. In patients with PD-L1<1%, no apparent benefit was observed with the addition of nivolumab to chemotherapy. As a result, the indication was restricted to patients with tumour cell PD-L1 expression ≥1%.

3.4. Unfavourable effects

In study CA209648, the most common AEs in the nivo + chemo arm were nausea (65.2%), decreased appetite (51.3%), anaemia (45.8%), constipation (44.2%), stomatitis (32.6%), diarrhoea (29.4%), fatigue (25.8%), vomiting (22.6%), and neutrophil count decreased (22.3%). Grade 3-4 AEs were reported by 69.7% subjects in the nivo + chemo arm compared with a 54.3% of subjects from the chemo arm.

Drug-related AEs were reported more frequently in the nivo + chemo arm (95.8% vs. 90.5%), being the most common events in the nivo + chemo arm: nausea (58.7%), decreased appetite (42.6%), and stomatitis (31.6%).

SAEs were observed in 58.1% subjects in the nivo + chemo arm compared with the 42.1% in the chemo arm and same differences were observed for drug-related SAEs (23.9% vs. 16.1%). The most common drug-related SAEs reported in the nivo + chemo arm were acute kidney injury (1.9%); colitis, pneumonia, and stomatitis (1.6% each); febrile neutropenia, pneumonitis, vomiting, hyponatraemia, and deceased appetite (1.3% each).

There were 5 (1.6%) subjects for which primary reason for death was recorded as study drug toxicity in the nivo + chemo arm and 4 (1.3%) subjects in the chemo arm.

IMAEs observed were in line with other already approved nivolumab therapeutic indications. Laboratory abnormalities were also more frequent in the nivo + chemo arm although it is difficult to distinguish their clinical relevance.

The proportion of subjects with AEs leading to discontinuation was higher in the nivo + chemo arm vs the chemo arm (40.6% vs. 25.3%). Also, for drug-related AEs leading to discontinuation, the same trend was observed (34.2% vs. 19.4% respectively).

3.5. Uncertainties and limitations about unfavourable effects

High incidences of liver tests abnormalities were reported for both treatment arms. Higher frequency of AST, ALT, ALP and bilirubin elevations were reported in the nivo + chemo arm compared with the chemo arm but not all reported laboratory abnormalities were translated into hepatic adverse events although liver enzymes and bilirubin monitoring are useful for early identification of these events. Recommendations for management of immuno-related hepatitis are already included in section 4.4 of the SmPC.

Vital signs observations were submitted by individual patient listings in the initial application so a proper assessment of the possible changes has not been performed. Instead, a manual review of PTs that could be linked to vital sign-related AEs was presented.

Some differences were identified in the incidences of all-causality any-grade AEs by sex but no particular trend could be identified.

3.6. Effects Table

Effects Table for Opdivo (nivolumab) for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (data cut-off: 18 Jan 2021) – Study CA209648

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoints (PD-L1≥1%; N=315)						
OS	Overall survival; Time from randomisation until death from any cause	Median, months (95%CI)	15.44 (11.93, 19.52)	9.07 (7.69, 9.95)	HR 0.54 (99.5% CI: 0.37, 0.80); p[a] < 0.0001	CSR
PFS	Progression free survival; Time until progressive disease (BICR-assessed per RECIST 1.1) or death from any cause, whichever occurs first	Median, months (95%CI)	6.93 (5.68, 8.34)	4.44 (2.89, 5.82)	HR 0.65 (98.5% CI: 0.46, 0.92); p[a] =0.0023	CSR
Secondary endpoints (All randomised patients; N= 645)						
OS	Overall survival	Median, months (95%CI)	13.21 (11.14, 15.70)	10.71 (9.40, 11.93)	HR 0.74 (99.1% CI: 0.58, 0.96); p[a] = 0.0021	CSR
PFS	Progression free survival	Median, months (95%CI)	5.82 (5.55, 7.00)	5.59 (4.27, 5.88)	HR 0.81 (98.5% CI: 0.64, 1.04) p[a] = 0.0355	CSR
ORR	Overall response rate per BICR (complete response + partial response)	% (95% CI)	47.4 (41.8, 53.0)	26.9 (22.1, 32.0)	Difference: 20.6 (95% CI: 13.4, 27.7)	CSR
Secondary endpoint (PD-L1≥1%); N= 315						
ORR	Overall response rate per BICR (complete response + partial response)	% (95% CI)	53.2 (45.1, 61.1)	19.7 (13.8, 26.8)	Difference: 33.4 (95% CI: 23.5, 43.4)	CSR
Unfavourable Effects[b]						
Grade 3-4 AEs	All causality (drug-related)	%	72.9 (48.7)	55.9 (36.2)		
Deaths	Due to study drug toxicity	%	1.6	1.6		
AE leading to DC	All causality (drug-related)	%	41.9 (34.2)	26.6 (20.7)		
SAEs	All causality (drug-related)	%	60.0 (23.9)	42.8 (16.1)		

Abbreviations: AE: adverse event; BICR: blinded independent central review; CSR: clinical study report; HR: hazard ratio; RECIST 1.1: Response Evaluation Criteria In Solid Tumours version 1.1; SAE: serious adverse event.

Notes: [a] Stratified 2-sided log-rank test p-value. [b] Safety data presented in the above table are based on a DBL of 04 Oct 2021

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In study CA209648 the first-line treatment of OSCC with nivolumab in combination with chemotherapy (fluorouracil plus cisplatin) showed a statistically significant improvement in OS compared with chemotherapy (fluorouracil plus cisplatin) alone in the all-randomised patient population. No statistically significant differences were observed between both treatment arms in PFS, as assessed by BICR (primary definition). However, results were considered to be driven by patients with tumour cells expressing PD-L1≥1% (primary efficacy population) with efficacy results in patients with tumour cell PD-L1<1% considered unconvincing. As a result, the indication was restricted to patients with tumour cells expressing PD-L1 ≥1%.

With regards to safety, the addition of nivolumab to platinum-based chemotherapy resulted in an increased toxicity, as shown by the higher rate of SAEs, Grade 3-4 AEs and discontinuation due to AEs. The safety profile combines the already known toxicities for both nivolumab and chemotherapy scheme used in this setting.

3.7.2. Balance of benefits and risks

Nivolumab in combination with chemotherapy demonstrated superiority over chemotherapy alone in OS, PFS and ORR in the first-line treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cells expressing PD-L1 ≥1%.

The proposed combination is more toxic and less well tolerated than chemotherapy alone although the safety profile can be considered manageable.

Therefore, the benefit/risk balance of nivolumab in combination with chemotherapy in the claimed indication is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Opdivo in the claimed indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include in combination with fluoropyrimidine- and platinum-based combination chemotherapy the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) with tumour cell PD-L1 expression ≥ 1% for OPDIVO based on study CA209648; 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 26.2 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'OPDIVO-H-C/003985/II-0107'