24 February 2022
EMA/155438/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yervoy	ipilimumab
OPDIVO	nivolumab

Procedure No. EMEA/H/C/xxxx/WS/2113

Note

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

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Table of contents

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

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 Tumors
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
UC	urothelial carcinoma
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 following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

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 treatment of first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) for Opdivo in combination with Yervoy; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 24.0 of the Opdivo RMP and version 33.0 of the Yervoy RMP have also been submitted.

The requested worksharing procedure 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 WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The 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

Appointed Rapporteur for the WS procedure: Blanca Garcia-Ochoa

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
WSA's responses submitted to the CHMP on	21 December 2021
CHMP Rapporteur's preliminary assessment report on the WSA's responses circulated on	1 February 2022
PRAC Rapporteur's preliminary assessment report on the WSA's responses circulated on	1 February 2022
PRAC RMP advice and assessment overview adopted by PRAC on	10 February 2022
CHMP Rapporteur's updated assessment report on the WSA's responses circulated on	18 February 2022
CHMP Opinion adopted on	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 ipilimumab, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (see section 5.1).

YERVOY in combination with nivolumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (see section 5.1).

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

OPDIVO in combination with ipilimumab 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%

YERVOY in combination with nivolumab 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 is either 3 mg/kg nivolumab every 2 weeks or 360 mg nivolumab every 3 weeks administered intravenously over 30 minutes in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment 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 an European Commission decision in 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-tumor 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.

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

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. Ipilimumab, as monotherapy, is approved for the treatment of advanced melanoma.

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

Both nivolumab and ipilimumab are proteins composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk. As a protein, nivolumab and ipilimumab are 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, ipilimumab 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 WSA.

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

- Tabular overview of clinical studies

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

The 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 ipilimumab 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. 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.

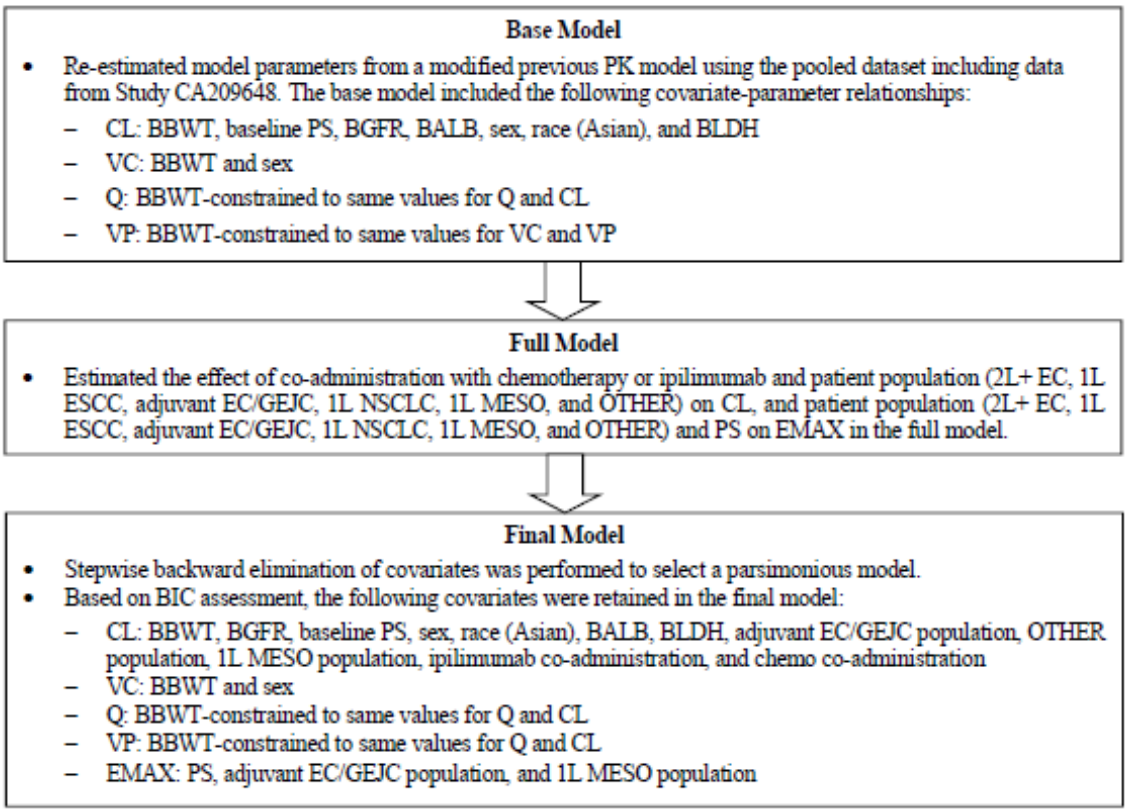
Abbreviations: Chemo = chemotherapy; GFR = glomerular filtration rate; Ipi = ipilimumab; Max = maximum; Min = minimum; n = number of subjects; Nivo = nivolumab; PD-L1 = Programmed death ligand-1; Q2W = every 2 weeks; Q6W = every 6 weeks; SD = standard deviation.

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:

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

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

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

[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

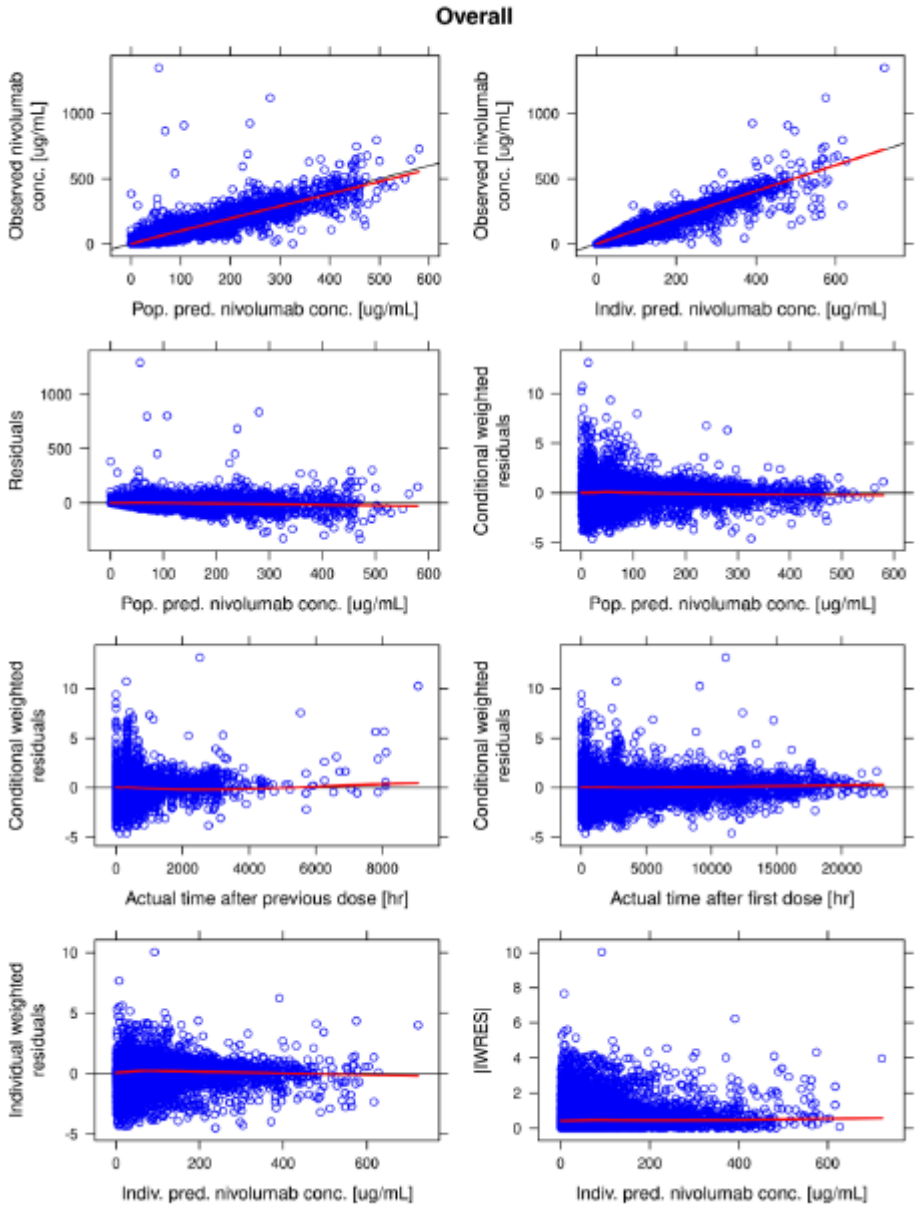


Figure 5.1.2-1: **Prediction-corrected Visual Predictive Check of Trough Concentrations (Log Scale) Versus Actual Time After First Dose for Data from the 1L ESCC Population by Treatment Using the Nivolumab Final Population Pharmacokinetic Model**

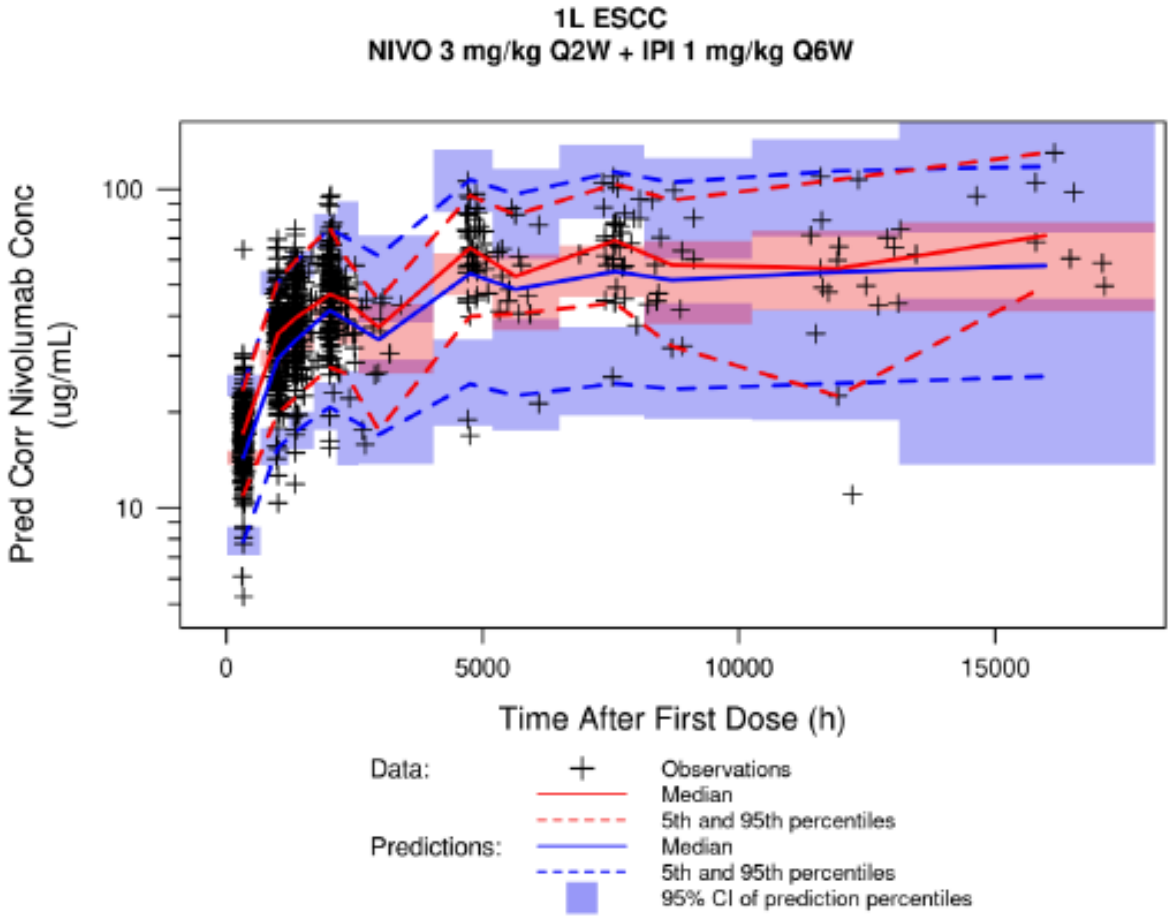
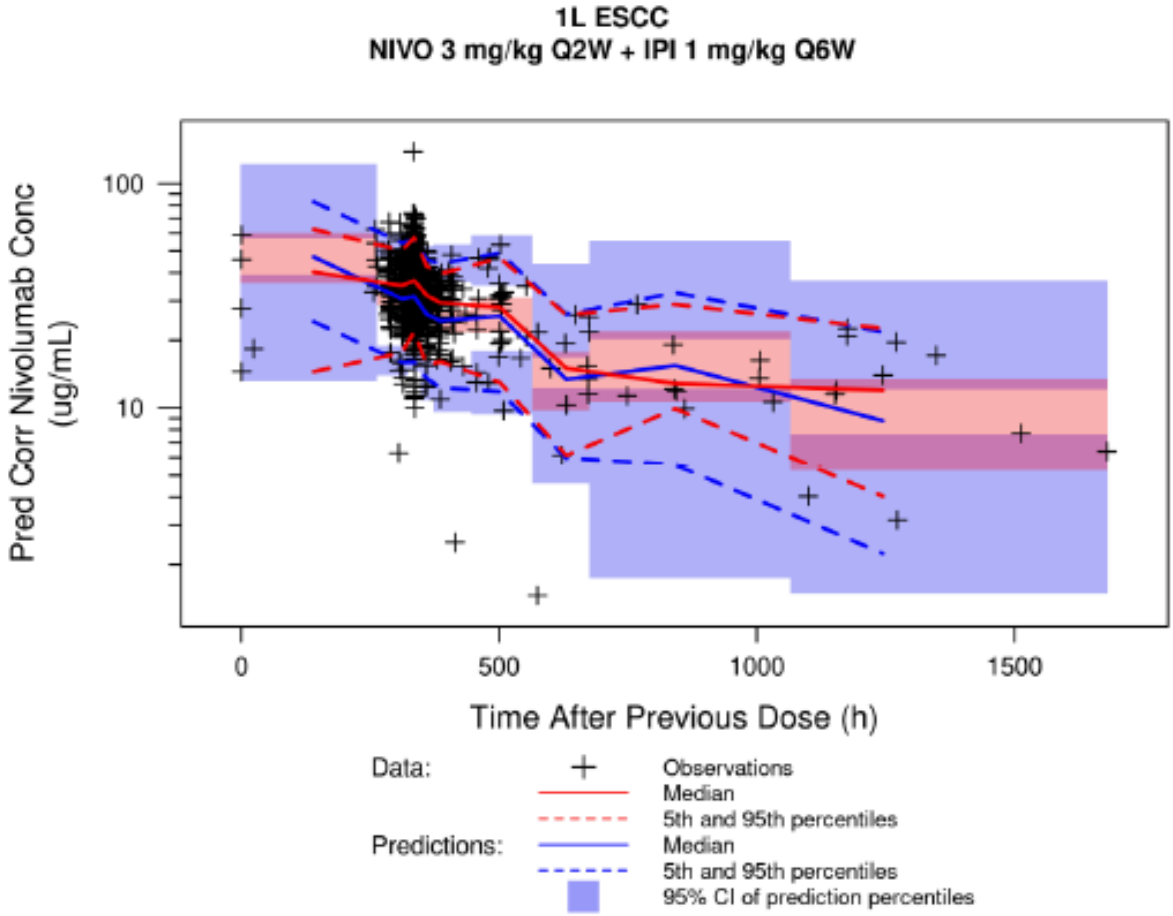
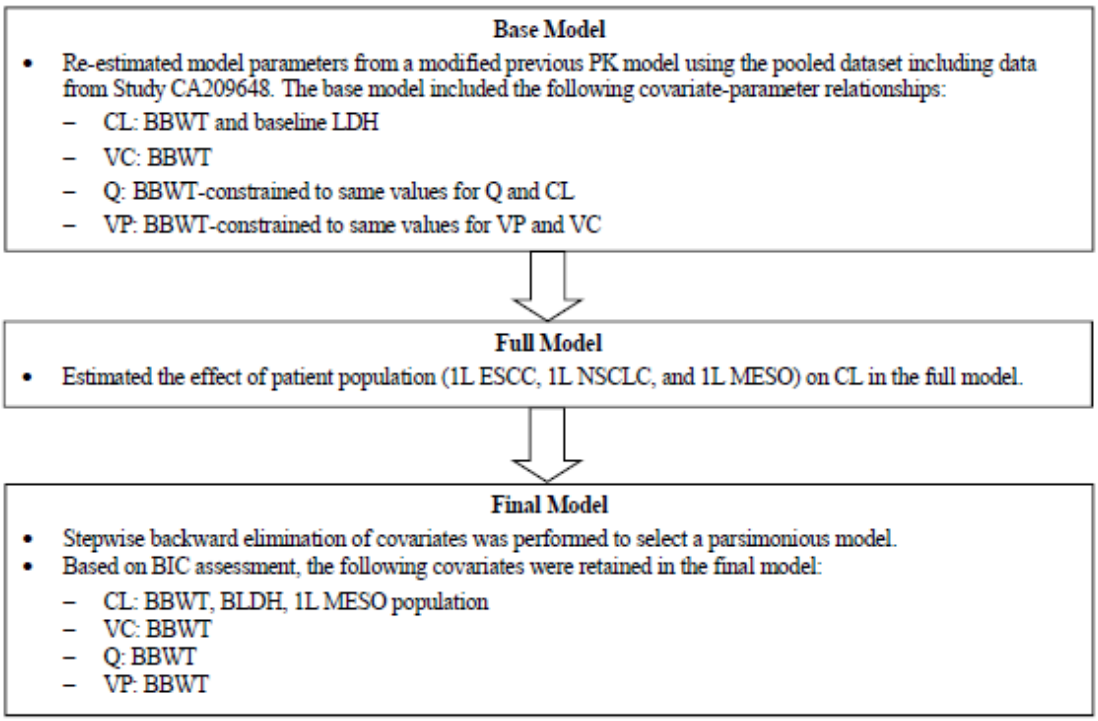


Figure 5.1.2-2: **Prediction-corrected Visual Predictive Check of All Concentrations (Log Scale) Versus Actual Time After Previous Dose for Data from the 1L ESCC Population by Treatment Using the Nivolumab Final Population Pharmacokinetic Model**



Ipilimumab

Figure 5.2.1-1: Schematic Overview of the Population Pharmacokinetic Model Development for Ipilimumab



Final Ipilimumab model

The final model for ipilimumab was developed from the full model by performing a stepwise backward elimination of the covariate effects of the full model (subject population on CL) to determine a parsimonious model. The final model estimated (typical value) Emax (-0.238) indicates that ipilimumab CL decreases with time, and that the maximal decrease is approximately 21% [calculated as: 1 −exp(Emax)]. The half-maximal change is estimated to occur at approximately 3.4 months (T50 = 2,480 hours) in all subjects.

Table 5.2.1.3-1: Parameter Estimates of the Ipilimumab Final Population Pharmacokinetic Model

Name [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval (Bootstrap Derived)[d]
		Fixed Effects		
CL0 [mL/h][e]	θ_1	15.2	0.274 (1.80)	14.6 - 15.6
VC [L][e]	θ_2	4.3	0.0512 (1.19)	4.19 - 4.40
Q [mL/h][e]	θ_3	25.0	2.45 (9.83)	19.8 - 29.8
VP [L][e]	θ_4	3.65	0.114 (3.13)	3.45 - 3.90
CL_{BBWT}[f]	θ_7	0.563	0.0462 (8.21)	0.474 - 0.66
VC_{BBWT}[f],	θ_8	0.529	0.0489 (9.24)	0.434 - 0.623

Table 5.2.1.3-1: Parameter Estimates of the Ipilimumab Final Population Pharmacokinetic Model

Name [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval (Bootstrap Derived)[d]
CL_{BLDH}[f]	θ_9	0.779	0.0462 (16.0)	0.543 - 1.01
EMAX[e]	θ_{10}	-0.238	0.0243(10.2)	(-0.297) - (-0.19)
T50 [h][e]	θ_{11}	2480	300 (10.5)	2330 - 3670
HILL [-]	θ_{12}	2.19	0.303 (13.9)	1.64 - 3.09
$CL_{POP1LMESO}$[g]	θ_{13}	0.178	0.0237 (13.3)	0.132 - 0.227
		Random Effects[h,i]		
ω^2 -CL [-]	$\omega_{1,1}$	0.106 (0.326)	0.00724 (6.81)	0.0921 - 0.12
ω^2 -VC [-]	$\omega_{2,2}$	0.0651 (0.255)	0.0148 (22.8)	0.0352 - 0.0945
ω^2 -EMAX [-]	$\omega_{3,3}$	0.0709 (0.266)	0.014 (19.7)	0.0461 - 0.104
ω^2 CL: ω^2 VC [-]	$\omega_{1,2}$	0.0316 (0.178)	0.00508 (16.1)	0.022 - 0.0419
		Residual Error		
Proportional [-]	θ_5	0.205	0.00751 (3.66)	0.189 - 0.22
Additive [-]	θ_6	0.194	0.0316 (16.3)	0.0764 - 0.252

[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 (986 runs successful out of a total of 1,000).

[e] CL0, VC, VP, and Q are typical values of CL, VC, VP, and Q at the reference covariate values. Covariate effects were estimated relative to a reference subject with baseline LDH of 200 IU/L and body weight of 80 kg.

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

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

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

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

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

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

$$CL_{TV,i} = CL_{REF} \times \left(e^{CL_{POP1LMESO}}\right)^{POP1LMESO_i}$$

[h] Eta shrinkage: ETA_CL: 11.2%, ETA_VC: 43.6%, ETA_EMAX: 56.5%; Epsilon shrinkage: 19.7%.

[i] The calculated correlation coefficient (r) of the off-diagonal omega was 0.380 for cov(IIV in VC, IIV in CL).

Figure 5.2.1.3-1: Goodness-of-Fit Plots for the Ipilimumab Final Population Pharmacokinetic Model, Overall, and by Population Groups

Overall

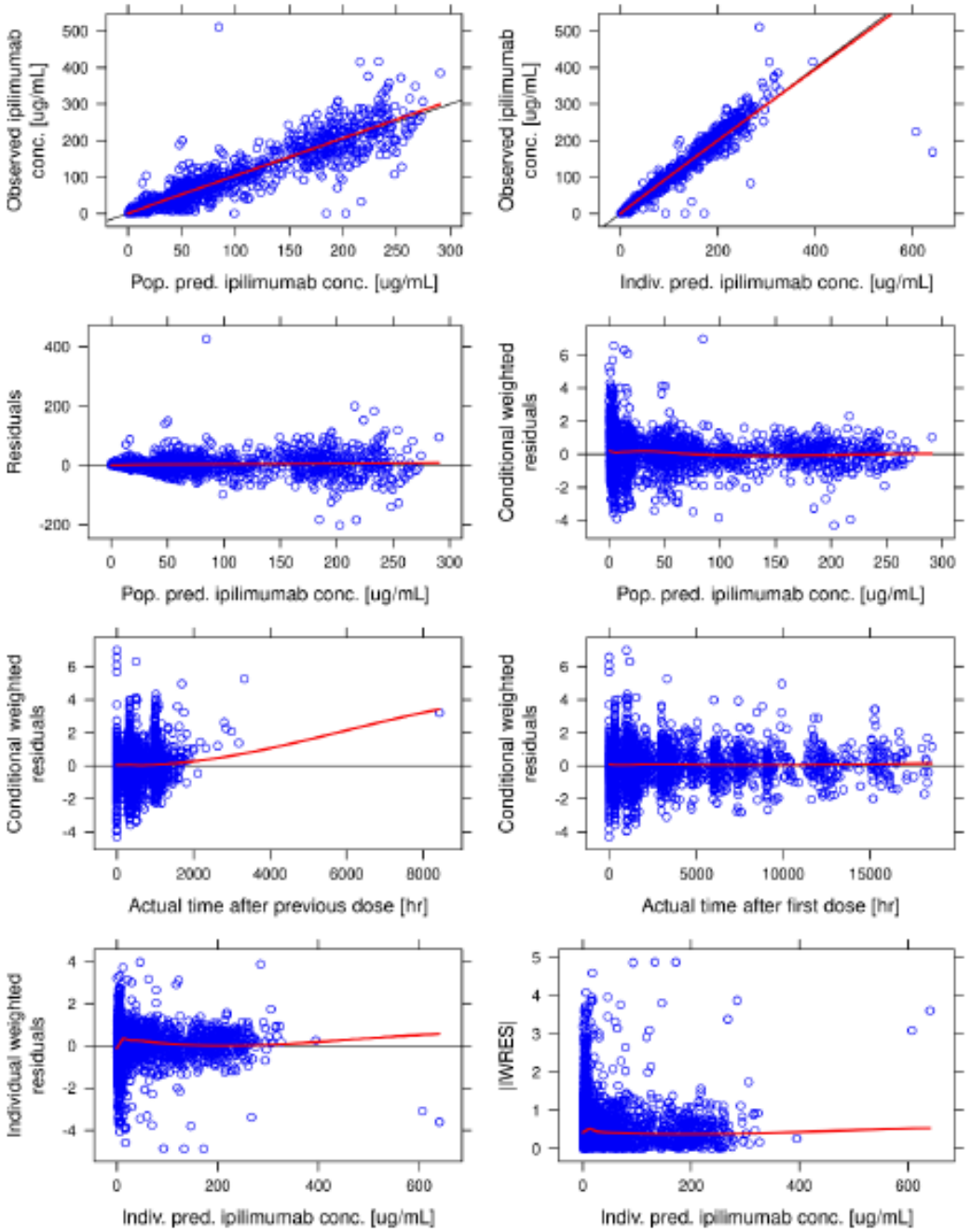
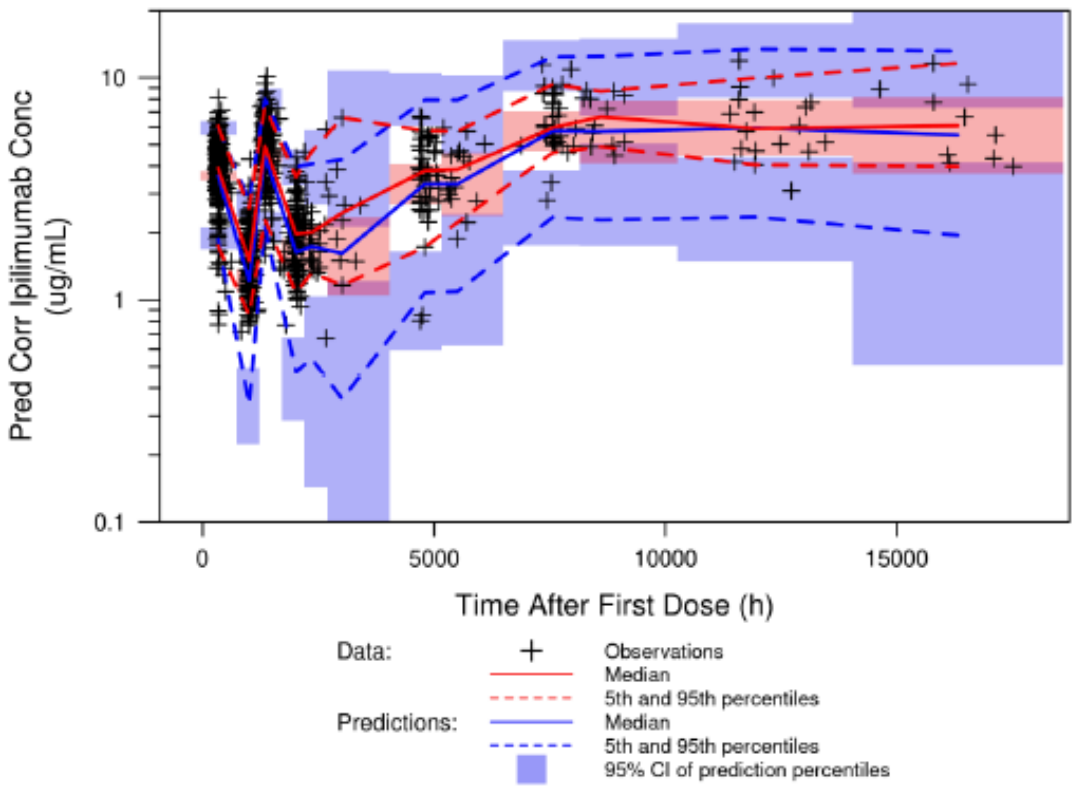


Figure 5.2.2-1: **Prediction-corrected Visual Predictive Check of All Concentrations (Log Scale) Versus Actual Time After First Dose for Data from the 1L ESCC Subject Population Using the Ipilimumab Final Population Pharmacokinetic Model**



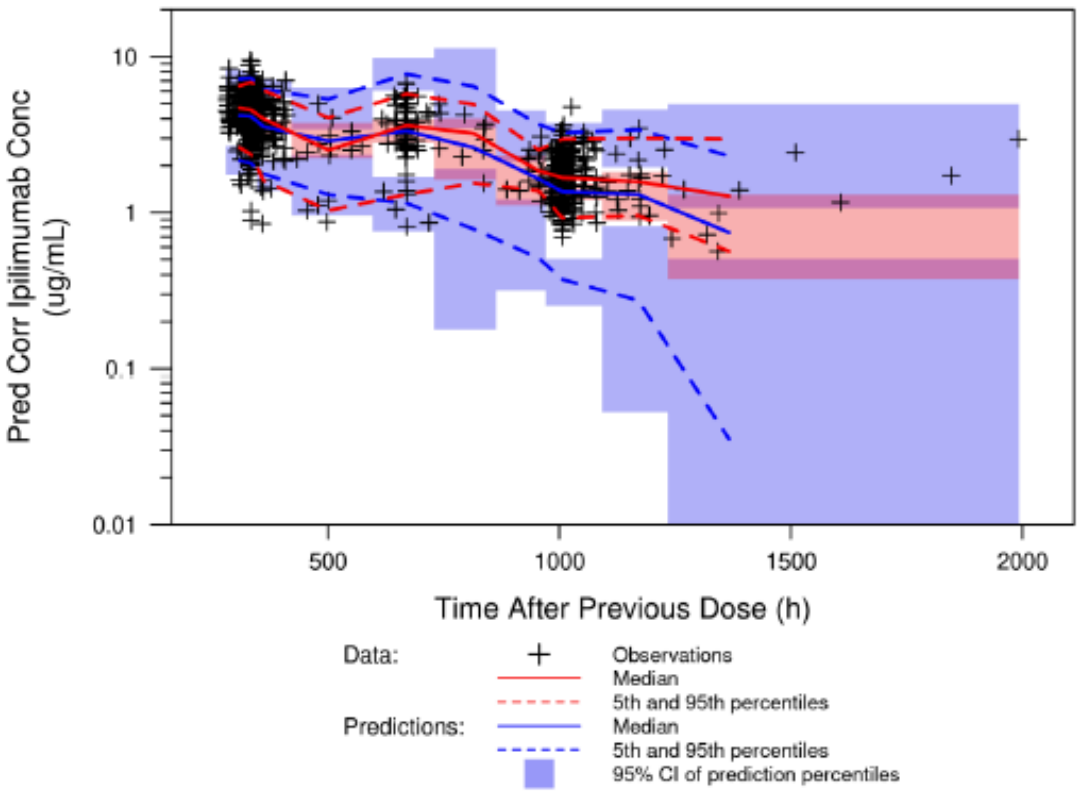
Abbreviations: 1L = first-line; CI = confidence interval; Conc = concentration; ESCC = esophageal squamous cell carcinoma; Pred Corr = prediction corrected.

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

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

Source: Analysis-Directory/d1pk-ipi/graphs/rmd-pnghi/vpc-ipi-s648only-final-02-atafd-001.png

Figure 5.2.2-2: **Prediction-corrected Visual Predictive Check of All Concentrations (Log Scale) Versus Actual Time After Previous Dose for Data from the 1L ESCC Population Using the Ipilimumab Final Population Pharmacokinetic Model**



Abbreviations: 1L = first-line; CI = confidence interval; Conc = concentration; ESCC = esophageal squamous cell carcinoma; Pred Corr = prediction corrected.
Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/
Program Source: Analysis-Directory/d1pk-ipi/R/ipi-cv209648-1l-escc-pmr-tfl-section-5-model-application.Rmd
Source: Analysis-Directory/d1pk-ipi/graphs/rmd-pnghi/vpc-ipi-s648only-final-02-atapd-001.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).

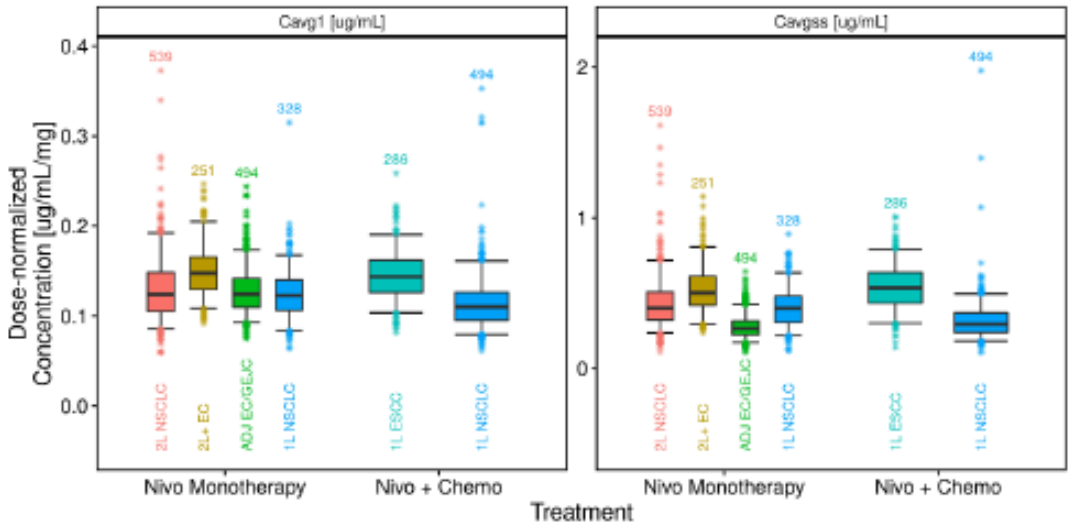
Abbreviations: 1L = first-line; 2L = second-line; Chemo = chemotherapy; CL0 = clearance at time 0; CLss = clearance at steady state; %CV = coefficient of variation expressed as a percentage; EC = esophageal cancer; ESCC = esophageal squamous cell carcinoma; GEJC = gastroesophageal junction cancer; IPI = 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/

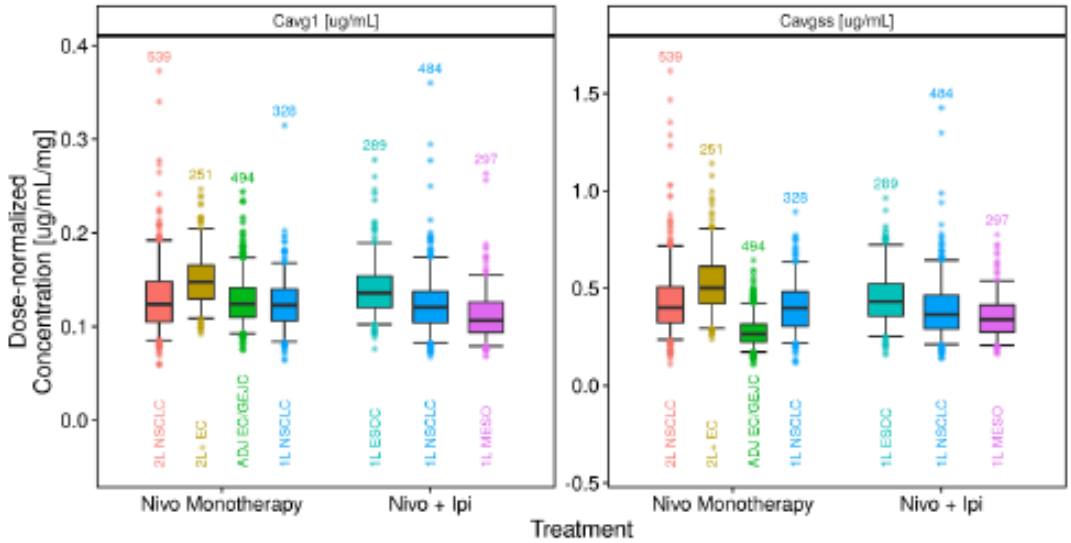
Program Source: Analysis-Directory/d1pk-nivo/R/nivo-cv209648-1l-escc-pmr-tfl-section-5-model-application.Rmd

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/

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/rpt-b-dncavg-by-popn-combo-v02.png and rpt-b-dncavg-by-popn-combo-v03.png

Table 5.2.3.1-1: Summary Statistics (Geometric Mean [%CV]) of Individual Ipilimumab Pharmacokinetic Parameter Estimates by Subject Population and Overall Population in the Population Pharmacokinetic Analysis (n = 1364)

Parameter	Geometric Mean (%CV)				
	Ipi Monotherapy	Nivo+Ipi			All (n = 1364)
	2L+ MEL (n = 327)	1L ESCC (n = 278)	1L NSCLC (n = 464)	1L MESO (n = 295)	
CL0 (mL/h)	15.5 (37.2)	12.8 (31.3)	14.5 (32.7)	17.2 (28)	14.9 (34.2)
CLss (mL/h)	12.3 (39.7)	10.1 (32.5)	11.5 (35.1)	13.5 (32.3)	11.8 (36.6)
Vss (L)	7.88 (15.1)	6.69 (10.9)	7.38 (12.1)	7.51 (14.5)	7.38 (14.3)
T1/2α,ss (h)	48.5 (10.8)	49.1 (2.92)	48.9 (4.26)	47.7 (12.8)	48.6 (8.48)
T1/2β,ss (days)	20.9 (29.5)	21.4 (23.8)	20.8 (26.8)	18.5 (25)	20.4 (27.1)

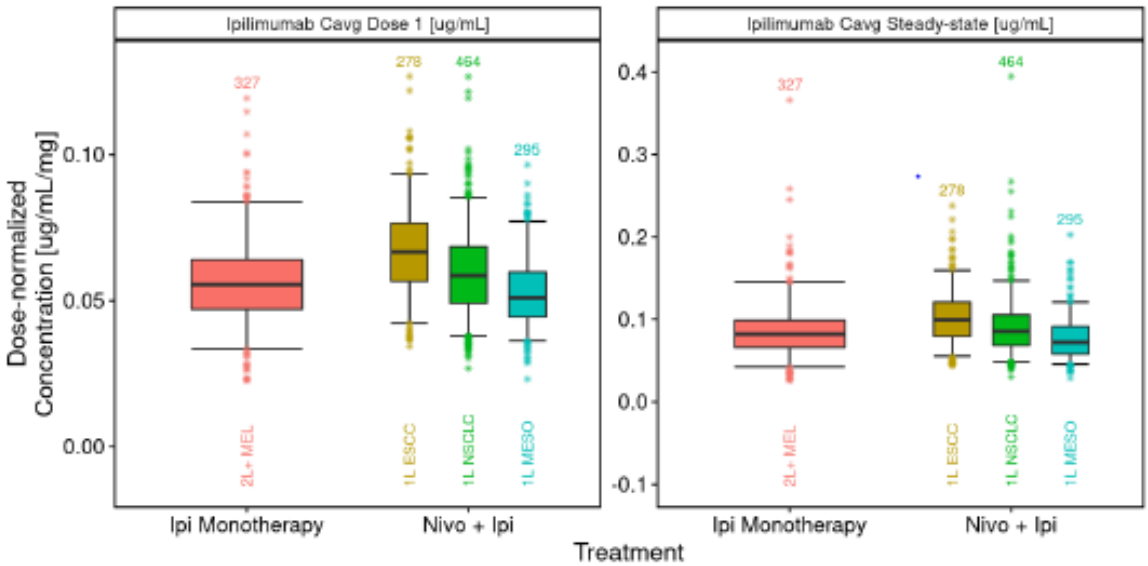
Abbreviations: 1L = first-line; 2L = second-line; CL0 = clearance at time 0; CLss = clearance at steady state; %CV = coefficient of variation expressed as a percent; ESCC = esophageal squamous cell carcinoma; Ipi = ipilimumab; MEL=melanoma; MESO = mesothelioma; n = number of subjects; NSCLC = non-small 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-ipi/R/ipi-cv209648-1l-escc-pmr-tfl-section-5-model-application.Rmd

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

Figure 5.2.3.1-1: Distributions of Dose-normalized Ipilimumab Cavg1 and Cavgss by Subject Populations and by Treatments



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. One 2L+ MEL and one 1L NSCLC subjects with dose-normalized Ipilimumab Cavg Steady-state > 20 were excluded from plot for better visualization.

Abbreviations: 1L = first-line; 2L = second-line; Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; ESCC = esophageal squamous cel carcinoma; Ipi = ipilimumab; MEL=melanoma; MESO = mesothelioma; Nivo = nivolumab; NSCLC = non-smal cell lung cancer.

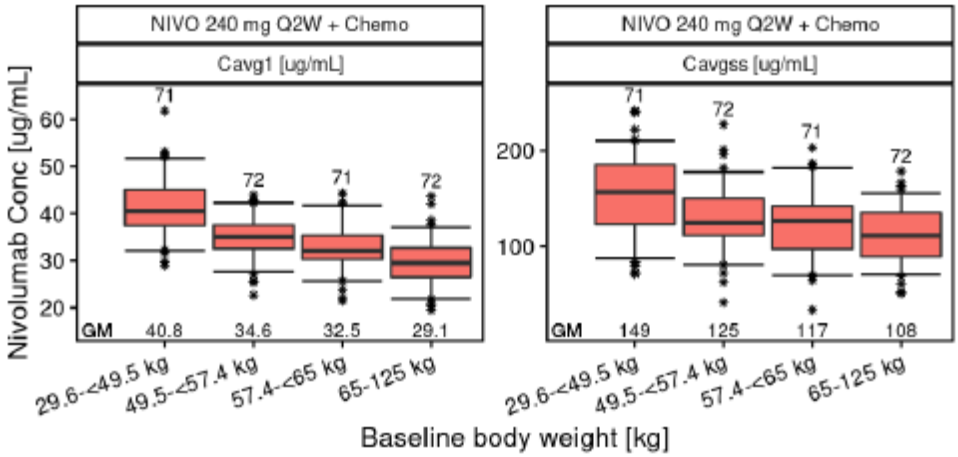
Analysis-Directory: /global/pkms/data/CA/209/ec-1l/prd/cognigen/sd/final/

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.

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

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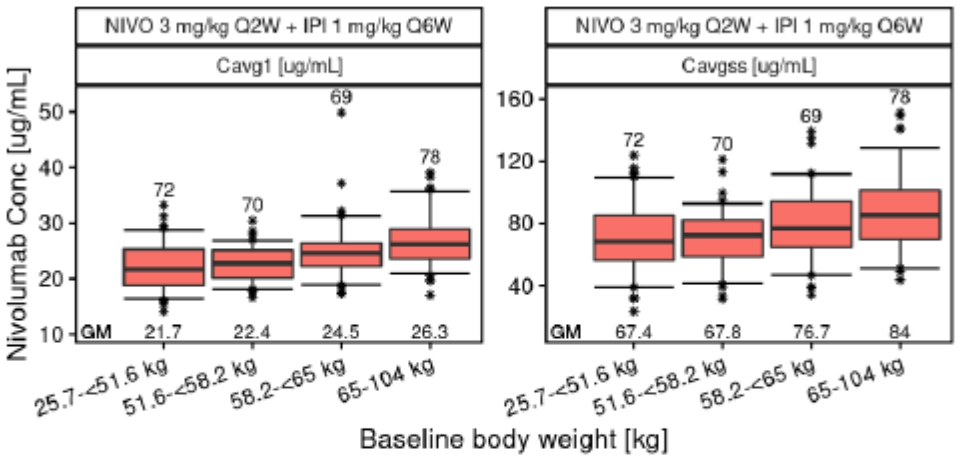
Source: Analysis-Directory/d1pk-nivo/graphs/rmd-pnglo/rpt-b-exp-by-WTQRT-cavg-NIVO240mgQ2WChemo-v01.png

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/

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

Table 5.1.3.2-2: Predicted Exposures for the 5th/95th Percentiles of Body Weight 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 (43.4 kg)	Median (58.2 kg)	P95 (78.9 kg)	% Difference (P05-Median)	% Difference (P95-Median)
Cavg1	20.3	23	26.1	-11.7	13.5
Cmin1	13.1	15	17.2	-12.7	14.7
Cmax1	43.2	48.3	54.2	-10.6	12.2
Cavgss	65.1	75.7	88.4	-14	16.8
Cminss	51.2	60	70.7	-14.7	17.8
Cmaxss	94.4	108	125	-12.6	15.7

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

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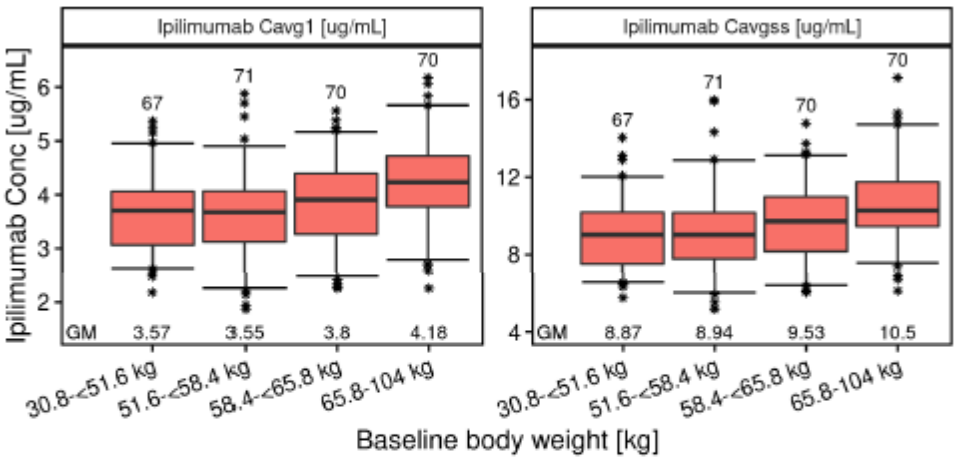
Baseline Body Weight Impact on Ipilimumab Exposure

Figure 5.2.3.2-1: Boxplots of Predicted Ipilimumab Exposures (Cavg1 and Cavgss) by Body Weight Quartiles for 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.

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

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Source: Analysis-Directory/d1pk-ipi/graphs/rmd-pnghi/rpt-b-exp-by-WTQRT-cavg-v01.png

Table 5.2.3.2-1: Predicted Ipilimumab Exposures for the 5th/95th Percentiles of Body Weight for a Typical Subject for the Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W

Exposure	P05 (43.7 kg)	Median (58.4 kg)	P95 (79.1 kg)	% Difference (P05-Median)	% Difference (P95-Median)
Cmax1 [µg/mL]	13.90	16.00	18.40	-13.1	15.0
Cmin1 [µg/mL]	1.13	1.28	1.45	-11.7	13.3
Cavg1 [µg/mL]	3.40	3.87	4.44	-12.1	14.7
Cmaxss [µg/mL]	16.10	18.40	21.20	-12.5	15.2
Cminss [µg/mL]	5.30	6.02	6.87	-12.0	14.1
Cavgss [µg/mL]	8.28	9.42	10.80	-12.1	14.6

Abbreviations: BBWT = baseline body weight; 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; 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/

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

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Baseline LDH Impact on Ipilimumab Exposure

Table 5.2.3.3-1: Predicted Exposures for the 5th/95th Percentiles of Baseline LDH for a Typical Subject in the Nivolumab 3 mg/kg Q2W + Ipilimumab 1 mg/kg Q6W Treatment Group

Exposure	P05 (128 U/L)	Median (197 U/L)	P95 (454 U/L)	% Difference P05-Median	% Difference P95-Median
Cavg1	4.28	4.09	3.78	4.65	-7.58
Cmin1	1.51	1.35	1.10	11.9	-18.5
Cmax1	16.9	16.9	16.9	0.00	0.00
Cavgss	10.4	9.95	9.23	4.52	-7.24
Cminss	6.82	6.36	5.63	7.23	-11.5
Cmaxss	19.8	19.4	18.9	2.06	-2.58

Abbreviations: 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; LDH = lactate dehydrogenase; P05 = 5th percentile; P95 = 95th percentile; Q2W = every 2 weeks; Q6W = every 6 weeks.

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

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Dose recommendations

Nivolumab

Nivolumab Exposures in Subjects with 1L OSCC When Administered as a Flat Dose (240 mg Q2W or 360 mg Q3W) Versus Weight-Based Dosing (3 mg/kg Q2W) In Combination with Ipilimumab

Nivolumab exposures were predicted for subjects with 1L OSCC in Study CA209648 following the nivolumab 3 mg/kg Q2W, 240 mg Q2W, or 360 mg Q3W in combination with ipilimumab treatment

regimens. 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 nivolumab 3 mg/kg Q2W and 240 mg Q2W regimens (Figure 5.1.3.8-1).

The geometric mean (with 90% PI) nivolumab concentration-time profiles in subjects with 1L OSCC for the first 42 days and at steady state are presented for the nivolumab 3 mg/kg Q2W and 360 mg Q3W regimens (Figure 5.1.3.8-2).

The steady-state exposure, including Cminss, Cmaxss, and Cavgss of nivolumab 240 mg Q2W was 37.3% to 38% higher compared to nivolumab 3mg/kg Q2W + ipilimumab dosing regimen. The steady-state exposure of nivolumab 360 mg Q3W was 62.7% higher for Cmaxss, 22.3% higher for Cminss, and 38% for Cavgss compared to nivolumab 3 mg/kg Q2W + ipilimumab dosing regimen.

Table 5.1.3.8-1: Summary of Nivolumab Exposures (Geometric Mean) for Nivolumab 3 mg/kg Q2W, Nivolumab 240 mg Q2W, or Nivolumab 360 mg Q3W in Combination With Ipilimumab 1 mg/kg Q6W in Subjects with 1L ESCC in Study CA209648

Time	Summary Exposure (µg/mL)	Geometric Mean (%CV)			% Difference (G2-G1)[a]	% Difference (G3-G1)[b]
		3 mg/kg Q2W + Ipi (n = 289)	240 mg Q2W + Ipi (n = 289)	360 mg Q3W + Ipi (n = 289)		
Week 0-2	CmaxW2	51.4 (13.7)	70.9 (18.9)	106 (18.9)[c]	37.9	106
	CminW2	15.1 (27.3)	20.8 (27.2)	NA	37.7	NA
	CavgW2	23.7 (17.9)	32.7 (19.7)	NA	38	NA
Week 0-3	CmaxW3	66.7 (15.4)	92.0 (19.3)	106 (18.9)[c]	37.9	58.9
	CminW3	NA	NA	22.8 (34.3)	NA	NA

Table 5.1.3.8-1: Summary of Nivolumab Exposures (Geometric Mean) for Nivolumab 3 mg/kg Q2W, Nivolumab 240 mg Q2W, or Nivolumab 360 mg Q3W in Combination With Ipilimumab 1 mg/kg Q6W in Subjects with 1L ESCC in Study CA209648

Time	Summary Exposure (µg/mL)	Geometric Mean (%CV)			% Difference (G2-G1)[a]	% Difference (G3-G1)[b]
		3 mg/kg Q2W + Ipi (n = 289)	240 mg Q2W + Ipi (n = 289)	360 mg Q3W + Ipi (n = 289)		
	CavgW3	NA	NA	41.7 (21.2)	NA	NA
Week 0-6	CmaxW6	75.5 (17.0)	104 (20.1)	130 (19.4)	37.7	72.2
	CminW6	29.6 (33.4)	40.9 (32.8)	34.2 (38.0)	38.2	15.5
	CavgW6	33.9 (21.7)	46.8 (22.5)	50.1 (23.1)	38.1	47.8
Steady State	Cmaxss	110 (23.6)	151 (25.1)	179 (23.4)	37.3	62.7
	Cminss	56.9 (39.6)	78.5 (39.1)	69.6 (43.3)	38	22.3
	Cavgss	73.9 (31.5)	102 (31.6)	102 (31.6)	38	38

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

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

[c] Equivalent.

Abbreviations: 1L = first-line; Cavgss = time-averaged serum concentration at steady state (2 weeks for Q2W and 3 weeks for Q3W); CavgW2 = average nivolumab concentration over the first dosing interval for Q2W (CavgW2 is equivalent to Cavg1 for Q2W; CavgW2 is not applicable for Q3W); CavgW3 = average nivolumab concentration over the first dosing interval for Q3W and not applicable for Q2W (CavgW3 is equivalent to Cavg1 for Q3W); CavgW6 = average nivolumab concentration over the first 2 dosing interval for Q3W and the first 3 dosing interval for Q2W; Cmaxss = peak serum concentration at steady state; CmaxW2 = maximum nivolumab serum concentration after the first dose (CmaxW2 is equivalent to Cmax1 for Q2W and Q3W); CmaxW3 = maximum nivolumab concentration after the first dose for Q3W and after the second dose for Q2W (CmaxW3 is equivalent to Cmax1 for Q3W; CmaxW2 and CmaxW3 are equivalent for Q3W); CmaxW6 = maximum nivolumab concentration after the second dose for Q3W and after the third dose for Q2W; CminW2 = minimum nivolumab concentration after the first nivolumab dose for Q2W (CminW2 is equivalent to Cmin1 for Q2W; Cminss = trough serum concentration at steady state; CminW2 is not applicable for Q3W); CminW3 = minimum nivolumab concentration after the first nivolumab dose for Q3W and not applicable for Q2W (CminW3 is equivalent to Cmin1 for Q3W); CminW6 = minimum nivolumab concentration after the second nivolumab dose for Q3W and after the third dose for Q2W; %CV = coefficient of variation expressed as a percent; ESCC = esophageal squamous cell carcinoma; Ipi = ipilimumab; n = number of subjects; NA = not applicable; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks.

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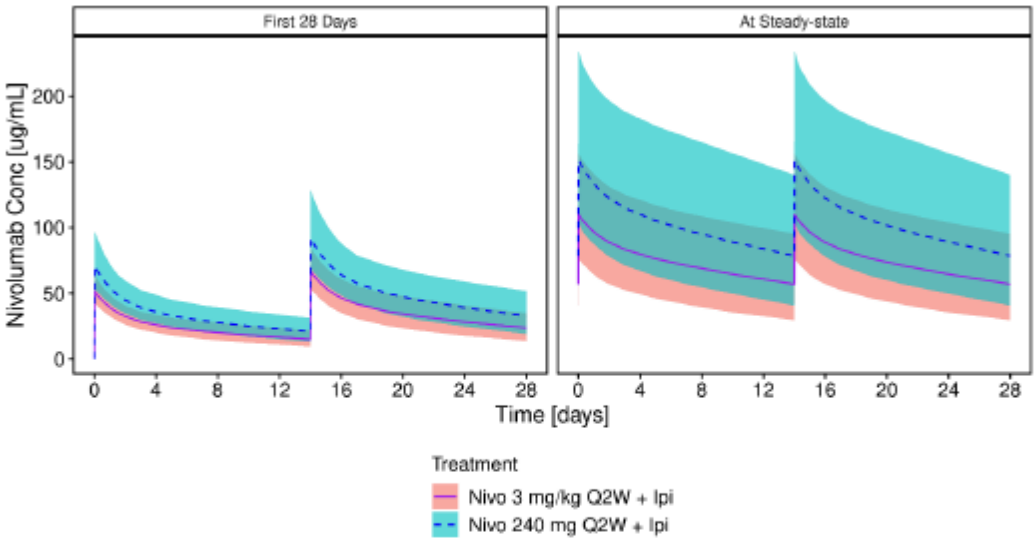
Figure 5.1.3.8-1: Predicted Geometric Mean (90% PI) Nivolumab Concentration-Time Profiles by Dosing Regimens (Nivolumab 3 mg/kg Q2W vs Nivolumab 240 mg Q2W) in Subjects with 1L ESCC



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

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

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

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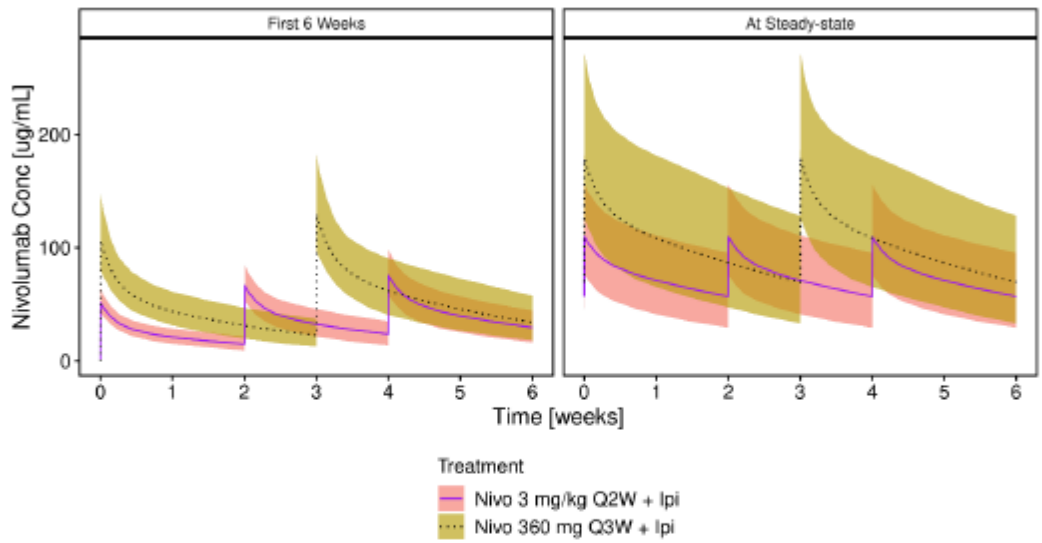
Figure 5.1.3.8-2: Predicted Geometric Mean (90% PI) Nivolumab Concentration-Time Profiles by Dosing Regimens (Nivolumab 3 mg/kg Q2W+Ipilimumab vs Nivolumab 360 mg Q3W+Ipilimumab) in Subjects with 1L ESCC



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

Abbreviations: 1L = first-line; Conc = concentration; ESCC = esophageal squamous cell carcinoma; Ipi = ipilimumab; Nivo = nivolumab; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 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-pnghi/1-cp-time-geomean-ci-3nivoipi-240nivoipi-v01.png

Ipilimumab

Ipilimumab exposures were predicted for subjects with 1L OSCC in Study CA209648 following the ipilimumab 1 mg/kg Q6W, in combination with nivolumab 3 mg/kg Q2W. The predicted concentration-time profiles were used to calculate key summary measures of ipilimumab exposure.

The geometric mean (with 90% PI) ipilimumab concentration-time profiles in subjects with 1L OSCC for the first 12 weeks and at steady state are presented (Figure 5.2.3.7-1).

Table 5.2.3.7-1: Summary Statistics (Geometric Mean [%CV]) of Ipilimumab Exposure in Subjects with 1L ESCC in Study CA209648 (n = 278)

Time	Exposure (µg/mL)	Geometric Mean (%CV)
		Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W
Week 0-6	CmaxW6	16.2 (11.2)
	CminW6	1.18 (52.2)
	CavgW6	3.77 (22.4)
Steady State	Cmaxss	18.8 (14.8)
	Cminss	5.92 (33.0)
	Cavgss	9.44 (22.4)

Abbreviations: 1L = first-line; Cavgss = time-averaged serum concentration at steady state; CavgW6 = average concentration after 2 doses of Q3W regimen or 3 doses of Q2W regimen over the dosing interval of Week 0-6; Cmaxss = steady state maximum nivolumab concentration; CmaxW6 = maximum concentration after the second dose for Q3W regimen or after the third dose for Q2W regimen at Week 0-6; Cminss = steady state minimum nivolumab concentration; CminW6 = minimum concentration after the second dose for Q3W regimen or after the third dose for Q2W regimen at Week 6; %CV = coefficient of variation expressed as a percent; ESCC = esophageal squamous cell carcinoma; Ipi = ipilimumab; n = number of subjects; 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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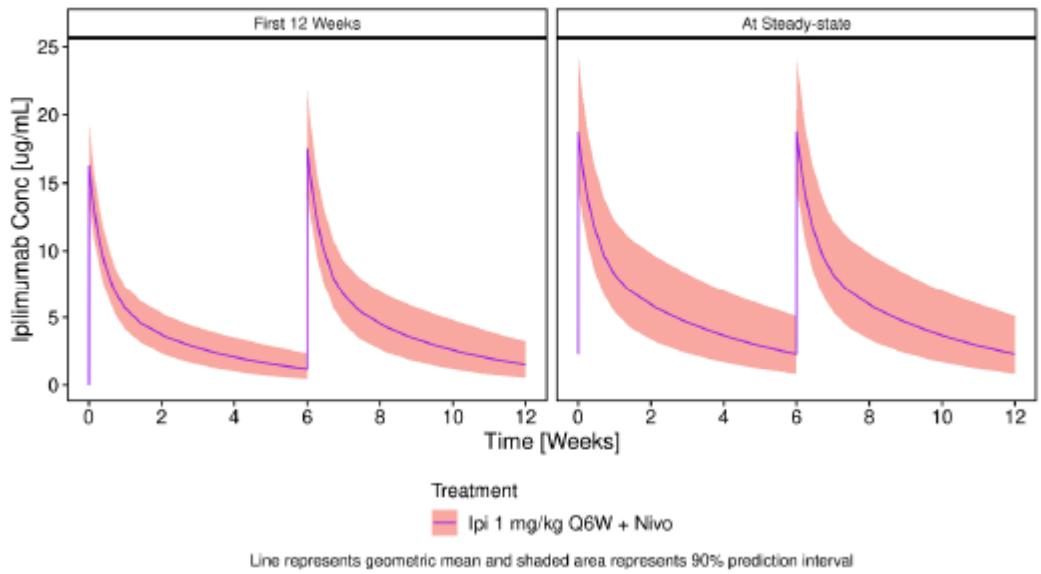
Source: Analysis-Directory/d1pk-ipi/tables/rmd-rtf/sumstat-pk-exp-1mpk-ipi-v01.rtf

Figure 5.2.3.7-1: Predicted Geometric Mean (90% PI) Ipilimumab Concentration-Time Profiles in Subjects with 1L ESCC



2.3.3. 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.

Ipilimumab is a soluble, fully human monoclonal immunoglobulin (IgG1κ) that selectively binds to the cytotoxic T-cell lymphocyte antigen 4 (CTLA-4; CD152) expressed on a subset of T-cells, thereby blocking the interaction between CTLA-4 and B7 molecules on antigen-presenting cells (APCs) and preventing the inhibitory modulation of T-cell activation promoted by such interaction. Ipilimumab monotherapy is currently approved in the US, EU, and several other countries for the treatment of metastatic melanoma and the adjuvant treatment of melanoma and is being investigated across tumor types in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

2.3.4. PK/PD modelling

Exposure-efficacy

E-R Analysis of Efficacy for OS - Nivo+Ipi - Overall Study Population: For the E-R OS model of nivo+ipi vs chemo, both linear and log-linear functional forms of nivolumab and ipilimumab CavgW6 were assessed in the full model for the overall study population. Due to a high correlation ($r > 0.97$) between nivolumab and ipilimumab exposures, ipilimumab CavgW6 was removed from the full model. Ipilimumab treatment was tested and still resulted in a high correlation with nivolumab exposure and was removed from the model. Among the evaluated functional forms of exposure effect, the linear function of nivolumab CavgW6 had the lowest BIC value but did not meet the criteria of a reduction in BIC of at least 2. Therefore, log-linear nivolumab CavgW6 was selected for the full model development.

The interaction between nivolumab CavgW6 and sex and nivolumab CavgW6 and age reduced BIC by 5 and 0.4, respectively. However, the interaction between nivolumab CavgW6 and age was not included in the model due to high correlations. No other significant covariates resulted in an interaction effect with nivolumab CavgW6 that decreased the BIC. Thus, the full model included only the interaction between nivolumab CavgW6 and sex. Figure 3 is a graphical presentation of the estimated effects in the full OS model for nivo+ipi in the overall study population, showing the HRs of OS across the predictor ranges and the associated 95% CIs, relative to the median value (for continuous covariates except CavgW6) or reference group (for categorical covariates). The effect of nivolumab CavgW6 on HR of OS was calculated relative to the chemo-only arm.

In the full model assessment, the relationship between nivolumab CavgW6 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 CavgW6. In male subjects, nivolumab CavgW6 exposures were associated with significantly (95% CI interval excluded 1) lower risk of death than the chemo alone (HR of 0.62 [95% CI: 0.5, 0.76] over chemo [CavgW6 = 0] at the 5th percentile of CavgW6 [CavgW6 = 24 µg/mL], and HR of 0.6 [95% CI: 0.47, 0.75] over chemo at the 95th percentile of CavgW6 [CavgW6 = 48 µg/mL]). In female subjects, nivolumab CavgW6 exposures were associated with lower risk of death than the chemo alone (HR of 0.828 [95% CI: 0.665, 1.03] over chemo [CavgW6 = 0] at the 5th percentile of

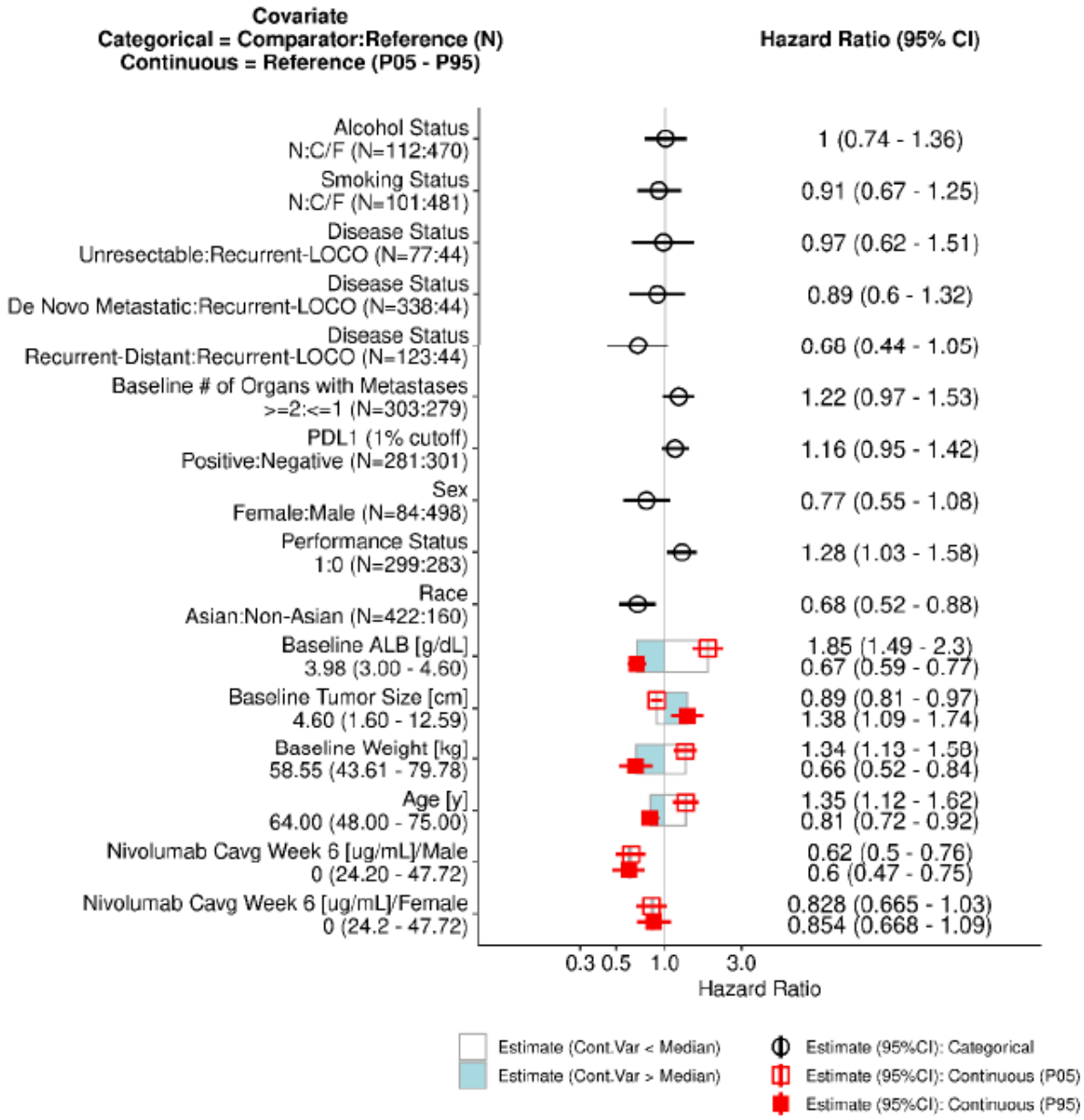
CavgW6 [CavgW6 = 24 µg/mL], and HR of 0.854 [95% CI: 0.668, 1.09] over chemo at the 95th percentile of CavgW6 [CavgW6 = 48 µg/mL]). The E-R relationship was relatively flat across the range of nivolumab CavgW6 in this study as evidenced by the limited range of HRs associated with the 5th and 95th percentiles of nivolumab CavgW6.

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

The continuous variables identified as significant predictors (95% CI of effect did not include 1) on OS in the full model were nivolumab CavgW6, age, baseline weight, baseline tumour size, and baseline ALB. The risk of death increased with higher baseline tumour size (HR of 1.38 [95% CI: 1.09, 1.74] for 95th percentile of baseline tumour size relative to the median), lower baseline weight (HR of 1.34 [95% CI: 1.13, 1.58] for 5th percentile of weight relative to the median weight), younger age (HR of 1.35 [95% CI: 1.12, 1.62] for 5th percentile of age relative to the median age), and lower baseline ALB (HR of 1.85 [95% CI: 1.49, 2.3] 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, sex, tumor PD-L1 1% status, 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. Model-predicted cumulative probabilities of OS using predicted CavgW6 for the nivo 3 mg/kg Q2W+ipi and nivo 360 mg every 3 weeks (Q3W)+ipi as well as the chemo-only arm in Study CA209648 are presented in Figure 4. Both nivolumab-treated regimens showed improved OS compared to the chemo-only group.

Figure 3: **Estimated Covariate Effects of the Exposure-Response of OS (Full Model) in Study CA209648 (Nivo+Ipi) - Overall Study Population**



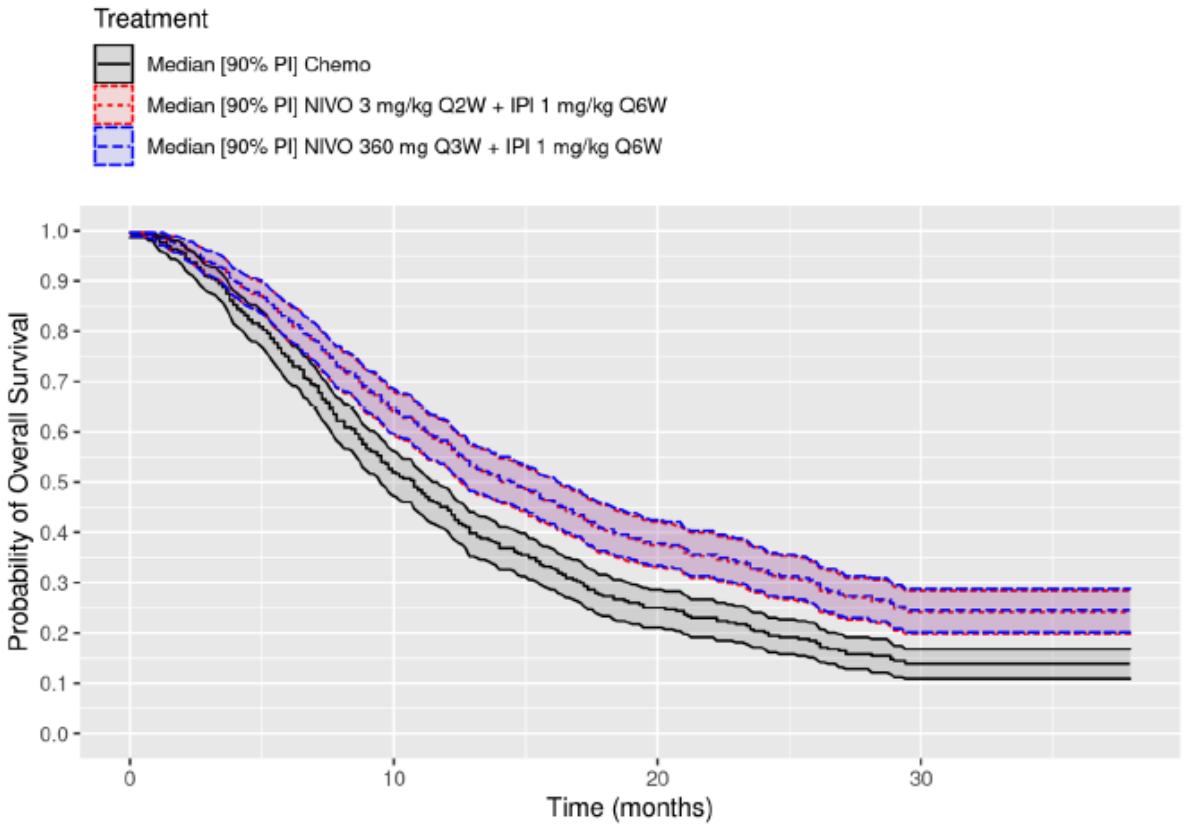
Note: The effect of nivolumab Cavg Week 6 in males was based on the nivolumab Cavg effect alone. The effect of nivolumab Cavg Week 6 in females was based on the nivolumab Cavg effect plus the interaction between nivolumab Cavg and females.

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

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

Figure 4: **Predicted Median [90% PI] Probability of OS Using Simulated CavgW6 from 2 Proposed Dosing Regimens (Nivo 3 mg/kg Q2W or Nivo 360 mg Q3W+Ipi) in Subjects with 1L ESCC in Study CA209648 - Overall Study Population**



Abbreviations: 1L = first-line; CavgW6 = average serum concentration at Week 6; Chemo = chemotherapy; ESCC = esophageal squamous cell carcinoma; Ipi = ipilimumab; Nivo = nivolumab; OS = overall survival; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 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-ni-360vs3mgkg-pi.png

E-R Analysis of Efficacy for OS - Nivo+Ipi - Tumor Cell PD-L1 Expression ≥ 1% Population:
For the E-R OS model of nivo+ipi vs chemo, both linear and log-linear functional forms of nivolumab and ipilimumab CavgW6 were assessed in the full model for the tumor cell PD-L1 expression ≥ 1% population. Due to a high correlation ($r > 0.97$) between nivolumab and ipilimumab exposures, ipilimumab CavgW6 was removed from the full model. Ipilimumab treatment was tested and still resulted in a high correlation with nivolumab exposure and was removed from the model. Among the evaluated functional forms of exposure effect, the linear function of nivolumab CavgW6 had the lowest BIC value but did not meet the criteria of a reduction in BIC of at least 2. Therefore, the log-linear effect of nivolumab CavgW6 was selected for inclusion in the full model. No significant covariates resulted in an interaction effect with nivolumab CavgW6 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 race and sex. The risk of death decreased with female sex and with Asian race.

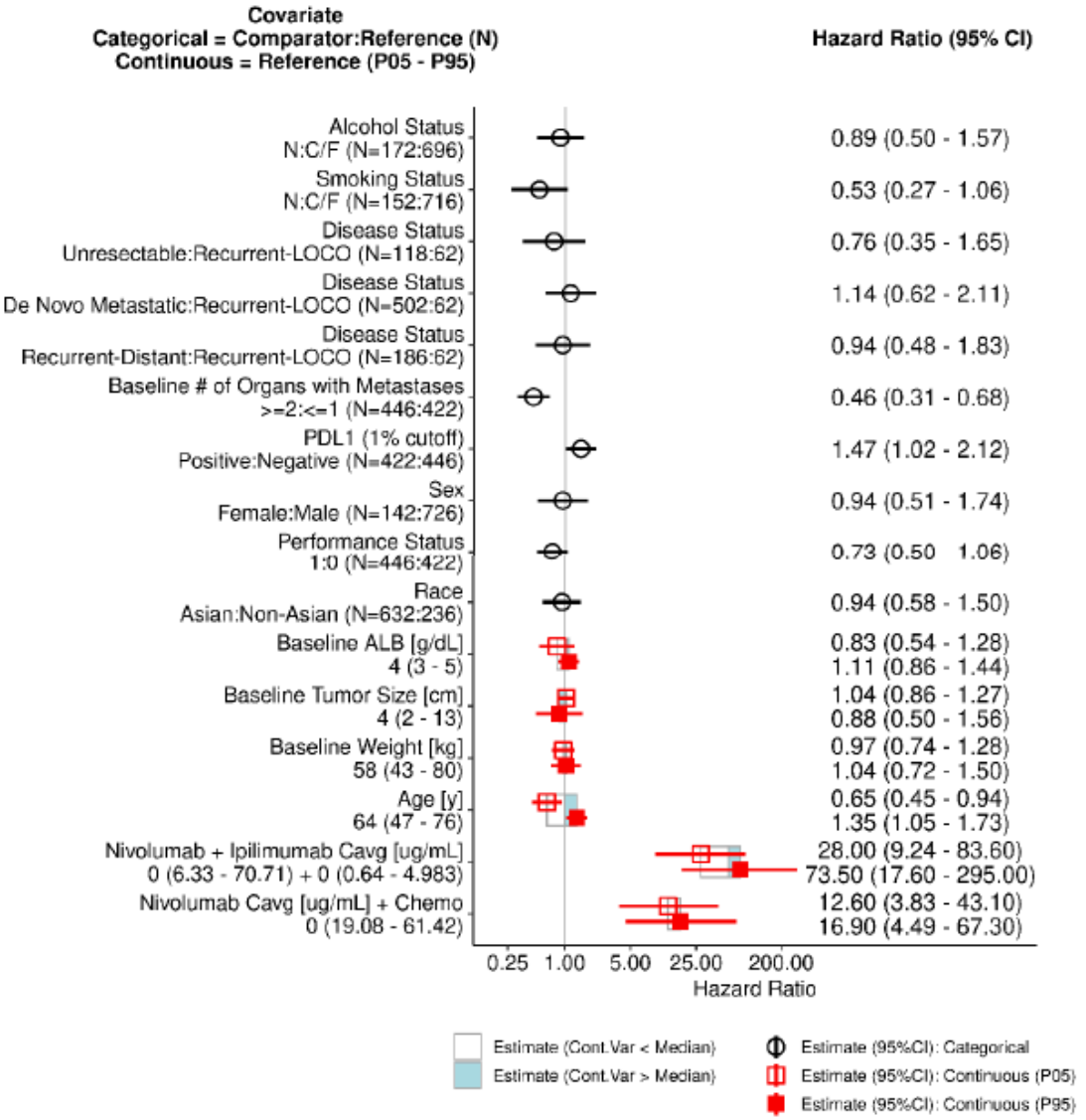
The continuous variables that were identified as significant predictors (95% CI of effect did not include 1) on OS in the full model were nivolumab CavgW6, baseline weight, and baseline ALB. Higher nivolumab CavgW6 exposures were associated with significantly (95% CI interval excluded 1) lower risk of death than the chemo alone (HR of 0.56 [95% CI: 0.42, 0.74] over chemo [CavgW6 = 0] at the 5th percentile of CavgW6 [CavgW6 = 24 µg/mL], and HR of 0.54 [95% CI: 0.4, 0.73] over chemo at the 95th percentile of CavgW6 [CavgW6 = 48 µg/mL]). The risk of death increased with lower baseline weight (HR of 1.34 [95% CI: 1.05, 1.71] for 5th percentile of weight relative to the median weight) and lower baseline ALB (HR of 1.82 [95% CI: 1.39, 2.39] 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 tumor size, PS, 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.

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.

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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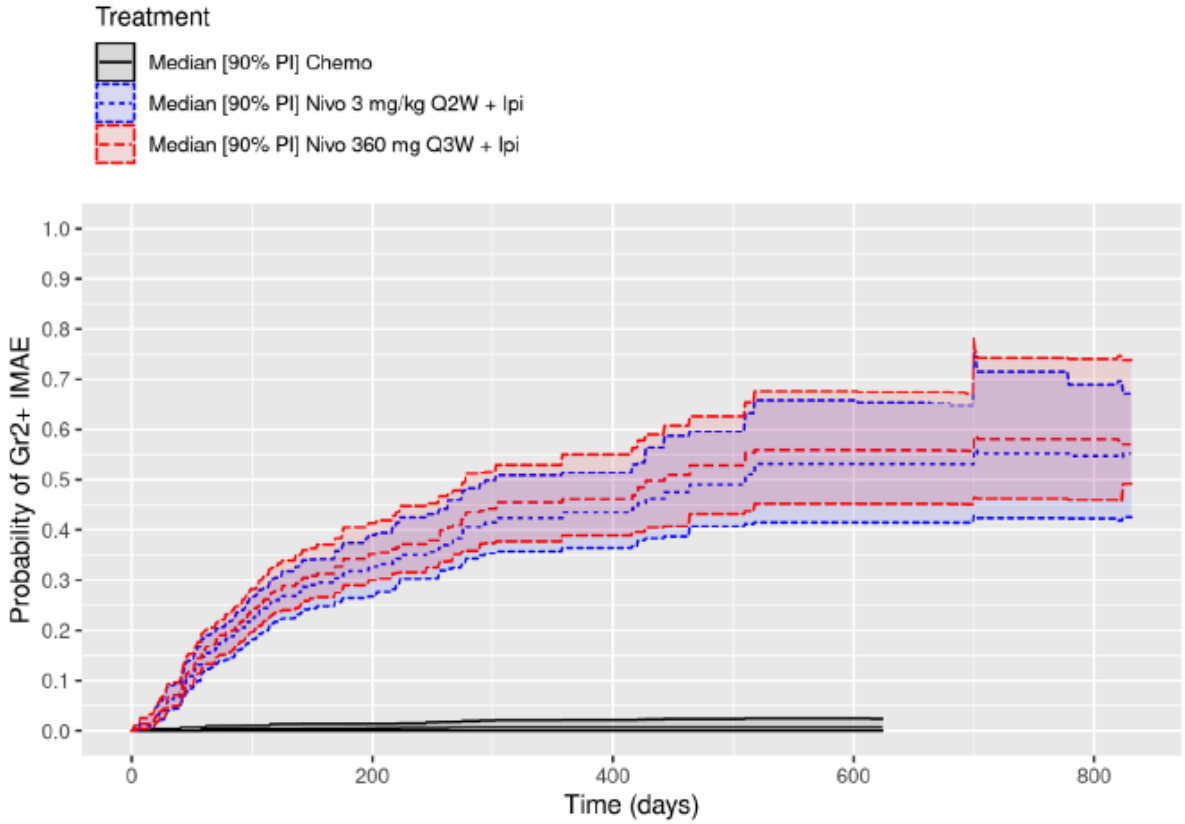
Figure 7: **Predicted Median [90% PI] Probability of Gr2+ IMAEs Using Simulated Nivolumab and Ipilimumab Cavg from 2 Proposed Dosing Regimens (Nivo 3 mg/kg Q2W or Nivo 360 mg Q3W+Ipi) in Subjects with 1L ESCC for Study CA209648 - Overall Study Population**



Abbreviations: 1L = first-line; Cavg = average concentration; Chemo = chemotherapy; ESCC = esophageal squamous cell carcinoma; Gr2+ IMAEs = Grade ≥ 2 immune-mediated adverse events; Ipi = ipilimumab; Nivo = nivolumab; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 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

Source: Analysis-Directory/010063/d1pkpd-saf/graphs/R/saf-model-app-km-pi-ni.png

2.3.5. 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.

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

No clinically relevant changes in ipilimumab exposure were predicted among the covariates tested in OSCC patients, suggesting that there is no need for ipilimumab dose adjustment in special sub-groups of populations.

Dosing regimens

The evaluation of alternative dosing schedules of nivolumab (3 mg/kg Q2W vs. 240 mg Q2W and 3 mg/kg Q2W vs. 360 mg Q3W) in combination with ipilimumab through a model-based approach is appreciated, but should be considered based on the impact in terms of efficacy or safety endpoints, which is unclear especially in patients with extreme baseline body-weight and baseline albumin levels. A clinically relevant increase in exposure at steady-state conditions has been predicted when 240 mg Q2W (37.3% on Cmax,ss, 38% on Cmin,ss, and 38% Cave,ss) and 360 mg Q3W (62.7% on Cmax,ss, 22.3% on Cmin,ss, and 38% Cave,ss).

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+ipilimumab vs. chemo alone arms are selected. The recommendation of nivolumab in combination with ipilimumab seems to be justified in the overall population and tumour cell PD-L1 expression ≥1% population based on the OS and PFS in adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma, although the predicted probability for OS is only slightly improved in the nivo+ipi arm vs. chemotherapy.

Exposure-safety

The exposure-safety evaluation revealed a higher probability of Grade2+ IMAE (50-60%) when nivolumab is co-administered with ipilimumab vs. the chemo group, suggesting a clear higher incidence when ipilimumab is selected vs. chemotherapy. A similar benefit/risk assessment was predicted when a flat dosing regimen (360 mg Q3W) of nivolumab was compared with a body weight regimen of 3 mg/kg Q2W of nivolumab.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of nivolumab+ipilimumab groups were evaluated through the implementation of a previously developed population PK model of nivolumab and ipilimumab, which has been adapted to patients with oesophageal squamous cell carcinoma. The pharmacokinetic characterization seems appropriate based on the evidence provided. The exposure-efficacy and exposure-safety analyses demonstrated the adequacy of the exposure metrics selected to predict the OS/PFS and the incidence of Grade2+ IMAE across the different sub-groups of patients.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

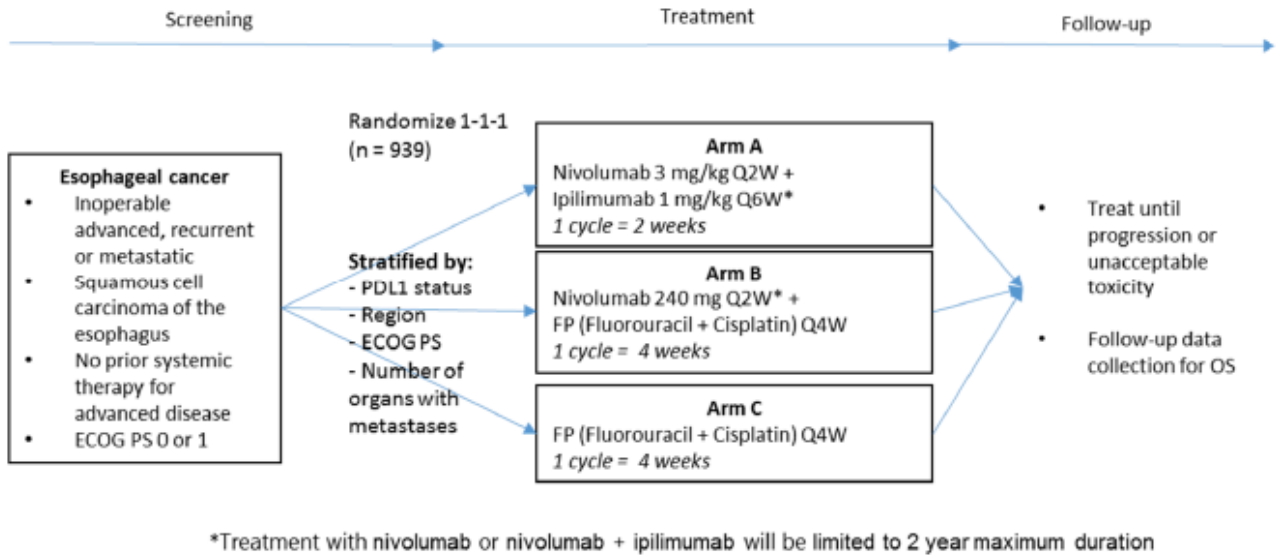
No dose-response studies were submitted as part of this application.

2.4.2. Main study

<u>Study CA209648</u>: 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

<u>Key inclusion criteria</u>

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.

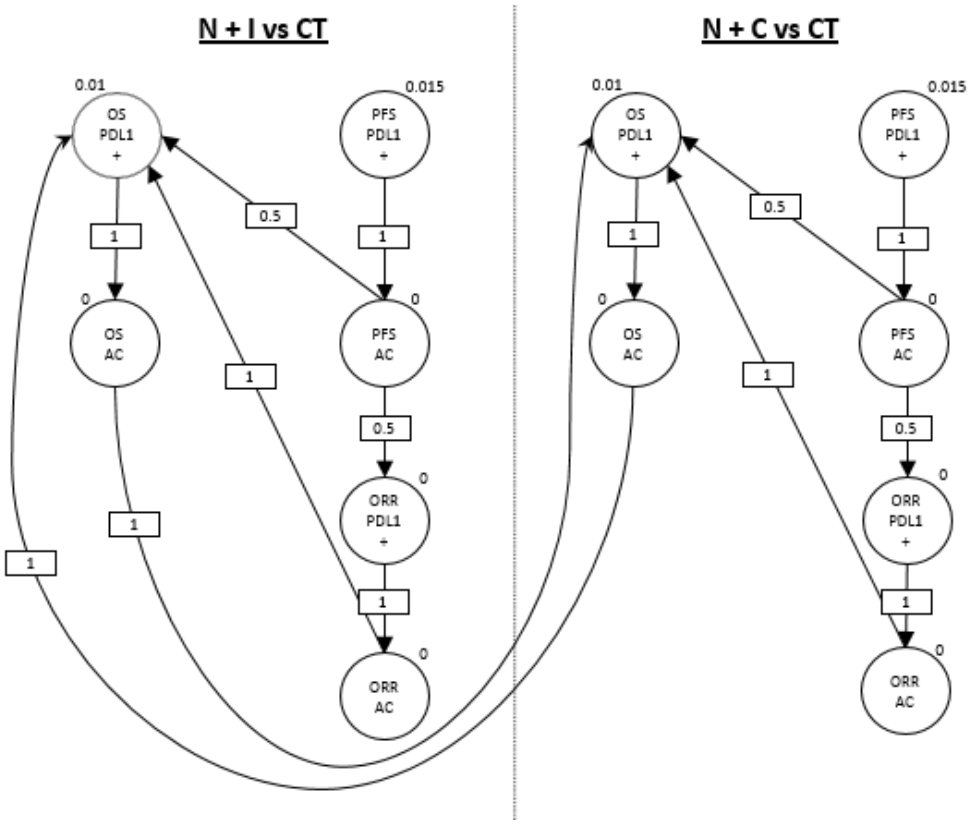
- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IRT
- All Randomized Subjects: All enrolled subjects who were randomized to any treatment arm in the study
- All Treated Subjects: All randomized subjects who received at least one dose of study drug 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 + ipi vs. chemo:

- For PFS: since the primary endpoint of PFS in all randomized subjects with tumor cell PD-L1 expression ≥ 1% was not significant at the 2-sided alpha level 0.015 (p-value: 0.8958), then the PFS and ORR secondary endpoints were not formally tested and no alpha was passed to the PFS/ORR secondary endpoints and OS primary endpoint from the secondary endpoint of PFS in all randomized subjects.
- For OS: the observed number of OS events in all randomized subjects with tumor cell PD-L1 expression ≥ 1% at IA was 227 [90.8% of the target final number of 250 OS events]. With the total overall alpha of 0.02 (initial allocated overall alpha of 0.01 plus 0.01 alpha passed from the secondary OS endpoint in all randomized subjects for nivo + chemo vs. chemo), the

significance level was 0.014 for OS IA in all randomized subjects with tumor cell PD-L1 expression ≥ 1%. Since the primary endpoint of OS was significant at the IA 2-sided alpha level 0.014 (p-value: 0.0010), then the secondary endpoint of OS in all randomized subjects was tested with the overall 2-sided alpha level 0.02. The observed number of OS events in all randomized subjects at IA was 448 [87.2% of the target final number of 514 OS events]. With the overall alpha of 0.02, the significance level was 0.018 for OS IA in all randomized subjects. The secondary endpoint of OS was significant at the IA 2-sided alpha level of 0.018 (p-value: 0.0110). Per testing procedure, the alpha can only be passed in one direction between 2 comparisons, therefore the alpha of 0.02 for OS in nivo + ipi vs. chemo cannot be passed back to OS in nivo + chemo 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 cellPD-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).

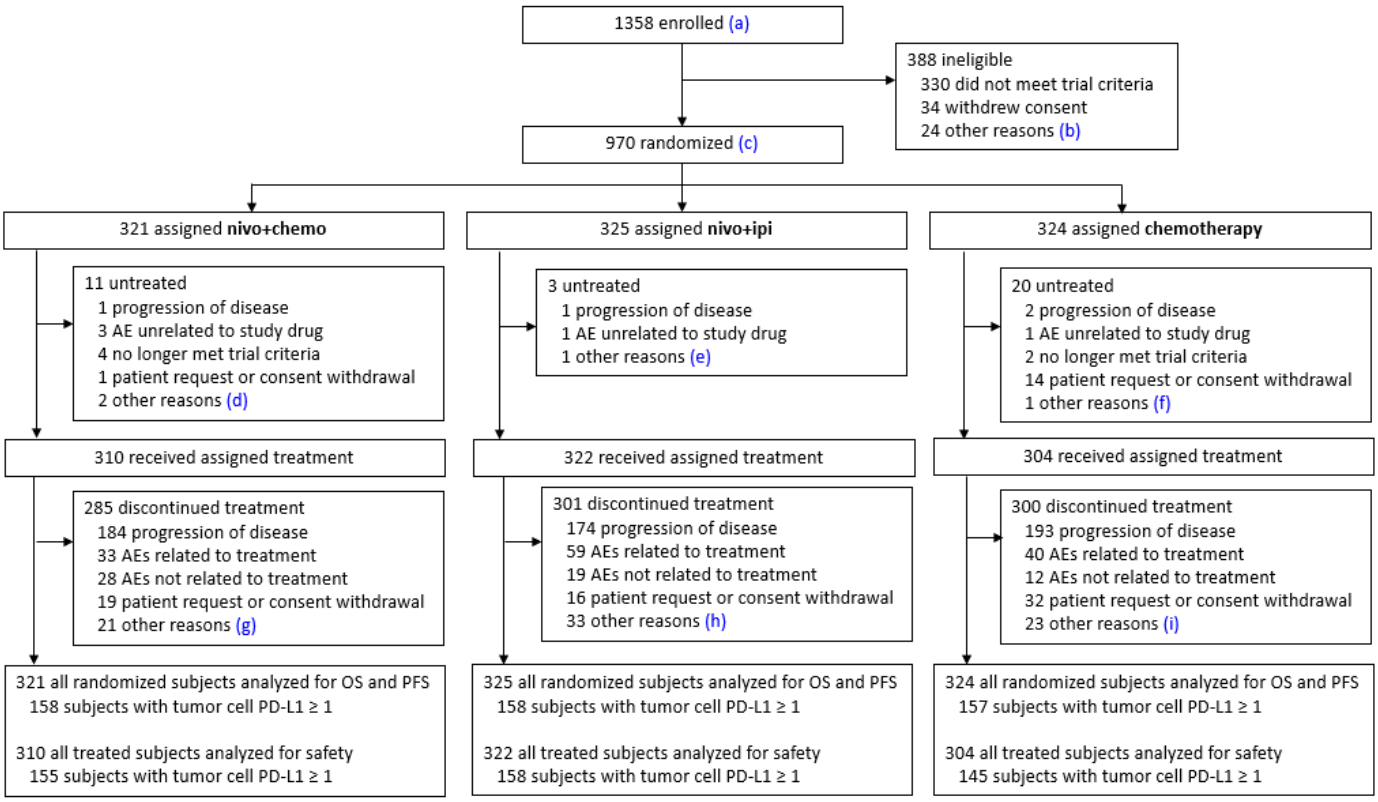
Analysis of PRO

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 P*anax 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 325 subjects in the nivo + ipi arm, 321 subjects in the nivo + chemo arm and 324 subjects in the chemo arm. A total of 936 subjects were treated; this includes 322 subjects in the nivo +ipi arm, 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 oesophageal 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 oesophageal 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 oesophageal 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.	939	316

Document (Amendment) / Date	Summary of Key Global Changes	Planned Sample Size	Total No. of Subjects Randomized Prior to Protocol Revision or Amendment
	• 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. • 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

Protocol Deviation Category	Protocol Deviation	Not randomized	Randomized to Nivo + Chemo	Randomized to Nivo + Ipi	Randomized to Chemo	Total No. of IPDs
	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
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 oesophagus 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)

	Nivo+Ipi N=325	Nivo+Chemo N=321	Chemo N=324	Total N=970
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				
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)

	Nivo+Ipi N=325	Nivo+Chemo N=321	Chemo N=324	Total N=970
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				
< 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 current 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 +Ipilimumab vs. Chemotherapy - All Randomized Subjects with Tumour Cell PD-L1 ≥1% and All Randomized Subjects

	All Randomized Subjects with Tumor Cell PD-L1 ≥1%		**All Randomized Subjects**	
Efficacy Parameter	**Nivo+Ipi N = 158**	**Chemo N = 157**	**Nivo+Ipi N = 325**	**Chemo N = 324**
OS	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	106 (67.1)	121 (77.1)	216 (66.5)	232 (71.6)
HR (alpha-adjusted CI)[a]	0.64 (98.6% CI: 0.46, 0.90)		0.78 (98.2% CI: 0.62, 0.98)	
HR (95% CI)[a]	0.64 (0.49, 0.84)		0.78 (0.65, 0.95)	
Stratified 2-sided log-rank test p-value[b]	0.0010		0.0110	
Median OS, mo (95% CI)[c]	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)	12.75 (11.27, 15.47)	10.71 (9.40, 11.93)
OS Rate (95% CI),[c] %				
At 6 mo.	74.44 (66.84, 80.55)	72.80 (64.83, 79.26)	74.03 (68.85, 78.49)	75.85 (70.65, 80.26)
At 12 mo.	57.11 (48.97, 64.44)	37.07 (29.22, 44.91)	53.50 (47.83, 58.83)	44.32 (38.63, 49.85)
PFS per BICR	**Primary Endpoint**		**Secondary Endpoint**	
Events, n (%)	123 (77.8)	100 (63.7)	258 (79.4)	210 (64.8)
HR (98.5% CI)[a]	1.02 (0.73, 1.43)		1.26 (NA, NA)	
HR (95% CI)[a]	1.02 (0.78, 1.34)		1.26 (1.04, 1.52)	
Stratified 2-sided log-rank test p-value[b]	0.8958		NA	
Median PFS, mo. (95% CI)[c]	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)	2.92 (2.66, 4.17)	5.59 (4.27, 5.88)
PFS Rate (95% CI)[c], %				
At 6-mo.	34.83 (27.26, 42.48)	39.04 (30.07, 47.90)	31.69 (26.50, 37.00)	43.15 (36.96, 49.19)
At 12-mo.	26.40 (19.45, 33.85)	10.45 (4.71, 18.84)	22.70 (17.99, 27.75)	16.02 (11.02, 21.86)
ORR per BICR	**Secondary Endpoint**		**Secondary Endpoint**	
N Responders (%)[d]	56 (35.4)	31 (19.7)	90 (27.7)	87 (26.9)
95% CI	(28.0, 43.4)	(13.8, 26.8)	(22.9, 32.9)	(22.1, 32.0)

	All Randomized Subjects with Tumor Cell PD-L1 ≥1%		All Randomized Subjects	
Efficacy Parameter	**Nivo+Ipi N = 158**	**Chemo N = 157**	**Nivo+Ipi N = 325**	**Chemo N = 324**
ORR Difference (95% CI)[e]	15.7 (5.9, 25.4)		0.9 (-5.9, 7.6)	
Complete Response, n (%)	28 (17.7)	8 (5.1)	36 (11.1)	20 (6.2)
DOR per BICR	**Exploratory Endpoint**		**Exploratory Endpoint**	
n events/N responders (%)	31/56 (55.4)	17/31 (54.8)	53/90 (58.9)	51/87 (58.6)
Median, mo. (95% CI)	11.83 (7.10, 27.43)	5.68 (4.40, 8.67)	11.07 (8.31, 14.00)	7.13 (5.65, 8.21)
Min, Max, mo.	1.4+, 34.5+	1.4+, 31.8+	1.4+, 34.5+	1.4+, 31.8+
Proportion (95% CI)[c] with DOR of:				
≥6 mo.	0.67 (0.52, 0.77)	0.39 (0.19, 0.59)	0.66 (0.55, 0.75)	0.54 (0.41, 0.65)
≥12 mo.	0.49 (0.35, 0.62)	0.13 (0.02, 0.33)	0.48 (0.36, 0.58)	0.23 (0.13, 0.34)
PFS per Investigator	**Exploratory Endpoint**		**Exploratory Endpoint**	
Events, n (%)	127 (80.4)	122 (77.7)	268 (82.5)	249 (76.9)
HR (95.0% CI)[a]	0.83 (0.64, 1.07)		1.01 (0.85, 1.21)	
Median PFS, mo. (95% CI)[c]	4.01 (2.66, 5.42)	4.21 (3.06, 5.39)	3.52 (2.76, 4.24)	5.39 (4.21, 5.68)
PFS Rate (95% CI)[c], %				
At 6 mo.	36.16 (28.64, 43.71)	32.94 (24.95, 41.14)	33.19 (28.03, 38.44)	39.36 (33.52, 45.13)
At 12 mo.	26.25 (19.48, 33.50)	6.24 (2.65, 11.98)	21.94 (17.44, 26.78)	9.52 (6.14, 13.78)
PFS2/TSST per Investigator	**Exploratory Endpoint**		**Exploratory Endpoint**	
Events, n (%)	115 (72.8)	131 (83.4)	239 (73.5)	260 (80.2)
HR (95.0% CI)[a]	0.59 (0.45, 0.76)		0.74 (0.62, 0.88)	
Median PFS, mo. (95% CI)[c]	9.86 (8.48, 12.16)	7.06 (6.54, 7.82)	9.72 (8.48, 11.24)	7.89 (7.13, 8.44)

Stratified Cox proportional hazards model. HR is Nivo + Ipi 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 Tumor Cell PD-L1 ≥1%, and stratified by ECOG PS, number of organs with metastases, and tumor 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+ipi - chemo) based on CMH method of weighting. Stratified by ECOG PS (0 vs 1) and number of organs with metastases (≤1 vs ≥2) per IRT for all randomized subjects with tumor cell PD-L1 ≥1%, and stratified by ECOG PS, number of organs with metastases, and tumor cell PD-L1 expression (≥1% or <1% and indeterminate) per IRT for all randomized subjects.

Symbol + indicates a censored value

Database lock: 01-Mar-2021. Minimum follow-up for OS was 13.1 months.

Primary endpoints

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

At DBL (01-Mar-2021), minimum follow-up for OS among all randomized subjects with tumor cell PD-L1 expression ≥ 1% was 13.1 months.

In all randomized subjects with tumor cell PD-L1 expression ≥ 1%, a statistically significant and clinically relevant improvement in OS was observed with nivo + ipi vs. chemo. The OS HR was 0.64 (98.6% CI: 0.46, 0.90) with a stratified 2-sided log-rank test p-value = 0.0010. Median OS (95% CI) was longer in the nivo + ipi arm compared with the chemo arm: 13.70 (11.24, 17.02) vs. 9.07 (7.69, 9.95) months, with non-overlapping CIs. OS rates (95% CI) in the nivo + ipi vs. chemo arms were as follows:

- At 6 months: 74.44% (66.84, 80.55) vs. 72.80% (64.83, 79.26)
- At 12 months: 57.11% (48.97, 64.44) vs. 37.07% (29.22, 44.91)

The KM curves crossed at approximately 6 months favoring nivo + ipi over chemo, with an increased separation over time.

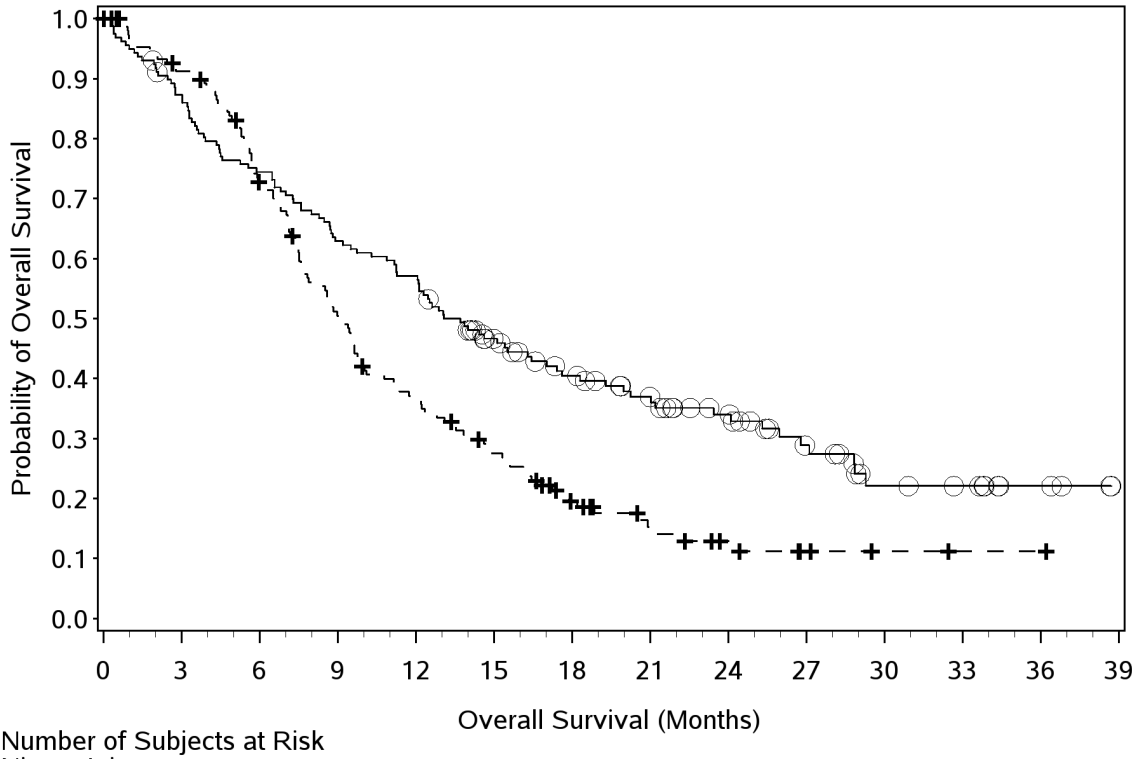
52 (32.9%) subjects in the nivo + ipi arm and 36 (22.9%) subjects in the chemo arm were censored for OS at DBL. Of the censored subjects, 11/52 (21.2%) and 0 subjects in the nivo + ipi and chemo arms, respectively, were continuing on-treatment and 37/52 (71.2%) and 19/36 (52.8%) subjects in the nivo + ipi and chemo arms, respectively, were in follow-up. Of the subjects off study in the nivo + ipi (n = 4) and chemo (n = 17) arms, all 4 of the subjects in the nivo + chemo arm and 15/17 subjects in the chemo arm withdrew consent.

Follow-up for OS was current for the majority of subjects: 98.1% of subjects in the nivo + ipi arm and 89.8% of subjects in the chemo arm either died or had a last known alive date on or after the clinical cutoff 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 = 0.62 (98.6% CI: 0.45, 0.87); 2-sided unstratified log-rank test descriptive p-value = 0.0005.
- Max-combo analysis of OS data: HR = 0.52 (adjusted 95% CI: 0.39, 0.69), descriptive p-value < 0.0001.
- In the *post-hoc analysis* of piecewise HRs for the nivo + ipi vs. chemo comparison, HRs were > 1.00 from study start to 4 months and < 1.00 thereafter. HRs (95% CI) by interval: 1.45 (0.59, 3.54) for 0 to ≤ 2 months, 1.57 (0.51, 4.82) for > 2 to ≤ 3 months, 3.15 (1.02, 9.78) for > 3 to ≤ 4 months, 0.64 (0.21, 1.96) for > 4 to ≤ 5 months, 0.21 (0.06, 0.71) for > 5 to ≤ 6 months, and 0.50 (0.35, 0.69) for > 6 months.
- In a multivariate analysis of OS, the treatment effect of nivo + ipi vs chemo was consistent with the primary OS analysis: HR = 0.62, 95.0% CI: 0.47, 0.82; multivariate Cox model descriptive p-value = 0.0007.

Figure 4: Kaplan-Meier Plot of Overall Survival - Nivolumab + Ipilimumab vs. Chemotherapy - All Randomized Subjects with Tumor Cell PD-L1 ≥1%



Number of Subjects at Risk

Nivo + Ipi	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemotherapy	157	135	105	72	52	36	21	12	8	4	2	1	1	0

Nivo + Ipi (events : 106/158), median and 95% CI : 13.70 (11.24, 17.02)
Chemotherapy (events : 121/157), median and 95% CI : 9.07 (7.69, 9.95)
Nivo + Ipi vs Chemotherapy - hazard ratio (98.6% CI): 0.64 (0.46, 0.90)
Nivo + Ipi vs Chemotherapy - hazard ratio (95% CI): 0.64 (0.49, 0.84)
Stratified log-rank test p-value : 0.0010

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.

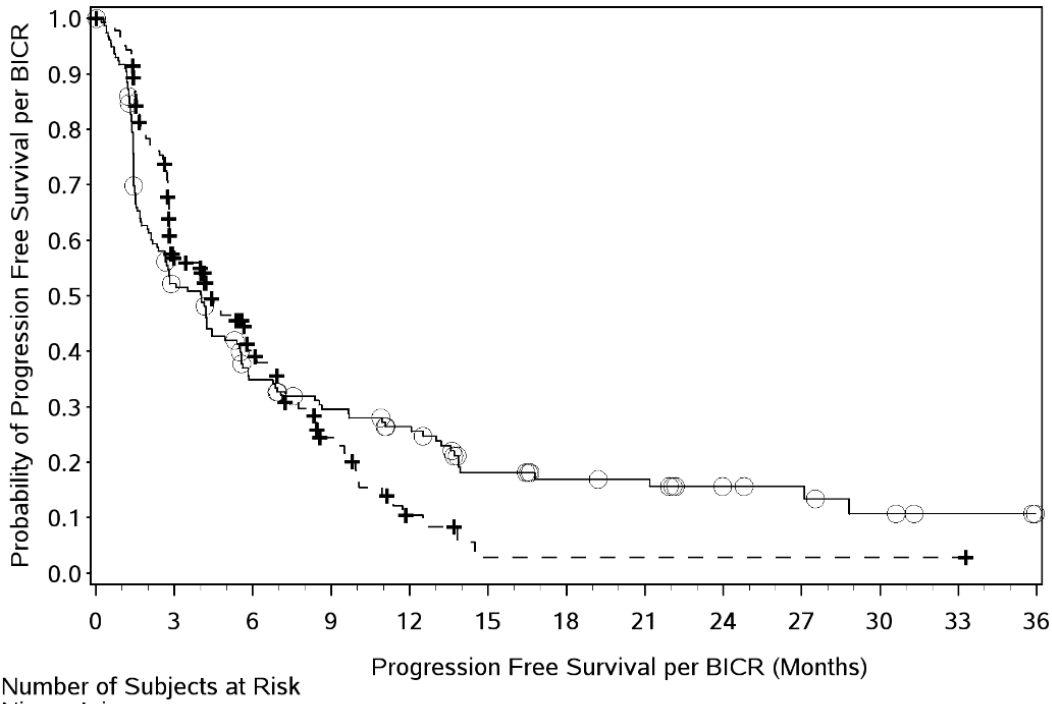
- ***Progression-free Survival*** *per BICR - All Randomized Subjects with Tumour Cell* ***PD-L1 ≥ 1%***

In all randomized subjects with tumor cell PD-L1 expression ≥ 1%, the PFS per BICR (primary definition) results for nivo + ipi vs. chemo did not meet the criteria for statistical significance: HR = 1.02 (98.5% CI: 0.73, 1.43; p = 0.8958). Median PFS per BICR (95% CI) was 4.04 (2.40, 4.93) and 4.44 (2.89, 5.82) months in the nivo + ipi vs. chemo arms, respectively. PFS rates (95% CI) in the nivo + ipi and chemo arms were as follows:

- At 6 months: 34.83% (27.26, 42.48) vs. 39.04% (30.07, 47.90)
- At 12 months: 26.40% (19.45, 33.85) vs. 10.45% (4.71, 18.84)

Results for PFS per BICR accounting for assessment on/after subsequent therapy (ie, including events and disease assessments that occurred on or after subsequent anti-cancer therapy) were as follows: HR = 0.85 (98.5% CI: 0.63, 1.15).

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



Number of Subjects at Risk

Nivo + Ipi	158	78	48	38	31	18	14	13	8	7	4	2	0
Chemotherapy	157	67	35	17	5	1	1	1	1	1	1	1	0

Nivo + Ipi (events : 123/158), median and 95% CI : 4.04 (2.40, 4.93)

Chemotherapy (events : 100/157), median and 95% CI : 4.44 (2.89, 5.82)

Nivo + Ipi vs Chemotherapy - hazard ratio (98.5% CI): 1.02 (0.73, 1.43)

Nivo + Ipi vs Chemotherapy - hazard ratio (95% CI): 1.02 (0.78, 1.34)

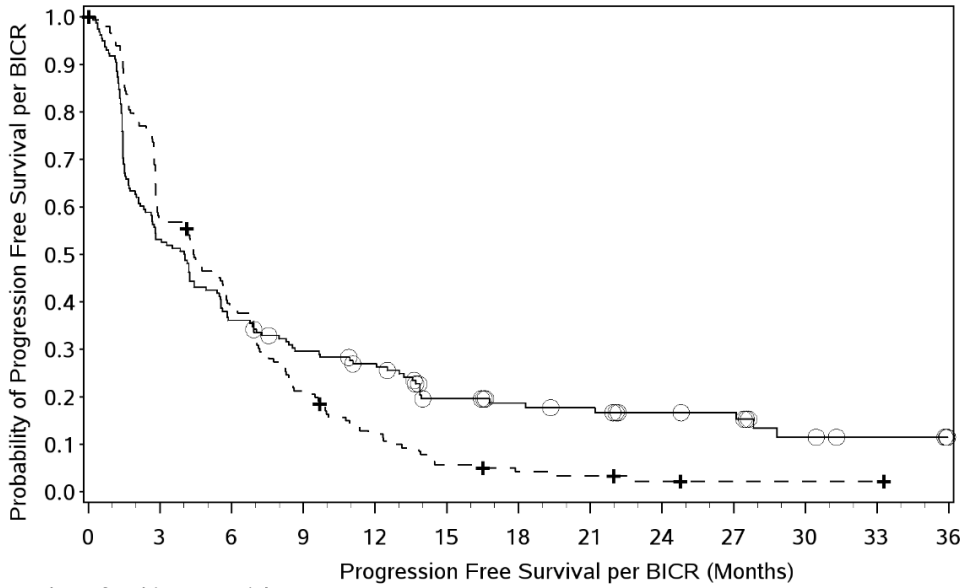
Stratified log-rank test p-value : 0.8958

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 + Ipilimumab over Chemotherapy - Analysis Accounting for Assessment on/after Subsequent Therapy - All Randomized Subjects with Tumor Cell PD-L1 ≥1%



Number of Subjects at Risk

Nivo + Ipi	158	84	57	45	39	24	20	17	13	12	6	4	0
Chemotherapy	157	85	57	31	17	8	5	4	2	1	1	1	0

Nivo + Ipi (events : 131/158), median and 95% CI : 4.02 (2.66, 4.93)
Chemotherapy (events : 142/157), median and 95% CI : 4.40 (2.92, 5.78)
Nivo + Ipi vs Chemotherapy - hazard ratio (98.5% CI): 0.85 (0.63, 1.15)
Nivo + Ipi vs Chemotherapy - hazard ratio (95% CI): 0.85 (0.67, 1.09)
Stratified log-rank test p-value : 0.1879

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 + Ipi 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 + Ipi N = 158	**Chemo**[b] **N = 157**	**Nivo + Ipi N = 158**	**Chemo**[b] **N = 157**
Overall survival				
Events, n (%)	106 (67.1)	121 (77.1)	119 (75.3)	130 (82.8)
Hazard ratio (95% CI)[c]	0.64 (0.49, 0.84)		0.63 (0.49, 0.82)	
Median (95% CI),[d] months	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)	13.700 (11.236, 17.413)	9.068 (7.688, 10.021)

	01-Mar-2021 DBL		04-Oct-2021 DBL[a]	
	Nivo + Ipi N = 158	**Chemo[b] N = 157**	**Nivo + Ipi N = 158**	**Chemo[b] N = 157**
OS Rate (95% CI),[d] %				
At 6 months	74.44 (66.84, 80.55)	72.80 (64.83, 79.26)	74.44 (66.84, 80.55)	73.17 (65.27, 79.55)
At 12 months	57.11 (48.97, 64.44)	37.07 (29.22, 44.91)	57.11 (48.97, 64.44)	37.26 (29.45, 45.06)
At 18 months	-	-	40.92 (33.15, 48.52)	21.09 (14.85, 28.08)
Progression-free survival per BICR				
Events, n (%)	123 (77.8)	100 (63.7)	128 (81.0)	101 (64.3)
Hazard ratio (95% CI)[c]	1.02 (0.78, 1.34)		1.02 (0.77, 1.34)	
Median (95% CI),[d] months	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)	4.041 (2.398, 4.928)	4.435 (2.891, 5.815)
PFS Rate (95% CI),[d] %				
At 6 months	34.83 (27.26, 42.48)	39.04 (30.07, 47.90)	34.83 (27.26, 42.48)	39.58 (30.62, 48.39)
At 12 months	26.40 (19.45, 33.85)	10.45 (4.71, 18.84)	26.45 (19.50, 33.88)	10.30 (4.64, 18.59)
At 18 months	-	-	17.56 (11.67, 24.45)	2.75 (0.27, 11.28)
Objective response rate per BICR,[e] n (%)	56 (35.4)	31 (19.7)	56 (35.4)	31 (19.7)
(95% CI)[e]	(28.0, 43.4)	(13.8, 26.8)	(28.0, 43.4)	(13.8, 26.8)
Complete response	28 (17.7)	8 (5.1)	27 (17.1)	8 (5.1)
Partial response	28 (17.7)	23 (14.6)	29 (18.4)	23 (14.6)
Difference (95% CI),[f] %	15.7 (5.9, 25.4)		15.7 (5.9, 25.4)	
Duration of response per BICR				
Median (95% CI),[d] months	11.83 (7.10, 27.43)	5.68 (4.40, 8.67)	12.649 (7.097, 18.628)	5.684 (4.402, 8.674)
Min, Max,[g] months	1.4+, 34.5+	1.4+, 31.8+	1.4+, 35.8+	1.4+, 40.1+
Proportion (95% CI)[d] with DOR of:				
≥ 6 months	0.67 (0.52, 0.77)	0.39 (0.19, 0.59)	0.67 (0.52, 0.77)	0.39 (0.19, 0.59)
≥ 12 months	0.49 (0.35, 0.62)	0.13 (0.02, 0.33)	0.50 (0.36, 0.63)	0.13 (0.02, 0.33)

Minimum follow-up for 01-Mar-2021 DBL: 13.1 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 + Ipi 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.

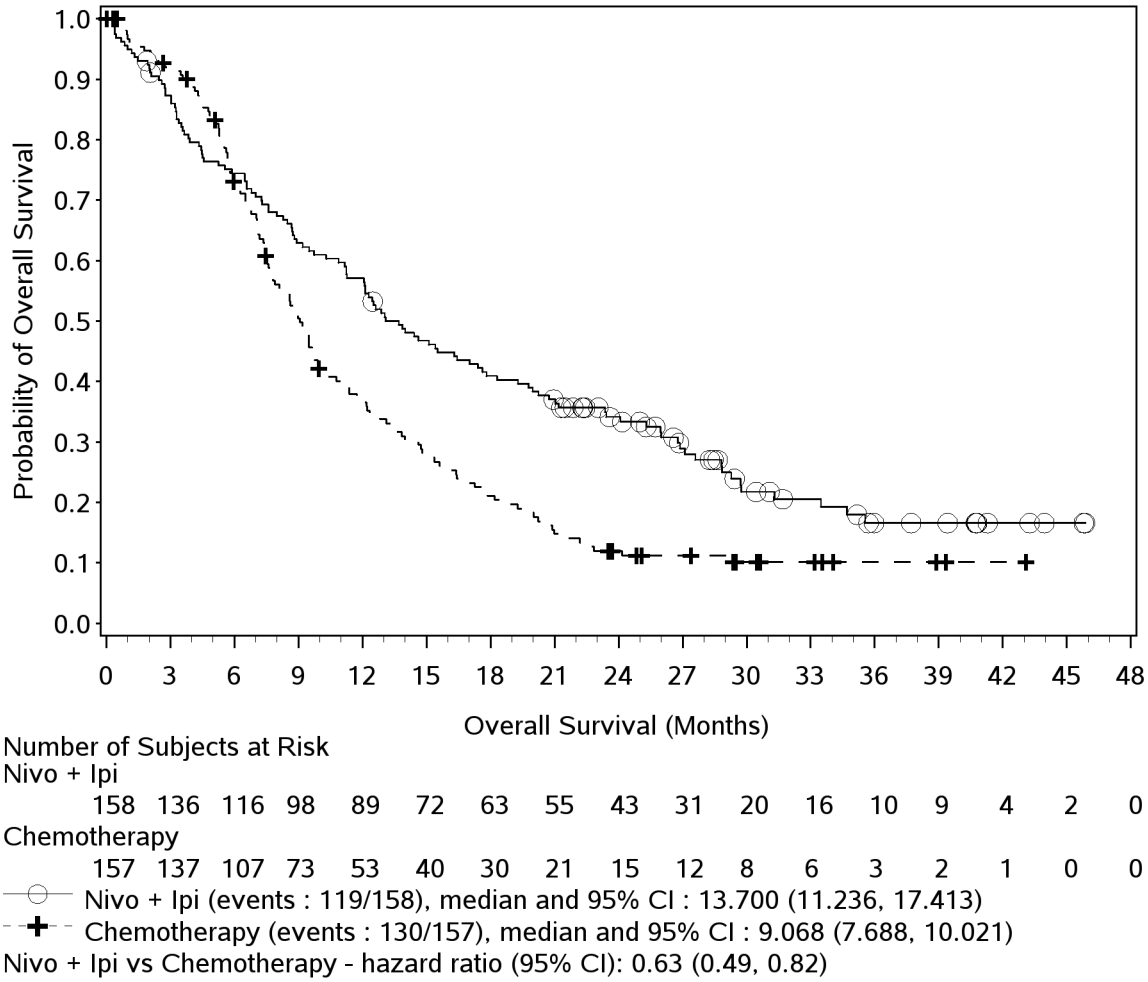
[d] Based on Kaplan-Meier estimates.

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

[f] Strata adjusted difference in objective response rate (Nivo + Ipi - 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

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



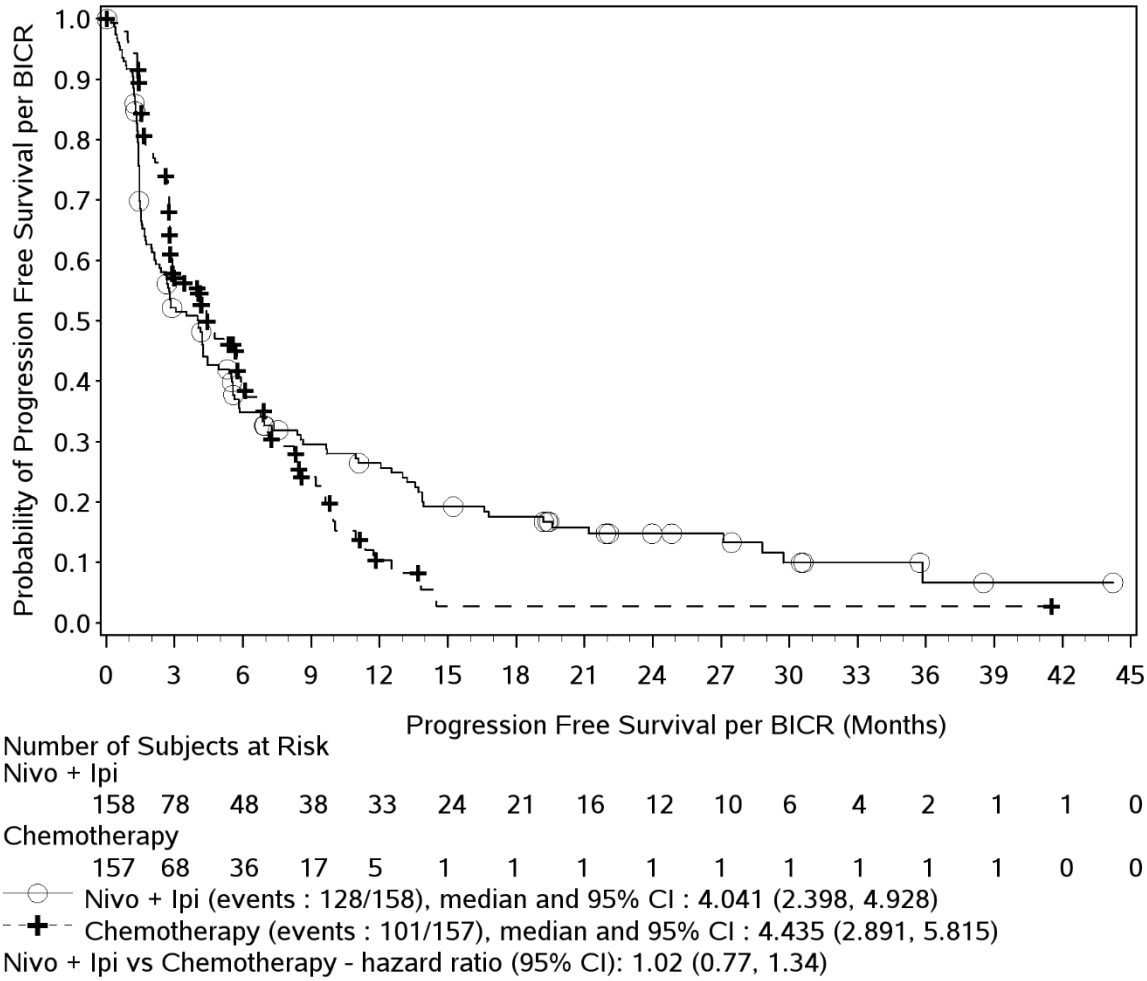
Statistical model for hazard ratio: Stratified Cox proportional hazard model.

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.

Figure 8. Kaplan-Meier Plot of Progression-free Survival per BICR for Nivo + Ipi 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***

A statistically significant improvement in OS was observed for all randomized subjects with nivo + ipi vs. chemo. Minimum follow-up for OS in the nivo + ipi and chemo arms was 13.1 months. The OS HR was 0.78 (98.2% CI: 0.62, 0.98); stratified 2-sided log-rank test p-value = 0.0110. Median OS (95% CI) was approximately 2 months longer in the nivo + ipi arm compared to the chemo arm: 12.75 (11.27, 15.47) vs. 10.71 (9.40, 11.93) months. Landmark OS rates (95% CI) for nivo + ipi vs. chemo were as follows:

- At 6 months: 74.03% (68.85, 78.49) vs. 75.85% (70.65, 80.26)
- At 12 months: 53.50% (47.83, 58.83) vs. 44.32% (38.63, 49.85)

The KM curves for nivo + ipi over chemo crossed at approximately 6.5 months, with an increased separation over time favoring nivo + ipi over chemo.

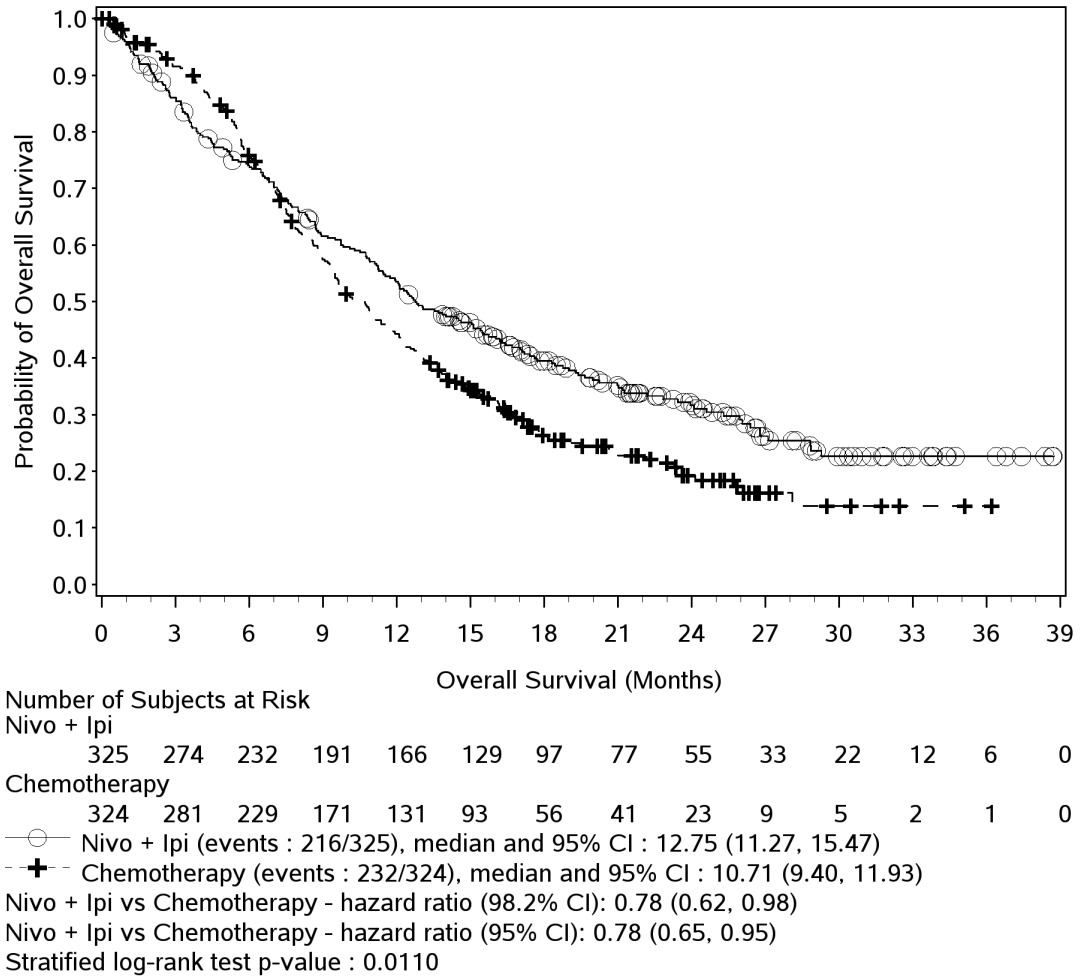
109 (33.5%) subjects in the nivo + ipi arm and 92 (28.4%) subjects in the chemo arm were censored for OS at DBL. Of the censored subjects, 21/109 (19.3%) and 4/92 (4.3%) subjects in the nivo + ipi and chemo arms, respectively, were continuing on-treatment and 72/109 (66.1%) and 57/92 (62.0%) subjects in the nivo + ipi and chemo arms, respectively, were in follow-up. The majority of subjects who were off study in the nivo + ipi (N = 16) and chemo (N = 31) arms, withdrew consent: 10/16 (62.5%) and 27/31 (87.1%), respectively.

Follow-up for OS was current for the majority of subjects: 95.4% of subjects in the nivo + ipi arm and 91.0% of subjects in the chemo arm either died or had a last known alive date on or after the clinical cutoff 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 = 0.78 (98.2% CI: 0.62, 0.98); 2-sided unstratified log-rank descriptive p-value = 0.0088.
- Max-combo analysis of OS data: HR = 0.67 (adjusted 95% CI: 0.55, 0.81), descriptive p-value < 0.0001.
- In the *post-hoc* analysis of piecewise HRs for the nivo + ipi vs chemo comparison, HRs were > 1.00 from study start to 4 months and < 1.00 thereafter. HRs (95% CI) by interval: 2.02 (1.07, 3.82) for 0 to ≤ 2 months, 1.36 (0.64, 2.88) for > 2 to ≤ 3 months, 1.96 (0.94, 4.09) for > 3 to ≤ 4 months, 0.79 (0.33, 1.87) for > 4 to ≤ 5 months, 0.39 (0.18, 0.83) for > 5 to ≤ 6 months, and 0.63 (0.49, 0.79) for > 6 months.
- In a multivariate analysis of OS, the treatment effect of nivo + ipi vs chemo was consistent with the primary OS analysis: HR = 0.77, 95.0% CI: 0.63, 0.93; multivariate Cox model descriptive p value = 0.0064.

Figure 9: Kaplan-Meier Plot of Overall Survival - Nivolumab + Ipilimumab 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% vs. <1% or indeterminate) as recorded in IRT.

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

In all randomized subjects, the HR for PFS per BICR for nivo + ipi vs. chemo was 1.26 (95% CI: 1.04, 1.52). Median PFS per BICR (95% CI) was 2.92 (2.66, 4.17) and 5.59 (4.27, 5.88) months in the nivo + ipi and chemo arms, respectively. PFS rates (95% CI) in the nivo + ipi and chemo arms were as follows, respectively:

- At 6 months: 31.69% (26.50, 37.00) vs. 43.15% (36.96, 49.19)
- At 12 months: 22.70% (17.99, 27.75) vs. 16.02% (11.02, 21.86)

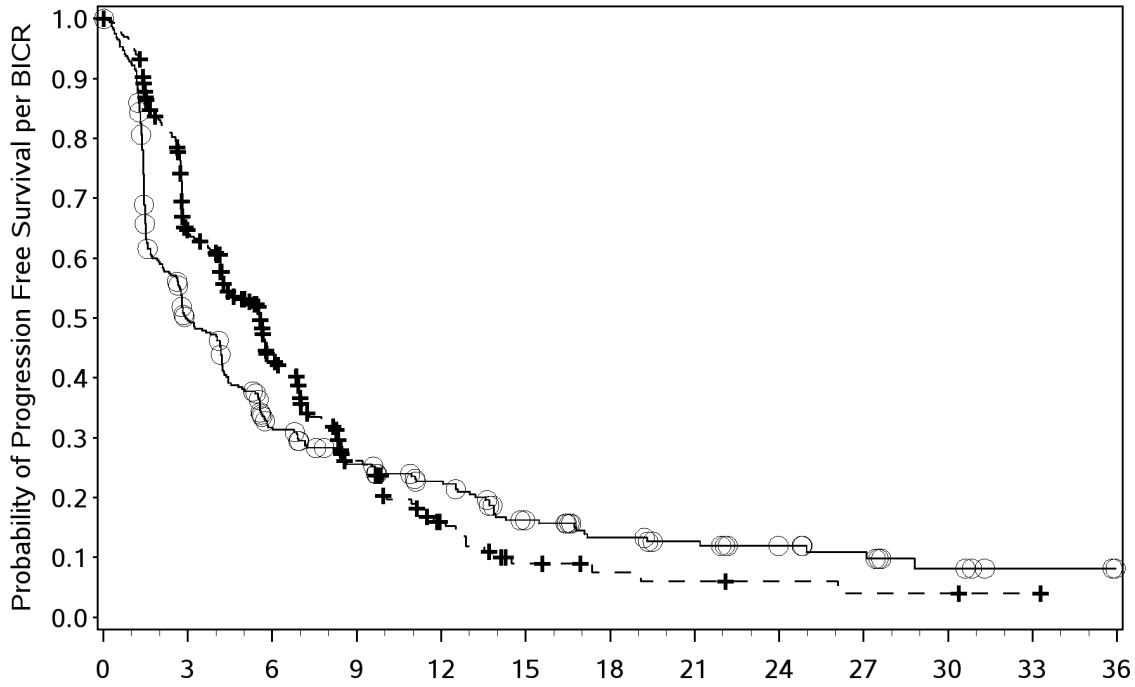
Results for the sensitivity analyses were as follows:

- Max-combo analysis when the proportionality assumption did not hold: HR = 0.81 (adjusted 95% CI: 0.65, 1.01).
- The post-hoc analysis comparing the RMST of PFS per BICR between nivo + ipi and chemo was performed when the proportionality assumption did not hold. Long-term PFS benefit was demonstrated with nivo + ipi vs chemo, with a difference over time favoring nivo + ipi over

chemo: -0.83 (-1.15, -0.51) at 6 months, 0.90 (1.58, -0.22) at 12 months, -0.11 (1.34, 1.11) at 24 months, and 0.35 (1.27, 1.98) at 33.3 months

Results for the PFS analysis accounting for assessment on/after subsequent therapy (ie, including events and disease assessments that occurred on or after subsequent anti-cancer therapy) were as follows: HR =1.09 (95% CI: 0.92, 1.29).

Figure 10: Kaplan-Meier Plot of Progression-Free Survival per BICR - Nivolumab + Ipilimumab vs. Chemotherapy - All Randomized Subjects



Number of Subjects at Risk

Nivo + Ipi	325	149	86	65	52	31	22	18	13	10	5	2	0
Chemotherapy	324	170	90	43	19	8	5	4	3	2	2	1	0

Nivo + Ipi (events : 258/325), median and 95% CI : 2.92 (2.66, 4.17)

Chemotherapy (events : 210/324), median and 95% CI : 5.59 (4.27, 5.88)

Nivo + Ipi vs Chemotherapy - hazard ratio (98.5% CI): N.A.

Nivo + Ipi vs Chemotherapy - hazard ratio (95% CI): 1.26 (1.04, 1.52)

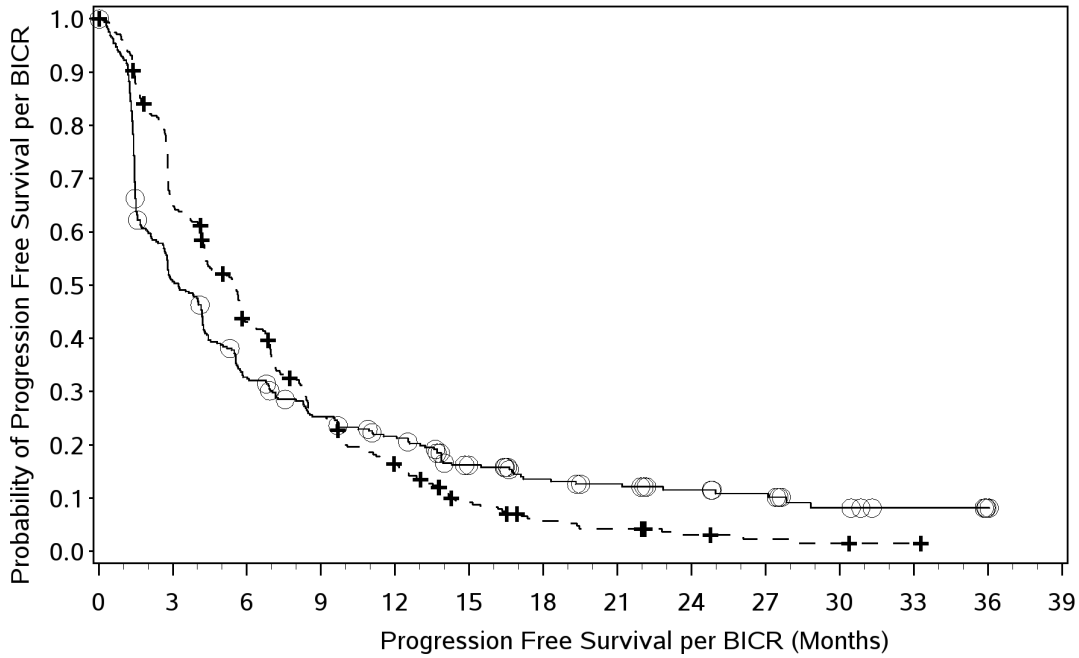
Stratified log-rank test p-value : N.A.

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



Number of Subjects at Risk

Nivo + Ipi	325	162	103	77	63	40	30	24	19	16	8	5	1	0
Chemotherapy	324	200	127	73	45	22	12	9	5	3	2	1	0	0

Nivo + Ipi (events : 279/325), median and 95% CI : 3.22 (2.76, 4.17)
Chemotherapy (events : 284/324), median and 95% CI : 5.55 (4.30, 5.78)
Nivo + Ipi vs Chemotherapy - hazard ratio (95% CI): 1.09 (0.92, 1.29)
Nivo + Ipi vs Chemotherapy - hazard ratio (98.5% CI): N.A.
Stratified log-rank test p-value : N.A.

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 tumor cell PD-L1 expression ≥ 1%, an improvement in BICR-assessed ORR (95% CI) was observed with nivo + ipi vs. chemo, with non-overlapping CIs: 35.4% (28.0, 43.4) vs 19.7% (13.8, 26.8), respectively. CRs per BICR were observed in 28 (17.7%) subjects in the nivo + ipi arm vs. 8 (5.1%) subjects in the chemo arm.

ORR (95% CI) per investigator for nivo + ipi and chemo were comparable to those per BICR 39.9% (32.2, 48.0) and 22.9% (16.6, 30.3).

Table 13: Best Overall Response per BICR - Nivolumab + Ipilimumab over Chemotherapy - All Randomized Subjects with Tumor PD-L1 ≥ 1%

	Number of Subjects (%)	
	Nivo + Ipi N = 158	Chemotherapy N = 157
BEST OVERALL RESPONSE		

COMPLETE RESPONSE (CR)	28 (17.7)	8 (5.1)
PARTIAL RESPONSE (PR)	28 (17.7)	23 (14.6)
STABLE DISEASE (SD)	43 (27.2)	72 (45.9)
PROGRESSIVE DISEASE (PD)	48 (30.4)	24 (15.3)
UNABLE TO DETERMINE (UTD)	11 (7.0)	30 (19.1)
OBJECTIVE RESPONSE RATE (1)	56/158 (35.4%)	31/157 (19.7%)
(95% CI)	(28.0, 43.4)	(13.8, 26.8)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	15.7%	
(95% CI)	(5.9, 25.4)	
(99.25% CI)	N.A.	
ESTIMATE OF ODDS RATIO (3, 4)	2.26	
(95% CI)	(1.35, 3.78)	
(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 + Ipi - 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 + Ipi 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, BICR-assessed ORR (95% CI) was similar in the nivo + ipi and chemo arms: 27.7% (22.9, 32.9) vs. 26.9% (22.1, 32.0). CRs by BICR were observed in 36 (11.1%) subjects treated with nivo + ipi and 20 (6.2%) subjects treated with chemo.

ORRs (95% CI) per investigator for nivo + ipi (31.1%; 26.1, 36.4) and chemo (28.7%; 23.8, 34.0) were comparable to those per BICR.

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

	Number of Subjects (%)	
	Nivo + Ipi N = 325	Chemotherapy N = 324
BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	36 (11.1)	20 (6.2)
PARTIAL RESPONSE (PR)	54 (16.6)	67 (20.7)
STABLE DISEASE (SD)	103 (31.7)	148 (45.7)
PROGRESSIVE DISEASE (PD)	103 (31.7)	38 (11.7)
UNABLE TO DETERMINE (UTD)	29 (8.9)	51 (15.7)
OBJECTIVE RESPONSE RATE (1)	90/325 (27.7%)	87/324 (26.9%)
(95% CI)	(22.9, 32.9)	(22.1, 32.0)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	0.9%	
(95% CI)	(-5.9, 7.6)	
(99.25% CI)	N.A.	
ESTIMATE OF ODDS RATIO (3, 4)	1.04	
(95% CI)	(0.74, 1.47)	
(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 + Ipi - 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 + Ipi 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 + Ipi 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 + Ipi N = 325	**Chemo[b] N = 324**	**Nivo + Ipi N = 325**	**Chemo[b] N = 324**
Overall survival				
Events, n (%)	216 (66.5)	232 (71.6)	236 (72.6)	250 (77.2)
Hazard ratio (95% CI)[c]	0.78 (0.62, 0.98)		0.77 (0.65, 0.93)	
Median (95% CI),[d] months	12.75 (11.27, 15.47)	10.71 (9.40, 11.93)	12.813 (11.269, 15.507)	10.710 (9.363, 11.926)
OS Rate (95% CI),[d] %				
At 6 months	74.03 (68.85, 78.49)	75.85 (70.65, 80.26)	74.06 (68.89, 78.51)	76.01 (70.83, 80.39)
At 12 months	53.50 (47.83, 58.83)	44.32 (38.63, 49.85)	53.66 (48.00, 58.98)	44.36 (38.69, 49.87)
At 18 months	-	-	39.96 (34.51, 45.34)	27.54 (22.61, 32.69)
Progression-free survival per BICR				
Events, n (%)	258 (79.4)	210 (64.8)	266 (81.8)	214 (66.0)
Hazard ratio (95% CI)[c]	1.26 (1.04, 1.52)		1.24 (1.03, 1.50)	
Median (95% CI),[d] months	2.92 (2.66, 4.17)	5.59 (4.27, 5.88)	2.924 (2.661, 4.172)	5.618 (4.271, 5.914)
PFS Rate (95% CI),[d] %				
At 6 months	31.69 (26.50, 37.00)	43.15 (36.96, 49.19)	31.69 (26.50, 37.00)	43.61 (37.43, 49.61)
At 12 months	22.70 (17.99, 27.75)	16.02 (11.02, 21.86)	22.73 (18.03, 27.78)	16.41 (11.39, 22.23)
At 18 months	-	-	14.25 (10.32, 18.79)	7.99 (4.18, 13.38)
Objective response rate per BICR,[e] n (%)	90 (27.7)	87 (26.9)	90 (27.7)	86 (26.5)
(95% CI)[e]	(22.9, 32.9)	(22.1, 32.0)	(22.9, 32.9)	(21.8, 31.7)
Complete response	36 (11.1)	20 (6.2)	36 (11.1)	20 (6.2)
Partial response	54 (16.6)	67 (20.7)	54 (16.6)	66 (20.4)
Difference (95% CI),[f %]	0.9 (-5.9, 7.6)		1.2 (-5.6, 7.9)	
Duration of response per BICR				
Median (95% CI),[d] months	11.07 (8.31, 14.00)	7.13 (5.65, 8.21)	11.072 (8.312, 14.259)	7.129 (5.651, 8.214)
Min, Max,[g] months	1.4+, 34.5+	1.4+, 31.8+	1.4+, 35.8+	1.4+, 40.1+
Proportion (95% CI)[d] with DOR of:				
≥ 6 months	0.66 (0.55, 0.75)	0.54 (0.41, 0.65)	0.67 (0.56, 0.76)	0.54 (0.41, 0.65)

	01-Mar-2021 DBL		04-Oct-2021 DBL[a]	
	Nivo + Ipi N = 325	Chemo[b] N = 324	Nivo + Ipi N = 325	Chemo[b] N = 324
≥ 12 months	0.48 (0.36, 0.58)	0.23 (0.13, 0.34)	0.49 (0.37, 0.59)	0.23 (0.13, 0.34)

Minimum follow-up for 01-Mar-2021 DBL: 13.1 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 + Ipi 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.

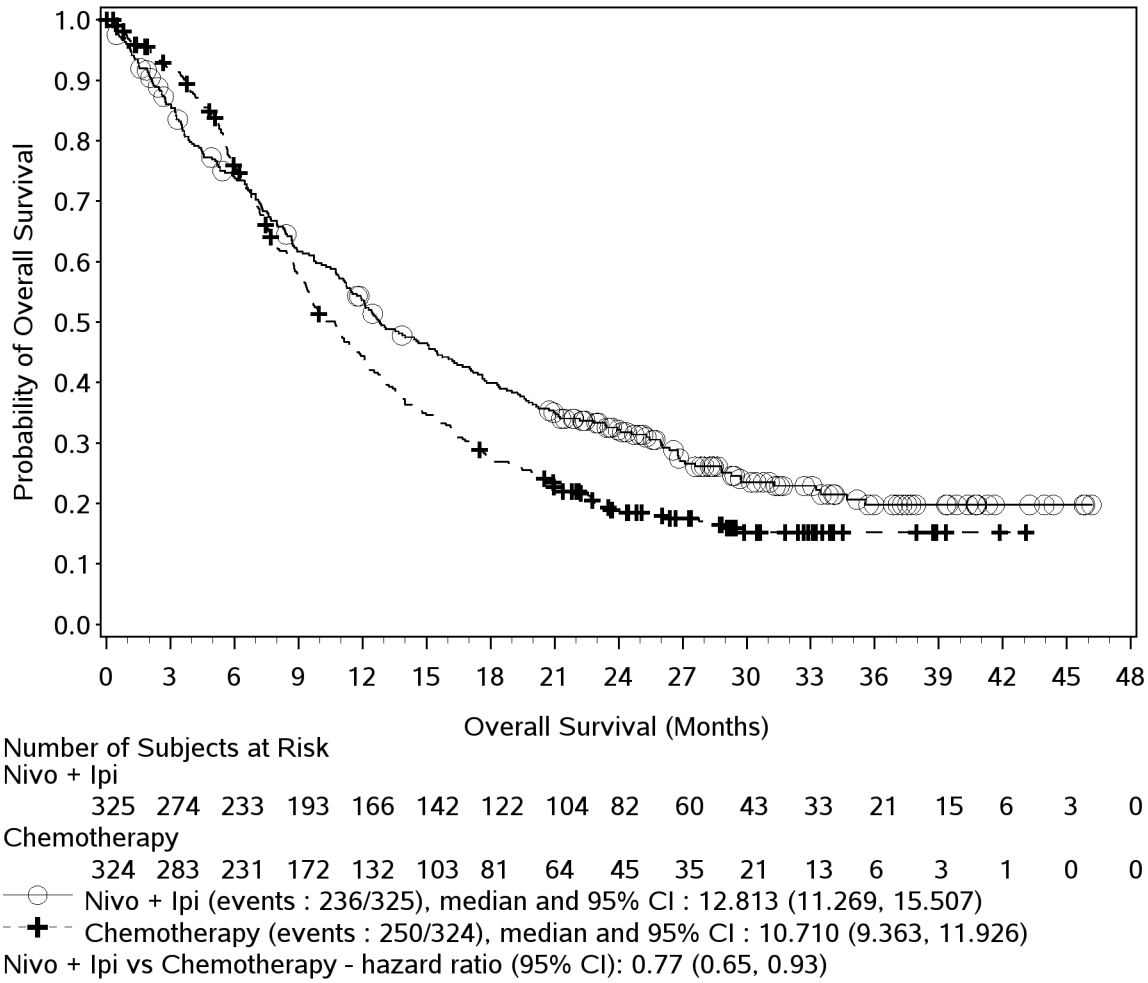
[d] Based on Kaplan-Meier estimates.

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

[f] Strata adjusted difference in objective response rate (Nivo + Ipi - 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 + Ipi vs Chemo - All Randomized Subjects in CA209648 (04-Oct-2021 Database Lock)



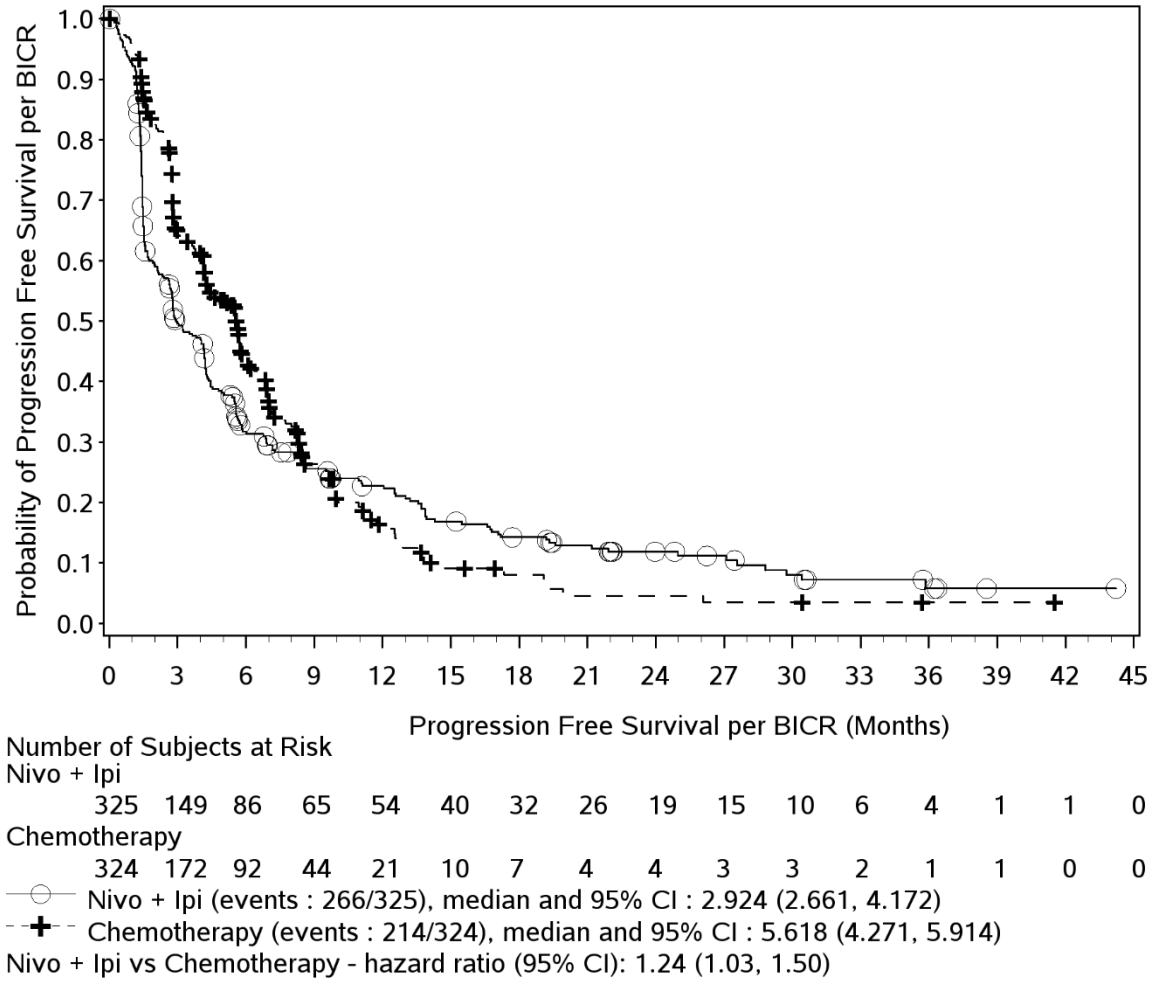
Statistical model for hazard ratio: Stratified Cox proportional hazard model.

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 + Ipi vs Chemo - All Randomized Subjects in CA209648 (04-Oct-2021 Database Lock)



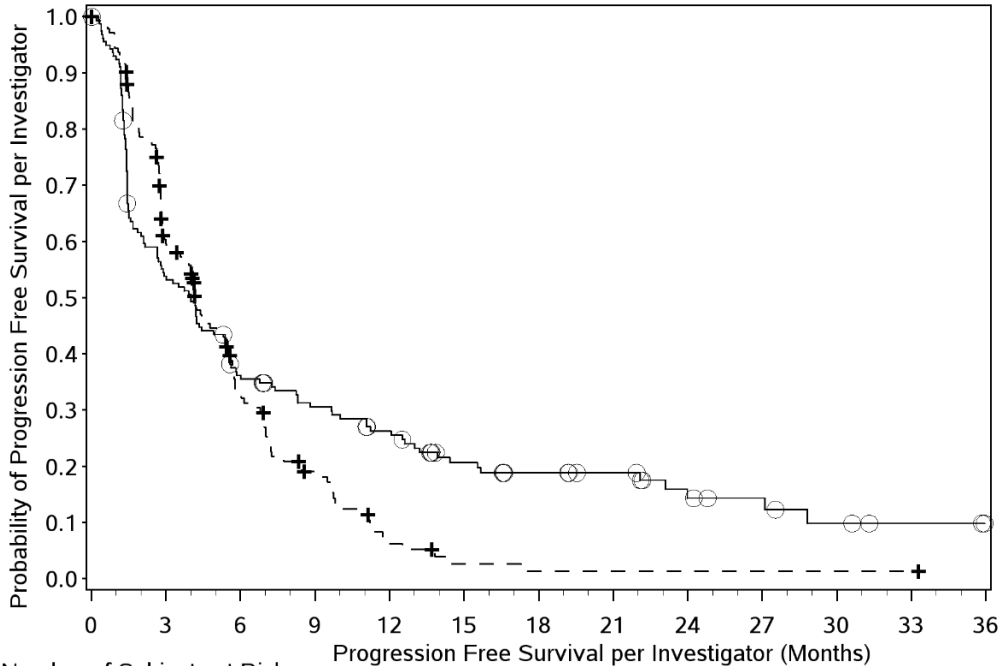
Statistical model for hazard ratio: Stratified Cox proportional hazard model.
Symbols represent censored observations.
Stratification factors are ECOG Performance Status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2), PD-L1 status (>= 1% vs. < 1% or indeterminate) as recorded in IRT.
Region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

Exploratory endpoints

- ***PFS by Investigator*** *in All Randomized Subjects with Tumour Cell* ***PD-L1 ≥ 1%***

In all randomized subjects with tumor cell PD-L1 ≥ 1%, analysis of PFS assessed by investigator showed an improved HR compared with the BICR-based primary analysis, favoring nivo + ipi over chemo: HR = 0.83 (95% CI: 0.64, 1.07). Median PFS (95% CI) in the nivo + ipi and chemo arms was 4.01 (2.66, 5.42) vs. 4.21 (3.06, 5.39) months. Landmark rates of PFS by investigator in the nivo + ipi vs. chemo arms were 36.16% (95% CI: 28.64, 43.71) vs 32.94% (95% CI: 24.95, 41.14) at 6 months and 26.25% (95% CI: 19.48, 33.50) vs. 6.24% (95% CI: 2.65, 11.98) at 12 months, respectively.

Figure 14: Kaplan-Meier Plot of Progression Free Survival per Investigator: Nivolumab + Ipilimumab over Chemotherapy - All Randomized Subjects with Tumour Cell PD-L1 ≥ 1%



Number of Subjects at Risk

Nivo + Ipi	158	83	54	43	35	23	18	15	9	7	4	2	0
Chemotherapy	157	79	39	20	6	2	1	1	1	1	1	1	0

Nivo + Ipi (events : 127/158), median and 95% CI : 4.01 (2.66, 5.42)

Chemotherapy (events : 122/157), median and 95% CI : 4.21 (3.06, 5.39)

Nivo + Ipi vs Chemotherapy - hazard ratio (95% CI): 0.83 (0.64, 1.07)

Statistical model for hazard ratio: Stratified Cox proportional hazard model

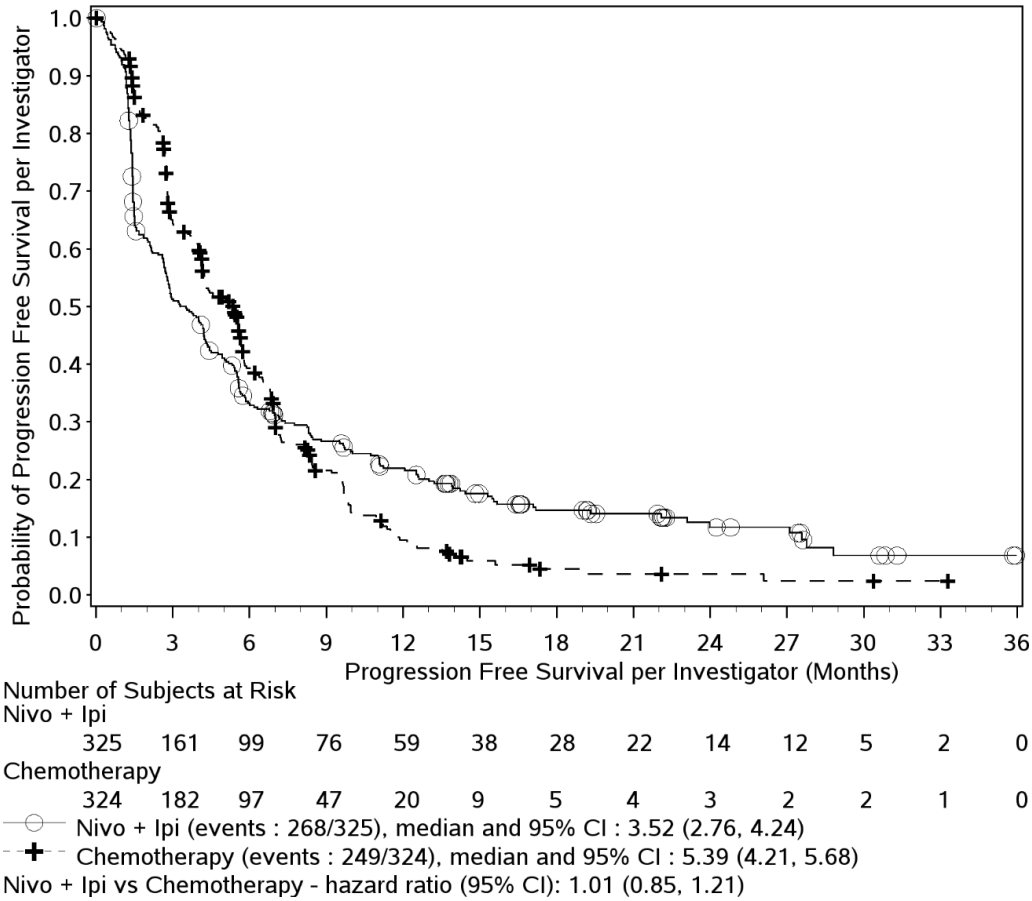
Symbols represent censored observations.

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

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

In all randomized subjects, analysis of PFS assessed by investigator for nivo + ipi vs chemo compared resulted in a HR = 1.01 (95% CI: 0.85, 1.21). Median PFS (95% CI) in the nivo + ipi and chemo arms was 3.52 (2.76, 4.24) vs. 5.39 (4.21, 5.68) months. Landmark rates of PFS by investigator in the nivo + ipi vs. chemo arms were 33.19% (95% CI: 28.03, 38.44) vs 39.36% (95% CI: 33.52, 45.13) at 6 months and 21.94% (95% CI: 17.44, 26.78) vs. 9.52% (95% CI: 6.14, 13.78) at 12 months, respectively.

Figure 15: Kaplan-Meier Plot of Progression Free Survival per Investigator - Nivolumab + Ipilimumab 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), PD-L1 status (>= 1% vs. < 1% or indeterminate) as recorded in IRT.

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

Among responders per BICR in the nivo + ipi (N = 90) vs. chemo (N = 87) arms:

Median TTR (min, max) per BICR was similar in the nivo + ipi (1.51 [1.2, 8.4] months) and chemo (1.51 [1.1, 9.7] months) arms.

Median DOR (95% CI) was numerically longer with nivo + ipi vs. chemo: 11.07 (8.31, 14.00) vs. 7.13 (5.65, 8.21) months and separation of the KM curves favoring nivo + ipi over chemo began at approximately 6 months. In the nivo + ipi vs. chemo arms, 66% (55%, 75%) vs. 54% (41%, 65%) of subjects had a DOR (95% CI) of at least 6 months, and 48% (36%, 58%) vs. 23% (13%, 34%) of subjects had a DOR (95% CI) of at least 12 months.

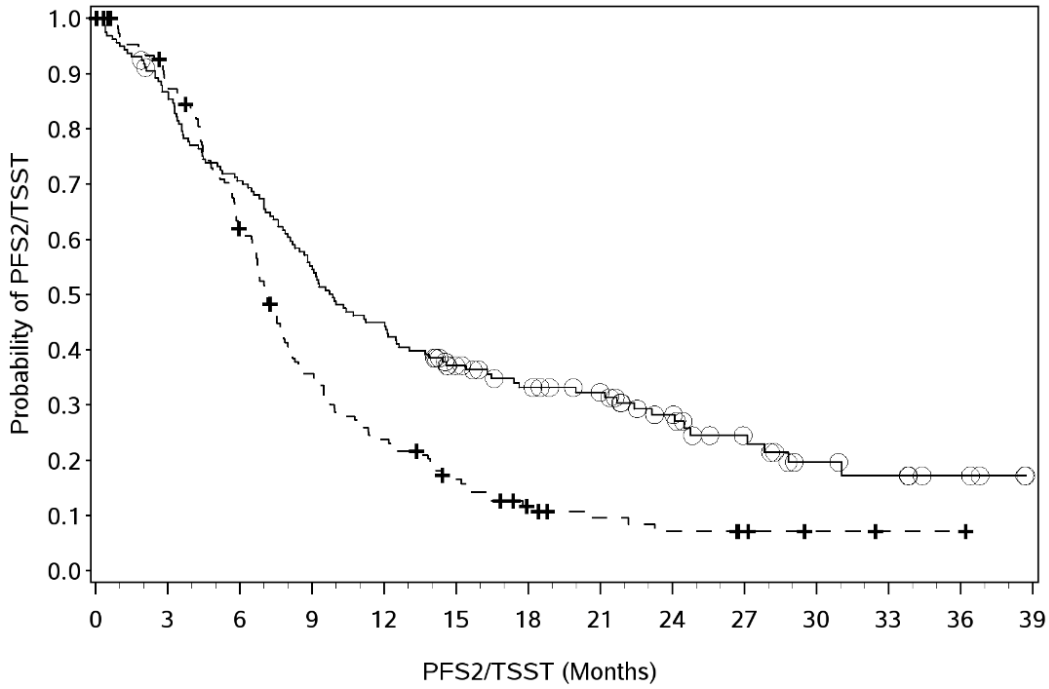
- ***PFS2/TSST -*** *All Randomized Subjects with Tumor Cell* ***PD-L1 ≥ 1%***

A numerical improvement in PFS2/TSST per investigator was observed with nivo + ipi compared to chemo in all randomized subjects with tumor cell PD-L1 ≥ 1%:

Median PFS2/TSST (95% CI) per investigator was numerically longer with nivo + ipi vs. chemo: 9.86 (8.48, 12.16) vs. 7.06 (6.54, 7.82) months. The HR favored nivo + ipi over chemo, with the upper bound

of the 95% CI below 1: 0.59 (95% CI: 0.45, 0.76). The 12-month PFS2/TSST rates (95% CI) were 44.92% (37.00, 52.52) vs. 23.77% (17.19, 30.97), respectively.

Figure 16: Kaplan-Meier Plot of PFS on Next-line Therapy/Time to Second Subsequent Therapy per Investigator - Nivolumab + Ipilimumab over Chemotherapy - All Randomized Subjects with Tumour Cell PD-L1 ≥1%



Number of Subjects at Risk

Nivo + Ipi	158	135	110	86	70	50	41	35	25	16	9	7	4	0
Chemotherapy	157	130	90	51	34	21	12	8	6	4	2	1	1	0

Nivo + Ipi (events : 115/158), median and 95% CI : 9.86 (8.48, 12.16)
Chemotherapy (events : 131/157), median and 95% CI : 7.06 (6.54, 7.82)
Nivo + Ipi vs Chemotherapy - hazard ratio (95% CI): 0.59 (0.45, 0.76)

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.

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

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

Median PFS2/TSST (95% CI) per investigator was numerically longer with nivo + ipi vs. chemo: 9.72 (8.48, 11.24) vs. 7.89 (7.13, 8.44) months. The HR favoured nivo + ipi over chemo, with the upper bound of the 95% CI below 1: 0.74 (95% CI: 0.62, 0.88).

51.7% vs. 62.7% of subjects, respectively, received subsequent cancer therapy. Among subjects who did not receive any subsequent cancer therapy, 68 (20.9%) vs. 42 (13.0%) were censored, respectively (Table S.5.114.3). Among subjects who received at least 1 subsequent cancer therapy, 18 (5.5%) vs. 22 (6.8%) were censored, respectively.

Biomarker analysis

Efficacy by tumour cell PD-L1 expression

Table 16. Efficacy of Nivolumab + Ipilimumab vs. Chemotherapy by Baseline Tumour Cell PD-L1 Levels – All Randomized Subjects

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	Nivo+ Ipi N=164	Chemo N=166	Nivo+ Ipi N=158	Chemo N=156	Nivo+ Ipi N=202	Chemo N=207	Nivo+ Ipi N=120	Chemo N=115	Nivo+ Ipi N=219	Chemo N=225	Nivo+ Ipi N=103	Chemo N=97
OS												
HR (95% CI)[a]	0.96 (0.74, 1.25)		0.63 (0.48, 0.82)		0.86 (0.68, 1.09)		0.66 (0.48, 0.90)		0.82 (0.65, 1.02)		0.71 (0.51, 1.00)	
Events, n	108	111	106	120	134	146	80	85	145	161	69	70
Median OS, mo (95% CI)[b]	11.96 (10.09, 16.03)	12.16 (10.71, 14.00)	13.70 (11.24, 17.02)	9.20 (7.72, 10.02)	12.42 (10.74, 16.20)	11.14 (9.59, 12.88)	13.04 (11.17, 17.02)	9.49 (7.82, 11.37)	12.52 (10.91, 15.74)	10.84 (9.40, 12.35)	13.04 (9.49, 19.98)	9.49 (8.51, 12.19)
PFS per BICR												
HR (95% CI)[a]	1.45 (1.13, 1.88)		0.98 (0.75, 1.29)		1.35 (1.07, 1.70)		0.95 (0.70, 1.30)		1.30 (1.04, 1.62)		0.98 (0.70, 1.39)	
Events, n	132	108	123	100	161	134	94	74	175	147	80	61
Median PFS, mo. (95% CI)[b]	2.83 (1.68, 4.17)	5.75 (5.39, 6.97)	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)	2.79 (1.91, 4.04)	5.68 (4.44, 6.90)	4.24 (2.66, 5.55)	4.40 (2.83, 5.91)	2.83 (2.14, 4.04)	5.65 (4.27, 6.37)	4.24 (2.63, 5.55)	4.50 (2.86, 6.93)
ORR per BICR (CR + PR)[c]												
ORR (95% CI)	20.1 (14.3, 27.1)	33.7 (26.6, 41.5)	35.4 (28.0, 43.4)	19.9 (13.9, 27.0)	22.3 (16.7, 28.6)	30.9 (24.7, 37.7)	36.7 (28.1, 45.9)	20.0 (13.1, 28.5)	23.3 (17.9, 29.5)	29.3 (23.5, 35.8)	36.9 (27.6, 47.0)	21.6 (13.9, 31.2)
CR, n (%)	8 (4.9)	12 (7.2)	28 (17.7)	8 (5.1)	16 (7.9)	14 (6.8)	20 (16.7)	6 (5.2)	18 (8.2)	15 (6.7)	18 (17.5)	5 (5.2)
Partial Response, n (%)	25 (15.2)	44 (26.5)	28 (17.7%)	23 (14.7)	29 (14.4)	50 (24.2)	24 (20.0)	17 (14.8)	33 (15.1)	51 (22.7)	20 (19.4)	16 (16.5)
Stable Disease, n (%)	60 (36.6)	74 (44.6)	43 (27.2)	72 (46.2)	68 (33.7)	92 (44.4)	35 (29.2)	54 (47.0)	74 (33.8)	102 (45.3)	29 (28.2)	44 (45.4)
Progressive Disease, n (%)	53 (32.3)	14 (8.4)	48 (30.4)	24 (15.4)	71 (35.1)	22 (10.6)	30 (25.0)	16 (13.9)	76 (34.7)	24 (10.7)	25 (24.3)	14 (14.4)
Unable to Determine, n (%)	18 (11.0)	22 (13.3)	11 (7.0)	29 (18.6)	18 (8.9)	29 (14.0)	11 (9.2)	22 (19.1)	18 (8.2)	33 (14.7)	11 (10.7)	18 (18.6)

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

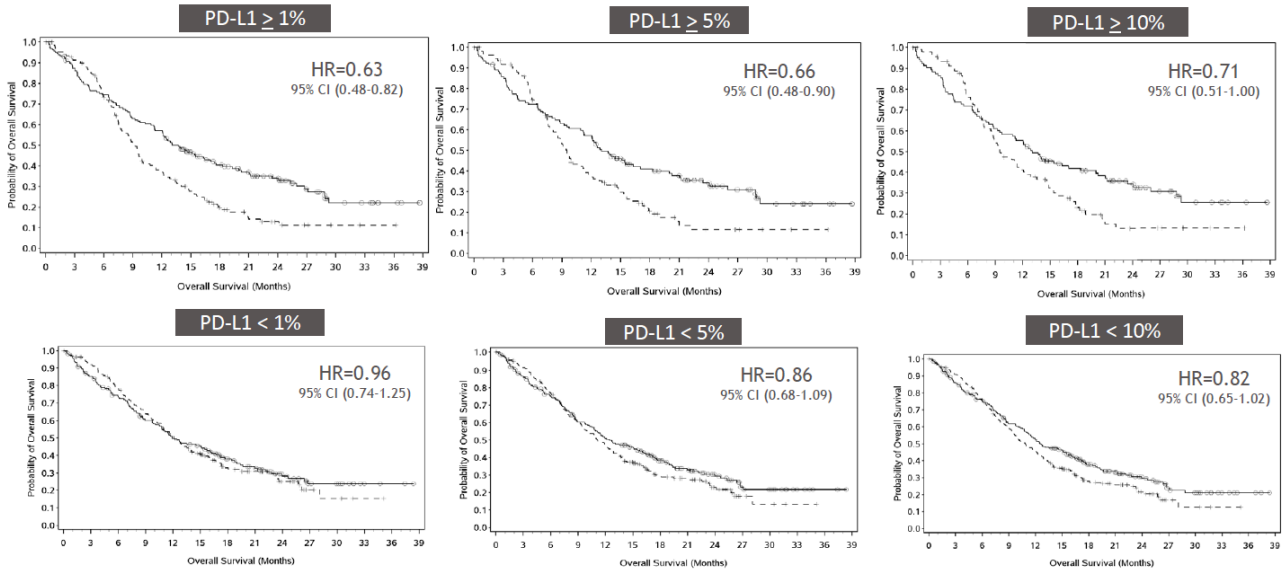
[a] Unstratified Cox proportional hazards model.

[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; Ipi - ipilimumab; Nivo - nivolumab; ORR - objective response rate; OS - overall survival, PD-L1- programmed death ligand 1; PFS - progression-free survival; PR - partial response

Figure 17: Nivo+Ipi vs. Chemo: OS KM by Tumour Cell PD-L1 (All Randomised Patients)



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.

Table 17. Predictive Relationship of PD-L1 status for efficacy endpoints: Nivo+Ipi over Chemo – All PD-L1 evaluable subjects

PD-L1 Expression Cutoff: 1%	
PROGRESSION-FREE SURVIVAL PER BICR (1)	
HAZARD RATIO (95% CI): NIVO + IPI VS. CHEMOTHERAPY (PD-L1 NEGATIVE)	1.47 (1.13, 1.89)
HAZARD RATIO (95% CI): NIVO + IPI VS. CHEMOTHERAPY (PD-L1 POSITIVE)	0.96 (0.73, 1.25)
HAZARD RATIO (95% CI): PD-L1 POSITIVE VS. PD-L1 NEGATIVE (NIVO + IPI)	0.80 (0.63, 1.03)
HAZARD RATIO (95% CI): PD-L1 POSITIVE VS. PD-L1 NEGATIVE (CHEMOTHERAPY)	1.23 (0.94, 1.61)
INTERACTION P-VALUE	0.0241
OVERALL SURVIVAL (1)	
HAZARD RATIO (95% CI): NIVO + IPI VS. CHEMOTHERAPY (PD-L1 NEGATIVE)	0.96 (0.73, 1.25)
HAZARD RATIO (95% CI): NIVO + IPI VS. CHEMOTHERAPY (PD-L1 POSITIVE)	0.63 (0.48, 0.82)
HAZARD RATIO (95% CI): PD-L1 POSITIVE VS. PD-L1 NEGATIVE (NIVO + IPI)	0.92 (0.71, 1.21)
HAZARD RATIO (95% CI): PD-L1 POSITIVE VS. PD-L1 NEGATIVE (CHEMOTHERAPY)	1.41 (1.09, 1.82)
INTERACTION P-VALUE	0.0278

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=0.0241 for PFS per BICR and p=0.0278 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 + Ipi 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+ Ipi N=164	Chemo N=166	Nivo+ Ipi N=158	Chemo N=156	Nivo+ Ipi N=202	Chemo N=207	Nivo+ Ipi N=120	Chemo N=115	Nivo+ Ipi N=219	Chemo N=225	Nivo+ Ipi N=103	Chemo N=97
01-Mar-2021 DBL												
HR (95% CI)[a]	0.96 (0.74, 1.25)		0.63 (0.48, 0.82)		0.86 (0.68, 1.09)		0.66 (0.48, 0.90)		0.82 (0.65, 1.02)		0.71 (0.51, 1.00)	
Events, n	108	111	106	120	134	146	80	85	145	161	69	70
Median OS, mo (95% CI)[b]	11.96 (10.09, 16.03)	12.16 (10.71, 14.00)	13.70 (11.24, 17.02)	9.20 (7.72, 10.02)	12.42 (10.74, 16.20)	11.14 (9.59, 12.88)	13.04 (11.17, 17.02)	9.49 (7.82, 11.37)	12.52 (10.91, 15.74)	10.84 (9.40, 12.35)	13.04 (9.49, 19.98)	9.49 (8.51, 12.19)
04-Oct-2021 DBL												
HR (95% CI)[a]	0.96 (0.74, 1.24)		0.64 (0.50, 0.83)		0.86 (0.69, 1.08)		0.68 (0.51, 0.92)		0.82 (0.66, 1.02)		0.75 (0.54, 1.03)	
Events, n	115	120	119	129	144	158	90	91	156	174	78	75
Median OS, mo (95% CI)[b]	11.959 (10.086, 16.197)	12.156 (10.710, 13.996)	13.700 (11.236, 17.413)	9.199 (7.721, 10.021)	12.682 (10.743, 16.427)	11.039 (9.495, 12.879)	13.043 (11.170, 18.300)	9.495 (8.115, 11.368)	12.682 (10.908, 16.033)	10.842 (9.363, 12.353)	13.043 (9.495, 19.778)	9.626 (8.509, 12.189)

Minimum follow-up for 01-Mar-2021 DBL: 13.1 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.

Minimum follow-up for 01-Mar-2021 DBL: 13.1 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 + Ipi vs Chemo - All Randomized Subjects (by Tumor Cell PD-L1 Expression) in CA209648 (04-Oct-2021 Database Lock) - Exploratory Analysis

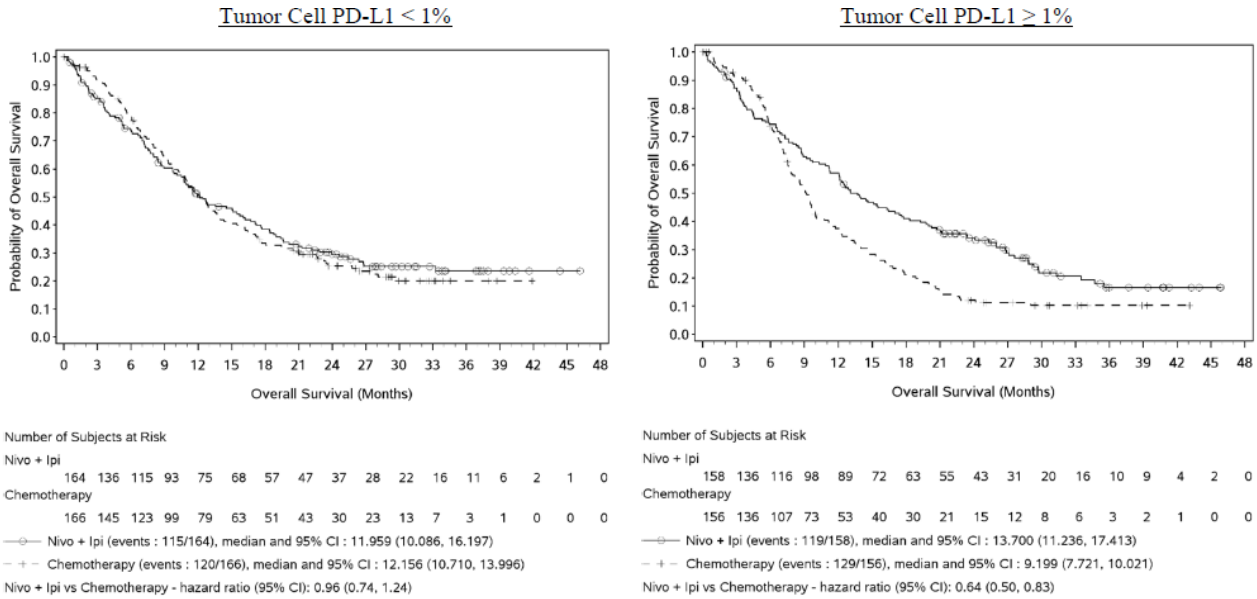


Table 19. Progression-free Survival (per BICR) of Nivo + Ipi vs Chemotherapy by Baseline Tumor Cell PD-L1 Levels - All Randomized Subjects (01-Mar-2021 and 04-Oct-2021 Database Locks) - Exploratory Analysis

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	Nivo+ Ipi N=164	Chemo N=166	Nivo+ Ipi N=158	Chemo N=156	Nivo+ Ipi N=202	Chemo N=207	Nivo+ Ipi N=120	Chemo N=115	Nivo+ Ipi N=219	Chemo N=225	Nivo+ Ipi N=103	Chemo N=97
01-Mar-2021 DBL												
HR (95% CI)[a]	1.45 (1.13, 1.88)		0.98 (0.75, 1.29)		1.35 (1.07, 1.70)		0.95 (0.70, 1.30)		1.30 (1.04, 1.62)		0.98 (0.70, 1.39)	
Events, n	132	108	123	100	161	134	94	74	175	147	80	61
Median PFS, mo. (95% CI)[b]	2.83 (1.68, 4.17)	5.75 (5.39, 6.97)	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)	2.79 (1.91, 4.04)	5.68 (4.44, 6.90)	4.24 (2.66, 5.55)	4.40 (2.38, 5.91)	2.83 (2.14, 4.04)	5.65 (4.27, 6.37)	4.24 (2.63, 5.55)	4.50 (2.86, 6.93)
04-Oct-2021 DBL												
HR (95% CI)[a]	1.44 (1.12, 1.85)		0.98 (0.75, 1.29)		1.34 (1.06, 1.68)		0.95 (0.70, 1.31)		1.29 (1.04, 1.61)		0.98 (0.69, 1.38)	
Events, n	135	111	128	101	168	138	95	74	183	151	80	61
Median PFS, mo. (95% CI)[b]	2.825 (1.676, 4.172)	5.749 (5.487, 6.998)	4.041 (2.398, 4.928)	4.435 (2.891, 5.815)	2.793 (1.906, 4.041)	5.717 (4.435, 6.899)	4.238 (2.661, 5.552)	4.402 (2.825, 5.914)	2.825 (2.136, 4.041)	5.684 (4.304, 6.374)	4.238 (2.628, 5.552)	4.501 (2.858, 6.932)

Minimum follow-up for 01-Mar-2021 DBL: 13.1 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 + Ipi vs Chemo - All Randomized Subjects (by Tumour Cell PD-L1 Expression) in CA209648 (04-Oct-2021 Database Lock) – Exploratory Analysis

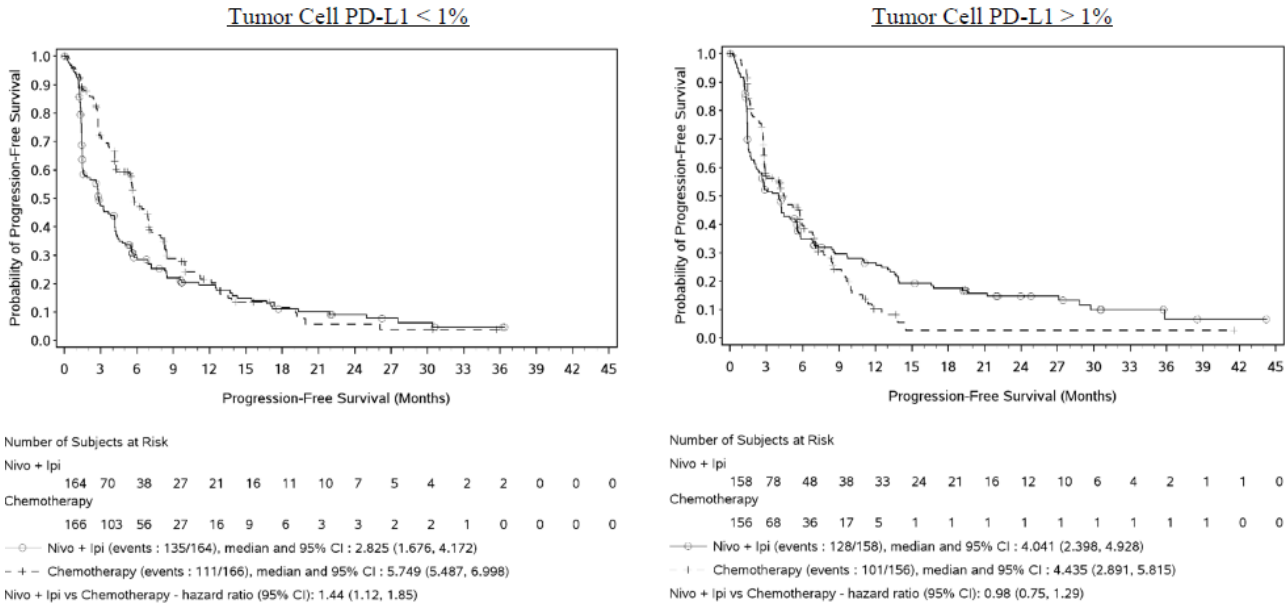


Table 20. Objective Response Rate (per BICR) and Duration of Response (per BICR) of Nivo + Ipi vs Chemotherapy by Baseline Tumour Cell PD-L1 Levels - All Randomized Subjects (01-Mar-2021 and 04-Oct-2021 Database Locks) - Exploratory Analysis

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	Nivo+ Ipi N=164	Chemo N=166	Nivo+ Ipi N=158	Chemo N=156	Nivo+ Ipi N=202	Chemo N=207	Nivo+ Ipi N=120	Chemo N=115	Nivo+ Ipi N=219	Chemo N=225	Nivo+ Ipi N=103	Chemo N=97
01-Mar-2021 DBL												
ORR (CR+PR)[a], % (95% CI)	20.1 (14.3, 27.1)	33.7 (26.6, 41.5)	35.4 (28.0, 43.4)	19.9 (13.9, 27.0)	22.3 (16.7, 28.6)	30.9 (24.7, 37.7)	36.7 (28.1, 45.9)	20.0 (13.1, 28.5)	23.3 (17.9, 29.5)	29.3 (23.5, 35.8)	36.9 (27.6, 47.0)	21.6 (13.9, 31.2)
CR, n (%)	8 (4.9%)	12 (7.2%)	28 (17.7%)	8 (5.1%)	16 (7.9%)	14 (6.8%)	20 (16.7%)	6 (5.2%)	18 (8.2%)	15 (6.7%)	18 (17.5%)	5 (5.2%)
Median DoR (95% CI),[b] months	11.07 (5.68, 14.26)	7.16 (5.68, 9.72)	11.83 (7.10, 27.43)	5.68 (4.40, 8.67)	NA	NA	NA	NA	NA	NA	NA	NA
04-Oct-2021 DBL												
ORR (CR+PR)[a], % (95% CI)	20.1 (14.3, 27.1)	33.1 (26.0, 40.8)	35.4 (28.0, 43.4)	19.9 (13.9, 27.0)	22.3 (16.7, 28.6)	30.4 (24.2, 37.2)	36.7 (28.1, 45.9)	20.0 (13.1, 28.5)	23.3 (17.9, 29.5)	28.9 (23.1, 35.3)	36.9 (27.6, 47.0)	21.6 (13.9, 31.2)
CR, n (%)	9 (5.5%)	12 (7.2%)	27 (17.1%)	8 (5.1%)	17 (8.4%)	14 (6.8%)	19 (15.8%)	6 (5.2%)	19 (8.7%)	15 (6.7%)	17 (16.5%)	5 (5.2%)
Median DoR (95% CI),[b] months	11.07 (6.70, 14.26)	7.16 (5.68, 9.72)	12.65 (7.10, 18.63)	5.68 (4.40, 8.67)	12.62, (8.31, 17.97)	7.16 (5.59, 9.72)	10.25 (5.91, 15.34)	5.68 (4.30, 8.71)	12.25 (6.70, 17.97)	7.13 (5.68, 8.67)	10.84 (6.83, 15.34)	5.68 (4.27, 8.71)

Minimum follow-up for 01-Mar-2021 DBL: 13.1 months. Minimum follow-up for 04-Oct-2021 DBL: 20 months.

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

[b] Based on Kaplan-Meier estimates.

NA = not available.

Biomarker result as recorded in CRF.

Efficacy in PD-L1 by CPS subgroups

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

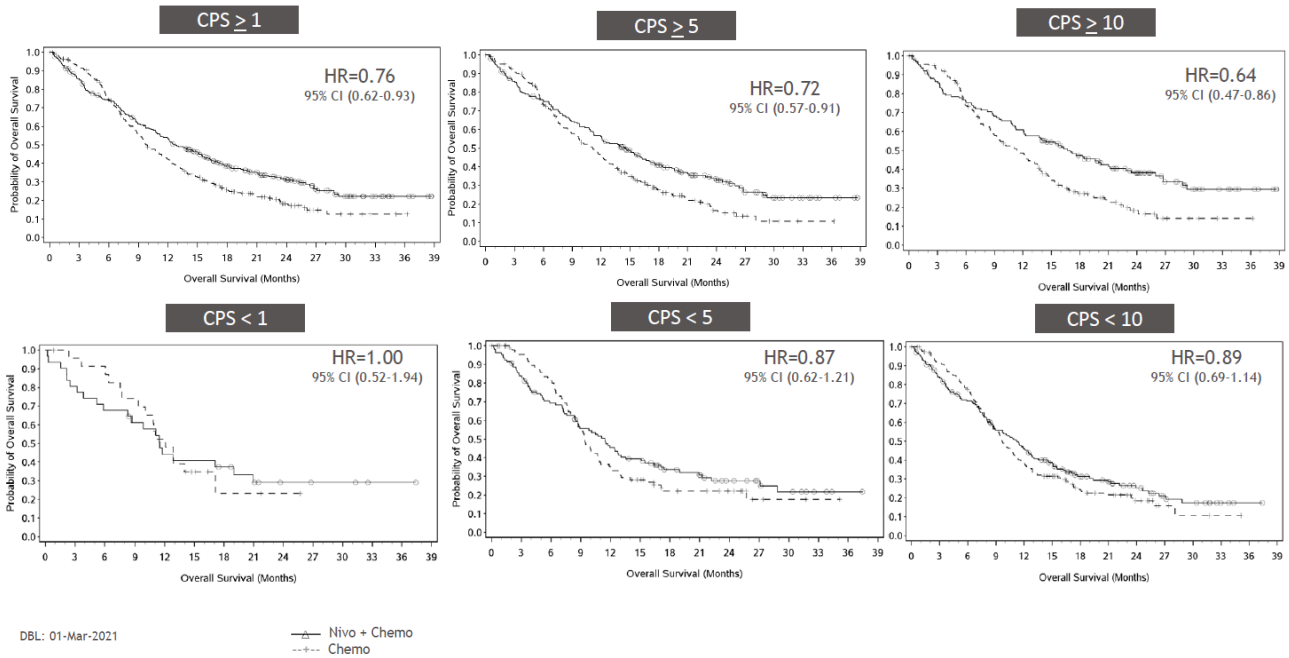
	CPS < 1		CPS ≥ 1		CPS < 5		CPS ≥ 5		CPS < 10		CPS ≥ 10	
	Nivo+ Ipi N=31	Chemo N=24	Nivo+ Ipi N=266	Chemo N=280	Nivo+ Ipi N=106	Chemo N=91	Nivo+ Ipi N=191	Chemo N=213	Nivo+ Ipi N=171	Chemo N=159	Nivo+ Ipi N=126	Chemo N=145
OS												
HR (95% CI)[a]	1.00 (0.52, 1.94)		0.76 (0.62, 0.93)		0.87 (0.62, 1.21)		0.72 (0.57, 0.91)		0.89 (0.69, 1.14)		0.64 (0.47, 0.86)	
Events, n	21	16	179	205	73	66	127	155	121	118	79	103
Median OS, mo (95% CI)[b]	11.47 (5.88, 20.96)	12.09 (9.33, 17.12)	12.75 (10.91, 15.47)	9.76 (8.84, 11.63)	11.43 (8.48, 13.08)	9.40 (8.44, 10.84)	14.52 (11.24, 17.02)	11.14 (9.20, 12.55)	11.24 (8.67, 12.81)	9.69 (8.61, 10.97)	16.69 (12.12, 21.19)	11.63 (8.84, 13.54)
PFS per BICR (primary definition)												
HR (95% CI)[a]	1.49 (0.78, 2.85)		1.18 (0.97, 1.45)		1.41 (1.00, 1.97)		1.11 (0.88, 1.40)		1.45 (1.11, 1.88)		0.98 (0.73, 1.30)	
Events, n	29	14	206	184	88	56	147	142	138	99	97	99
Median PFS, mo. (95% CI)[b]	3.22 (1.54, 4.80)	5.68 (2.86, 11.24)	2.83 (2.60, 4.17)	5.55 (4.24, 5.91)	2.79 (1.51, 4.14)	4.27 (3.22, 5.88)	3.65 (2.63, 4.44)	5.62 (4.27, 6.90)	2.60 (1.51, 2.89)	4.76 (4.17, 5.75)	4.44 (2.79, 5.82)	5.78 (4.24, 7.06)

[a] Unstratified Cox proportional hazards model.

[b] Based on Kaplan-Meier estimates.

Abbreviations: BICR - Blinded Independent Central Review; Chemo - chemotherapy; CI - confidence interval; CPS - combined positive score; CSR - clinical study report; HR - hazard ratio; Ipi - ipilimumab; Nivo - nivolumab; OS - overall survival, PD-L1- programmed death ligand 1; PFS - progression-free survival

Figure 20. Nivo+Ipi vs. Chemo: Subgroup Analyses of OS by PD-L1 CPS Cut-offs



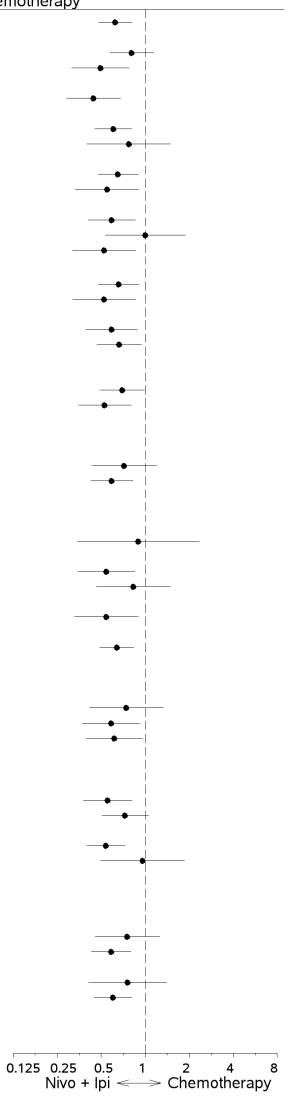
Ancillary analyses

Subgroup analyses

In a subgroup analysis of all randomized subjects with **tumour cell PD-L1 expression ≥ 1**%, OS HRs (95% CIs) for all but one subgroup favoured nivo + ipi over chemo (point estimate of HR < 1). The point estimate of HR for the Rest of Asia region subgroup was 1.00. However, the number of subjects in this subgroup was small (n = 48), and the 95% CI of the HR was wide (0.53, 1.88); thus, interpretation of this result is limited.

Figure 21. Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - Nivolumab + Ipilimumab vs. Chemotherapy - All Randomized Subjects with Tumor Cell PD-L1 ≥1%

	N	Nivo + Ipi N of Events (N of Subjects)	Nivo + Ipi mOS (95% CI)	Chemotherapy N of Events (N of Subjects)	Chemotherapy mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs. Chemotherapy
Overall	315	106 (158)	13.70 (11.24, 17.02)	121 (157)	9.07 (7.69, 9.95)	0.62 (0.48, 0.81)
Age Categorization						
< 65	177	68 (95)	12.88 (8.67, 15.51)	61 (82)	9.49 (7.43, 12.22)	0.81 (0.57, 1.14)
>= 65 and < 75	115	35 (55)	14.62 (10.87, 25.30)	49 (60)	8.57 (7.36, 11.37)	0.49 (0.31, 0.77)
>= 75	23	3 (8)	N.A. (2.00, N.A.)	11 (15)	9.76 (5.75, 14.00)	
>= 65	138	38 (63)	17.02 (11.24, 27.10)	60 (75)	8.84 (7.46, 11.14)	0.44 (0.29, 0.68)
Sex						
Male	262	87 (131)	13.86 (11.24, 17.41)	103 (131)	8.80 (7.52, 9.76)	0.60 (0.45, 0.81)
Female	53	19 (27)	12.12 (8.71, 19.98)	18 (26)	13.11 (7.13, 18.86)	0.77 (0.40, 1.49)
Race						
Asian	230	76 (117)	15.11 (11.27, 18.30)	82 (113)	9.92 (8.11, 12.19)	0.65 (0.47, 0.89)
Non-Asian	85	30 (41)	12.06 (6.57, 19.98)	39 (44)	7.61 (6.80, 9.49)	0.55 (0.33, 0.90)
Region (per CRF)						
J/K/T	181	54 (91)	17.61 (12.29, 25.95)	63 (90)	9.92 (8.57, 12.81)	0.59 (0.41, 0.85)
Rest of Asia	48	21 (25)	8.67 (7.26, 13.70)	19 (23)	8.77 (3.88, 13.83)	1.00 (0.53, 1.88)
Rest of World	86	31 (42)	12.09 (6.80, 19.98)	39 (44)	7.61 (6.80, 9.49)	0.52 (0.32, 0.86)
Region						
Asia	229	75 (116)	14.62 (11.27, 18.30)	82 (113)	9.92 (8.11, 12.19)	0.66 (0.48, 0.90)
Non-Asia	86	31 (42)	12.09 (6.80, 19.98)	39 (44)	7.61 (6.80, 9.49)	0.52 (0.32, 0.86)
ECOG PS (per CRF)						
0	142	45 (72)	17.61 (13.08, 24.08)	50 (70)	10.09 (7.82, 13.40)	0.59 (0.39, 0.88)
1	172	61 (86)	11.17 (7.29, 13.70)	70 (86)	7.89 (6.80, 9.49)	0.66 (0.47, 0.94)
Not Reported	1	0 (0)	N.A.	1 (1)	14.75 (N.A., N.A.)	
Weight						
< 60 kg	179	68 (96)	12.62 (8.74, 17.02)	62 (83)	9.07 (7.49, 10.09)	0.70 (0.49, 0.99)
>= 60 kg	136	38 (62)	14.42 (12.06, 25.30)	59 (74)	8.97 (7.46, 12.19)	0.53 (0.35, 0.80)
Disease Stage at Initial Diagnosis						
Stage I	10	3 (5)	29.27 (12.12, N.A.)	3 (5)	17.77 (9.49, N.A.)	
Stage II	11	4 (5)	9.72 (5.26, N.A.)	4 (6)	5.29 (0.72, N.A.)	
Stage III	82	25 (33)	11.27 (7.98, 15.51)	39 (49)	9.40 (7.06, 13.11)	0.72 (0.43, 1.20)
Stage IV	211	73 (114)	14.42 (11.24, 19.98)	75 (97)	8.80 (7.52, 9.92)	0.59 (0.43, 0.82)
Not Reported	1	1 (1)	6.57 (N.A., N.A.)	0 (0)	N.A.	
Histologic Grade at Initial Diagnosis						
Gx	25	7 (11)	11.24 (2.00, N.A.)	11 (14)	7.62 (5.62, 17.25)	0.90 (0.34, 2.33)
G1	16	5 (8)	12.57 (2.46, N.A.)	7 (8)	9.12 (4.76, 10.09)	
G2	114	39 (58)	12.52 (8.71, 25.95)	44 (56)	8.57 (6.51, 12.81)	0.54 (0.35, 0.85)
G3	68	22 (28)	14.42 (5.88, 24.08)	28 (40)	10.02 (8.61, 14.78)	0.83 (0.47, 1.48)
G4	2	1 (2)	N.A. (20.24, N.A.)	0 (0)	N.A.	
Not Otherwise Specified	90	32 (51)	14.62 (10.28, 19.29)	31 (39)	7.82 (6.28, 12.09)	0.54 (0.33, 0.90)
Histological Classification at Initial Diagnosis						
Squamous Cell Carcinoma	312	106 (157)	13.08 (11.24, 17.02)	119 (155)	9.20 (7.72, 10.02)	0.64 (0.49, 0.83)
Adenosquamous Carcinoma	3	0 (1)	N.A.	2 (2)	4.73 (3.94, 5.52)	
Other	0	0 (0)	N.A.	0 (0)	N.A.	
Location at Initial Diagnosis						
Upper Thoracic	66	24 (37)	17.02 (7.59, 21.03)	22 (29)	9.12 (7.06, 15.31)	0.74 (0.41, 1.33)
Middle Thoracic	108	34 (50)	12.29 (8.74, 17.61)	46 (58)	8.57 (6.80, 9.95)	0.59 (0.37, 0.92)
Lower Thoracic	120	37 (59)	14.00 (9.20, 26.78)	46 (61)	9.63 (7.43, 11.73)	0.62 (0.40, 0.96)
Gastroesophageal Junction	20	10 (11)	8.80 (3.02, 21.19)	7 (9)	9.63 (5.68, 12.81)	
Not Reported	1	1 (1)	12.52 (N.A., N.A.)	0 (0)	N.A.	
Number of Organs with Metastases at Baseline (per IRT)						
<= 1	159	49 (80)	17.61 (12.88, 25.30)	58 (79)	9.49 (7.13, 12.22)	0.56 (0.38, 0.82)
>= 2	156	57 (78)	9.49 (7.59, 13.08)	63 (78)	8.61 (7.52, 9.92)	0.73 (0.50, 1.05)
Time from Initial Disease Diagnosis to Randomization						
< 1 Year	254	82 (128)	14.42 (11.27, 20.24)	100 (126)	8.80 (7.49, 9.92)	0.54 (0.40, 0.73)
1 - < 3 Years	47	20 (25)	9.72 (5.26, 15.11)	16 (22)	9.02 (5.29, 14.75)	0.96 (0.50, 1.85)
3 - < 5 Years	8	4 (4)	13.77 (2.04, 25.95)	2 (4)	15.38 (8.11, N.A.)	
>= 5 Years	5	0 (0)	N.A.	3 (5)	16.07 (5.39, N.A.)	
Not Reported	1	0 (1)	N.A.	0 (0)	N.A.	
Prior Surgery (Excluding Biopsy)						
Yes	85	29 (41)	12.88 (7.26, 17.41)	32 (44)	9.49 (7.36, 12.81)	0.75 (0.45, 1.25)
No	230	77 (117)	13.70 (11.27, 19.29)	89 (113)	8.80 (7.49, 9.95)	0.58 (0.43, 0.80)
Prior Radiotherapy						
Yes	54	20 (26)	12.11 (4.34, 16.43)	22 (28)	7.52 (5.95, 11.14)	0.76 (0.41, 1.40)
No	261	86 (132)	13.86 (11.24, 19.29)	99 (129)	9.43 (7.82, 11.37)	0.60 (0.45, 0.81)

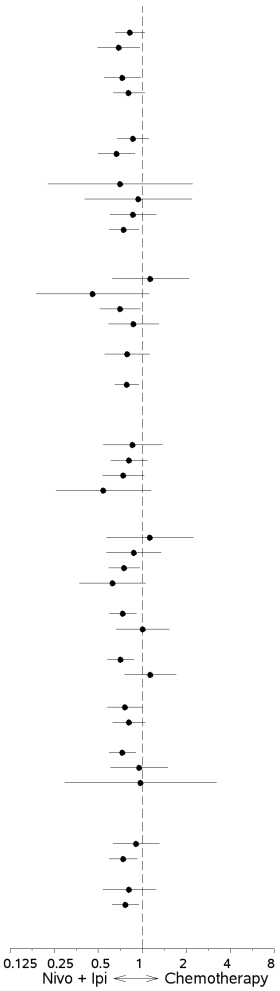


In a subgroup analysis of **all randomized subjects**, OS HRs (95% CIs) for most subgroups favored nivo + ipi over chemo (point estimate of HR < 1).

Figure 22. Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets - Nivolumab + Ipilimumab over Chemotherapy - All Randomized Subjects

	N	Nivo + Ipi N of Events (N of Subjects)	Nivo + Ipi mOS (95% CI)	Chemotherapy N of Events (N of Subjects)	Chemotherapy mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Ipi vs. Chemotherapy
Overall	649	216 (325)	12.75 (11.27, 15.47)	232 (324)	10.71 (9.40, 11.93)	0.78 (0.65, 0.94)
Age Categorization						
< 65	351	130 (185)	12.09 (8.71, 13.86)	118 (166)	10.18 (8.77, 12.25)	0.92 (0.72, 1.18)
>= 65 and < 75	245	73 (116)	15.47 (11.43, 21.26)	96 (129)	10.84 (8.80, 12.55)	0.65 (0.48, 0.89)
>= 75	53	13 (24)	24.61 (10.74, N.A.)	18 (29)	11.14 (7.06, 14.62)	0.55 (0.26, 1.15)
>= 65	298	86 (140)	16.03 (11.93, 22.83)	114 (158)	10.97 (8.97, 12.55)	0.63 (0.47, 0.84)
Sex						
Male	544	174 (269)	13.70 (11.27, 16.43)	203 (275)	9.95 (8.97, 11.37)	0.70 (0.57, 0.86)
Female	105	42 (56)	11.73 (8.02, 15.05)	29 (49)	14.75 (9.26, 20.90)	1.36 (0.85, 2.20)
Race						
Asian	458	150 (231)	14.00 (11.53, 17.08)	153 (227)	11.66 (9.92, 13.54)	0.81 (0.64, 1.01)
Non-Asian	191	66 (94)	11.43 (6.80, 15.05)	79 (97)	8.61 (7.43, 10.18)	0.73 (0.52, 1.02)
Region (per CRF)						
J/K/T	369	114 (185)	16.43 (12.12, 18.99)	119 (184)	12.09 (9.92, 14.78)	0.79 (0.61, 1.03)
Rest of Asia	86	35 (44)	10.97 (7.59, 13.70)	32 (42)	11.06 (6.37, 13.73)	0.94 (0.58, 1.53)
Rest of World	194	67 (96)	11.43 (7.23, 15.05)	81 (98)	8.51 (7.20, 9.69)	0.69 (0.50, 0.96)

Region							
Asia	455	149 (229)	13.70 (11.53, 17.02)	151 (226)	11.86 (10.02, 13.73)	0.83 (0.66, 1.04)	
Non-Asia	194	67 (96)	11.43 (7.23, 15.05)	81 (98)	8.51 (7.20, 9.69)	0.69 (0.50, 0.96)	
ECOG PS (per CRF)							
0	300	89 (149)	17.02 (14.62, 21.03)	99 (151)	12.35 (10.28, 14.98)	0.73 (0.55, 0.98)	
1	348	127 (176)	9.72 (8.02, 12.52)	132 (172)	8.97 (7.49, 10.02)	0.81 (0.63, 1.03)	
Not Reported	1	0 (0)	N.A.	1 (1)	14.75 (N.A., N.A.)		
Weight							
< 60 kg	363	132 (191)	11.47 (8.80, 14.62)	122 (172)	9.49 (8.48, 11.63)	0.86 (0.68, 1.11)	
>= 60 kg	286	84 (134)	15.47 (12.09, 18.76)	110 (152)	11.04 (9.63, 13.11)	0.67 (0.50, 0.89)	
Disease Stage at Initial Diagnosis							
Stage I	24	6 (13)	29.27 (12.12, N.A.)	6 (11)	17.77 (9.49, N.A.)	0.71 (0.23, 2.21)	
Stage II	40	17 (26)	14.52 (8.28, 26.38)	8 (14)	14.00 (2.37, N.A.)	0.94 (0.40, 2.18)	
Stage III	168	53 (76)	12.09 (9.82, 16.43)	67 (92)	11.14 (8.48, 13.83)	0.86 (0.60, 1.24)	
Stage IV	414	138 (208)	12.45 (9.20, 16.30)	150 (206)	9.69 (8.77, 10.97)	0.75 (0.59, 0.95)	
Not Reported	3	2 (2)	8.67 (6.57, 10.78)	1 (1)	13.73 (N.A., N.A.)		
Histologic Grade at Initial Diagnosis							
Gx	62	19 (27)	9.82 (4.50, 20.96)	24 (35)	12.71 (6.80, 17.25)	1.14 (0.62, 2.08)	
G1	30	8 (14)	14.97 (3.48, N.A.)	14 (16)	8.67 (4.76, 10.09)	0.46 (0.19, 1.12)	
G2	219	77 (119)	12.12 (8.71, 17.18)	75 (100)	9.43 (7.49, 12.19)	0.71 (0.51, 0.97)	
G3	147	44 (64)	14.42 (7.00, 18.76)	60 (83)	11.37 (9.63, 13.67)	0.87 (0.59, 1.30)	
G4	3	1 (2)	N.A. (20.24, N.A.)	1 (1)	9.69 (N.A., N.A.)		
Not Otherwise Specified	188	67 (99)	12.68 (11.10, 17.61)	58 (89)	10.87 (8.44, 14.00)	0.79 (0.55, 1.12)	
Histological Classification at Initial Diagnosis							
Squamous Cell Carcinoma	640	214 (322)	12.81 (11.27, 15.51)	227 (318)	10.78 (9.43, 12.09)	0.78 (0.65, 0.95)	
Adenosquamous Carcinoma	9	2 (3)	2.79 (2.14, N.A.)	5 (6)	6.03 (3.94, N.A.)		
Other	0	0 (0)	N.A.	0 (0)	N.A.		
Location at Initial Diagnosis							
Upper Thoracic	115	39 (64)	17.02 (12.09, 24.61)	33 (51)	13.83 (7.98, 20.90)	0.86 (0.54, 1.37)	
Middle Thoracic	265	90 (131)	11.27 (8.71, 14.52)	101 (134)	9.49 (8.02, 12.35)	0.81 (0.61, 1.08)	
Lower Thoracic	222	67 (103)	12.81 (10.74, 21.26)	82 (119)	10.97 (9.76, 13.24)	0.74 (0.54, 1.03)	
Gastroesophageal Junction	43	18 (25)	11.79 (3.65, 21.19)	14 (18)	7.69 (5.49, 11.37)	0.54 (0.26, 1.15)	
Not Reported	4	2 (2)	8.92 (5.32, 12.52)	2 (2)	12.07 (6.83, 17.31)		
Disease Status at Current Diagnosis							
Recurrent - Loco-Regional	50	17 (25)	13.86 (6.01, 20.96)	16 (25)	13.54 (7.13, 24.15)	1.13 (0.57, 2.23)	
Recurrent - Distant	133	46 (73)	15.47 (11.47, 25.95)	39 (60)	12.81 (9.49, 17.31)	0.88 (0.57, 1.35)	
De Novo Metastatic	383	130 (196)	12.06 (8.80, 14.42)	136 (187)	9.43 (8.51, 10.74)	0.75 (0.59, 0.96)	
Unresectable Advanced	83	23 (31)	17.41 (10.78, 23.43)	41 (52)	12.09 (7.06, 13.83)	0.63 (0.37, 1.05)	
Smoking Status							
Current/Former	524	174 (268)	14.42 (12.09, 16.43)	184 (256)	10.02 (8.97, 11.86)	0.74 (0.60, 0.91)	
Never/Unknown	125	42 (57)	9.82 (7.00, 12.75)	48 (68)	11.14 (7.72, 13.73)	1.01 (0.66, 1.53)	
Alcohol Use							
Current/Former	510	169 (260)	13.54 (11.93, 16.69)	184 (250)	10.09 (9.26, 11.73)	0.71 (0.58, 0.88)	
Never/Unknown	139	47 (65)	9.82 (7.23, 16.30)	48 (74)	11.66 (7.52, 14.75)	1.14 (0.76, 1.70)	
Number of Organs with Metastases at Baseline (per IRT)							
<= 1	318	100 (160)	16.03 (12.75, 20.24)	107 (158)	11.63 (9.49, 13.73)	0.76 (0.58, 1.00)	
>= 2	331	116 (165)	10.28 (8.28, 13.04)	125 (166)	9.63 (8.51, 11.14)	0.81 (0.63, 1.05)	
Time from Initial Disease Diagnosis to Randomization							
< 1 Year	501	162 (243)	12.45 (10.28, 16.20)	191 (258)	9.89 (8.90, 11.37)	0.73 (0.59, 0.91)	
1 - < 3 Years	115	46 (66)	12.68 (10.74, 16.03)	32 (49)	11.66 (7.36, 17.31)	0.95 (0.61, 1.49)	
3 - < 5 Years	22	6 (12)	20.96 (3.25, 25.95)	5 (10)	15.38 (5.49, N.A.)	0.98 (0.30, 3.22)	
>= 5 Years	10	2 (3)	15.47 (1.28, N.A.)	4 (7)	16.07 (5.39, N.A.)		
Not Reported	1	0 (1)	N.A.	0 (0)	N.A.		
Prior Surgery (Excluding Biopsy)							
Yes	186	63 (100)	15.05 (10.91, 18.99)	55 (86)	12.81 (10.02, 17.31)	0.91 (0.63, 1.31)	
No	463	153 (225)	12.29 (10.74, 15.51)	177 (238)	9.63 (8.61, 11.37)	0.74 (0.60, 0.92)	
Prior Radiotherapy							
Yes	133	48 (74)	15.05 (9.72, 16.69)	42 (59)	9.92 (6.80, 14.00)	0.82 (0.54, 1.24)	
No	516	168 (251)	12.62 (10.91, 15.74)	190 (265)	10.78 (9.40, 12.09)	0.77 (0.62, 0.95)	



Additional analyses

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

	Nivo + Ipi N = 325	Chemotherapy N = 324	
	RMST (95% CI)	RMST (95% CI)	Difference (95% CI)
6 MONTHS	5.15 (4.97, 5.33)	5.45 (5.30, 5.59)	-0.30 (-0.53, -0.06)
12 MONTHS	8.95 (8.50, 9.39)	8.95 (8.56, 9.35)	0.00 (-0.60, 0.59)
24 MONTHS	13.80 (12.83, 14.77)	12.43 (11.56, 13.29)	1.37 (0.07, 2.67)
36 MONTHS	16.78 (15.31, 18.24)	14.23 (12.90, 15.57)	2.54 (0.56, 4.52)
36.2 MONTHS (A)	16.82 (15.35, 18.30)	14.26 (12.92, 15.60)	2.56 (0.57, 4.55)

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 + Ipi 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 + Ipi over Chemo All Randomized Subjects

	Nivo + Ipi N = 325	Chemotherapy N = 324	
	RMST (95% CI)	RMST (95% CI)	Difference (95% CI)
6 MONTHS	3.49 (3.26, 3.73)	4.32 (4.10, 4.54)	-0.83 (-1.15, -0.51)
12 MONTHS	5.08 (4.59, 5.56)	5.98 (5.51, 6.45)	-0.90 (-1.58, -0.22)
24 MONTHS	6.85 (5.95, 7.74)	6.96 (6.13, 7.79)	-0.11 (-1.34, 1.11)
33.3 MONTHS (A)	7.72 (6.54, 8.91)	7.37 (6.26, 8.48)	0.35 (-1.27, 1.98)
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 + Ipi over Chemo.
(A) The minimum of the longest survival time in each treatment arm, regardless of censoring.

Early deaths

Based on visual evaluation of the OS Kaplan-Meier (K-M) curves, an early crossing in the OS K-M curves between nivo +ipi and chemo arms occurred at approximately 6.5 months, suggesting an initial higher survival rate with the chemo arm compared with the nivo + ipi arm. Thus, exploratory post-hoc analyses were conducted in CA209648, to identify the first timepoint when the smoothed hazards were equal thus define the timing cut-off of early death, to assess the potential risks of early death for nivo + ipi vs. chemo, and to investigate baseline demographic and disease characteristics of patients for whom nivo + ipi may not provide a treatment benefit due to the initial increase in the risk of early death. The analyses conducted are based on data from CA209648 with the DBL of 01-Mar-2021. The population for analyses was limited to all randomized subjects in the nivo + ipi and chemo arms for the study.

A stratified piecewise Cox-regression model with treatment arm as covariate was produced for all randomized subjects of the nivo + ipi and chemo arms. Piecewise time intervals were defined as 0-2, > 2-3, > 3-4, > 4-5, > 5-6, and > 6 months. The point estimate of the piecewise HR of death between the 2 arms was evaluated for each of these time intervals. Based on the stratified piecewise Cox-regression model, a higher piecewise HR was noted for nivo + ipi arm vs. chemo arm up to 4 months (HR between 0-2 months: 2.02, 95% CI: 1.07 - 3.82; HR between 2-3 months: 1.36, 95% CI: 0.64 - 2.88; and HR between 3-4 months: 1.96, 95% CI: 0.94 - 4.09). The piecewise HRs became < 1 in favour of nivo + ipi starting from Month 4, and remained < 1 between 5-6 months, and > 6 months.

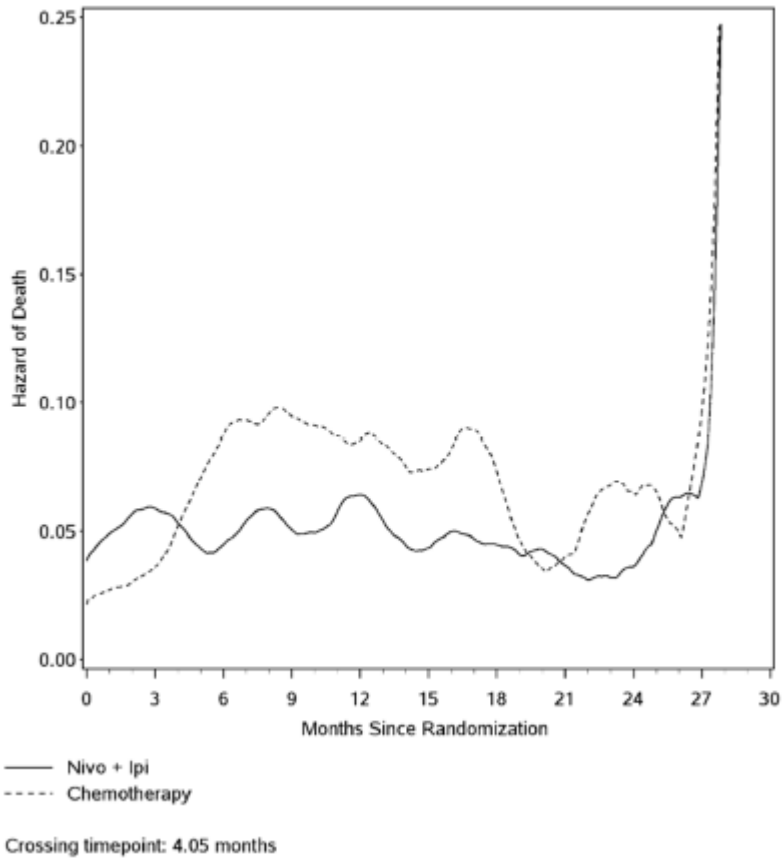
Table 24. Piecewise Hazard Ratios of Overall Survival - All Randomized Subjects in the Nivolumab + Ipilimumab and Chemotherapy Arms

Overall Survival Interval in Months	Nivo + Ipi N = 325 # EVENTS / # SUBJECTS (%)	Chemotherapy N = 324 # EVENTS / # SUBJECTS (%)	HR (95% CI)
0 to <= 2	29/325 (8.9)	14/324 (4.3)	2.02 (1.07, 3.82)
> 2 to <= 3	16/325 (4.9)	12/324 (3.7)	1.36 (0.64, 2.88)
> 3 to <= 4	20/325 (6.2)	11/324 (3.4)	1.96 (0.94, 4.09)
> 4 to <= 5	9/325 (2.8)	12/324 (3.7)	0.79 (0.33, 1.87)
> 5 to <= 6	9/325 (2.8)	25/324 (7.7)	0.39 (0.18, 0.83)
> 6	133/325 (40.9)	158/324 (48.8)	0.63 (0.49, 0.79)

Stratified Cox proportional hazard model. Hazard Ratio is over Chemotherapy.
Stratification factors are ECOG performance status (0 vs 1), number of organs with metastases (<= 1 vs. >= 2), tumor cell 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.

A plot of smoothed instantaneous hazard of death for each treatment arm was produced in all randomized subjects of the nivo + ipi and chemo arms. The first time point when the smoothed curves of instantaneous hazard of death for two treatment arms crossed (i.e., hazards of death were equal) was at 4.05 months. An early death was defined as a death of a subject with a death date prior to or on 4.05 months (subjects censored prior to or on 4.05 months were considered as having non-early deaths), after which any potential risk of death was no longer higher in the nivo + ipi arm. The instantaneous hazard rates were equal at 19.5, 21 and 25 months, which reflected fluctuations in the hazard of death driven by the small numbers of events.

Figure 23. Plot of Smoothed Instantaneous Hazard of Death over Time – All Randomized Subjects in the Nivolumab + Ipilimumab and Chemotherapy Arms



The piecewise HRs and instantaneous hazards in the subgroups of subjects with tumour cell PD-L1 ≥1% or <1% were consistent with the results in all randomized subjects.

Early deaths (i.e. a death prior to or on 4.05 months after randomization) were reported for 66/325 (20.3%) and 38/324 (11.7%) randomized subjects, in the nivo + ipi and chemo arms, respectively.

The cause of death in the early-death population was summarized by treatment arm in the table below.

Table 25. Early Deaths - All Randomized Subjects in the Nivolumab + Ipilimumab and Chemotherapy Arms

	Nivo + Ipi N = 66	Chemotherapy N = 38
NUMBER OF SUBJECTS WITH EARLY DEATH (%)	66 (100.0)	38 (100.0)
PRIMARY REASON FOR DEATH (%)		
DISEASE	45 (68.2)	30 (78.9)
STUDY DRUG TOXICITY	4 (6.1)	4 (10.5)
PRIOR PD	3 (4.5)	1 (2.6)
RADIOGRAPHIC PD	2 (3.0)	0
NO PRIOR PD	1 (1.5)	3 (7.9)
OTHER	13 (19.7)	2 (5.3)
PRIOR PD	6 (9.1)	0
RADIOGRAPHIC PD	5 (7.6)	0
NO PRIOR PD	7 (10.6)	2 (5.3)
UNKNOWN	4 (6.1)	2 (5.3)
PRIOR PD	2 (3.0)	1 (2.6)
RADIOGRAPHIC PD	1 (1.5)	0
NO PRIOR PD	2 (3.0)	1 (2.6)

Early Death is defined as a subject who died prior to or on 4.05 months after randomization.
Cutoff defined based on smoothed hazard curves figure.
PRIOR PD (Progressive Disease) means progressive disease (the earliest occurrence of progression (clinical or radiographic) as assessed per investigator) had occurred before or on the death date. Otherwise NO PRIOR PD.

Table 26. Early Deaths with Reasons of "Other" / "Unknown" in the Nivolumab + Ipilimumab and Chemotherapy Arms

Early Death	Cause of Death	SAE with Fatal Outcome	Causality of SAE if Applicable	Disease Progression
Nivo + Ipi Arm				
1	Other	Bacteriemia	not related	Yes
2	Other	Worsening of pneumonia aspiration	not related	Yes*
3	Other	Pneumonia	not related	Yes
4	Other	Acute respiratory failure	not related	Yes
5	Other	High digestive bleeding	not related	Yes
6	Other	Esophageal hemorrhage	not related	Yes (clinical)
7	Other	Lung infection	not related	Yes
8	Other	Pneumonia	not related	Death prior to disease assessment
9	Other	Respiratory insufficiency	not related	Death prior to disease assessment
10	Other	Death not otherwise specified	not related	Death prior to disease assessment
11	Other	Dyspnea	not related	Death prior to disease assessment
12	Other	Sepsis	not related	Death prior to disease assessment
13	Other	Internal bleeding	related	Death prior to disease assessment
14	Unknown	Lung infection	not related	Yes
15	Unknown	Death due to unknown cause	not related	Death prior to disease assessment
16	Unknown	Death due to unknown cause	not related	Yes (clinical)
17	Unknown	Death due to unknown cause	not related	Death prior to disease assessment
Chemo Arm				
1	Other	acute hypoxic respiratory failure	not related	Death prior to disease assessment
2	Other	sudden death	not related	Death prior to disease assessment
3	Unknown	death due to unknown cause	related	Death prior to disease assessment
4	Unknown	no AE/SAE leading to death	n/a	Yes (clinical)

* Progressive disease per Blinded Independent Central Review (BICR). This case was categorized as a case without prior progression per investigator in Table 3.2-1.
Deaths may be captured on death, adverse event, ECOG performance status, status and follow-up CRF pages. The primary source of Death date is the death CRF.
Early Death is defined as a subject who died prior to or on 4.05 months after randomization. Cutoff is defined based on smoothed hazard curves in all randomized subjects.

There were 7 baseline demographic and disease variables identified with imbalance ≥ 10% in early-death rate between the nivo + ipi and chemo arms.

Table 27. Incidence of Early Death with ⩾ 10% Difference in Pre-defined Subsets - All Randomized Subjects in the Nivolumab + Ipilimumab and Chemotherapy Arms

		Nivo + Ipi Arm N=325		Chemo Arm N=324	
Parameter	**Subgroup Category**	**Early Death n=66**	**Non-Early Death n=259**	**Early Death n=38**	**Non-Early Death n=286**
Overall		66/325 (20.3)	259/325 (79.7)	38/324 (11.7)	286/324 (88.3)
Liver Metastases per Investigator	Yes	33/66 (50.0)	57/259 (22.0)	8/38 (21.1)	83/286 (29.0)
	No	33/66 (50.0)	202/259 (78.0)	30/38 (78.9)	203/286 (71.0)
Weight	< 60 KG	44/66 (66.7)	147/259 (56.8)	18/38 (47.4)	154/286 (53.8)
	≥ 60 KG	22/66 (33.3)	112/259 (43.2)	20/38 (52.6)	132/286 (46.2)
Alcohol Use	Current/former	48/66 (72.7)	212/259 (81.9)	33/38 (86.8)	217/286 (75.9)
	Never/unknown	18/66 (27.3)	47/259 (18.1)	5/38 (13.2)	69/286 (24.1)
Disease Stage at Initial Diagnosis	Stage I	0/66	13/259 (5.0)	0/38	11/286 (3.8)
	Stage II	4/66 (6.1)	22/259 (8.5)	3/38 (7.9)	11/286 (3.8)
	Stage III	15/66 (22.7)	61/259 (23.6)	12/38 (31.6)	80/286 (28.0)
	Stage IV	47/66 (71.2)	161/259 (62.2)	23/38 (60.5)	183/286 (64.0)
	Not reported	0/66	2/259 (0.8)	0/38	1/286 (0.3)
Tumor Cell PD-L1 Expression from Lab	≥ 5%	27/66 (40.9)	93/259 (35.9)	11/38 (28.9)	104/286 (36.4)
	< 5%	38/66 (57.6)	164/259 (63.3)	27/38 (71.1)	180/286 (62.9)
	≥ 10%	23/66 (34.8)	80/259 (30.9)	8/38 (21.1)	89/286 (31.1)
	< 10%	42/66 (63.6)	177/259 (68.3)	30/38 (78.9)	195/286 (68.2)
	Indeterminate/not evaluable/missing	1/66 (1.5)	2/259 (0.8)	0/38	2/286 (0.7)
PD-L1 by CPS from CRF	≥ 5	39/66 (59.1)	152/259 (58.7)	26/38 (68.4)	187/286 (65.4)
	< 5	26/66 (39.4)	80/259 (30.9)	9/38 (23.7)	82/286 (28.7)
	Indeterminate/not evaluable/missing	1/66 (1.5)	27/259 (10.4)	3/38 (7.9)	17/286 (5.9)
Region (per CRF)	J/K/T	28/66 (42.4)	157/259 (60.6)	12/38 (31.6)	172/286 (60.1)
	Rest of Asia	7/66 (10.6)	37/259 (14.3)	8/38 (21.1)	34/286 (11.9)
	ROW	31/66 (47.0)	65/259 (25.1)	18/38 (47.4)	80/286 (28.0)

Percentages for OVERALL are based on N. Percentages for subsets are based on n.
Early Death is defined as a subject who died prior to or on 4.05 months after randomization.
Cutoff defined based on smoothed hazard curves figure.

The identified treatment-specific risk factors were included in the multivariate logistic model along with their interaction with treatment in all randomized subjects pooling the nivo + ipi and the chemo arms together. The final multivariate logistic regression model included risk factors identified within each treatment arm and their interaction terms with treatment if the p-value was less than 0.15.

The final model identified the following poor prognostic factors: non-Asia region ($p < 0.001$), baseline neutrophil/lymphocyte ratio ≥ 4 ($p = 0.001$), baseline tumour burden (≥ Q3, $p = 0.003$), ECOG PS of 1 ($p = 0.006$), and male ($p = 0.088$). The final model included the interactions of treatment arm with liver metastases ($p < 0.001$), never/unknown alcohol use ($p = 0.078$), and weight ($p = 0.123$), which had p-values less than 0.15. Neither tumour cell PD-L1 nor PD-L1 by CPS was identified as a risk factor for early death, in either univariate or multivariate logistic model.

Table 28. Final Multivariate Logistic Regression - Death Occurring in ≤4.05 Months from Randomization – Risk Factors in All Randomized Subjects in the Nivolumab + Ipilimumab and Chemotherapy Arms

	Odds Ratio (95% Wald CI)	P-value	No. of Early Death/ No. Randomized Subjects	
			Nivo + Ipi	Chemotherapy
TREATMENT (NIVOLUMAB 3 MG/KG + IPILIMUMAB 1 MG/KG, REFERENCE = CHEMOTHERAPY)		<0.001		
REGION (PER CRF) (J/K/T & REST OF ASIA, REFERENCE = ROW)		<0.001		
BASELINE NEUTROPHIL/LYMPHOCYTE RATIO (< 4, REFERENCE = >= 4 & NR)		0.001		
BASELINE TUMOR BURDEN PER BICR (>= Q3, REFERENCE = < Q3 & NR)		0.003		
ECOG PS (PER CRF) (0, REFERENCE = 1 & NR)		0.006		
SEX (MALE, REFERENCE = FEMALE)		0.088		
PRESENCE OF LIVER METASTASES PER INV (YES, REFERENCE = NO)		0.932		
TREATMENT * PRESENCE OF LIVER METASTASES PER INV		<0.001		
PRESENCE OF LIVER METASTASES PER INV (YES, REFERENCE = NO)				
AT TREATMENT VALUE NIVOLUMAB 3 MG/KG + IPILIMUMAB 1 MG/KG	2.64 (1.39, 5.04)			
AT TREATMENT VALUE CHEMOTHERAPY	0.40 (0.16, 0.99)			
ALCOHOL USE (CURRENT/FORMER, REFERENCE = NEVER/UNKNOWN)		0.126		
TREATMENT * ALCOHOL USE		0.078		
ALCOHOL USE (CURRENT/FORMER, REFERENCE = NEVER/UNKNOWN)				
AT TREATMENT VALUE NIVOLUMAB 3 MG/KG + IPILIMUMAB 1 MG/KG	0.96 (0.45, 2.06)			
AT TREATMENT VALUE CHEMOTHERAPY	2.95 (1.04, 8.36)			
WEIGHT (>= 60 KG, REFERENCE = < 60 KG)		0.214		
TREATMENT * WEIGHT		0.123		
WEIGHT (>= 60 KG, REFERENCE = < 60 KG)				
AT TREATMENT VALUE NIVOLUMAB 3 MG/KG + IPILIMUMAB 1 MG/KG	0.50 (0.26, 0.95)			
AT TREATMENT VALUE CHEMOTHERAPY	1.06 (0.51, 2.22)			
TREATMENT (NIVOLUMAB 3 MG/KG + IPILIMUMAB 1 MG/KG, REFERENCE = CHEMOTHERAPY)				
AT WEIGHT VALUE >= 60 KG, AT ALCOHOL USE VALUE CURRENT/FORMER, AT PRESENCE OF LIVER METASTASES PER INV VALUE YES	4.04 (1.42, 11.52)		11/ 32	3/ 29
AT WEIGHT VALUE >= 60 KG, AT ALCOHOL USE VALUE CURRENT/FORMER, AT PRESENCE OF LIVER METASTASES PER INV VALUE NO	0.61 (0.27, 1.36)		6/ 81	14/ 87
AT WEIGHT VALUE >= 60 KG, AT ALCOHOL USE VALUE NEVER/UNKNOWN, AT PRESENCE OF LIVER METASTASES PER INV VALUE YES	12.36 (2.97, 51.53)		2/ 9	1/ 14
AT WEIGHT VALUE >= 60 KG, AT ALCOHOL USE VALUE NEVER/UNKNOWN, AT PRESENCE OF LIVER METASTASES PER INV VALUE NO	1.86 (0.49, 7.10)		3/ 12	2/ 22
AT WEIGHT VALUE < 60 KG, AT ALCOHOL USE VALUE CURRENT/FORMER, AT PRESENCE OF LIVER METASTASES PER INV VALUE YES	8.59 (2.94, 25.08)		13/ 34	3/ 36
AT WEIGHT VALUE < 60 KG, AT ALCOHOL USE VALUE CURRENT/FORMER, AT PRESENCE OF LIVER METASTASES PER INV VALUE NO	1.29 (0.62, 2.71)		18/113	13/ 98
AT WEIGHT VALUE < 60 KG, AT ALCOHOL USE VALUE NEVER/UNKNOWN, AT PRESENCE OF LIVER METASTASES PER INV VALUE YES	26.30 (6.48, >99.99)		7/ 15	1/ 12
AT WEIGHT VALUE < 60 KG, AT ALCOHOL USE VALUE NEVER/UNKNOWN, AT PRESENCE OF LIVER METASTASES PER INV VALUE NO	3.96 (1.13, 13.84)		6/ 29	1/ 26

Prognostic covariates identified within each arm using backward selection method (SLSTAY=0.25). Covariates with p-value < 0.15 and treatment arm by covariate interaction effects with a p-value <0.15 included. P-values and odds ratios from multivariate logistic regression model. Reference level for covariates are Region from CRF (ref=ROW); Baseline ECOG from CRF (ref=1 & NR); Sex (ref=Female); Weight (ref=<60KG); Alcohol Use (ref=Never/Unknown); Presence of Liver Metastases per INV (ref=No); Baseline Neutrophil/Lymphocyte Ratio (ref=>=4 & NR); Baseline Tumor Burden per BICR (ref=<Q3 & NR).

Table 29. Univariate Logistic Regression - Death Occurring ≤ 4.05 Months from Randomization Including Treatment, One Risk Factor and its Interaction with Treatment - All Randomized Subjects in the Nivolumab + Ipilimumab and Chemotherapy Arms

Subgroup	N	Nivo + Ipi Total Subjects With an Event (N Subjects)	Chemotherapy Total Subjects With an Event (N Subjects)	Nivo + Ipi vs Chemotherapy Odds Ratio (95% Wald CI)	P-value	Test for Interaction P-value
PRESENCE OF LIVER METASTASES PER INV					0.099	<0.001
YES	181	33 (90)	8 (91)	6.01 (2.59, 13.95)		
NO	468	33 (235)	30 (233)	1.11 (0.65, 1.88)		
ALCOHOL USE					0.717	0.033
CURRENT/FORMER	510	48 (260)	33 (250)	1.49 (0.92, 2.41)		
NEVER/UNKNOWN	139	18 (65)	5 (74)	5.28 (1.83, 15.21)		
WEIGHT					0.720	0.131
< 60 KG	363	44 (191)	18 (172)	2.56 (1.42, 4.63)		
>= 60 KG	286	22 (134)	20 (152)	1.30 (0.67, 2.50)		

Odds Ratios and p-values based on univariate logistic model
Reference level for covariates are Region from CRF ROW; Baseline ECOG 1 & NR from CRF; Number of Organs with Metastases at Baseline from IRT <= 1; Tumor PD-L1 Expression Level from lab with cutoffs >= 1%, 5% and 10%; PD-L1 by CPS from CRF with cutoffs >= 1, 5 and 10; Age Categorization I < 65; Sex Female; RACE Non-Asian; Region Non-Asia; Weight < 60 KG; Disease Stage at Initial Diagnosis Stage IV; Histologic Grade at Initial Diagnosis NOS & Non-G3/G4; Location at Initial Diagnosis Gastroesophageal Junction & NR; Disease Status at Current Diagnosis Non-De Novo Metastatic; Smoking Status and Alcohol Use Never/Unknown; Time from Initial Disease Diagnosis to Randomization >= 1 Year & NR; Prior Surgery (Excluding Biopsy) No; Prior Radiotherapy No; Presence of Liver Metastases per INV No; Presence of Bone Metastases per INV No; Baseline Neutrophil/Lymphocyte Ratio >= 4 & NR; Baseline Tumor Burden per BICR < Q3 & NR; Baseline Lung Immune Prognostic Index 1 & 2 & NR.

Analyses to support contribution of components

In order to evaluate the contribution of the ipilimumab component in the nivo + ipi regimen in CA209648, analyses were pre-specified in the CSR SAP version 4.0 Section 8.0 to compare the efficacy data descriptively between the nivo + ipi and nivo + chemo arms.

Table 30. Summary of Key Efficacy Results Including Descriptive Comparison of Nivo + Ipi and Nivo + Chemo Arms - All Randomized Subjects

Efficacy Parameter	Nivo+Ipi N=325	Nivo+Chemo N=321	Chemo N=324
OS			
Events, n (%)	216 (66.5)	209 (65.1)	232 (71.6)
HR **vs Chemo**[a]	0.78	0.74	--
	(98.2% CI: 0.62, 0.98)	(99.1% CI: 0.58, 0.96)	--
	(95% CI: 0.65, 0.95)	(95% CI: 0.61, 0.90)	--
Stratified log-rank p-value **vs Chemo**	0.0110[b]	0.0021[b]	--
HR (CI) **Nivo+Ipi vs Nivo+Chemo**	1.04 (95% CI: 0.86, 1.26)		--
0 to ≤ 2 months	2.43 (95% CI: 1.24, 4.77)		--
> 2 to ≤ 3 months	1.45 (95% CI: 0.69, 3.08)		--
> 3 to ≤ 4 months	1.70 (95% CI: 0.85, 3.42)		--
> 4 to ≤ 5 months	0.76 (95% CI: 0.32, 1.78)		--
> 5 to ≤ 6 months	0.85 (95% CI: 0.36, 2.01)		--
> 6 months	0.88 (95% CI: 0.69, 1.12)		--
Median OS, mo.[c] (95% CI)	12.75 (11.27, 15.47)	13.21 (11.14, 15.70)	10.71 (9.40, 11.93)
Restricted mean OS time (95% CI)[d]			
12 mo.	8.95 (8.50, 9.39)	9.50 (9.12, 9.88)	--

Efficacy Parameter	Nivo+Ipi N=325	Nivo+Chemo N=321	Chemo N=324
Difference (95% CI)[e]	-0.56 (-1.14, 0.03)		--
24 mo.	13.80 (12.83, 14.77)	14.36 (13.46, 15.27)	--
Difference (95% CI)[e]	-0.56 (-1.89, 0.76)		--
36 mo.	16.78 (15.31, 18.24)	17.25 (15.81, 18.70)	--
Difference (95% CI)[e]	-0.48 (-2.53, 1.58)		--
38.7 mo.[f]	17.39 (15.79, 18.98)	17.52 (15.96, 19.09)	--
Difference (95% CI)[e]	-0.14 (-2.37, 2.10)		--
ORR per BICR[g]			
N Responders (%)	90 (27.7)	152 (47.4)	87 (26.9)
95% CI[h]	(22.9, 32.9)	(41.8, 53.0)	(22.1, 32.0)
Complete Response, n (%)	36 (11.1)	43 (13.4)	20 (6.2)
Partial Response, n (%)	54 (16.6)	109 (34.0)	67 (20.7)
Stable disease, n (%)	103 (31.7)	103 (32.1)	148 (45.7)
Progressive disease, n (%)	103 (31.7)	42 (13.1)	38 (11.7)
Unable to determine, n (%)	29 (8.9)	24 (7.5)	51 (15.7)
ORR Difference (95% CI) **vs Chemo**[i]	0.9 (-5.9, 7.6)[j]	20.6 (13.4, 27.7)[j]	--
Odds Ratio (95% CI) **vs Chemo**[k]	1.04 (0.74, 1.47)[j]	2.48 (1.78, 3.45)[j]	--
DOR per BICR			
N Events/N Responders (%)	53 (58.9)	96 (63.2)	51 (58.6)
Median, mo.[c] (95% CI)	11.07 (8.31, 14.00)	8.18 (6.90, 9.69)	7.13 (5.65, 8.21)
Min, Max, mo.[l]	1.4+, 34.5+	1.4+, 35.9+	1.4+, 31.8+
Proportion (95% CI) with DOR ≥ 12 mo	0.48 (0.36, 0.58)	0.39 (0.30, 0.47)	0.23 (0.13, 0.34)

Stratified Cox proportional hazard model. Hazard ratio is Nivo+ipi over Chemo

[b] 2-sided log-rank test 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.

[c] Based on Kaplan-Meier estimates

[d] Restricted mean survival time (RMST) is based on trapezoidal integration of the area under the Kaplan-Meier estimated curve until restricted time point.

[e] The difference of RMST is nivo + ipi over nivo + chemo.

[f] The minimum of the longest survival time in each treatment arm, regardless of censoring

[g] Per RECIST 1.1; ORR = CR+PR.

[h] Confidence interval based on the Clopper and Pearson method.

[i] Strata adjusted difference in ORR (Nivo+ipi - chemo or Nivo+chemo - chemo) based on Cochran-Mantel-Haenszel (CMH) method of weighting

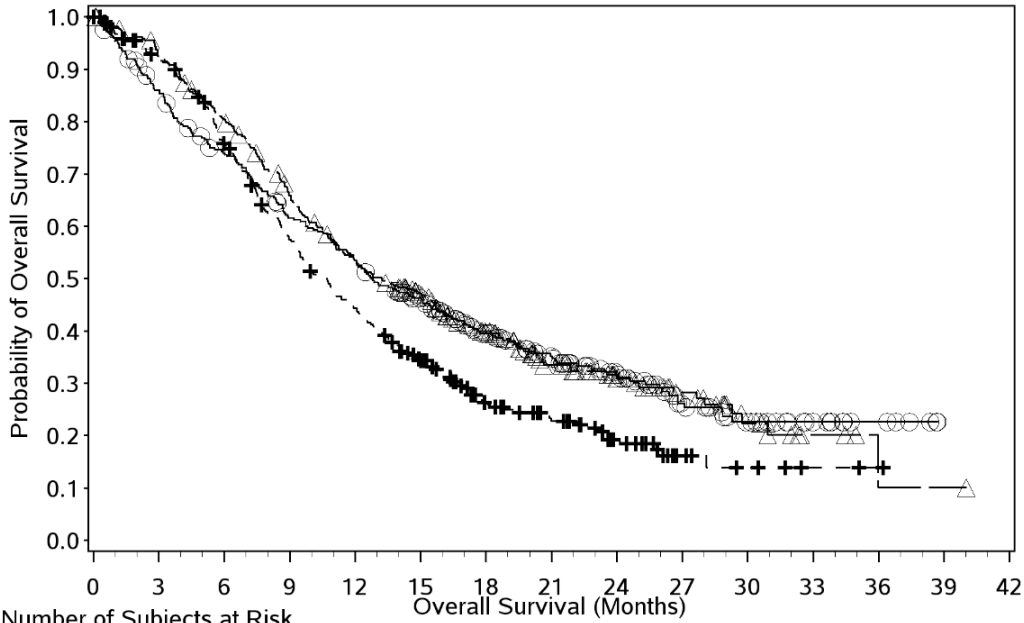
[j] Stratified by ECOG Performance Status (0 vs 1), number of organs with metastases (≤ 1 vs ≥ 2), PD-L1 status (≥ 1% vs < 1% or indeterminate) as recorded in IRT.

[k] Strata adjusted odds ratio (Nivo+ipi over chemo or Nivo+chemo over chemo) using Mantel-Haenszel method

[l] Symbol + indicates a censored value.

Abbreviations: BICR - blinded independent central review, Chemo - chemotherapy, CI - confidence interval, CR - complete response, CSR - clinical study report, DOR - duration of response, ECOG - Eastern Cooperative Oncology Group, HR - hazard ratio, Ipi - ipilimumab, IRT - interactive response technology, Nivo - nivolumab, ORR - objective response rate, OS - overall survival, PS - performance status, RECIST - Response Evaluation Criteria in Solid Tumors, PFS - progression-free survival, PR - partial response

Figure 24. Kaplan-Meier Plot of Overall Survival - Nivo + Ipi, Nivo + Chemo, and Chemo - 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 tumour cell PD-L1 expression (≥ 1% or < 1% and indeterminate) as recorded in IRT.

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 31. 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:	From 29 Jun 2017 (FPFV) to 18 Jan 2021 (LPLV)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	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+Ipi	Chemo
	Number of subjects	325 All randomised 158 PD-L1≥1%	324 All randomised 157 PD-L1≥1%

	OS (**PD-L1≥1%**) (median, months)	13.70	9.07
	95% CI	11.24, 17.02	7.69, 9.95
	PFS (**PD-L1≥1%**) (median, months)	4.04	4.44
	95% CI	2.40, 4.93	2.89, 5.82
	OS (**all randomised**) (median, months)	12.75	10.71
	95% CI	11.27, 15.47	9.40, 11.93
	PFS (**all randomised**) (median, months)	2.92	5.59
	95% CI	2.66, 4.17	4.27, 5.88
	ORR (PD-L1≥1%) (%)	35.4	19.7
	95% CI	28.0, 43.4	13.8, 26.8
	ORR (All randomised) (%)	27.7	26.9
	95% CI	22.9, 32.9	22.1, 32.0
Effect estimate per comparison	Primary endpoint **OS (PD-L1≥1%)**	Comparison groups	Nivo+Ipi vs. Chemo
		Hazard ratio (HR)	0.64
		98.6% CI	0.46, 0.90
		p value (stratified 2-sided)	0.0010
	Primary endpoint **PFS (PD-L1≥1%)**	Comparison groups	Nivo+Ipi vs. Chemo
		Hazard ratio (HR)	1.02
		98.5% CI	0.73, 1.43
		p value (stratified 2-sided)	0.8958
	Secondary endpoint **OS (all randomised)**	Comparison groups	Nivo+Ipi vs. Chemo
		Hazard ratio (HR)	0.78
		98.2% CI	0.62, 0.98
		p value (stratified 2-sided)	0.0110
	Secondary endpoint **PFS (all randomised)**	Comparison groups	Nivo+Ipi vs. Chemo
		Hazard ratio (HR)	1.26
		98.5% CI	NA, NA
		p value (stratified 2-sided)	NA
	Secondary endpoint **ORR (PD-L1≥1%)**	Comparison groups	Nivo+Ipi vs. Chemo
		Difference	15.7
		95% CI	5.9, 25.4
		P-value	Not applicable
	Secondary endpoint **ORR (all randomised)**	Comparison groups	Nivo+Ipi vs. Chemo
		Difference	0.9
		95% CI	-5.9, 7.6
		P-value	Not applicable
Notes			

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

Not applicable

Clinical studies in special populations

Table 32: 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 Yervoy (ipilimumab) 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 chemotherapy for the same target population (EMEA/H/C/3985/II/107).

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 standard of care.

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 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W. This regimen has been used in previous clinical trials (e.g. study CA209743 in patients with malignant pleural mesothelioma) and therefore is considered acceptable.

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 recommend 5-FU (750 - 1000 mg/m² on Days 1 - 4) plus cisplatin (75 - 100 mg/m² on Day 1) every 4 weeks. The proposed regimen is considered acceptable.

Further, the proposed posology in the PI is 3 mg/kg nivolumab Q2W or 360 mg Q3W in combination with 1 mg/kg ipilimumab Q6W. The justification for the additional posology for nivolumab (i.e. 360 mg Q3W) 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. There were 81 patients (42 patients with tumour cell PD-L1 expression ≥1%) in the nivo+ipi arm who were treated beyond progression, with a median treatment duration of 1.12 months (range: 0.1, 22.6). 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 stated that treatment beyond progression was not allowed in the chemo arm, however, investigator could continue study therapy while awaiting the RECIST 1.1 assessment. There were 23 patients in the chemo arm that received treatment beyond progression. In response to the follow-up request received the MAH provided the total duration of treatment and duration of post-progression treatment in patients with tumor cell PD-L1 expression ≥ 1% and in patients with tumor cell PD-L1 < 1%. The data presented for both tumor cell PD-L1 ≥ 1% and tumor cell PD-L1 < 1% show that some patients treated with nivo + ipi or nivo + chemo received therapy up to several months after investigator-assessed progression. The continuation of therapy beyond progression in this subset of patients indicates the investigator's assessment of continued benefit, as treatment was to be discontinued at the time of progression in the absence of ongoing clinical benefit.

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 42 patients in the nivo+ipi arm who were treated beyond progression, with a median treatment duration of 1.10 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, investigator could continue study therapy while awaiting the RECIST 1.1 assessment. There were 13 patients with PD-L1≥1% in the chemo arm 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 was low (only 5 patients in the nivo+ipi arm received treatment for more than 4 months, which was the maximum

[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

reported in the chemo arm where treatment beyond progression was not allowed), it is considered unlikely that this may have impacted the (OS) results. No further actions are considered 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 PRO 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 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 has considered the hypothetical strategy; in particular the MAH has censored the intercurrent events which deals with the administration of subsequent therapy and withdrawal of consent. Sensitivity analyses 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). No relevant protocol deviations were reported in the nivo+ipi arm. Taking into account the low number of patients with protocol deviations 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 this 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.

The proportion of patients that received subsequent systemic therapy was comparable between treatment arms (51.7% nivo+ipi and 55.9% chemo). In the chemo group, a higher number of patients received anti-PD-(L)1 therapy (15.7% vs. 4.3%), mainly nivolumab. In contrast, 5-FU and cisplatin were among the most frequent subsequent therapies received in the nivo+ipi arm.

Efficacy outcomes

The efficacy data provided are 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 since the combination of nivo+ipi demonstrated a statistically significant improvement in OS compared with chemo (HR 0.64; 98.6% CI: 0.46, 0.90) in the primary efficacy population (i.e. PD-L1≥1%). The median OS was of 13.7 (95% CI: 11.24, 17.02) months in the nivo+ipi arm vs. 9.07 (95% CI: 7.69, 9.95) months in the chemo arm. However, no statistically significant differences were observed in PFS, as assessed by BICR (HR 1.02; 98.5% CI: 0.73, 1.43). PFS analysis according to the investigator was consistent with the primary analysis (HR 0.83; 95% CI: 0.64, 1.07). Sensitivity analyses, including PFS per BICR accounting for assessment on/after subsequent therapy (HR 0.85; 98.5% CI: 0.63, 1.15), were overall in line with the primary analysis.

Since PFS did not meet the criteria for statistical significance in the PD-L1≥1% population, as per the hierarchical testing strategy, PFS in the all-randomised patients was not formally tested (HR 1.26; 95% CI: 1.04, 1.52); neither was ORR.

In the all-randomised patients, with 216 (66.5%) events in the nivo+ipi arm and 232 (71.6%) in the chemo arms (87.2% of the target final number of OS events), a statistically significant improvement in OS was observed with nivo+ipi over chemo (HR 0.78; 98.2% CI: 0.62, 0.98). Median OS was of 12.75 months vs. 10.71 months, respectively. Sensitivity analyses were consistent with the primary analysis.

Notwithstanding the above, there was a higher rate of early deaths in the nivo+ipi arm, with crossing of the KM curves at approximately 6.5 months. Exploratory post-hoc analyses were carried out. Early deaths were defined as deaths that occurred during the first 4 months (4.05 moths). During this period, 66 patients died in the nivo+ipi arm compared with 38 patients in the chemo arm. The main cause of death was disease progression (45 [68.2%] vs. 30 [78.9%], respectively), followed by a cause named as "other" (13 [19.7% nivo+ipi vs. 2 [5.3%] chemo). According to these analyses, the

presence of liver metastasis was identified as a risk factor for early death in the nivo+ipi arm vs. chemo arm. Further, body weight (low) and alcohol use (never/unknown) were also associated with early death among patients treated with nivo+ipi in the exploratory multivariate logistic analyses, although results may be influenced by some imbalances in baseline characteristics and the small sample size of some subgroups (i.e. never/unknown alcohol use). The highest risk is observed among patients with liver metastases, low body weight (<60 kg) and alcohol use value never/unknown. Tumour cell PD-L1 was not identified as a predictive risk factor for early death. A warning has been included in section 4.4 of the SmPC regarding the higher number of early deaths within 4 months and that physicians should consider the delayed onset of effect of nivolumab in combination with ipilimumab before initiating treatment in patients with poorer prognostic features and/or aggressive disease.

The OS subgroup analysis was overall consistent with the primary analysis (all-randomised population) for most of the subgroups analysed, except for the subgroup of female patients, where no apparent benefit was observed with the combination of nivo+ipi over chemo (HR 1.36; 95% CI: 0.85, 2.20). It is acknowledged this is a relatively small subgroup (n=105) and as stated by the MAH, the control arm performed better in female patients compared with the overall population (median OS 14.75 months vs. 10.71 in the overall population). Nevertheless, CIs barely overlap, suggesting differences observed by gender might not be a chance finding. The MAH argued there were some imbalances in prognostic factors between both treatment arms, although it is not clear how these imbalances may have impacted the results. In the subgroup of female patients with PD-L1≥1%, a more favourable effect was observed (HR 0.77; 95%CI: 0.40, 1.49) while clearly not in patients with PD-L1<1% (HR 2.44; 95% CI: 1.18, 5.04), although these subgroups are even smaller, thus results should be interpreted with caution. A similar pattern was observed with pembrolizumab in study KEYNOTE-590, in patients with oesophageal cancer[3]. The KM curves for the subgroup of female patients suggest a lower OS with nivo+ipi during all study period. However, taking into account this is a subgroup analysis, with important inherent limitations, the relatively small sample size of this subgroup and the fact that a biological rationale cannot be confirmed, no conclusions can be drawn.

With regards to the subgroup analysis by PD-L1 expression, which was in fact one of the stratification factors, there is an apparent lack of benefit in the subgroup of patients with PD-L1 <1% in OS (HR; 0.96; 95% CI: 0.74, 1.25) and PFS (HR 1.45; 95% CI: 1.13, 1.88). Moreover ORR was lower in the nivo+ipi arm compared with the chemo arm (20.1% vs. 33.7%). Further, no clear separation of the OS KM curves in favour of the experimental arm is observed. Besides, as for the overall population, crossing of the KM curves is observed at approximately 9 months. 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 after approximately 9 months (with crossing of KM curves at 6.5 months). Bearing in mind the above results, only an indication restricted to patients with tumour cell PD-L1 expression ≥ 1% could be envisaged. The MAH was requested to further discuss the benefit in the PD-L1<1% population to justify an 'all comers' indication. The MAH argues that the proposed combination is a non-chemotherapy containing regimen which may be an option for patients unwilling to receive chemo and that the use of nivo + ipi "will be best tailored at the patient level". This is not considered a convincing argumentation. Even if it is agreed that this combination may be an alternative regimen to chemotherapy, with a different safety profile which can be considered reasonably manageable, the reported efficacy results do not support a positive benefit/risk in the proposed broad indication with updated efficacy data confirming the results initially observed in the PD-L1<1% population, see below. Further, the increased rate of early deaths in patients treated with nivo+ipi is also of concern, particularly in the subgroup of patients with PD-L1<1% in whom the initial lack of control of the

[3] European Public Assessment Report Keytruda (pembrolizumab). Available in: https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-3820-ii-0097-epar-assessment-report-variation_en.pdf

disease together with the reported lower effect do not allow to conclude that this combination is able to provide benefit. As a result the indication has been restricted to patients with tumour cell PD-L1 expression ≥1% (see below).

Regarding ORR (by BICR), in patients with PD-L1≥1% a higher ORR was reported in the nivo+ipi arm vs. chemo (35.4% vs. 19.7%). However, ORR was comparable between treatment arms in the all-randomised patient population (27.7% nivo+ipi vs. 26.9% chemo). The MAH argues that median DoR was slightly longer in the nivo+ipi arm (11.07 months vs. 7.13 months), with a DoR rate at 12 months of 48% in the nivo+ipi arm vs. 23% in the chemo arm. It should however be noted that comparing median DoR lacks value as this is a non-randomised comparison (i.e. deriving from objective responses which are a post-baseline event), while OS and PFS data are available in the context of a randomized clinical trial.

Other exploratory endpoints, such as PFS2/TTST favoured the nivo+ipi arm (HR 0.74; 95% CI: 0.62, 0.88).

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 (HR 0.63; 95% CI: 0.49, 0.82) and ORR (35.4% vs. 19.7%) in patients with tumour cell PD-L1≥1% (i.e. the primary efficacy population). However, no benefit was observed in PFS (HR 1.02; 95% CI: 0.77, 1.34). In the all randomised patients (the intended target population) the combination of nivo+ipi resulted in improved OS (HR 0.77; 95% CI: 0.65, 0.93), but no benefit was observed in PFS, with even a detrimental effect (HR 1.24; 95% CI: 1.03, 1.50), and ORR was similar between arms (27.7% vs. 26.5%). In patients with PD-L1<1% results were also consistent with prior data. Even if the exploratory nature of data reported in this subgroup analysis is acknowledged, no apparent benefit was observed with nivo+ipi over chemo in OS (HR 0.96; 95% CI: 0.74, 1.24), a detrimental effect in PFS with the combination was observed (HR 1.44; 95% CI: 1.12, 1.85) and the ORR was also lower in the nivo+ipi arm (20.1% nivo+ipi vs. 33.1% chemo).

Biomarker analysis

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.

Contribution of the monocomponents

A justification on the combination of nivolumab plus ipilimumab has been provided. The rationale for the dual checkpoint inhibition is acknowledged and the combination is currently approved in a variety of tumour types (i.e. NSCLC, melanoma, RCC, MSI-H/dMMR CRC). The MAH argues that neither nivolumab nor ipilimumab alone are expected to improve the efficacy of chemotherapy. However, this statement is based on efficacy data from studies carried out in a different setting (i.e. later lines of OSCC or gastric cancer and even squamous NSCLC) and therefore it is not known whether different (better) results may have been reached with nivolumab as monotherapy in treatment naïve patients with oesophageal cancer. Nivolumab, as monotherapy, is currently approved in patients with OSCC after prior fluoropyrimidine- and platinum-based chemotherapy. In order to further support the contribution of ipilimumab to the combination, comparative efficacy data (descriptive) of the nivo+chemo arm (which has demonstrated superiority over chemo alone) versus nivo+ipi arm have

been provided. This descriptive analysis was pre-specified in the SAP. Efficacy data shows no differences between nivo+ipi vs. nivo+chemo in OS (HR 1.04; 95%CI: 0.86, 1.26). According to an exploratory analysis of piecewise OS HRs, a higher benefit may be expected with nivo+ipi after the first 4 months. However, the ORR was higher in the nivo+chemo arm compared with the nivo+ipi (47.4% vs. 27.7%), although DoR appears longer with nivo+ipi (8.18 months chemo vs. 11.07 months nivo+ipi). Having all considered, the contribution of nivolumab can be considered demonstrated based on the results of the nivo+chemo arm over chemo alone. Further, and as mentioned above, OS results are consistent between both combinations (i.e. nivo+ipi and nivo+chemo) also supporting that the contribution of ipilimumab can be considered established.

The finally agreed **indication** is:

OPDIVO in combination with ipilimumab 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%.

YERVOY in combination with nivolumab 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%.

As discussed above, based on the available data, a broad indication regardless of PD-L1 expression was not considered acceptable and therefore the indication was restricted to patients with tumour cell PD-L1 expression ≥1%.

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 ipilimumab showed a statistically significant clinically relevant OS improvement compared with chemotherapy alone in patients with tumour cell PD-L1 expression ≥ 1%. No statistically significant differences were observed in PFS, although lack of correlation between PFS and OS has been previously observed with immunotherapy. These results can be considered of clinical relevance.

A higher rate of early deaths in the nivo+ipi arm was observed during the first months of treatment. These early deaths were observed regardless of tumour cell PD-L1 expression and are compatible with lack of control of the disease during the first months. This issue has been observed in other clinical trials with immunotherapy. A warning has been included in section 4.4 of the SmPC.

2.5. Clinical safety

Introduction

Safety assessment for this application is based on All Treated Population (N=936) in study CA209648. In particular, safety data from 322 subjects treated with 1L nivo + ipi (nivo 3 mg/kg IV Q2W + ipi 1 mg/kg IV Q6W) from treatment arm A 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 + Ipi arm were to receive nivolumab 3 mg/kg as a 30-minute IV infusion Q2W and ipilimumab 1 mg/kg as an IV infusion Q6W. Patients in the Chemo arm were to receive 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.

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 and a summary of these results are 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 33.

Table 33. 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)

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(a) Percentages based on subjects entering period.
(b) Percentages based on number of randomized subjects
(c) Percentages based on number of treated subjects
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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 proportion of subjects with treatment durations >3 months was higher in the chemo arm (54.3%) compared with the nivo + ipi arm (47.8%) while this trend is reversed when we look at long-term data. 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%).

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 34 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 35. 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)

Safety Parameter	No. of Subjects (%)					
	Nivo+Ipi (N=322)		Nivo+Chemo (N=310)		Chemo (N=304)	
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)
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)

Safety Parameter	No. of Subjects (%)					
	Nivo+Ipi (N=322)		Nivo+Chemo (N=310)		Chemo (N=304)	
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 + Ipi vs Chemo in CA209648 (04 Oct 2021 DBL)

Table 36: Updated Safety Results of Nivo + Ipi vs Chemo - All Treated Subjects in CA209648 (04-Oct-2021 Database Lock)

	No. of Subjects (%)			
Safety Parameter	**Nivo+Ipi N = 322**		**Chemo N = 304**	
Deaths	234 (72.7)		242 (79.6)	
Primary Reason for Death				
Disease	190 (59.0)		222 (73.0)	
Study Drug Toxicity	6 (1.9)[a]		5 (1.6)[b]	
Unknown	13 (4.0)		6 (2.0)	
Other	25 (7.8)[c]		9 (3.0)[d]	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	219 (68.0)	160 (49.7)	130 (42.8)	100 (32.9)
Drug-related SAEs	105 (32.6)	75 (23.3)	49 (16.1)	40 (13.2)
All-causality AEs leading to DC	85 (26.4)	57 (17.7)	81 (26.6)	33 (10.9)
Drug-Related AEs leading to DC	59 (18.3)	43 (13.4)	63 (20.7)	18 (5.9)
All-causality AE	317 (98.4)	204 (63.4)	301 (99.0)	170 (55.9)
Drug-related AEs	256 (79.5)	105 (32.6)	275 (90.5)	110 (36.2)
≥ 15% Drug-related AEs in Any Treatment Arm				
Rash	56 (17.4)	7 (2.2)	5 (1.6)	0
Diarrhoea	32 (9.9)	2 (0.6)	46 (15.1)	6 (2.0)
Fatigue	29 (9.0)	4 (1.2)	50 (16.4)	11 (3.6)
Nausea	26 (8.1)	1 (0.3)	158 (52.0)	8 (2.6)
Decreased appetite	19 (5.9)	5 (1.6)	130 (42.8)	9 (3.0)
Vomiting	18 (5.6)	4 (1.2)	49 (16.1)	9 (3.0)
Stomatitis	14 (4.3)	0	71 (23.4)	5 (1.6)
Anaemia	13 (4.0)	2 (0.6)	67 (22.0)	17 (5.6)
Constipation	7 (2.2)	1 (0.3)	66 (21.7)	1 (0.3)
Neutrophil count decreased	2 (0.6)	0	52 (17.1)	24 (7.9)
Hiccups	2 (0.6)	0	53 (17.4)	0
All-causality Select AEs by Category				
Endocrine	92 (28.6)	19 (5.9)	5 (1.6)	0
Gastrointestinal	78 (24.2)	10 (3.1)	62 (20.4)	7 (2.3)
Hepatic	67 (20.8)	24 (7.5)	22 (7.2)	5 (1.6)
Pulmonary	34 (10.6)	13 (4.0)	6 (2.0)	2 (0.7)
Renal	18 (5.6)	3 (0.9)	63 (20.7)	5 (1.6)
Skin	137 (42.5)	13 (4.0)	38 (12.5)	0
Hypersensitivity/Infusion Reactions	14 (4.3)	0	1 (0.3)	0
Drug-Related Select AEs by Category				
Endocrine	88 (27.3)	19 (5.9)	1 (0.3)	0
Gastrointestinal	38 (11.8)	5 (1.6)	47 (15.5)	7 (2.3)
Hepatic	42 (13.0)	14 (4.3)	12 (3.9)	2 (0.7)
Pulmonary	28 (8.7)	10 (3.1)	1 (0.3)	0
Renal	8 (2.5)	2 (0.6)	57 (18.8)	5 (1.6)
Skin	111 (34.5)	13 (4.0)	12 (3.9)	0
Hypersensitivity/Infusion Reactions	9 (2.8)	0	1 (0.3)	0

Table 36: Updated Safety Results of Nivo + Ipi vs Chemo - All Treated Subjects in CA209648 (04-Oct-2021 Database Lock)

Safety Parameter	No. of Subjects (%)			
	Nivo+Ipi N = 322		Chemo N = 304	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality IMAEs within 100 d of last dose treated with IMM by Category				
Diarrhea/Colitis	13 (4.0)	5 (1.6)	0	0
Hepatitis	15 (4.7)	11 (3.4)	0	0
Pneumonitis	16 (5.0)	10 (3.1)	0	0
Nephritis/Renal Dysfunction	4 (1.2)	2 (0.6)	0	0
Rash	48 (14.9)	9 (2.8)	3 (1.0)	1 (0.3)
Hypersensitivity/Infusion Reactions	3 (0.9)	0	0	0
All-causality Endocrine IMAEs within 100 d of last dose by Category				
Adrenal Insufficiency	17 (5.3)	7 (2.2)	0	0
Hypophysitis	22 (6.8)	10 (3.1)	0	0
Hypothyroidism/Thyroiditis	50 (15.5)	1 (0.3)	0	0
Diabetes Mellitus	5 (1.6)	2 (0.6)	0	0
Hyperthyroidism	19 (5.9)	2 (0.6)	1 (0.3)	0
All-causality OESIs within 100 d of last dose with/without IMM by Category				
Pancreatitis	5 (1.6)	4 (1.2)	0	0
Encephalitis	3 (0.9)	3 (0.9)	0	0
Myositis/Rhabdomyolysis	2 (0.6)	0	0	0
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0
Uveitis	2 (0.6)	1 (0.3)	0	0
Myocarditis	2 (0.6)	0	0	0
Graft Versus Host Disease	0	0	0	0

[a] In the nivo + ipi arm, there were 2 additional "Study Drug Toxicity" deaths as of the 04-Oct-2021 DBL, one subject had the cause of death updated from "Other" at the 01-Mar-2021 DBL to "Study Drug Toxicity" as of the 04-Oct-2021 DBL, and there was one new "Study Drug Toxicity" case reported after the 01-Mar-2021 DBL. See Appendix 1.2.1 for details of changes in cause of death between the two DBLs.

[b] 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 further details.

[c] In the nivo + ipi arm, there were 3 additional "Other" deaths as of the 04-Oct-2021 DBL, 2 subjects had the cause of death updated from "Disease" at the 01-Mar-2021 DBL to "Other" as of the 04-Oct-2021 DBL, 1 subject had the cause of death updated from "Study Drug Toxicity" at the 01-Mar-2021 DBL to "Other" as of the 04-Oct-2021 DBL, and there was one new "Other" death reported after the 01-Mar-2021 DBL. See Appendix 1.2.1 for further details.

[d] In the chemo arm, there was one additional "Other" death after the 01-Mar-2021 DBL.

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 35). 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%), nausea (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 37. 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 gastrointestinal disorders (648.8 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. Pyrexia was the most frequently reported PT for nivo + ipi (67.0/100 P-Y) and 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 636.3 with nivo + ipi vs 1893.5 with chemo treatment. In the nivo + ipi arm, the most frequently reported SOC was investigations (125.8/100 P-Y), and the most frequently reported PT was rash (41.8/100 P-Y). In the chemo arm, the most frequently reported SOC was gastrointestinal disorders (625.2/100 P-Y) with nausea as the most frequently reported PT (266.0/100 P-Y).

Serious adverse event/deaths/other significant events

Serious Adverse Events

Between the nivo + ipi and chemo arms, the overall proportion of subjects with all-causality and drug-related SAEs were numerically higher in the nivo + ipi arm vs the chemo arm. The proportions of subjects with drug-related SAEs were higher with nivo + ipi vs chemo in the SOCs of Endocrine Disorders (6.8% vs 0.3%) and Respiratory, Thoracic and Mediastinal Disorders (6.2% vs 1.6%), largely due to immune-related AEs coincident with immunotherapy treatment.

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 38). 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 39). 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 38. 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 39. 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 40).

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 40. 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.

Deaths 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.

There were some changes in the causes of death between the 1-Mar-2021 DBL and the 4-Oct-2021 DBL. In the nivo + ipi arm, two deaths were re-assessed as "due to drug toxicity" in the latest DBL, one due to internal bleeding and the other one due to pneumonitis. On the contrary, one death caused by acute respiratory syndrome was reassessed and considered not related to treatment within the data update.

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 + ipi arm: skin (34.2%), endocrine (27.3%), and hepatic (13.0%)
- 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 + ipi arm: rash (17.1%), hypothyroidism and pruritis (13.4% each), and diarrhoea (9.9%)
- 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 + ipi arm: pneumonitis (3.7%), adrenal insufficiency (2.2%), and hypophysitis (1.9%)
- 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 + ipi arm (ranging from 62.5% to 100% across categories). The median time to resolution of drug-related select AEs ranged from 0.14 to 12.14 weeks in the nivo + ipi arm. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy (Table 41).

Table 41: Onset, Management, and Resolution of Drug-Related Select AEs - All Subjects Treated with Nivolumab + Ipilimumab (N=322) 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	27.3 / 5.9	8.21 (1.9-72.9)	3.4	38.6 / 9.1	N.E. (0.4+-154.0+)	28.4
Gastrointestinal	11.8 / 1.6	9.14 (0.6-50.3)	1.2	26.3 / 10.5	2.93 (0.3-79.1+)	94.7
Hepatic	13.0 / 4.3	5.00 (1.0-50.1)	2.8	31.0 / 21.4	5.14 (1.1-30.9+)	88.1

Table 41: Onset, Management, and Resolution of Drug-Related Select AEs - All Subjects Treated with Nivolumab + Ipilimumab (N=322) 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]
Pulmonary	8.1 / 2.8	11.86 (1.9-72.3)	3.4	34.6 / 15.4	12.14 (0.1+-119.3+)	65.4
Renal	2.5 / 0.6	7.14 (1.1-47.1)	0.6	50.0 / 37.5	9.57 (0.7-142.3+)	62.5
Skin	34.2 / 4.0	3.93 (0.1-54.3)	0.9	50.9 / 7.3	11.43 (0.3-146.6+)	70.0
Hypersensitivity / Infusion Reaction	2.8 / 0	0.14 (0.1-10.0)	0	11.1 / 0	0.14 (0.1-2.1)	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 8.5.1-2 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 + ipi and chemo arms were 131 (40.7%) 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 + ipi arm (any Grade): hypothyroidism/thyroiditis (15.5%), rash (13.7%), hypophysitis (6.5%), hyperthyroidism (5.9%), adrenal insufficiency (5.6%), hepatitis (4.0%), pneumonitis (3.7%), and diarrhea/colitis (3.4%)

- Proportion of subjects with Grade 3-4 IMAEs, by category: hypophysitis (3.1%); rash (2.5%); hepatitis (2.8%); pneumonitis and adrenal insufficiency (2.2% each); diarrhea/colitis (1.2%); nephritis/renal dysfunction, diabetes mellitus, and hyperthyroidism (0.6% each)

- 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 42). 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 + ipi 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 42: Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - All Subjects Treated with Nivolumab + Ipilimumab (N=322) 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 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	3.7 / 2.2	11.00 (3.6-36.6)	2.8 / 0.3	100 / 50.0	3.64 (0.1-115.3)	50.0	13.71 (0.3+-117.1+)	0 (0/0)
Diarrhea/Colitis	3.4 / 1.2	9.43 (1.7-37.1)	1.2 / 1.6	100 / 36.4	8.14 (0.6-112.9)	100	13.57 (0.7-25.3)	66.7 (2/3)
Hepatitis	4.0 / 2.8	4.29 (2.1-64.3)	1.9 / 2.2	100 / 69.2	6.71 (0.1-69.1)	84.6	8.14 (1.3-30.1)	33.3 (1/3)
Nephritis/Renal Dysfunction	1.2 / 0.6	7.21 (4.1-13.0)	0 / 0.6	100 / 75.0	4.43 (2.6-10.9)	75.0	9.57 (0.9-14.1)	100 (2/2)
Rash	13.7 / 2.5	5.07 (0.3-80.0)	0.6 / 2.8	100 / 20.5	5.57 (0.1-129.6)	68.2	11.86 (0.3-122.1+)	37.5 (3/8)
Hypersensitivity	0.3 / 0	2.14 (2.1-2.1)	0 / 0	100 / 0	0.14 (0.1-0.1)	100	0.14 (0.1-0.1)	0 (0/0)
Adrenal Insufficiency	5.6 / 2.2	14.71 (6.1-72.9)	1.6 / 2.8	77.8 / 5.6	65.36 (0.6-143.9)	16.7	N.A. (0.7-144.7+)	0 (0/4)

Table 42: Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - All Subjects Treated with Nivolumab + Ipilimumab (N=322) 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 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)
Hypophysitis	6.5 / 3.1	12.00 (2.7-63.3)	0.9 / 4.3	81.0 / 23.8	65.14 (3.1-142.0)	23.8	N.A. (1.9-142.0+)	0 (0/5)
Hypothyroidism/ Thyroiditis	15.5 / 0.3	7.86 (2.1-36.4)	0.6 / 3.1	10.0 / 2.0	30.71 (2.3-92.0)	26.0	N.A. (0.6-148.7+)	33.3 (1/3)
Hyperthyroidism	5.9 / 0.6	6.14 (1.9-16.3)	0.3 / 1.2	10.5 / 5.3	5.21 (3.3-7.1)	78.9	7.36 (0.4+-48.4+)	0 (0/3)
Diabetes Mellitus	1.6 / 0.6	39.29 (4.3-59.4)	0.6 / 0.9	0 / 0	N.A. (N.A.-N.A.)	0	N.A. (11.0+-138.6+)	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 8.5.2-2 of CA209648 Primary CSR

Other Events of Special Interest

OESIs do not fulfill all criteria to qualify as IMAEs but may require immunosuppression 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 43):

- 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 43. 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 44 (30-day follow-up, SI units):

Table 44. 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 45).

Table 45. 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 46). 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 46. 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 + ipi vs chemo arms, frequencies of subjects with all-causality (Table 47) and drug-related AEs (Table 48) in the subgroups of sex, age category, race, and region were comparable overall to the frequencies of subjects with AE 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 and ≥85 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 47. 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 48. 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 + Ipilimumab

Of the 281 nivolumab ADA-evaluable subjects in the nivo + ipi arm, 19 (6.8%) subjects were nivolumab ADA positive at baseline, and 68 (24.2%) subjects were nivolumab ADA positive after start of treatment (Table 49).

- 1 (0.4%) subject was considered persistent positive, and 6 (2.1%) subjects were neutralizing ADA positive.
- Two subjects were positive for nivolumab ADA at baseline, but the titers of post-baseline ADA and neutralizing ADA samples did not exceed ≥ 4-fold titer increase from baseline. Thus, both subjects were not qualified for the definition of ADA-positive or NAb-positive.
- The highest nivolumab ADA titer values observed were 256 and 512, which occurred in 1 subject each. All other titers were low, ranging from 1 to 64.

Of the 282 ipilimumab ADA-evaluable subjects in the nivo + ipi arm, 6 (2.1%) subjects were ipilimumab ADA-positive at baseline and 17 (6.0%) subjects were ipilimumab ADA-positive after the start of treatment (Table 49).

- 1 (0.4%) subject was considered persistent positive for ipilimumab ADA only, and 1 (0.4%) subject was neutralizing ADA positive for ipilimumab ADA only.
- Ipilimumab ADA titers were low, ranging from 1 to 64.

Table 49. 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 and/or ipilimumab ADAs and NAbs continued treatment with clinical benefit, and there was no apparent trend showing an effect of positive ADA or NAbs on the efficacy of nivo + ipi.

A BOR of CR or PR per BICR was reported in 24 out of 68 nivolumab ADA-positive subjects and in 7 out of 17 ipilimumab ADA-positive subjects. The ADA titers among all ADA-positive subjects ranged from 1 to 512 for nivolumab and 1 to 64 for ipilimumab. Though these results are based on small sample sizes and should be interpreted with caution, these results are consistent with the ORR observed for all randomized subjects in the nivo + ipi arm (27.7%), which included subjects negative for ADA.

Overall, the incidences of nivolumab and ipilimumab NAbs were low.

- Of the 6 subjects with nivolumab NAbs (Table 49):
    - BORs per BICR were SD for 4 subjects (66.7%) and PD for 2 subjects (33.3%). There were no subjects with CR or PR per BICR.
    - The nivolumab ADA titers in these subjects ranged from 1 to 256.
- For the 1 subject in the nivo + ipi arm with ipilimumab NAbs, BOR per BICR was SD.
    - The ipilimumab ADA titers in this subject ranged from 4 to 64.

Effect of Immunogenicity on Safety

Overall, an effect of ADA on the safety of nivo + ipi treatment was not observed (Table 50).

Among the nivo + ipi-treated subjects evaluable for nivolumab ADA, the proportions of subjects with hypersensitivity/infusion-related reaction select AEs was 4/68 (5.9%) subjects in the nivolumab ADA-

positive subgroup vs 8/213 (3.8%) subjects in the nivolumab ADA-negative subgroup. However, though the sample size of the ADA-positive group limits interpretation, all of these hypersensitivity/infusion reactions were Grade 1 or 2, and all events resolved.

Among the nivo + ipi-treated subjects evaluable for ipilimumab ADA, the proportion of subjects with hypersensitivity/infusion-related reaction select AEs was higher in the ipilimumab ADA positive subgroup (2/17 subjects, 11.8%) vs ipilimumab ADA-negative subgroup (10/265 subjects, 3.8%) (Table 50). However, though the sample size of the ADA-positive group limits interpretation, all of these hypersensitivity/infusion reactions were Grade 1 or 2, and all events resolved.

Table 50. 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.

Between the nivo + ipi and chemo arms, the overall proportions of subjects were comparable for all-causality AEs leading to discontinuation (25.2% vs 25.3%) and for drug-related AEs leading to discontinuation (17.7% vs 19.4%).

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 51). 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 52). 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 51. 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
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 52. 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 53).

Table 53: Summary of Safety - All Treated Subjects with Tumor 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 53: Summary of Safety - All Treated Subjects with Tumor 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 53: Summary of Safety - All Treated Subjects with Tumor 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
	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)

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 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W for Section 4.8 of the OPDIVO SmPC and Section 4.8 of the YERVOY SmPC.

- Integrate all-causality AEs data from CA209648 and CA209743 (1L unresectable malignant pleural mesothelioma) for the intended dose and regimen of nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W.
- Programmatically remap MedDRA PTs representing the same or similar clinical conditions for the integrated AE data and generate summary tables.
- Identify clinically relevant events based on BMS medical review of the all-causality re-mapped AE summary table.
- Present resulting clinically relevant re-mapped events by SOC and all-causality frequency in the final adverse drug reaction (ADR) table.
- To calculate the frequencies of laboratory ADR, BMS used the laboratory abnormality change from baseline tables.

As explained above, for labeling 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 nivolumab and ipilimumab SmPC, selection of specific ADRs (Section 4.8 of the nivolumab and ipilimumab SmPC) is based on clinical relevance as determined by the BMS medical reviewer.

A review of all-causality AEs was conducted for CA209648 and the integrated safety data from CA209648 and CA209743 to ensure that the 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 for both nivolumab and ipilimumab reflects the ADRs that were observed with nivo + ipi 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. In line with the above mentioned guidelines, frequency of ADR is presented based on all-causality AEs. To calculate the frequencies of laboratory ADR, BMS used the laboratory abnormality change from baseline tables for the pooled subjects from CA209648 + CA209743 (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. Also note: CA209648 scheduled safety assessment did not include the collection of amylase and lipase data; hence, the total amylase and total lipase in Section 4.8 of the SmPC under nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in the 3rd column of Table 7 remain unchanged and are based only on data from CA209743 (MPM).

OPDIVO SmPC

The presentation of ADRs in Section 4.8 of the current approved OPDIVO SmPC displays 3 columns in Table 7, one for nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, one for nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in renal cell carcinoma (RCC) and dMMR or MSI-H colorectal cancer (CRC), and one for nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in malignant pleural mesothelioma (MPM).

With the current application, the 3rd column in the ADR table is updated with pooled data from 1L treatment of OSCC (n=322 of treated patients from CA209648) and 1L treatment of MPM (n=300 of treated patients from CA209743) for nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W. The intended dose regimen and/or schedule of administration for OSCC was the same as the approved regimen for MPM. 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.

YERVOY SmPC

The presentation of ADRs in Section 4.8 of the current approved YERVOY SmPC displays 3 columns in Table 5, one for ipilimumab 3 mg/kg in combination with nivolumab 1 mg/kg in melanoma, one for ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in RCC and dMMR or MSI-H CRC, and one for ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg in MPM.

With the current application, the 3rd column in the ADR table is updated with pooled data from 1L treatment of OSCC (n=322 of treated patients from CA209648) and 1L treatment of MPM (n=300 of treated patients from CA209743) for ipilimumab 1 mg/kg Q6W in combination with nivolumab 3 mg/kg Q2W. The intended dose regimen and/or schedule of administration for OSCC was the same as the approved regimen for MPM. The patient population with tumor cell PD L1 ≥ 1% from CA209648 presented with a similar safety profile, and a qualitative statement was added in the Section 4.8 of the YERVOY SmPC.

OPDIVO and YERVOY Package Leaflets (PL)

In line with the approach for the SmPC, PL Sections 4 is updated. With this application, the list of side effects reported in 'clinical trials with nivolumab in combination with ipilimumab' is updated with highest frequency, as needed.

Presentation of Clinically Relevant Adverse Reactions

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

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

Safety Results of Nivolumab in Combination with Ipilimumab in First-Line OSCC (CA209648) and Pooled Studies across Tumour Types

Safety data for 1L treatment of OSCC with nivo + ipi from CA209648 were pooled with safety data for 1L treatment of MPM with Nivo + ipi from CA209743. The intended dose regimen and/or schedule of administration for OSCC was the same as the approved regimen for MPM: nivolumab 3 mg/kg Q2W in combination with ipilimumab 1 mg/kg Q6W.

A summary of re-mapped all-causality, and drug-related AEs (within 30 days of the last dose) for nivo + ipi arm in CA209648 (n=322) is shown side-by-side with the integrated safety data from CA209743 (n=300), and pooled analysis of the nivo + ipi arm from CA209648 and CA209743 (n=622) in Table 54 and Table 55, respectively. Overall, the types of AEs reported in CA209648 were consistent with CA209743 and the pooled analysis of CA209648 and CA209743 for nivolumab in combination with ipilimumab.

The frequencies of any grade, all-causality, and drug-related AEs were comparable or lower in nivo + ipi treated subjects in CA209648 when compared with the pooled analysis except the following differences:

- The frequencies of any grade all-causality AEs were higher in nivo + ipi treated subjects in CA209648 vs the pooled for dysphagia (11.8% vs 7.2%), anaemia (23.0% vs 19.1%), pneumonia (14.3% vs 10.5%), transaminase increased (15.2% vs 12.2%), and weight decreased (12.1% vs 8.8%) (Table 54).
- The frequencies of drug-related AEs were higher in nivo + ipi treated subjects in CA209648 vs the pooled for, transaminases increased (10.9% vs 8.8%) and stomatitis (5.9% vs 4.0%) (Table 55).

Table 54. Summary of Any Adverse Events using Re-mapped Terms Occurring in At Least 10% of Subjects – All Nivolumab + Ipilimumab Treated Subjects from CA209748, CA209743 and Pooled Analysis (CA209648 + CA209743)

	CA209648			CA209743			Nivo + Ipi Pooled		
	Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 322			Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 300			Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 622		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	316 (98.1)	192 (59.6)	31 (9.6)	299 (99.7)	159 (53.0)	25 (8.3)	615 (98.9)	351 (56.4)	56 (9.0)
Gastrointestinal disorders	219 (68.0)	52 (16.1)	2 (0.6)	186 (62.0)	28 (9.3)	0	405 (65.1)	80 (12.9)	2 (0.3)
Diarrhoea	71 (22.0)	6 (1.9)	0	94 (31.3)	12 (4.0)	0	165 (26.5)	18 (2.9)	0
Nausea	72 (22.4)	2 (0.6)	0	73 (24.3)	2 (0.7)	0	145 (23.3)	4 (0.6)	0
Constipation	66 (20.5)	1 (0.3)	0	56 (18.7)	1 (0.3)	0	122 (19.6)	2 (0.3)	0
Vomiting	47 (14.6)	5 (1.6)	0	43 (14.3)	0	0	90 (14.5)	5 (0.8)	0
Abdominal pain	33 (10.2)	3 (0.9)	0	46 (15.3)	3 (1.0)	0	79 (12.7)	6 (1.0)	0
Stomatitis	35 (10.9)	2 (0.6)	0	15 (5.0)	0	0	50 (8.0)	2 (0.3)	0
Dysphagia	38 (11.8)	17 (5.3)	0	7 (2.3)	1 (0.3)	0	45 (7.2)	18 (2.9)	0
General disorders and administration site conditions	159 (49.4)	13 (4.0)	4 (1.2)	206 (68.7)	28 (9.3)	0	365 (58.7)	41 (6.6)	4 (0.6)
Fatigue	69 (21.4)	8 (2.5)	0	129 (43.0)	13 (4.3)	0	198 (31.8)	21 (3.4)	0
Pyrexia	73 (22.7)	3 (0.9)	0	55 (18.3)	4 (1.3)	0	128 (20.6)	7 (1.1)	0
Oedema	24 (7.5)	0	0	52 (17.3)	0	0	76 (12.2)	0	0
Chest pain	11 (3.4)	1 (0.3)	0	61 (20.3)	9 (3.0)	0	72 (11.6)	10 (1.6)	0
Skin and subcutaneous tissue disorders	154 (47.8)	14 (4.3)	0	154 (51.3)	12 (4.0)	0	308 (49.5)	26 (4.2)	0
Rash	99 (30.7)	10 (3.1)	0	91 (30.3)	7 (2.3)	0	190 (30.5)	17 (2.7)	0
Pruritus	56 (17.4)	3 (0.9)	0	62 (20.7)	3 (1.0)	0	118 (19.0)	6 (1.0)	0
Respiratory, thoracic and mediastinal disorders	124 (38.5)	28 (8.7)	4 (1.2)	169 (56.3)	27 (9.0)	2 (0.7)	293 (47.1)	55 (8.8)	6 (1.0)
Cough	42 (13.0)	1 (0.3)	0	69 (23.0)	2 (0.7)	0	111 (17.8)	3 (0.5)	0
Dyspnoea	27 (8.4)	2 (0.6)	0	82 (27.3)	7 (2.3)	0	109 (17.5)	9 (1.4)	0
Metabolism and nutrition disorders	160 (49.7)	63 (19.6)	0	122 (40.7)	22 (7.3)	1 (0.3)	282 (45.3)	85 (13.7)	1 (0.2)
Decreased appetite	56 (17.4)	13 (4.0)	0	71 (23.7)	3 (1.0)	0	127 (20.4)	16 (2.6)	0

System Organ Class (%) Preferred Term (%)	CA209648 Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 322			CA209743 Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 300			Nivo + Ipi Pooled Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 622		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Infections and infestations	119 (37.0)	47 (14.6)	2 (0.6)	130 (43.3)	25 (8.3)	2 (0.7)	249 (40.0)	72 (11.6)	4 (0.6)
Pneumonia	46 (14.3)	25 (7.8)	2 (0.6)	19 (6.3)	8 (2.7)	0	65 (10.5)	33 (5.3)	2 (0.3)
Upper respiratory	23 (7.1)	4 (1.2)	0	36 (12.0)	1 (0.3)	0	59 (9.5)	5 (0.8)	0
Investigations	129 (40.1)	34 (10.6)	0	100 (33.3)	31 (10.3)	0	229 (36.8)	65 (10.5)	0
Transaminases increased	49 (15.2)	12 (3.7)	0	27 (9.0)	8 (2.7)	0	76 (12.2)	20 (3.2)	0
Weight decreased	39 (12.1)	6 (1.9)	0	16 (5.3)	0	0	55 (8.8)	6 (1.0)	0
Musculoskeletal and connective tissue disorders	78 (24.2)	6 (1.9)	0	117 (39.0)	13 (4.3)	0	195 (31.4)	19 (3.1)	0
Musculoskeletal pain	46 (14.3)	2 (0.6)	0	72 (24.0)	4 (1.3)	0	118 (19.0)	6 (1.0)	0
Arthralgia	20 (6.2)	0	0	52 (17.3)	5 (1.7)	0	72 (11.6)	5 (0.8)	0
Blood and lymphatic system disorders	99 (30.7)	32 (9.9)	0	69 (23.0)	19 (6.3)	0	168 (27.0)	51 (8.2)	0
Anaemia	74 (23.0)	20 (6.2)	0	45 (15.0)	8 (2.7)	0	119 (19.1)	28 (4.5)	0
Endocrine disorders	85 (26.4)	19 (5.9)	0	57 (19.0)	5 (1.7)	1 (0.3)	142 (22.8)	24 (3.9)	1 (0.2)
Hypothyroidism	45 (14.0)	0	0	39 (13.0)	0	0	84 (13.5)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	65 (20.2)	27 (8.4)	18 (5.6)	42 (14.0)	12 (4.0)	19 (6.3)	107 (17.2)	39 (6.3)	37 (5.9)
Malignant neoplasm	43 (13.4)	22 (6.8)	18 (5.6)	32 (10.7)	9 (3.0)	19 (6.3)	75 (12.1)	31 (5.0)	37 (5.9)

MedDRA Version: 23.1; CTC Version 4.0
Includes events reported between first dose and last dose of therapy + 30 days.
Some preferred terms are re-mapped based on BMS medical review.
Nivo + Ipi pooled group consists of Nivo + Ipi treatment group from studies CA209743 and CA209648.
Source: Appendix GI.145A-EUSMPC.1.1 in Appendix 1

Table 55. Summary of Drug-related Adverse Events using Re-mapped Terms Occurring in At Least 5% of Subjects – All Nivolumab + Ipilimumab Treated Subjects from CA209648, CA209743 and Pooled Analysis (CA209743 + CA209648)

System Organ Class (%) Preferred Term (%)	CA209648 Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 322			CA209743 Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 300			Nivo + Ipi Pooled Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 622		
	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)	240 (80.0)	91 (30.3)	1 (0.3)	496 (79.7)	193 (31.0)	3 (0.5)
Skin and subcutaneous tissue disorders	118 (36.6)	14 (4.3)	0	116 (38.7)	10 (3.3)	0	234 (37.6)	24 (3.9)	0
Rash	81 (25.2)	10 (3.1)	0	74 (24.7)	6 (2.0)	0	155 (24.9)	16 (2.6)	0
Pruritus	43 (13.4)	3 (0.9)	0	49 (16.3)	3 (1.0)	0	92 (14.8)	6 (1.0)	0
Gastrointestinal disorders	95 (29.5)	15 (4.7)	0	102 (34.0)	17 (5.7)	0	197 (31.7)	32 (5.1)	0
Diarrhoea	32 (9.9)	2 (0.6)	0	62 (20.7)	10 (3.3)	0	94 (15.1)	12 (1.9)	0
Nausea	26 (8.1)	1 (0.3)	0	30 (10.0)	1 (0.3)	0	56 (9.0)	2 (0.3)	0
Vomiting	18 (5.6)	4 (1.2)	0	8 (2.7)	0	0	26 (4.2)	4 (0.6)	0
Stomatitis	19 (5.9)	0	0	6 (2.0)	0	0	25 (4.0)	0	0
General disorders and administration site conditions	68 (21.1)	7 (2.2)	0	88 (29.3)	3 (1.0)	0	156 (25.1)	10 (1.6)	0
Fatigue	36 (11.2)	5 (1.6)	0	65 (21.7)	3 (1.0)	0	101 (16.2)	8 (1.3)	0
Pyrexia	26 (8.1)	1 (0.3)	0	16 (5.3)	0	0	42 (6.8)	1 (0.2)	0
Endocrine disorders	83 (25.8)	19 (5.9)	0	51 (17.0)	5 (1.7)	0	134 (21.5)	24 (3.9)	0
Hypothyroidism	43 (13.4)	0	0	33 (11.0)	0	0	76 (12.2)	0	0
Hyperthyroidism	20 (6.2)	2 (0.6)	0	11 (3.7)	0	0	31 (5.0)	2 (0.3)	0
Investigations	63 (19.6)	17 (5.3)	0	59 (19.7)	22 (7.3)	0	122 (19.6)	39 (6.3)	0
Transaminases increased	35 (10.9)	8 (2.5)	0	20 (6.7)	6 (2.0)	0	55 (8.8)	14 (2.3)	0
Amylase increased	8 (2.5)	4 (1.2)	0	17 (5.7)	7 (2.3)	0	25 (4.0)	11 (1.8)	0
Lipase increased	5 (1.6)	5 (1.6)	0	20 (6.7)	13 (4.3)	0	25 (4.0)	18 (2.9)	0
Metabolism and nutrition disorders	47 (14.6)	20 (6.2)	0	37 (12.3)	7 (2.3)	0	84 (13.5)	27 (4.3)	0
Decreased appetite	19 (5.9)	5 (1.6)	0	29 (9.7)	2 (0.7)	0	48 (7.7)	7 (1.1)	0
Respiratory, thoracic and mediastinal disorders	39 (12.1)	11 (3.4)	1 (0.3)	32 (10.7)	2 (0.7)	0	71 (11.4)	13 (2.1)	1 (0.2)

System Organ Class (%) Preferred Term (%)	CA209648 Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 322			CA209743 Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 300			Nivo + Ipi Pooled Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W N = 622		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Pneumonitis	26 (8.1)	9 (2.8)	0	19 (6.3)	2 (0.7)	0	45 (7.2)	11 (1.8)	0
Musculoskeletal and connective tissue disorders	21 (6.5)	0	0	44 (14.7)	6 (2.0)	0	65 (10.5)	6 (1.0)	0
Musculoskeletal pain	9 (2.8)	0	0	25 (8.3)	1 (0.3)	0	34 (5.5)	1 (0.2)	0
Arthralgia	4 (1.2)	0	0	23 (7.7)	2 (0.7)	0	27 (4.3)	2 (0.3)	0
Hepatobiliary disorders	23 (7.1)	13 (4.0)	0	23 (7.7)	14 (4.7)	0	46 (7.4)	27 (4.3)	0
Hepatic function abnormal	16 (5.0)	7 (2.2)	0	9 (3.0)	5 (1.7)	0	25 (4.0)	12 (1.9)	0
Injury, poisoning and procedural complications	9 (2.8)	0	0	26 (8.7)	3 (1.0)	0	35 (5.6)	3 (0.5)	0
Infusion related reaction	8 (2.5)	0	0	24 (8.0)	3 (1.0)	0	32 (5.1)	3 (0.5)	0

MedDRA Version: 23.1; CTC Version 4.0
Includes events reported between first dose and last dose of therapy + 30 days.
Some preferred terms are re-mapped based on BMS medical review.
Nivo + Ipi pooled group consists of Nivo + Ipi treatment group from studies CA209743 and CA209648.
Source: Appendix GI.143-EUSMPC.1.1 in Appendix 1

Additional safety data for nivo+ipi treated subjects in CA209648 vs pooled analysis of all nivo + ipi treated subjects in CA209648 and CA209743 (N=622) have been generated to support the SmPC.

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 + ipi arm were to receive nivolumab 240 mg as a 30-min IV infusion Q2W and ipilimumab 1 mg/kg as a 30-minute IV infusion Q6W. Patients in the chemo arm received 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. At the time of the DBL (1-Mar-2021), with a minimum follow-up of 12.9 months, a total of 886 subjects (94.7%) had discontinued treatment, 301 (93.5%) from the nivo + ipi arm and 300 (98.7%) from the chemotherapy treatment arm. The main reason for not continuing in the treatment period was disease progression in all cases but, for 59 (18.3%) subjects from the nivo + ipi arm and 40 (13.2%) from the chemotherapy arm, the reason for not continuing in the treatment period was reported as study drug toxicity. The median duration of study therapy was 2.79 (0 -24.0) months in the nivo + ipi arm and 3.35 (0-19.0) months in the chemo arm. The median number of treatment doses received by subjects in the nivo + ipi arm was 6 (1-52) for nivolumab and 3 (1-18) for ipilimumab while, in the chemotherapy arm, the median number of doses was 4 for each component (1-17 cisplatin, 1-21 fluorouracil), partly due to higher rate of disease progression (54% vs. 63.5%) reported by subjects from the chemo arm. The proportion of patients who received ≥90% of the planned relative dose intensity was comparable between both treatment groups but these figures are difficult to be interpreted, as in the nivo + ipi arm relative dose intensity accounts for dose delays (no dose reductions are allowed) and in the chemo arm, variations from the planned relative dose intensity account for dose reductions and cycle delays. 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 + ipi arm were nausea and pyrexia (22.4% each), diarrhoea and anaemia (22.0% each), rash (21.7%), constipation (20.5%) and neoplasms (20.2%) 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 59.6% of subjects in the nivo + ipi arm and 54.3% in the chemo arm. The most common (>5%) Grade 3-4 AEs were pneumonia (6.8%), malignant neoplasm progression (6.5%), anaemia (6.2%), and dysphagia (5.3%) in the nivo + ipi 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 79.5% of subjects in the nivo + ipi arm

and 90.5% subjects in the chemo arm, being the most commonly reported: rash (17.1%), and pruritus and hypothyroidism (13.4% each) in the nivo + ipi 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 31.7% of subjects in the nivo + ipi arm and the 35.5% subjects from the chemo arm, being the most common: hyponatraemia (2.5%); and rash, adrenal insufficiency, pneumonitis, alanine aminotransferase increased, and hepatic function abnormal (2.2% each) in the nivo + ipi 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 + ipi arm compared with the chemo arm (66.5% vs. 42.1%). The most frequently reported were malignant neoplasm progression (12.4%), pneumonia (7.5%), and pneumonitis and pyrexia (3.7% each) in the nivo + ipi arm; and malignant neoplasm progression (4.9%), dysphagia and pneumonia (3.6% each), oesophageal stenosis (3.3%) in the chemo treatment arm. Focusing on drug-related SAEs, they were reported by 32% subjects in the nivo + ipi arm and 16.1% in the chemo arm, being the most common SAEs pneumonitis (3.7%), hepatic function abnormal (2.5%), adrenal insufficiency (2.2%) in the nivo + ipi arm and vomiting (3.0%), and pulmonary embolism, diarrhoea, nausea, hyponatraemia, dehydration, atrial fibrillation, and acute kidney injury (1.0% each) in the chemo treatment arm.

Up to the data cut-off (DCO), the number of patients who died was numerically lower in the nivo + ipi arm compared with the chemo arm (66.8% 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 + ipi arm and 4 (1.3%) in the chemo treatment arm. The SAEs reported as primary reason for death in the nivo + ipi arm were: pneumonitis (2 subjects), interstitial lung disease, pulmonary embolism and acute respiratory syndrome. Up to the latest DBL (4 Oct 2021), 72.7% subjects in the nivo + ipi arm and 79.6% subjects in the chemo arm had died. The main reasons of death were generally consistent with the previous ones although there were two deaths reassessed as drug toxicity in the nivo + ipi arm.

Adverse events of special interest (AESI) for nivolumab and ipilimumab are classified into Select Adverse Events, immune-mediated AEs (IMAEs) and other events of special interest (OESIs). The most frequently reported drug-related select AE categories were skin (34.2%), endocrine (27.3%) and hepatic (13.0%) in the nivo + ipi arm, and renal (18.8%), gastrointestinal (15.5%), and hepatic (3.9%) in the chemo arm. By PT, the most common select AEs were rash (17.1%), hypothyroidism and pruritus (13.4% each), and diarrhoea (9.9%), and diarrhoea (15.1%), blood creatinine increased (10.5%), and acute kidney injury (3.3%) in the chemotherapy treatment arm. As seen with other nivolumab therapeutic indications, endocrine AEs tend to have the lowest rate resolved events (28.6% of subjects), followed by renal (62.5%) and pulmonary (65.4%) in the nivo + ipi treatment arm. Regarding IMAEs, analyses included endocrine events in addition to all events which required immunosuppressive therapy for their management. As expected, incidence of IMAEs was higher in the nivo + ipi arm compared with the chemo arm where rash (0.7%) was the only reported event of this type. In the nivo + ipi arm, 40.7% of subjects reported any IMAE being the most common: hypothyroidism/thyroiditis (15.5%), rash (13.7%), hypophysitis (6.5%), hyperthyroidism (5.9%), adrenal insufficiency (5.6%), hepatitis (4.0%), pneumonitis (3.7%), and diarrhoea/colitis (3.4%). The proportion of subjects who reported Grade 3-4 IMAEs (by category) was hypophysitis (3.1%), rash (2.5%), hepatitis (2.8%), pneumonitis and adrenal insufficiency (2.2% each), diarrhoea/colitis (1.2%), nephritis/renal dysfunction, diabetes mellitus, and hyperthyroidism (0.6% each). OESIs, events that do not fulfil all criteria to be considered IMAEs but which may require immunosuppression for their management, were reported by 14 subjects from the nivo + ipi group. These events were Grade 2-4 pancreatitis, Grade 1 myocarditis, Grade 1-4 uveitis, Grade 2-4 encephalitis and Grade 1-2 myositis. All of them were considered resolved except for a Grade 1 event of myocarditis, one Grade 2 event of uveitis and Grade 1 myositis.

Focusing on laboratory abnormalities (up to 30 days after last treatment dose), reported increases in hepatic parameters were higher in the nivo + ipi arm compared with the chemo arm, while this trend was not observed regarding hematology values whose alterations are generally attributed to chemotherapy. 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 3/306 (1%) in the nivo + ipi 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 22.8% and the 7.6% of subjects from the nivo + ipi arm and the chemo arm, respectively. Electrolytes alterations were also slightly higher in the nivo + ipi arm compared with the chemo arm, although differences were not as remarkable as those observed for the third treatment arm (nivo + chemo). 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. Vital signs observations were submitted by individual patient listings in the initial application. Upon request, the MAH performed a manual review of PTs that could be linked to vital sign-related AEs. Overall, reported incidences of these events were comparable between both treatment arms with no relevant differences.

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 (24 subjects in each arm) and no data is available for ≥85.

The proportion of subjects with drug-related AEs leading to discontinuation was similar in the nivo + ipi arm vs. the chemo arm (17.7% vs. 19.4%). The most frequently reported drug-related AEs leading to discontinuation of study therapy were pneumonitis (2.5%), and adrenal insufficiency and hepatic function abnormal (1.6% each) in the nivo + ipi 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. Drug-related Grade 3-4 AEs leading to discontinuation were reported in 41 (12.7%) subjects from the nivo + ipi 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 PI, pooling of safety results from studies CA209648 (current application) and CA209743 (Malignant Pleural Mesothelioma therapeutic indication) has been proposed. This approach seems reasonable due to the fact that both studies were performed using the same posology (nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W). Detailed justification for the proposed information to be included in the PI has been submitted, comparing frequencies of AEs between both studies and the pooled analysis using the already explained re-mapping methodology. When comparing safety results from study CA209648 vs. the pooled dataset, some differences were identified: the incidences of any grade all-causality AEs were higher in nivo + ipi treated subjects in CA209648 for dysphagia (11.8% vs 7.2%), anaemia (23.0% vs 19.1%), pneumonia (14.3% vs 10.5%), transaminase increased (15.2% vs 12.2%), and weight decreased (12.1% vs 8.8%). Also, drug-related AEs were higher in nivo + ipi treated subjects in CA209648 vs the pooled for, transaminases increased (10.9% vs 8.8%) and stomatitis (5.9% vs 4.0%). These differences are not considered clinically relevant and the pooling strategy is endorsed.

2.5.2. Conclusions on clinical safety

The safety profile of nivolumab in combination with ipilimumab for the 1L treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC has been characterised based on the results from study CA209648, by comparison with subjects who received standard chemotherapy.

Subjects treated with nivolumab + ipilimumab reported less all-causality and drug-related AEs but considerably higher rates of SAEs, including drug-related SAEs. There was also high incidence of discontinuations due to drug-related Grade 3-4 AEs. Deaths attributable to treatment were comparable between arms. As expected, select AEs, IMAEs and OESIs were frequently reported with this combination, especially regarding endocrine, hepatic, pulmonary and skin categories. Early detention and management of these toxicities continue to be crucial for patients receiving this combination treatment.

For the purpose of including identified ADRs in the PI, safety results from study CA209648 have been pooled with those from study CA209743 (MPM), as both studies used the same posology.

Overall, the combination of nivolumab and ipilimumab in this OSCC setting presents considerable toxicity that, compared with standard chemotherapy, seems to be manageable but especial attention must be drawn to IMAEs and their established clinical management and follow-up.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted updated RMP versions with this application.

OPDIVO

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

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

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

Safety concerns

Table 56: 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

Table 56:	Summary of Safety Concerns
	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

The safety concerns remain unchanged.

Pharmacovigilance plan

Table 57: 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	Post-marketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and VKH), and infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCTOngoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission	With PSUR starting at DLP 03-Jul-2017 06-2019 4Q2022

The pharmacovigilance activities remain unchanged

Risk minimisation measures

Table 58: 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: Patient Alert Card	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Severe Infusion Reactions	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: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: 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
	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

Table 58: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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

The risk minimization measures and pharmacovigilance activities remain unchanged

Yervoy

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 35.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 35.0 with the following content:

Safety concerns

Table 59: Summary of Safety Concerns

Important identified risks	• GI irARs (eg, diarrhoea, colitis, GI perforation) • Hepatic irARs (eg, hepatitis) • Skin irARs (eg, rash, pruritus, TEN, and DRESS) • Neurologic irARs (eg, neuropathy) • Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency) • Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis) • Severe infusion reactions
Important potential risks	• Immunogenicity
Missing information	• Long-term safety in adolescent patients > 12 years of age • Potential PD interaction with systemic immunosuppressants • Patients with severe hepatic impairment • Patients with severe renal impairment • Patients with autoimmune disease

The safety concerns remain unchanged.

Pharmacovigilance plan

Table 60: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
MAH to sponsor extension of the Dutch Melanoma Treatment Registry (DMTR) to include paediatric subjects and to collect their safety data (CA184557)[i]	To obtain additional safety information in paediatric patients	Long-term safety in adolescent patients > 12 years of age	1. Synopsis of the DMTR	16-Apr-2018
			2. Submission of protocol	02-Nov-2019
			3. Start of data collection	End of 2Q 2019
			4. Recruitment period[a]	2Q 2019 until 1Q 2029
			5. Progress Report	End of 2Q 2022
			6. Interim Study Report	End of 2Q 2024
			7. End of data collection	End of Q1 2029
			6. Final report of study results	End of 2Q 2029

[a] The recruitment period began in 2Q 2019, when the Princess Maxima Center officially confirmed its collaboration to the paediatric extension of the DMTR, but the data will include all paediatric patients entered in the DMTR who received ipilimumab prior to the start of data collection.

The pharmacovigilance activities remain unchanged

Risk minimisation measures

Table 61: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Identified Risks Immune-related Adverse Reactions (GI irARs, hepatic irARs, skin irARs, neurological irARs, endocrine irARs, and other irARs)	Routine risk minimisation measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring, diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures:Patient Information Guide and Alert Card	Additional pharmacovigilance activities: None
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Section 4.3 Contraindication, Section 4.4 Special warnings, Section 4.8 Undesirable effects	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: • Patient Information Guide and Alert Card	Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 4.8 Immunogenicity	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Long-term safety in adolescent patients > 12 years of age	Routine risk minimisation measures: SmPC Section 4.2, 4.4, 4.8, and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A PIP for ipilimumab in malignant neoplasms (except melanoma, nervous system, haematopoietic, and lymphoid tissue) and a second PIP in melanoma have been completed in the EU. • Reporting of long-term safety data in paediatric patients in studies of nivolumab and ipilimumab combination therapy (CA209070 and CA209908[a]). • Monitoring of initial AEs and continued follow-up while on therapy and/or 100 days after the last dose by the treating physician. Follow-up information obtained by BMS using specified procedures (telephone interviews or

Table 61: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		mailing a questionnaire to the treating physician).
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: MAH to sponsor extension of the DMTR to include paediatric subjects and to collect their safety data (CA184557).
Potential PD interaction with systemic immunosuppressants	Routine risk minimisation measures: SmPC Section 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe renal impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

[a] The primary CSR for CA209908 was completed and reported to fulfil the obligation set out by Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation') for both OPDIVO and YERVOY. In the YERVOY PSUR #14, this study was listed as completed.

The risk minimization measures remain unchanged

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 agreed 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 WSA and has been found <acceptable> <unacceptable> for the following reasons:

The inclusion of the new proposed indication for Opdivo (i.e. in combination with ipilimumab 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 (nivolumab) in combination with Yervoy (ipilimumab) 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)[4]. 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[5].

The main risk factors for SCC 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 SCC, the value of palliative chemotherapy is less proved and best supportive care (BSC) or palliative monotherapy can also be considered[6]. 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[7]. 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

[4] GLOBOCAN 2020 (accessed October 2021)
[5] Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet. 2017 Nov 25;390(10110):2383-2396.
[6] 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
[7] NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric junction cancers. Version 4.2021.

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 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+ipi 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 67.1% nivo+ipi vs. 77.1% chemo) showed a statistically significant improvement in favour of the nivo+ipi arm over chemo arm (HR 0.64; 98.6% CI: 0.46, 0.90). Median OS was of 13.70 (95% CI: 11.24, 17.02) months in the nivo+ipi group and 9.07 (95% CI: 7.69, 9.95) months in the chemo group.

Regarding **PFS** (event rate 77.8% nivo+ipi vs. 63.7% chemo) no statistically significant differences were observed between treatment arms (HR 1.02; 98.5% CI: 0.73, 1.43). Median PFS was 4.04 (95% CI: 2.40, 4.93) months and 4.44 (95% CI: 2.89, 5.82) months, in the nivo+ipi and chemo groups, respectively.

Secondary endpoints

OS in the **all-randomised patients** (event rate of 66.5% in the nivo+ipi arm and 71.6% in the chemo arm), showed a statistically significant benefit of nivo+ipi over chemo (HR 0.78; 98.2% CI: 0.62, 0.98). Median OS was of 12.75 (95% CI: 11.27, 15.47) 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 1.26; 98.5% CI: NA, NA). Median PFS was 2.92 (95%CI: 2.66, 4.17) months in the nivo+ipi arm versus 5.59 (95% CI: 4.27, 5.88) months in the chemo arm.

The **ORR** (by BICR) was higher in the nivo+ipi arm compared with the chemo arm in patients with PD-L1≥1% (35.4% vs. 19.7%) while no differences were observed in the all-randomised patients (27.7% 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 the primary analysis.

3.3. Uncertainties and limitations about favourable effects

The combination of nivo+ipi demonstrated a statistically significant improvement in OS in the all-randomised patient population. However, this effect appears to be driven mostly by patients with tumour cell PD-L1 expression ≥1%. In patients with PD-L1<1%, the benefit of the combination of nivo+ipi over chemotherapy is not justified. As a result the indication was restricted to patients with tumour cell PD-L1 expression ≥1%.

Further, there was a higher rate of early deaths in the nivo+ipi arm compared with the chemo arm, being disease progression the main cause of these deaths. The delay in the onset of action of immunotherapy along with some prognostic factors appear the most plausible explanation. This issue has been observed in previous clinical trials with immunotherapy.

3.4. Unfavourable effects

In study CA209648, 98.1% of subjects in the nivo + ipi arm and 99% in the chemo arm reported any AEs. The most common AEs in the nivo + ipi arm were nausea and pyrexia (22.4% each), diarrhoea and anaemia (22.0% each), rash (21.7%), constipation (20.5%) and neoplasms (20.2%). Grade 3-4 AEs were reported by 59.6% subjects in the nivo + ipi arm compared with a 54.3% of subjects from the chemo arm.

Drug-related AEs were reported more frequently in the chemo arm (79.5% vs. 90.5%), being the most common events in the nivo + ipi arm: rash (17.1%), and pruritus and hypothyroidism (13.4% each).

SAEs were observed in 66.5% subjects in the nivo + ipi arm compared with the 42.1% in the chemo arm and same differences were observed for drug-related SAEs (32% vs. 16.1%). The most common drug-related SAEs reported in the nivo + ipi arm were pneumonitis (3.7%), hepatic function abnormal (2.5%) and adrenal insufficiency (2.2%). There were 5 (1.6%) subjects for which primary reason for death was recorded as study drug toxicity in the nivo + ipi arm and 4 (1.3%) subjects in the chemo arm.

IMAEs observed were in line with other already approved nivolumab and ipilimumab therapeutic indications.

The proportion of subjects with AEs leading to discontinuation was similar in both treatment arms (25.2% vs. 25.3%). Also, for drug-related AEs leading to discontinuation, the same trend was observed (17.7% vs. 19.4%).

3.5. Uncertainties and limitations about unfavourable effects

Liver tests abnormalities were more commonly reported in the nivo + ipi arm compared with the chemo arm but not all these 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 4.8 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) in combination with Yervoy (ipilimumab) 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)	13.70 (11.24, 17.02)	9.07 (7.69, 9.95)	HR 0.64 (98.6% CI: 0.46, 0.90); p[a] < 0.0010	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)	4.04 (2.40, 4.93)	4.44 (2.89, 5.82)	HR 1.02 (98.5% CI: 0.73, 1.43); p[a] =0.8958	CSR
Secondary endpoints (All randomised patients; N= 649)						
OS	Overall survival	Median, months (95%CI)	12.75 (11.27, 15.47)	10.71 (9.40, 11.93)	HR 0.78 (98.2% CI: 0.62, 0.98); p[a] = 0.0110	CSR
PFS	Progression free survival	Median, months (95%CI)	2.92 (2.66, 4.17)	5.59 (4.27, 5.88)	HR 1.26 (98.5% CI: NA, NA) p[a] = NA	CSR
ORR	Overall response rate per BICR (complete response + partial response)	% (95% CI)	27.7 (22.9, 32.9)	26.9 (22.1, 32.0)	Difference: 0.9 (95% CI: -5.9, 7.6)	CSR
Secondary endpoint (PD-L1≥1%); N= 315						
ORR	Overall response rate per BICR (complete response + partial response)	% (95% CI)	35.4 (28.0, 43.4)	19.7 (13.8, 26.8)	Difference: 15.7 (95% CI: 5.9, 25.4)	CSR
Unfavourable Effects[b]						
AEs	All causality (drug-related)	%	98.4 (79.5)	99 90.5)		
Grade 3-4 AEs	All causality (drug-related)	%	63.4 (32.6)	55.9 (36.2)		
Deaths	Due to study drug toxicity	%	1.9	1.6		
AE leading to DC	All causality (drug-related)	%	26.4 (18.3)	26.6 (2.7)		
SAEs	All causality (drug-related)	%	68 (32.6)	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 treatment with nivolumab in combination with ipilimumab showed a statistically significant improvement in OS compared with chemotherapy (fluorouracil plus cisplatin) in the all-randomised patient population. No statistically significant differences were observed between both treatment arms in PFS, as assessed by BICR. However, results in the overall population are considered

to be driven by patients with tumour cell PD-L1≥1% (primary efficacy population). In patients with PD-L1<1%, the benefit of the combination of nivo+ipi over chemotherapy is not justified and therefore the indication has been restricted to patients with tumour cell PD-L1 expression ≥1%.

From a safety point of view the combination of nivo+ ipi is characterised by substantial toxicity, with a higher rate of SAEs compared with chemotherapy. The most commonly reported drug-related AEs with nivo+ipi were rash, pruritus and hypothyroidism. As expected, select AEs, IMAEs and OESIs were frequently reported with this combination, especially regarding endocrine, hepatic, pulmonary and skin categories. However, overall the safety profile appears in line with the already known safety profile of this combination.

3.7.2. Balance of benefits and risks

Nivolumab in combination with ipilimumab has demonstrated superiority over chemotherapy in OS (and ORR) in patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥1%. Moreover, while this combination entails an important toxicity it may be an alternative treatment option for this patient population with a different safety profile.

Having all considered, the benefit/risk balance of nivolumab in combination with ipilimumab in the claimed indication is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk of Opdivo and Yervoy in the currently applied 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 treatment of 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 in combination with Yervoy; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 26.2 of the Opdivo RMP and version 35.0 of the Yervoy RMP have also been submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to 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 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'OPDIVO/Yervoy-H-C-3985/2213/WS/2113'

[i] Protocol CA184557: Long-term Follow-up of Ipilimumab-treated Pediatric Patients Enrolled in the Dutch Melanoma Treatment Registry (DMTR). Bristol Myers Squibb Company; 2019. Document Control No. 930139126.