16 September 2021
EMA/556100/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0096

Note

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

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List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BIRC	blinded independent review committee
Chemo	chemotherapy
CI	confidence interval
CNS	central nervous system
CPS	combined positive score
CSR	clinical study report
CTC	Common Terminology Criteria
DBL	database lock
DMC	data monitoring committee
FOLFOX	folinic acid, fluorouracil and oxaliplatin
GC	gastric cancer
GCP	good clinical practice
GEJC	gastric oesophageal junction carcinoma
GI	gastrointestinal
HLGT	high-level group term
HR	hazard ratio
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IR	infusion reaction
ISR	incurred sample reanalysis
IV	intravenous
LLN	lower limit of normal
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimum important difference
NA	not available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Nivo	nivolumab
Nivo+chemo	nivolumab + chemotherapy
OAC/EAC	oesophageal adenocarcinoma
OESI	other events of special interest
ORR	overall response rate
OS	overall survival
PBRER	Periodic Benefit-Risk Evaluation Report
PD-L1	programmed cell death ligand 1
PFS	progression free survival
PK	pharmacokinetics

PT	preferred term
QD	daily
RMP	Risk Management Plan
SAE	serious adverse event
SCS	Summary of Clinical Safety
SI	International System of Units
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	system organ class
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
XELOX	capecitabine and oxaliplatin

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 25 November 2020 an application for a variation.

The following changes were proposed:

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

Extension of indication to use OPDIVO (nivolumab) in combination with fluoropyrimidine- and platinum-based combination chemotherapy, in first-line treatment of adult patients with advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma (Study CA209649); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21.0 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0432/2020, P/0433/2020, on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application P/0433/2020, was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek scientific advice at the CHMP.

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

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: Paula Boudewina van Hennik

Timetable	**Actual dates**
Submission date	25 November 2020
Start of procedure:	26 December 2020

Timetable	Actual dates
CHMP Rapporteur's preliminary assessment report circulated on:	24 February 2021
CHMP Co-Rapporteur's Rapporteur's preliminary assessment report circulated on:	24 February 2021
PRAC Rapporteur's preliminary assessment report circulated on:	26 February 2021
PRAC RMP advice and assessment overview adopted by PRAC on:	11 March 2021
CHMP Rapporteurs' updated joint assessment report circulated on:	19 March 2021
Request for supplementary information adopted by the CHMP on:	25 March 2021
MAH's responses submitted to the CHMP on:	19 May 2021
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on:	6 July 2021
CHMP Rapporteurs' updated joint assessment report on the MAH's responses circulated on:	16 July 2021
2nd Request for supplementary information adopted by the CHMP on:	22 July 2021
MAH's responses submitted to the CHMP on:	13 August 2021
CHMP Rapporteurs' preliminary joint assessment report on the MAH's responses circulated on:	1 September 2021
CHMP Rapporteurs' updated joint assessment report on the MAH's responses circulated on:	15 September 2021
CHMP Opinion adopted on:	16 September 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Gastric cancer (GC) is the 5th leading cancer and the 3rd leading cause of cancer-related deaths worldwide[1]. Oesophageal cancer is the 7th leading cancer and the 6th leading cause of cancer-related deaths worldwide. GC/gastric oesophageal junction carcinoma (GEJC)/oesophageal adenocarcinoma (OAC) remain a leading cause of cancer-related mortality worldwide, with an estimated 1 million deaths worldwide in 2018.[2]

Adenocarcinoma is the most common (> 90%) histological subtype for GCs worldwide and OAC has increased in North America and Europe (EU)[3,4]. GEJC anatomically straddles the distal oesophagus and proximal stomach and due to its location and the same adenocarcinoma histology, GEJ tumours are

[1] Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol. 2019; 14: 26–38.
[2] Lin D, Khan U, Goetze TO, et al. Gastroesophageal Junction Adenocarcinoma: Is There an Optimal Management? American Society of Clinical Oncology Educational Book 2019; 39, e88-e95.
[3] Ajani JA, Lee J, Sano T, et al. Gastric adenocarcinoma. Nat Rev Dis Primers 2017; 3:17036.
[4] Rustgi AK and El-Serag HB. Esophageal carcinoma. N Engl J Med 2014; 371:2499-2509.

frequently grouped together with GC. Advanced or metastatic OAC, GEJC, and GC are considered similar diseases and the same treatment approach is recommended.[5,6,7,8,9]

GC, including GEJ carcinoma, is a heterogeneous disease with several established risk factors, including environmental, genetic, and behavioural risks. The aetiology of this disease is complex and multifactorial. Environmental and lifestyle factors such as Helicobacter pylori infection, smoking, high salt intake, low vegetable intake, and obesity have been associated with GC. There has been a steady decline in GC mortality attributable to dietary and lifestyle changes worldwide and to decreasing infection with H. pylori, which is considered the main cause in Asian countries. However, the incidence of GEJ tumours has increased in the US and Europe (~35%) considerably due to increases in risk factors such as obesity and gastroesophageal reflux disease, while remaining only 20% in Asian countries.

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 persons. OAC is three to four times as common in men as it is in women.

Claimed therapeutic indication

The new claimed indication for OPDIVO is:

- *OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy, is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS)≥5.*

Proposed dosage and administration:

The recommended dose is 360 mg nivolumab administered intravenously (IV) over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy Q3W or 240 mg nivolumab administered IV over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy Q2W (see Section 5.1 of the SmPC). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Management

Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil [5-FU], capecitabine, and tegafur/gimeracil/oteracil potassium [S1]) are considered first-line standard-of-care

[5] National Comprehensive Cancer Network (NCCN) Guideline Esophageal and Esophagogastric Junction cancer (Version 3.2020).
[6] Lordick F, Mariette C, Haustermans K, R. et al. Oesophageal Cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2016; 27 (suppl 5): v50-v57.
[7] National Comprehensive Cancer Network (NCCN) Guideline Gastric cancer (Version 2.2019).
[8]Smyth EC, VerheijnM, Allum W, et al. Gastric cancer: European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2016; 27:38-49.
[9] Cunningham D, Rao S, Starling N, et al. Randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric (OG) cancer: The REAL 2 trial. Journal of Clinical Oncology 2006; 24: Abstract LBA4017.

treatments for metastatic GC/GEJC/OAC across geographic regions.[10,11,12,13,14] With GC/GEJC/OAC, different survival outcomes have been reported across regions; the median OS ranges from 12 to 14 months in Asian countries and from 8 to 11 months in the United States (US) and Europe.[15,16,17]

In the past decade, multiple new investigational drugs with mainly molecular targets have been investigated in the first-line setting as add-ons to backbone platinum and fluoropyrimidine treatment. These agents, with the exception of trastuzumab, which targets and benefits only the human epidermal growth factor receptor 2 (HER2)-positive population (approximately 20% of subjects are HER2 positive in first-line GC/GEJC), have failed to show a survival benefit in randomized trials. Trastuzumab + chemotherapy provided an improvement in survival over chemotherapy in subjects who were HER2 positive; at a median follow up of 17.1 months, median OS was 13.5 vs. 11.0 months (HR = 0.74).[18]

To date, no immunotherapy agents with or without chemotherapy have been approved for the first-line treatment of GC/GEJC/OAC in the EU.

[10]Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3).Gastric Cancer 2011; 14:113-123.
[11] Ohtsu A, Shah MA, Cutsem EV, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: A randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011; 29:3968-3976.
[12] Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358:36-46.
[13] Yamada Y, Higuchi K, Nishikawa K, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. Annals of Oncology 2015; 26:141-148.
[14] Van Cutsem E, Kang Y, Chung H, et al. T Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). J Clin Oncol 2009; 27: Abstract LBA4509.
[15] Bang YJ, Cutsem EV, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastrooesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376:687-97.
[16] HERCEPTIN® (trastuzumab) USPI. Genentech, Inc. 2010.
[17] Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14:490-499.
[18] Fuchs C , Shitara K, Di Bartolomeo M et al RAINFALL: A randomized, double-blind, placebo-controlled phase III study of cisplatin (Cis) plus capecitabine (Cape) or 5FU with or without ramucirumab (RAM) as first-line therapy in patients with metastatic gastric or gastroesophageal junction (G-GEJ) adenocarcinoma. ASCO GI Cancers Symposium2018, abstract # 5.

Agents Relevant to First-line Advanced or Metastatic Gastric Cancer, Gastroesophageal Junction Cancer, or Oesophageal Adenocarcinoma (GC/GEJC/OAC)

Product (s) Name	Reference	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
HER2 inhibitor + chemotherapy						
Herceptin (trastuzumab) + chemotherapy	Van Cutsem E, et al. 2009[17] Trastuzumab USPI[18]	HER2-over-expressing metastatic gastric or GEJ adeno-carcinoma	2010 in US and EU	Trastuzumab 8 mg/kg Q3W followed by 6 mg/kg Q3W + chemotherapy (cisplatin + capecitabine or 5-FU)	Trastuzumab + chemo mOS: 13.5 months ORR: 47% updated mOS: 13.1 months	Most common Grade 3/4 AEs: neutropenia (27%), anemia (12%), diarrhea (9%), nausea (7%), and anorexia and vomiting (6% each), and asthenia, febrile neutropenia, and thrombocytopenia (5% each).
Chemotherapy: Platinum + fluoropyrimidine-containing regimens						
Fluorouracil (FU)+ leucovorin+ oxaliplatin (FOLFOX) FU + leucovorin+ cisplatin (FLP)	Al-Batran S-E, et al. 2008[25] Enzinger, et al.[26] NCCN Guidelines[8,10] ESMO Guide-lines[9,11]	Untreated gastric or esophago-gastric adeno-carcinoma	2006 in US and 2011 in EU FU, as a component of a platinum-containing multidrug chemotherapy regimen. FOLFOX is recommended in the NCCN and ESMO guidelines	FOLFOX: FU 2,600 mg/m^2 via 24-hour infusion, leucovorin 200 mg/m^2 + oxaliplatin 85 mg/m^2 Q2W FLP: FU 2,000 mg/m^{2}via 24-hour infusion, leucovorin 200 mg/m^2 QW + cisplatin 50 mg/m^2 Q2W	FOLFOX vs FLP mOS: 10.7 vs 8.8 months ORR: 41.3% vs 16.7%	Most common Grade 3/4 AEs (FLP vs FOLFOX): neutropenia (14.7% vs 11.6%), leukopenia (11.8% vs 6.3%), anemia (6.9% vs 2.7%), nausea (8.8% vs 4.5%), vomiting (5.9% vs 2.7%), thromboembolic (5.9% vs 0.9%), and fatigue (6.9% vs 3.6%).
			Modified FOLFOX6: oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours (or per local standard) on Days 1 and 2 cycled every 14 days			
Chemotherapy: Platinum + fluoropyrimidine-containing regimens (continued)						
Capecitabine + oxaliplatin (XELOX or CapeOx)	Park YH, et al. 2008[27]	Advanced gastric cancer	Not approved, but XELOX (CapeOx) is recommended in NCCN guidelines and ESMO Guidelines	Capecitabine (1,000 mg/m^2 BID, Days 1–14) + oxaliplatin (130 mg/m^2 IV infusion on Day 1) Q3W	mOS: 11.9 months ORR: 63%	Most common Grade 3/4 AEs: thrombocytopenia (11%), neutropenia (8%), diarrhea and bleeding (7% each), and leukopenia (6%).
Docetaxel + cisplatin + fluorouracil (DCF) Cisplatin + fluorouracil (CF)	Van Cutsem E, et al. 2006[28,]	First-line treatment of advanced GC/GEJC Docetaxel +cisplatin + fluorouracil	2006 in US and 2007 in EU Docetaxel +cisplatin + fluorouracil	Docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 (Day 1) + fluorouracil 750 mg/m^2/day (Days 1-5) Q3W Cisplatin 100 mg/m^2 (Day 1) + fluorouracil 1,000 mg/m^2/day (Days 1-5) Q4W	DCF and CF mOS: 9.2 and 8.6 months ORR: 37% and 25%	Most common Grade 3/4 AEs (DCF vs CF): neutropenia (82% vs 57%), leukopenia (65% vs 31%), anemia (18% vs 26%), stomatitis (21% vs 27%), diarrhea (19% vs 8%), lethargy (19% vs14%), nausea and vomiting (both: 14% vs 17%), and anorexia (10% vs 9%).
Capecitabine + cisplatin	Lordick F, et al. 2013[20] Kang et al. 2009[29] NCCN Guidelines[8,10] ESMO Guide-lines[9,11]	Previously untreated advanced gastric cancer	Not approved, but capecitabine + cisplatin is recommended in NCCN guidelines and ESMO guidelines	3-wk cycles of capecitabine BID 1000 mg/m^2 (on Days 1-14) + cisplatin 80 mg/m^2 (on Day 1)	Capecitabine + cisplatin mOS: 10.7 months ORR: 29%	Most common Grade 3/4 AEs: neutropenia (32%), anemia (11%), hypokalemia and nausea (9% each), vomiting (8%), and fatigue, asthenia, hyponatremia, and decreased appetite (6% each).

Abbreviations: AEs - adverse events, BID - twice daily, CF - cisplatin + fluorouracil, chemo - chemotherapy, DCF - docetaxel + cisplatin + fluorouracil, ESMO - European Society for Medical Oncology, FLP - FU + leucovorin+ cisplatin, FOLFOX - folinic acid (leucovorin) "FOL", fluorouracil (5-FU) "F", and oxaliplatin (eloxatin) "OX", FU - fluorouracil, GC - gastric cancer, GEJC - gastroesophageal junction cancer, HER2 - human epidermal growth factor receptor 2, HR - hazard ratio, mOS - median overall survival, NCCN - National Comprehensive Cancer Network, ORR - objective response rate, QXW - every X weeks, XELOX - Xeloda (capecitabine)"XEL" and oxaliplatin "OX"

2.1.2. About the product

OPDIVO (nivolumab) is a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab

potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

In the EU nivolumab as monotherapy has been approved for the treatment of melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin's lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma, oesophageal squamous cell carcinoma (OSCC), and adjuvant treatment of oesophageal or gastro-osesophageal junction cancer (OC or GEJC) (OPDIVO SmPC). The combination of nivolumab with ipilimumab (Yervoy) has been approved for the treatment of melanoma, RCC, malignant pleural mesothelioma (MPM) and colorectal cancer (CRC) and in combination with ipilimumab and platinum-based chemotherapy for the first-line treatment of metastatic NSCLC. The combination of nivolumab with cabozantinib has been approved for the treatment of RCC.

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

The MAH did not seek scientific advice at the CHMP concerning the current procedure.

2.1.4. General comments on compliance with GCP

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

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

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

2.2.2. Discussion and conclusion on non-clinical aspects

Not applicable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

BMS-Sponsored Phase 3 Study Supporting the Proposed Indication of Nivolumab + Chemotherapy for the Treatment of GC/GEJC/EAC

Study/Phase/ Status	Population	Design*	Endpoints	Test Drugs and Dose	Number of Subjects
CA209649 Phase 3 Ongoing Database lock: 10-Jul-2020 for the primary analysis of PFS per BICR and OS for nivo+chemo vs chemo	Subjects with previously untreated advanced or metastatic GC/GEJC/EAC	Phase 3, randomized, open-label, 3-arm study of nivo+ipi or nivo+chemo (XELOX or FOLFOX) or chemo (XELOX or FOLFOX)	For nivo+chemo vs chemo ***Primary*:** OS and PFS (per BICR) in subjects with PD-L1 CPS ≥ 5 ***Secondary:*** OS in subjects with PD-L1 CPS ≥ 1 and in all randomized subjects (hierarchically tested); OS in subjects with PD-L1 CPS ≥ 10; PFS (per BICR) in subjects with PD-L1 CPS ≥ 10, CPS ≥ 1, or all randomized subjects; ORR (per BICR) in subjects with PD-L1 CPS ≥ 10, CPS ≥ 5, CPS ≥ 1, or all randomized subjects	**Nivo+Chemo Arm** Nivolumab + XELOX (Q3W): Nivo 360 mg IV over 30 min on Day 1 + oxaliplatin 130 mg/m^2 IV on Day 1 + capecitabine 1000 mg/m^2 PO BID on Days 1 to 14 Nivolumab + FOLFOX (Q2W): Nivo 240 mg IV over 30 min on Day 1 + oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours or per local standard on Days 1 and 2 **Chemo Arm** XELOX (Q3W): Oxaliplatin 130 mg/m^2 IV on Day 1 + capecitabine 1000 mg/m^2 PO BID on Days 1 to 14 FOLFOX (Q2W): Oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours or per local standard on Days 1 and 2	2031 subjects randomized in all 3 arms 1581 concurrently randomized to the nivo+chemo or chemo arms: 789 in the nivo+chemo arm 792 in the chemo arm

Abbreviations: BICR - blinded independent central review, BID - twice daily, chemo - chemotherapy, BMS - Bristol-Myers Squibb, CPS - combined positive score, EAC - esophageal adenocarcinoma, FOLFOX - leucovorin + fluorouracil + oxaliplatin, GC - gastric cancer, GEJC - gastroesophageal junction cancer, IV - intravenous, ipi - ipilimumab, nivo - nivolumab, ORR - objective response rate, OS - overall survival, PD-L1 - programmed death ligand 1, PFS - progression-free survival, PO - orally, QXW - every X weeks, XELOX - capecitabine + oxaliplatin
* This submission is only for nivo+chemo vs chemo
Source: summarized based on CA209649 Primary Clinical Study Report

2.3.2. Pharmacokinetics

PK analytical methods

Pre-study validation

In support of study CA209649, human serum samples for nivolumab were analyzed at either PPD, Inc. (Richmond, VA) or at WuXi AppTec (Shanghai, P. R. China; for subjects from China) using validated ECL Methods, ICD 416 or 14BASM122, respectively.

In-study validation

The details of the assay and sample analysis as well as management details are provided in the respective bioanalytical reports.

Clinical Study CA209649

For both methods, the quantification of BMS-936558 in human serum samples was performer by ECL Method over a quantitative range of 0.2 µg/mL and 6.5 µg/mL. In addition, each batch consisted of one set of standards [0.100 (anchor), 0.200, 0.300, 1.000, 2.500, 4.000, 5.500 and 6.500 µg/mL] and

two sets of three QCs (0.600, 1.500 and 4.800 µg/mL) and 3 sets of DQC (for study sample which requires dilution).

PPD Project RHDS Bioanalytical Report

Sample analysis for the quantification of BMS-936558 in human serum samples was performed at PPD Laboratories, 2244 Dabney Road, Richmond, Virginia 23230 (804) 359-1900, USA from January 15th, 2018 to June 10th, 2020.

A total of 3842 samples were received and 3825 samples were analysed (17 samples were not analysed per protocol SOP) in 183 bioanalytical runs (175 runs met the acceptance criteria). Out of 3825 samples, 3787 samples were reported and 38 samples were not reported in data transfer files (sample outstanding reconciliation with Watson database).

The between-run precision (%CV) and accuracy (%Bias) of the calibration curve standards ranged from 0.945% to 4.92% and from -0414% to 3.98%, respectively. A total of seven calibration standards were rejected. In all valid runs, no more than one was rejected at the same run. In three runs the ULOQ and in one run the LLOQ was rejected.

The between-run precision (%CV) and accuracy (%Bias) of the QCs ranged from 5.28% to 6.36% and from 0.706% to 6.93%, respectively (including all QCs). A total of fifteen QCs was outside the acceptance range. In all valid runs, no more than two QCs was outside the acceptance range at the same run, and not at the same concentration level.

A total of 326 samples were re-analysed due to the following reasons: sample result above upper limit of ULOQ, diluted sample quantitated below limit of quantitation, inadvertently re-assayed at incorrect dilution, re-assayed inadvertently (for all these samples the original values were reported), limit of quantitation (LLOQ) raised due to deletion of calibration standard and confirmatory potential quantitating pre-dose.

A total of 441 samples were subjected for ISR. Out these, 434 samples met the ISR acceptance criteria (± 30%), which has resulted in 98.4% ISR pass rate for study samples.

The maximum storage for samples was 1690 days at nominally -80 ºC. The long-term stability of nivolumab in human plasma covers 2373 days at nominally -80 ºC.

WuXi AppTec Study Number: 400040-181151-PSA

Sample analysis for the quantification of BMS-936558 in human serum samples by ECL Method over a quantitative range of 0.2 µg/mL and 6.5 µg/mL was performed at WuXi AppTec in Shanghai from July 25th, 2019 to May 25th, 2020.

A total of 599 samples were analysed in 26 bioanalytical runs (all runs met the acceptance criteria) and all of them were reported.

The between-run precision (%CV) and accuracy (%Bias) of the calibration curve standards ranged from 0.4% to 2.0% and from 0.0% to 3.0%, respectively. No calibration curve standard was rejected.

The between-run precision (%CV) and accuracy (%Bias) of the QCs ranged from 4.4% to 5.5% and from -7.5% to -2.6%, respectively). No QC was outside the acceptance range

A total of 51 samples were re-analysed due to sample result above ULOQ (48 samples) and sample re-assayed inadvertently (3 samples; for these samples the original values were reported),

A total of 60 samples were subjected for ISR. All the samples met the ISR acceptance criteria (± 30%), which has resulted in 100.0% ISR pass rate for study samples.

Study samples analysed and reported for Nivolumab (BMS-936558) in support of study CA209649

were covered by 2373 days of long-term stability at nominal at -70 ºC.

Pharmacokinetics in the target population

Pharmacokinetic data from Study CA209649 were pooled with data from 6 other studies for an updated PPK analysis. In total, the updated PPK dataset included data from 1825 subjects with either 2L NSCLC (reference population), 1L GC/GEJC/EAC, 2L+ GC, or other solid tumours from a total of 7 studies in which subjects received nivolumab monotherapy or nivo+chemo.

Table 3-1: Summary of Clinical Studies Included in Pharmacometric PPK Analyses

Protocol #: Title Study Population	Treatment	Planned Sample Size[a]	Nominal PK/PD Sampling Schedule	Analysis
MDX1106-01 (**CA209001**): Phase 1, open-label, multicenter, dose-escalation study to evaluate the safety and pharmacokinetics of BMS-936588 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*	Nivo Monotherapy 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: Pre-dose, 30 minutes into dosing, immediately post-infusion, and 30 minutes, 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: Pre-dose and peak on treatment Days 1 and 29; single samples on Days 8, 15, 22, 36, 43, 57, 85, and 113	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*	Nivo Monotherapy 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, 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, 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	PPK Only include subjects with melanoma, NSCLC, and RCC

Table 3-1: Summary of Clinical Studies Included in Pharmacometric PPK Analyses

Protocol #: Title Study Population	Treatment	Planned Sample Size[a]	Nominal PK/PD Sampling Schedule	Analysis
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*	Nivo Monotherapy Dose: 3 mg/kg, 1-hr IV infusion Regimen: Q2W	132 (nivolumab treated)	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	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*	Nivo Monotherapy Dose: 3 mg/kg, 1-hr IV infusion Regimen: Q2W	287 (nivolumab treated)	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	PPK
CA209032: A Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors *Subjects with pathologically confirmed locally advanced or metastatic disease of breast carcinoma, gastric or gastro-esophageal junction carcinoma, pancreatic adenocarcinoma, SCLC, urothelial carcinoma, ovarian carcinoma*	Nivo Monotherapy Dose: 3 mg/kg, 1-hr IV infusion Regimen: Q2W	58 (nivolumab treated GC cohort)	Pre-dose on C1D1, C4D1, C10D1, C13D1, C25D1 and on Day 1 of every 16th week thereafter until discontinuation of study treatment or completion of 2 years of study treatment	PPK (Nivo monotherapy arm only)
ONO-4538-12 (CA209316): A Phase 3, multicenter, double-blind, randomized study in patients with unresectable advanced or recurrent gastric cancer *Subjects with gastric cancer*	Nivo Monotherapy Dose: 3 mg/kg, 1-hr IV infusion Regimen: Every 2 weeks	290 (nivolumab treated)	Treatment period (Cycle 1): Day 1 pre-dose, Day 1 post dose (just before the end of infusion), Day 15 pre-dose, Day 29 pre-dose Treatment period (Cycles 2, 4, 5, 7, and 9): Day 1 pre-dose, Day 1 post dose (in Cycle 4, just before the end of infusion only) Post-treatment observation period: At the examination 28 days after the end of the treatment period (only in subjects proceeding to the post-treatment observation period by the end of Cycle 9), and 6–12 weeks after the last dose of the investigational product (as far as possible)	PPK

Table 3-1: Summary of Clinical Studies Included in Pharmacometric PPK Analyses

Protocol #: Title Study Population	Treatment	Planned Sample Size[a]	Nominal PK/PD Sampling Schedule	Analysis
CA209649: A randomized, multicenter, open-label, Phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine versus oxaliplatin plus fluoropyrimidine in subjects with previously untreated advanced or metastatic gastric or gastroesophageal junction cancer (nivolumab plus chemotherapy cohort only, DBL 07/2020) *Subjects with advanced or metastatic gastric or gastroesophageal junction or esophageal adenocarcinoma cancer*	Nivo+Chemo Dose: 240 mg, 30-min IV infusion Regimen: Q2W Or Dose: 360 mg, 30-min IV infusion Regimen: Q3W	791 (nivolumab plus chemotherapy treated)	Q2W Cycles 1, 2, 3, 7, 9, 17, 25, 37, and 49: Predose on Day 1 Q3W Cycles 1, 2, 5, 11, 17, 25, and 33: Predose on Day 1	PPK, E-R efficacy, and E-R safety

[a] As per protocol.

Abbreviations: C = cycle; D = day; DBL = database lock; E-R = exposure-response; GC = gastric cancer; hr = hour; IV = intravenous; min = minutes; Nivo = nivolumab; Nivo+Chemo = nivolumab in combination with oxaliplatin plus fluoropyrimidine; 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; RCC = renal cell carcinoma; SCLC = small cell lung cancer; SQ NSCLC = squamous cell non-small cell lung cancer.

Table 3.2.1.1-1: Subjects Included in the PPK Analysis Dataset

Study	# Subjects			
	Nivolumab Treated[a]	PK Database (eToolbox)[b]	Flagged	Included (% of Subjects in eToolbox)
MDX1106-01 (CA209001)	39	39	0	39 (100)
MDX1106-03 (CA209003)	269	269	1	268 (99.63)
CA209017	125	127	2	125 (98.43)
CA209032	58	58	0	58 (100)
CA209057	280	282	2	280 (99.29)
ONO-4538-12 (CA209316)	330	330	1	329 (99.7)
CA209649	763	773	47	726 (93.92)
Total	1878	1878	53	1825 (97.18)

[a] All studies were nivolumab monotherapy, with the exception of study CA209649, which was nivo+chemo combination therapy.

[b] 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.

Source: d1pk\asmbdat\10060-nivoppk-data-disposition.xlsx

Table 3.2.1.2-1: Samples Included in the PPK Analysis Dataset

Study	PK Database[a]	Day 1 Pre-Dose (FLG=3)	No Dosing (FLG=1)	Below LLOQ[b] (FLG=2)	Duplicate Samples at Same Time (Set Up for NCA) (FLG=4)	Conc > 2000 µg/mL (FLG=5)	Duplicate Sample (Different Conc) (FLG=6)	Error in Dose Amount (FLG=8)	Crossover PK Samples (FLG=9)	|CWRES| > 6 (FLG=25)	Included Samples (% of PK Database)
MDX1106-01 (CA209001)	915	40	33	42	0	0	0	0	0	1	799 (87.32)
MDX1106-03 (CA209003)	3363	295	22	73	76	2	71	0	0	9	2815 (83.71)
CA209017	585	122	0	9	0	0	1	0	0	1	452 (77.26)
CA209032	274	53	1	2	0	0	0	0	24	0	194 (70.8)
CA209057	1355	267	13	15	0	0	5	0	0	3	1052 (77.64)
ONO-4538-12 (CA209316)	1758	330	2	2	3	0	0	1	0	1	1419 (80.72)
CA209649	3115	726	18	29	0	0	0	1	0	1	2340 (75.12)
Total	11365	1833	89	172	79	2	77	2	24	16	9071 (79.82)

[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.

Abbreviations: Conc = concentration; |CWRES| = absolute conditional weighted residuals; LLOQ = lower limit of quantification; NCA = non-compartmental analysis; PK = pharmacokinetic; PPK = population pharmacokinetic.

Source: d1pk\asmbdat\10060-nivoppk-data-disposition.xlsx

Table 3.2.1.4-1: Summary of Covariates Included in PPK Analysis by Study and Overall

Subject Characteristic		CA209001 (n = 39)	CA209003 (n = 268)	CA209017 (n = 125)	CA209032 (n = 58)	CA209057 (n = 280)	CA209316 (n = 329)	CA209649 (n = 726)	Overall (n = 1825)
Baseline Body Weight (kg)	Mean (SD)	84.5 (18.5)	81.9 (19.2)	76.3 (17.1)	75 (14.7)	71.2 (15.3)	55.3 (10.2)	68.2 (16.8)	69.6 (18)
	Median	81.3	79.8	75	73.8	69.8	55	66	67.1
	Min, Max	54.8, 136	41.6, 153	46.3, 136	42, 112	43.5, 158	31.5, 91.8	36, 154	31.5, 158
	Missing n (%)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	11 (3.3)	0 (0.0)	12 (0.7)
Baseline GFR (mL/min/1.73 m^2)	Mean (SD)	77.5 (20.2)	80.3 (19.9)	83.3 (19.4)	95 (22.4)	83.1 (19.4)	92.1 (17)	91.5 (18.2)	87.9 (19.3)
	Median	85.4	82.6	83.6	96.2	84.7	94.9	93	90.5
	Min, Max	34.5, 104	31.2, 135	40.6, 128	45.2, 181	31.9, 128	36.6, 141	36.3, 236	31.2, 236
	Missing n (%)	0 (0.0)	5 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.3)
Baseline Tumor Burden (cm)	Mean (SD)	12.8 (9.65)	12.2 (8.31)	9.17 (4.59)	8.67 (6.72)	8 (4.91)	8.19 (5.73)	6.87 (4.46)	8.56 (6.11)
	Median	10.5	10.3	8.8	6.95	7.1	6.76	5.6	7.13
	Min, Max	2, 41.3	1, 61.5	1.2, 25	1, 25.9	1, 29.8	1, 31.3	1.1, 27.6	1, 61.5
	Missing n (%)	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	62 (18.8)	169 (23.3)[a]	235 (12.9)
Sex, n (%)	Male	22 (56.4)	176 (65.7)	102 (81.6)	44 (75.9)	144 (51.4)	228 (69.3)	498 (68.6)	1214 (66.5)
	Female	17 (43.6)	92 (34.3)	23 (18.4)	14 (24.1)	136 (48.6)	101 (30.7)	228 (31.4)	611 (33.5)
Baseline Performance Status, n (%)	0	13 (33.3)	111 (41.4)	27 (21.6)	29 (50.0)	81 (28.9)	87 (26.4)	304 (41.9)	652 (35.7)
	1	26 (66.7)	152 (56.7)	98 (78.4)	29 (50.0)	197 (70.4)	242 (73.6)	421 (58.0)	1165 (63.8)
	2	0 (0.0)	5 (1.9)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.1)	8 (0.4)
Race, n (%)	White	29 (74.4)	253 (94.4)	112 (89.6)	55 (94.8)	256 (91.4)	0 (0.0)	502 (69.1)	1207 (66.1)
	Black/African American	10 (25.6)	11 (4.1)	6 (4.8)	3 (5.2)	6 (2.1)	0 (0.0)	7 (1.0)	43 (2.4)
	Asian	0 (0.0)	1 (0.4)	4 (3.2)	0 (0.0)	9 (3.2)	328 (99.7)	183 (25.2)	525 (28.8)
	Others	0 (0.0)	2 (0.7)	1 (0.8)	0 (0.0)	8 (2.9)	1 (0.3)	32 (4.4)	44 (2.4)
	Unknown[b]	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.3)	4 (0.2)
	Missing n (%)[c]	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Baseline Serum Albumin [g/dL]	Mean (SD)	3.79 (0.375)	4.09 (0.476)	3.92 (0.538)	3.79 (0.427)	3.89 (0.492)	3.67 (0.517)	3.87 (0.457)	3.87 (0.495)
	Median	3.8	4.1	4	3.8	3.9	3.7	3.9	3.9
	Min, Max	2.3, 4.7	2.5, 5.1	2.2, 5.2	2.8, 4.7	1.9, 5.1	2.1, 5.1	2.3, 5.1	1.9, 5.2

Table 3.2.1.4-1: Summary of Covariates Included in PPK Analysis by Study and Overall

Subject Characteristic		CA209001 (n = 39)	CA209003 (n = 268)	CA209017 (n = 125)	CA209032 (n = 58)	CA209057 (n = 280)	CA209316 (n = 329)	CA209649 (n = 726)	Overall (n = 1825)
	Missing n (%)	0 (0.0)	5 (1.9)	4 (3.2)	18 (31.0)	7 (2.5)	0 (0.0)	26 (3.6)	60 (3.3)
Baseline Lactate Dehydrogenase [U/L]	Mean (SD)	352 (323)	263 (318)	349 (281)	366 (235)	378 (293)	335 (278)	309 (366)	323 (324)
	Median	198	187	273	327	277	238	212	225
	Min, Max	131, 1410	91, 2980	101, 2330	119, 1390	111, 3090	110, 2940	80, 4020	80, 4020
	Missing n (%)	0 (0.0)	8 (3.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	7 (1.0)	17 (0.9)
Combination Treatment, n (%)	Nivo Only	39 (100.0)	268 (100.0)	125 (100.0)	58 (100.0)	280 (100.0)	329 (100.0)	0 (0.0)	1099 (60.2)
	Nivo + Chemo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	726 (100.0)	726 (39.8)
Subject Population, n (%)	2L NSCLC	0 (0.0)	25 (9.3)	125 (100.0)	0 (0.0)	243 (86.8)	0 (0.0)	0 (0.0)	393 (21.5)
	2L+ GC	0 (0.0)	0 (0.0)	0 (0.0)	58 (100.0)	0 (0.0)	329 (100.0)	1 (0.1)	388 (21.3)
	1L GC/GEJC/EAC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	725 (99.9)	725 (39.7)
	OTHER[d]	39 (100.0)	243 (90.7)	0 (0.0)	0 (0.0)	37 (13.2)	0 (0.0)	0 (0.0)	319 (17.5)
Japanese Ethnicity, n (%)	Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	152 (46.2)	57 (7.9)	209 (11.5)
	Non-Japanese Asian	0 (0.0)	1 (0.4)	4 (3.2)	0 (0.0)	9 (3.2)	176 (53.5)	126 (17.4)	316 (17.3)
	Non-Asian	39 (100.0)	267 (99.6)	119 (95.2)	58 (100.0)	271 (96.8)	1 (0.3)	543 (74.8)	1298 (71.1)
	Missing n (%)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Chinese Ethnicity, n (%)	Chinese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	97 (13.4)	97 (5.3)
	Non-Chinese Asian	0 (0.0)	1 (0.4)	4 (3.2)	0 (0.0)	9 (3.2)	328 (99.7)	86 (11.8)	428 (23.5)
	Non-Asian	39 (100.0)	267 (99.6)	119 (95.2)	58 (100.0)	271 (96.8)	1 (0.3)	543 (74.8)	1298 (71.1)
	Missing n (%)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Primary Tumor Location at Study Entry, n (%)	EAC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	92 (12.7)	92 (5.0)
	GC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	515 (70.9)	515 (28.2)
	GEJC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	119 (16.4)	119 (6.5)
	Missing n (%)	39 (100.0)	268 (100.0)	125 (100.0)	58 (100.0)	280 (100.0)	329 (100.0)	0 (0.0)	1099 (60.2)
Presence of Liver Metastases, n (%)	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	275 (37.9)	275 (15.1)
	No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	429 (59.1)	429 (23.5)
	Missing n (%)	39 (100.0)	268 (100.0)	125 (100.0)	58 (100.0)	280 (100.0)	329 (100.0)	22 (3.0)	1121 (61.4)
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	133 (18.3)	133 (7.3)
	No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	593 (81.7)	593 (32.5)

Table 3.2.1.4-1: Summary of Covariates Included in PPK Analysis by Study and Overall

Subject Characteristic		CA209001 (n = 39)	CA209003 (n = 268)	CA209017 (n = 125)	CA209032 (n = 58)	CA209057 (n = 280)	CA209316 (n = 329)	CA209649 (n = 726)	Overall (n = 1825)
Histology Presence of Signet Ring Cell-N, n (%)	Missing n (%)	39 (100.0)	268 (100.0)	125 (100.0)	58 (100.0)	280 (100.0)	329 (100.0)	0 (0.0)	1099 (60.2)
Prior Surgery, n (%)	Yes	0 (0.0)	0 (0.0)	0 (0.0)	37 (63.8)	0 (0.0)	205 (62.3)	152 (20.9)	394 (21.6)
	No or Not Reported	0 (0.0)	0 (0.0)	0 (0.0)	21 (36.2)	0 (0.0)	124 (37.7)	574 (79.1)	719 (39.4)
	Missing n (%)	39 (100.0)	268 (100.0)	125 (100.0)	0 (0.0)	280 (100.0)	0 (0.0)	0 (0.0)	712 (39.0)
Immunogenicity by Visit Level, N (%)	Negative	689 (86.2)	1311 (46.6)	405 (89.6)	171 (88.1)	947 (90.0)	1338 (94.3)	2192 (93.7)	7053 (77.8)
	Positive	61 (7.6)	31 (1.1)	43 (9.5)	20 (10.3)	99 (9.4)	73 (5.1)	96 (4.1)	423 (4.7)
	Missing N (%)	49 (6.1)	1473 (52.3)	4 (0.9)	3 (1.5)	6 (0.6)	8 (0.6)	52 (2.2)	1595 (17.6)

[a] CA209649 allowed enrollment of subjects with non-measurable disease. Therefore, 'missing' tumor burden refers to subjects w/o reported BICR assessment.

[b] Unknown race was defined as race that could not be determined.

Abbreviations: 1L = first-line; 2L = second-line; 3L = third-line; ADA = anti-drug antibody; EAC = esophageal adenocarcinoma cancer; GC = gastric cancer; GEJC = gastroesophageal junction cancer; GFR = glomerular filtration rate; Max = maximum; Min = minimum; N = number of ADA measurements; n = number of subjects; Nivo = nivolumab; Nivo+Chemo = nivolumab in combination with oxaliplatin plus fluoropyrimidine; NSCLC = non-small cell lung cancer; PPK = population pharmacokinetic; SD = standard deviation.

[c] Missing race was defined as race criterion was not selected.

[d] The OTHER population included subjects with melanoma, or renal cell in Studies CA209001 and CA209003, colorectal or prostate cancer in Study CA209001, or 3L+ NSCLC in Studies CA209001, CA209003, and CA209057.

Note: The summary statistics for continuous covariates exclude missing values, however, the number (percentage) of missing values (if any) is shown in the table.

Source: d1pk\tables\rtf\sumstat-covs-bystudy.rtf

Base model

A previously developed 2L+ GC monotherapy final PPK model was revised and used as the base model for this updated analysis. The 1L GC/GEJC/EAC data, as a new patient population, was incorporated into the base and full model to obtain unbiased estimates of the magnitude of covariate effects on model parameters. Nivolumab PK, including data in 1L GC/GEJC/EAC, was well described by a linear 2 compartment model with time-varying CL in the full model.

The base model was a 2-compartment, zero-order IV infusion with time-varying elimination. The parameters of this model were re-estimated with the inclusion of data from Study CA209649. Log-normal random effects were estimated for CL, VC, and VP, a normally distributed random effect on Emax, and a correlation between the CL and VC random effects. The base model included covariate relationships between BBWT, BGFR, BALB, PS, sex, race, baseline LDH, tumour burden, and subject population and time-varying CL; BBWT and sex on VC as described in Section 4.1.1.1. Covariate relationships between BBWT and Q, and BBWT and VP were assumed to be identical to the relationships between BBWT and CL, and BBWT and VC. Parameter estimates and standard errors for this base model are presented in Table 5.1.1.1-1.

Table 5.1.1.1-1: Parameter Estimates of the Base PPK Model

Name [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval[d]
		Fixed Effects		
CL0 [mL/h][e]	θ_1	11.0	0.453 (4.13)	10.1 - 11.8
VC [L][e]	θ_2	4.67	0.0674 (1.44)	4.54 - 4.81
Q [mL/h][e]	θ_3	34.0	3.24 (9.53)	27.7 - 40.4
VP [L][e]	θ_4	2.91	0.155 (5.32)	2.61 - 3.21
CL_{BBWT}[f]	θ_6	0.557	0.0492 (8.84)	0.46 - 0.653
CL_{GFR}[f]	θ_7	0.109	0.0364 (33.4)	0.0376 - 0.18
CL_{SEX}[g]	θ_8	-0.126	0.0212 (16.7)	(-0.168) - (-0.0849)
CL_{PS}[g]	θ_9	0.0852	0.0181 (21.3)	0.0496 - 0.121
CL_{RAAS}[g]	θ_{10}	-0.0817	0.0237 (29)	(-0.128) - (-0.0352)
VC_{BBWT}[f]	θ_{11}	0.5	0.0403 (8.06)	0.421 - 0.579
VC_{SEX}[g]	θ_{12}	-0.215	0.027 (12.5)	(-0.268) - (-0.162)
EMAX[e]	θ_{13}	-0.277	0.0438 (15.8)	(-0.363) - (-0.192)
T50 [h][e]	θ_{14}	1410	158 (11.3)	1100 - 1720
HILL [-]	θ_{15}	2.89	0.752 (26)	1.41 - 4.36
CL_{BALB}[f]	θ_{16}	-0.939	0.0702 (7.48)	(-1.08) - (-0.801)
CL_{BLDH}[f]	θ_{17}	0.409	0.0918 (22.4)	0.229 - 0.589
CL_{BTSIZE}[f]	θ_{18}	0.0799	0.0147 (18.3)	0.0512 - 0.109
$CL_{MISSBTSIZE}$[g]	θ_{19}	0.00814	0.0269 (331)	(-0.0446) - 0.0609
$CL_{POPGC1L}$[g]	θ_{20}	-0.009	0.0253 (281)	(-0.0585) - 0.0405
$CL_{POPGC2L+}$[g]	θ_{21}	0.0988	0.0334 (33.8)	0.0334 - 0.164
CL_{POPOTH}[g]	θ_{22}	0.0815	0.0336 (41.3)	0.0156 - 0.147
		Random Effects[h,i]		
ω^2 -CL [-]	$\omega_{1,1}$	0.0855 (0.292)	0.00714 (8.34)	0.0716 - 0.0995

Table 5.1.1.1-1: Parameter Estimates of the Base PPK Model

Name [Units][a]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval[d]
ω^2 -VC [-]	$\omega_{2,2}$	0.121 (0.348)	0.0202 (16.7)	0.0813 - 0.16
ω^2 -VP [-]	$\omega_{3,3}$	0.204 (0.452)	0.0431 (21.1)	0.12 - 0.288
ω^2 -EMAX [-]	$\omega_{4,4}$	0.0586 (0.242)	0.0137 (23.3)	0.0319 - 0.0854
ω^2 CL: ω^2 VC [-]	$\omega_{1,2}$	0.0298 (0.173)	0.00566 (19)	0.0187 - 0.0409
		Residual Error		
Proportional [-]	θ_5	0.214	0.0089 (4.15)	0.197 - 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 intervals of random effects and residual error parameters are for variance or covariance.

[e] eCL_{REF}, VC_{REF}, VP_{REF}, and Q_{REF} are typical values of CL, VC, VP, and Q at the reference covariate values. Covariate effects were estimated relative to a reference subject who is a male, with baseline ALB of 4.0 g/dL, baseline LDH of 200 IU/L, tumor burden of 7.7 cm, weighing 80 kg, estimated GFR of 90 mL/min/1.73 m^2, PS of 0, race = white or other, defined as not Asian, and population type of 2L NSCLC.

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

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

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

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

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

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

$$CL_{TV,i} = CL_{REF} \times (e^{CL_{SEX}})^{SEX_i} \times (e^{CL_{PS}})^{PS_i} \times (e^{CL_{RAAS}})^{RAAS_i} \times (e^{CL_{POP1LGC}})^{POP1LGC_i} \times (e^{CL_{POP2L+GC}})^{POP2L+GC_i} \times (e^{CL_{POPOTH}})^{POPOTH_i} \times (e^{CL_{MISSBTSIZE}})^{MISSBTSIZE_i}$$

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

[h] Eta shrinkage: ETA_CL: 17.5%, ETA_VC: 29.2%, ETA_VP: 50.6%, ETA_EMAX: 50.5%; Epsilon shrinkage: 16.2%.

[i] The calculated correlation coefficient (r) of the off-diagonal omega was 0.293 for cov(IIV in VC, IIV in CL).

Note: The condition number was 201, indicating there was no evidence for ill-conditioning.

Source: KIWI Run ID 272809

Full model

Table 5.1.1.2-1: Parameter Estimates of the Full Nivolumab PPK 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	10.4	0.386 (3.71)	9.78 - 11.3
VC [L][e]	θ_2	4.64	0.0585 (1.26)	4.54 - 4.75
Q [mL/h][e]	θ_3	33.2	2.56 (7.7)	28.6 - 38.9
VP [L][e]	θ_4	3.02	0.149 (4.94)	2.71 - 3.29
CL_{BBWT}[f]	θ_6	0.543	0.0486 (8.96)	0.442 - 0.636
CL_{GFR}[f]	θ_7	0.131	0.0349 (26.6)	0.0609 - 0.204
CL_{SEX}[g]	θ_8	-0.133	0.0208 (15.6)	(-0.176) - (-0.0959)
CL_{PS}[g]	θ_9	0.115	0.0217 (18.8)	0.0725 - 0.159
CL_{RAAS}[g]	θ_{10}	-0.0808	0.0234 (28.9)	(-0.125) - (-0.0370)
VC_{BBWT}[f]	θ_{11}	0.465	0.0352 (7.58)	0.395 - 0.532
VC_{SEX}[g]	θ_{12}	-0.221	0.0222 (10.1)	(-0.263) - (-0.173)
EMAX[e]	θ_{13}	-0.157	0.0481 (30.5)	(-0.260) - (-0.0678)
T50 [h]	θ_{14}	1550	138 (8.94)	1280 - 1860
HILL [-]	θ_{15}	4.35	2.13 (48.9)	2.34 - 37.8
CL_{BALB}[f]	θ_{16}	-0.945	0.0669 (7.09)	(-1.08) - (-0.811)
CL_{BLDH}[f]	θ_{17}	0.410	0.0894 (21.8)	0.231 - 0.591
CL_{BTSIZE}[f]	θ_{18}	0.0799	0.0143 (17.9)	0.0513 - 0.109
$CL_{MISSBTSIZE}$[g]	θ_{19}	0.0138	0.0269 (195)	(-0.0435) - 0.0680
$CL_{POPGC1L}$[g]	θ_{20}	0.00613	0.0297 (485)	(-0.0470) - 0.0674
$CL_{POPGC2L+}$[g]	θ_{21}	0.0563	0.0369 (65.6)	(-0.0175) - 0.131
CL_{POPOTH}[g]	θ_{22}	0.112	0.0354 (31.6)	0.0384 - 0.181
$EMAX_{PS}$[g]	θ_{23}	-0.0821	0.0295 (36)	(-0.149) - (-0.0262)
$EMAX_{POPGC1L}$[g]	θ_{24}	-0.0824	0.037 (44.9)	(-0.165) - (-0.0124)

Name [Units][a]	Symbol	Estimate[b]	(%RSE)[c]	Derived)[d]
$EMAX_{POPGC2L+}$[g]	θ_{25}	0.0963	0.0467 (48.5)	(-0.00138) - 0.182
$EMAX_{POPOTH}$[g]	θ_{26}	-0.0417	0.048 (115)	(-0.143) - 0.0580
Random Effects[h,i]				
ω^2 -CL [-]	$\omega_{1,1}$	0.0874	0.00625 (7.15)	0.0742 - 0.0973
ω^2 -VC [-]	$\omega_{2,2}$	0.0827	0.0092 (11.1)	0.0654 - 0.0994
ω^2 -VP [-]	$\omega_{3,3}$	0.166	0.0386 (23.2)	0.111 - 0.278
ω^2 -EMAX [-]	$\omega_{4,4}$	0.0503	0.0112 (22.2)	0.0319 - 0.0784
ω^2 CL: ω^2 VC [-]	$\omega_{1,2}$	0.0298	0.00409 (13.7)	0.0221 - 0.0384
Residual Error				
Proportional [-]	θ_5	0.197	0.00427 (2.17)	0.188 - 0.205

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

[e] CL_{REF}, VC_{REF}, VP_{REF}, and Q_{REF} are typical values of CL, VC, VP, and Q at the reference covariate values. Covariate effects were estimated relative to a reference subject who is a male, with baseline ALB of 4.0 g/dL, baseline LDH of 200 IU/L, tumor burden of 7.7 cm, weighing 80 kg, estimated GFR of 90 mL/min/1.73 m^2, PS of 0, race = white or other, defined as not Asian, and population type of 2L NSCLC.

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

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

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

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

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

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

$$CL_{TV,i} = CL_{REF} \times (e^{CL_{SEX}})^{SEX_i} \times (e^{CL_{PS}})^{PS_i} \times (e^{CL_{RAAS}})^{RAAS_i} \times (e^{CL_{POP1LGC}})^{POP1LGC_i} \times (e^{CL_{POP2L+GC}})^{POP2L+GC_i} \times (e^{CL_{OTHER}})^{OTHER_i} \times (e^{CL_{MISSBTSIZE}})^{MISSBTSIZE_i}$$

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

$$EMAX_{TV,i} = EMAX_{REF} + (EMAX_{POP1LGC}) + (EMAX_{POP2L+GC}) + (EMAX_{POPOTH}) + (EMAX_{PS})$$

[h] Eta shrinkage: ETA_CL: 15.3%, ETA_VC: 30.3%, ETA_VP: 50.3%, ETA_EMAX: 50.2%; Epsilon shrinkage: 16.5%.

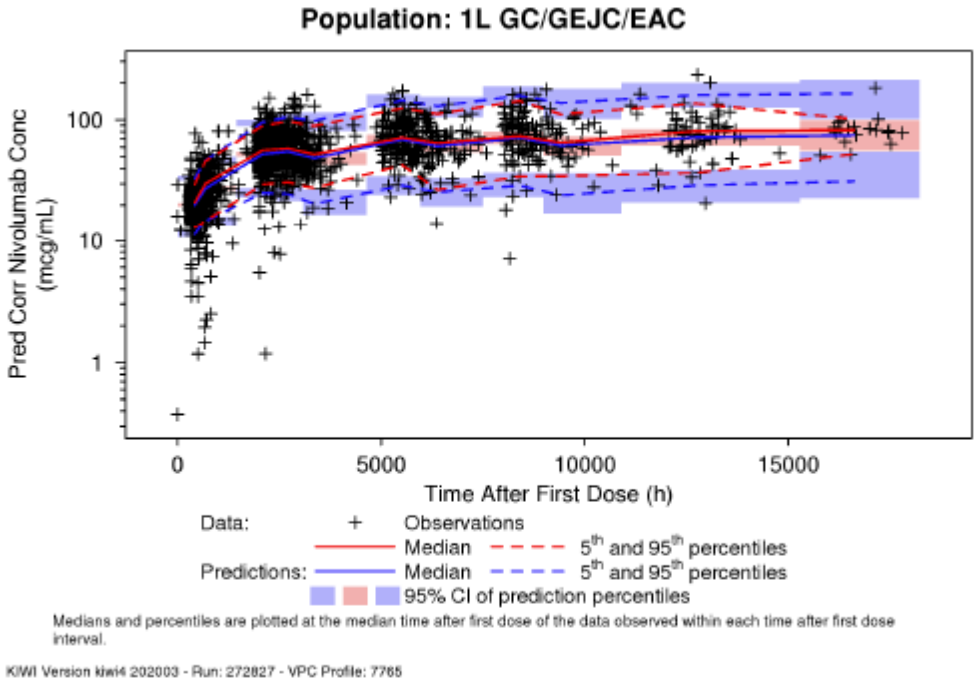
[i] The calculated correlation coefficient (r) of the off-diagonal omega was 0.351 for cov(IIV in VC, IIV in CL).

Note: Although 80 kg was the reference in NONMEM fitting, because the exponent would not change, all the model application was calculated based on the median BBWT of 67 kg.

Note: The condition number was 239, indicating there was no evidence for ill-conditioning.

Source: KIWI Run ID 272231

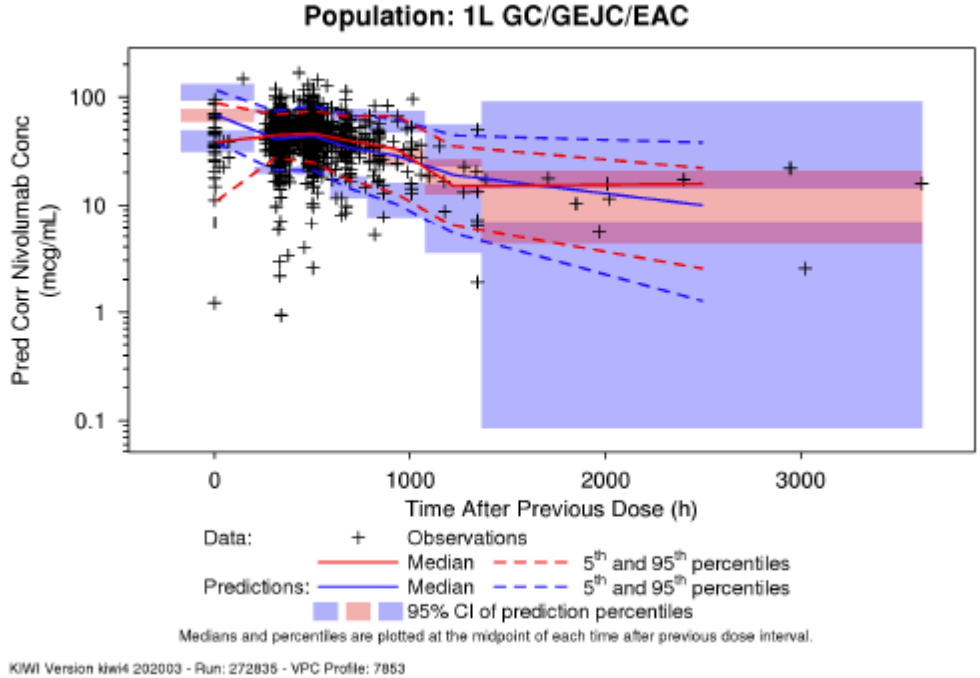
Figure 5.1.2-1: Prediction-corrected Visual Predictive Check of Trough Concentrations (Log Scale) Versus Actual Time After First Dose for Data from the 1L GC/GEJC/EAC Subject Population



Abbreviations: 1L = first-line; CI = confidence interval; Conc = concentration; EAC = esophageal adenocarcinoma cancer; GC = gastric cancer; GEJC = gastroesophageal junction cancer; Pred Corr = prediction corrected.

Source: d1pk\graphs\pnghi\vpc\vpc-r272827-vpc-final-pk-model-atafd-troughs-popn2-1lgc-t1-p7765-s1-001.png

Figure 5.1.2-2: Prediction-corrected Visual Predictive Check of All Concentrations (Log Scale) Versus Actual Time After Previous Dose for Data from the 1L GC/GEJC/EAC Subject Population

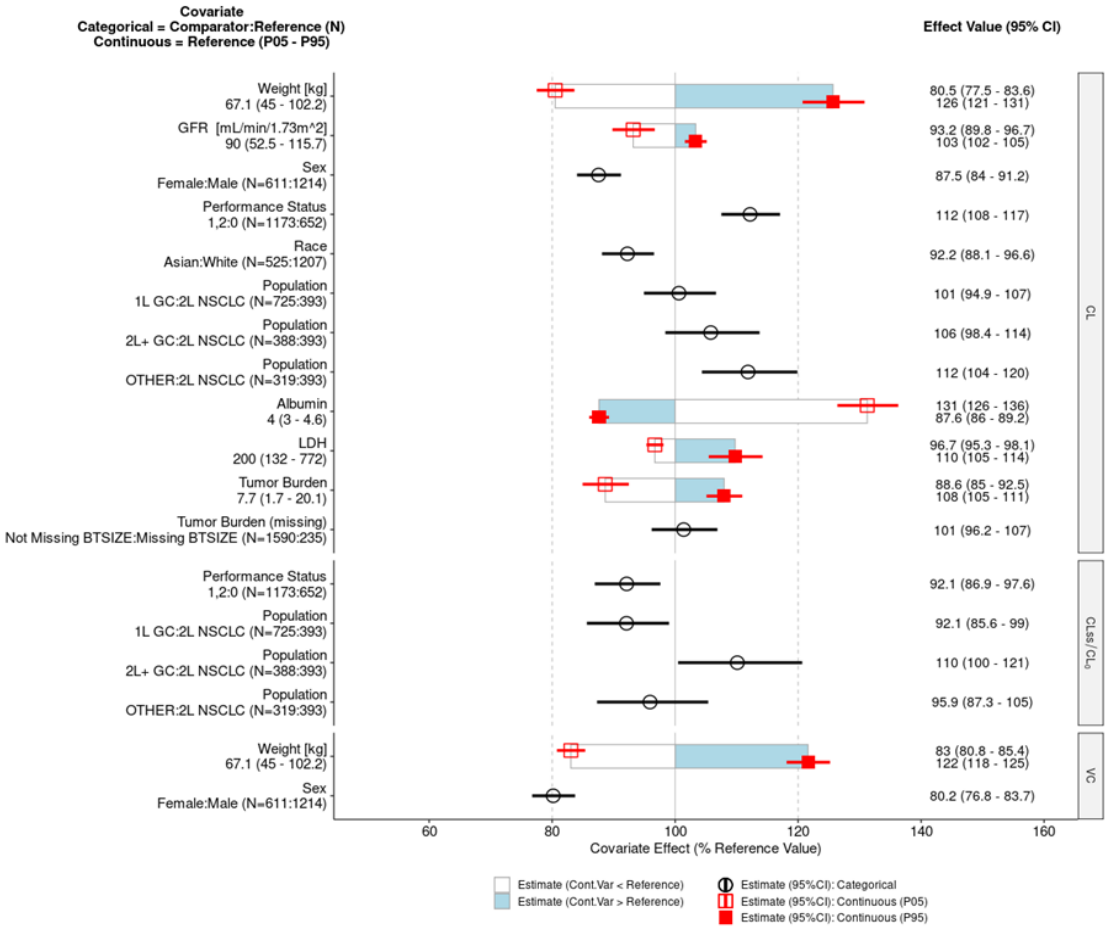


Abbreviations: 1L = first-line; CI = confidence interval; Conc = concentration; EAC = esophageal adenocarcinoma cancer; GC = gastric cancer; GEJC = gastroesophageal junction cancer; Pred Corr = prediction corrected.

Source: d1pk\graphs\pnghi\vpc\vpc-r272835-vpc-final-pk-model-atapd-stratbypopn-t1-p7853-s3-001.png

No covariates were found to have a clinically meaningful effect on nivolumab PK in this updated analysis. Graphical representations of the effect of categorical and continuous covariates on the typical value of the structural model parameters of CL, volume of central compartment (VC), and CLss/CL0 (EXP[EMAX]) are presented in Figure 3.1.1-1. All covariate effects were within ± 20% boundaries, except for the effect of baseline body weight on CL and VC and baseline albumin (ALB) on CL. Baseline body weight was associated with a 26% increase in CL and a 22% increase in VC in subjects with 95th percentile weight relative to subjects with median body weight. Nivolumab CL increased approximately 31% in subjects with 5th percentile baseline ALB relative to subjects with median baseline ALB value. However, the magnitudes of body weight, VC, and ALB effect on CL were consistent with findings of previous analyses. These findings were not considered to be clinically relevant, as the 95th percentile body weight or 5th percentile ALB only resulted in approximately 18.5% or 21.4% lower Cavgss, respectively, relative to those observed in subjects with median body weight or median ALB at baseline in Study CA209649.

Figure 3.1.1-1: Covariate Effects on Pharmacokinetic Model Parameters (Full Nivolumab Population Pharmacokinetic Model)



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

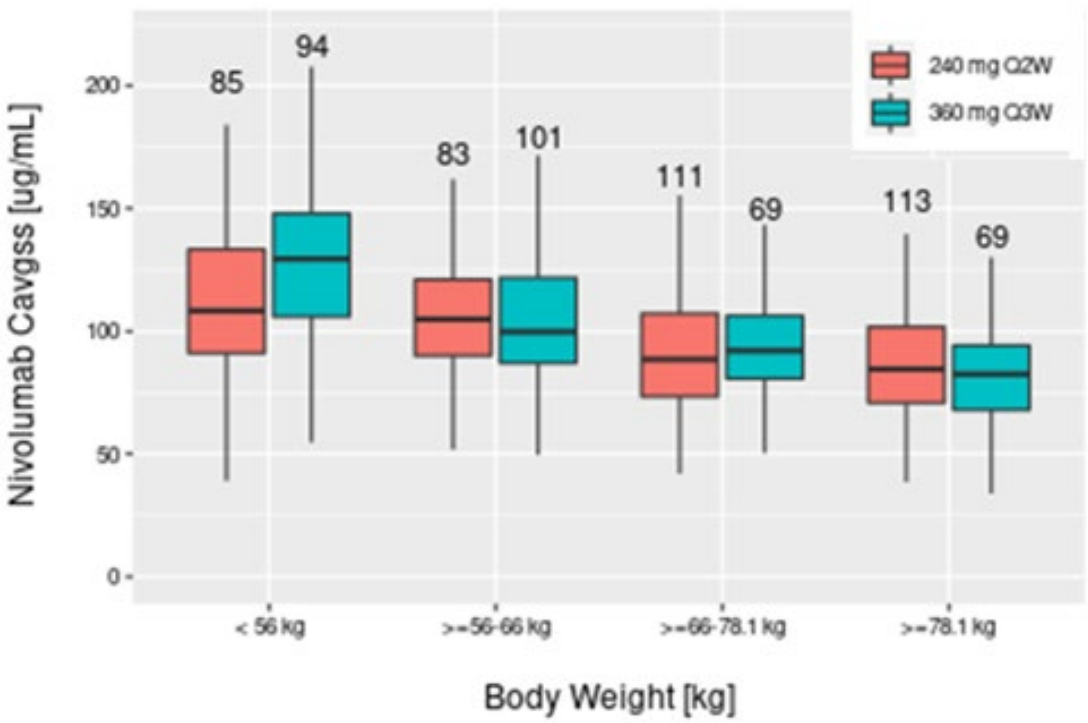
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is male, PS = 0, eGFR = 90 mL/min/1.73 m^2, with baseline ALB of 4.0 g/dL, baseline LDH of 200 IU/L, tumour burden of 7.7 cm, body weight = 67.1 kg, 2L NSCLC tumour type, and race = white or other, defined as not Asian. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Abbreviations: 1L =first-line; 2L = second-line; CI = confidence interval; CL = clearance; CLss = clearance at steady state; CL0 = clearance at time 0; eGFR = estimated glomerular filtration rate; GC = gastric cancer; GFR = glomerular filtration rate; LDH = lactate dehydrogenase; NSCLC = non-small cell lung cancer; PPK = population pharmacokinetic; PS = performance status; VC = volume of the central compartment

Source: Refer to Figure 5.1.1.2-1 in the PPK Analysis Report

Figure 3.1.3.1-2: Boxplots of Predicted Exposures (Cavgss) by Body Weight Quartiles (240 mg Q2W and 360 mg Q3W) for Subjects with 1L GC/GEJC/EAC



Abbreviations: 1L = first-line; Cavgss = time-averaged serum concentration at steady state; EAC = esophageal adenocarcinoma cancer; GC = gastric cancer; GEJC = gastroesophageal junction cancer; Q2W = every 2 weeks; Q3W = every 3 weeks.
Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. The number of subjects is above each box
Source: Refer to Figure 5.1.3.2-1 in the PPK Analysis Report

Table 5.1.3.3-1: Predicted Exposures for the 5th/95th Percentiles of Baseline Serum Albumin for a Typical Subject and % Differences in Relation to the Median for the Nivolumab 240 mg Q2W and 360 mg Q3W Treatment Groups

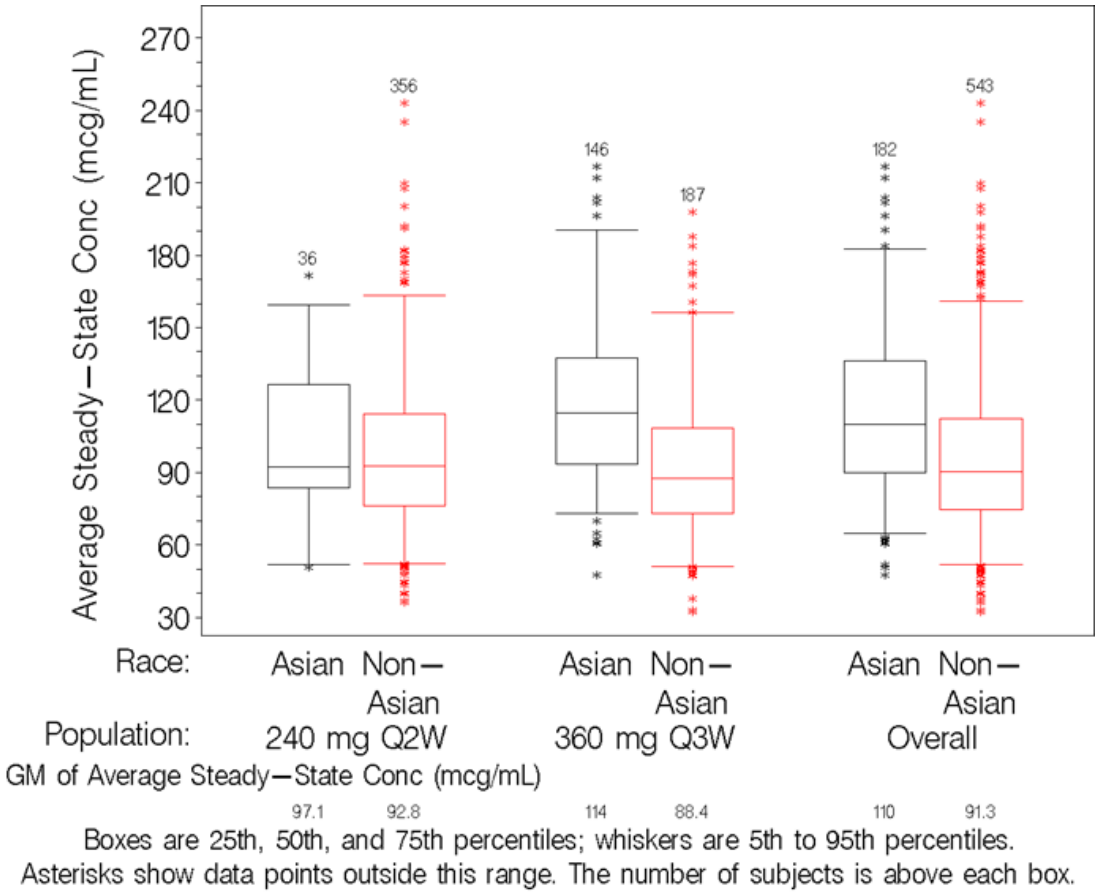
Exposure	P05	P95	P05	P95	P05-Median	P95-Median	P05-Median	P95-Median
	240 mg Q2W Arm		360 mg Q3W Arm		% Diff (240 mg)		% Diff (360 mg)	
Cavg1	27.1	29.9	34.8	39.6	-6.39	3.12	-8.48	4.25
Cmin1	17.5	21.4	20.1	26.6	-13	6.58	-17.5	9.29
Cmax1	56	56	84	84	-0.02	0.01	-0.02	0.01
Cavgss	76.1	111	76.1	111	-21.4	14.1	-21.4	14.1
Cminss	57.9	91.6	51.6	84.6	-25.9	17.2	-27.7	18.5
Cmaxss	114	148	136	169	-15.1	10	-12.8	8.52

Note: The BALB values for the 5th and 95th percentiles were 3.1 g/dl and 4.1 g/dl, respectively.

Abbreviations: BALB = baseline albumin; 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; Diff = difference; P05 = 5th percentile; P95 = 95th percentile; Q2W = every 2 weeks; Q3W = every 3 weeks

Source: dlpk\tables\rtf\sumstat-cavg1-med-balb.rtf

Figure 3.1.3.3-3: Distributions of Cavgss of Nivolumab by Dose Regimen and Overall in Study CA209649 in Relation to Asian Versus Non-Asian Subjects



Abbreviations: Cavgss = time-averaged serum concentration at steady state; Conc = concentration; GM = geometric mean; Q2W = every 2 weeks; Q3W = every 3 weeks.

Source: Refer to Figure 5.1.3.5-2 in the PPK Analysis Report

Dosing regimens

Results of the PPK analysis demonstrated that nivolumab PK in subjects with 1L GC/GEJC/EAC following nivo + chemo was consistent with the known PK characteristics of nivolumab, and were

similar to that of the 2L+ GC, 2L NSCLC, or OTHER populations following nivolumab monotherapy (Table 3.1.2-1). The OTHER population included subjects with melanoma, or renal cell in Studies CA209001 and CA209003, colorectal or prostate cancer in Study CA209001, or 3L+ NSCLC in Studies CA209001, CA209003, and CA209057.

Table 3.1.2-1: Summary Statistics of Nivolumab PK Parameter Estimates by Patient Population and Overall Population in the PPK Analysis by Tumour Type

Parameter	Geometric Mean (%CV)				
	1L GC/GEJC/EAC (n=725)	2L+ GC (n=387)	2L NSCLC (n=393)	OTHER (n=319)	ALL (n=1824)
CLss (mL/h)	7.46 (35.0)	9.06 (38.4)	8.22 (38.9)	9.3 (63.6)	8.25 (46.5)
Vs.s (L)	6.76 (19.0)	6.51 (21.7)	6.54 (22.0)	7.28 (28.0)	6.75 (22.7)
T1/2β,ss (days)	27.4 (25.4)	22 (49.7)	24.3 (27.6)	23.9 (65.5)	24.9 (40.9)

Note: n = 1824 is the sum of the 2L NSCLC, 2L+ GC, 1L GC/GEJC/EAC, and OTHER populations comprising the ALL population (overall PPK analysis population, except for 1 subject [NMID = 649134535] excluded from the model application).

Abbreviations: 1L = first-line; 2L = second-line; CLss = clearance at steady state; %CV = coefficient of variation expressed as a percentage; EAC = esophageal adenocarcinoma cancer; GC = gastric cancer; GEJC = gastroesophageal junction cancer; n = number of subjects; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; PPK = population pharmacokinetic; T1/2β,ss = terminal half-life at steady state; Vs.s = volume of distribution at steady state.

Source: Refer to Table 5.1.3.1-1 in the PPK Analysis Report.

The steady state exposure measures were comparable between the 2 regimens, with the differences in geometric mean values less than 20% for all exposure measures (Table 3.1.2-2).

Table 3.1.2-2: Geometric Mean Exposure for Nivolumab 240 mg Q2W and 360 mg Q3W Regimens in Combination with Chemotherapy in Subjects with 1L GC/GEJC/EAC

			GeoMean (% CV)[a]
Summary Exposure	Nivo 240 mg + FOLFOX Q2W GM [µg/mL] (%CV) (n=392)	Nivo 360 mg + XELOX Q3W GM [µg/mL] (%CV) (n=333)	%Diff GM (240 mg) G1-G2[a]
Cavgss	93.2 (33.6)	98.7 (33.3)	-5.57
Cmaxss	134 (28.4)	166 (26.6)	-19.3
Cminss	73.4 (38.5)	70.5 (40.1)	4.11
Cavg1	28.5 (21.7)	39.5 (21.2)	-27.8
Cmax1	58.7 (22.5)	93.3 (20.9)	-37.1
Cmin1	18.8 (26.3)	24.1 (27.3)	-22

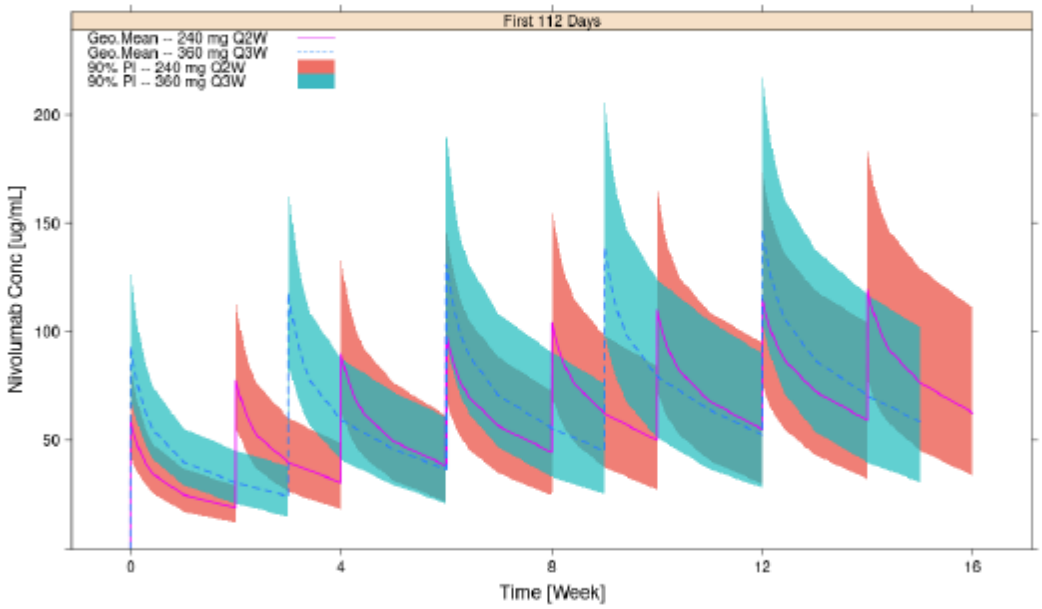
[a] Geometric mean (GM) difference in percentage of 240 mg Q2W (G1) relative to 360 mg Q3W (G2).

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; %CV = coefficient of variation expressed as a percentage; Diff = difference; EAC = esophageal adenocarcinoma cancer; GC = gastric cancer; GEJC = gastroesophageal junction cancer; GM = geometric mean; n = number of subjects; Nivo = nivolumab; p5 = 5th percentile; p95 = 95th percentile; Q2W = every 2 weeks; Q3W = every 3 weeks;

Source: Refer to Table 5.1.3.1-2 in the PPK Analysis Report

Figure 5.1.3.1-1: Predicted Geometric Mean (90% PI) Nivolumab Concentration-time Profiles (First 16 Weeks) (Linear Scale) by Dosing Regimen (Nivolumab 240 mg Q2W + FOLFOX and Nivolumab 360 mg Q3W + XELOX), in Subjects with 1L GC/GEJC/EAC



Abbreviations: 1L = first-line; Conc = concentration; EAC = esophageal adenocarcinoma cancer; GC = gastric cancer; GEJC = gastroesophageal junction cancer; Geo = geometric; PI = prediction interval; Q2W = every 2 weeks; Q3W = every 3 weeks.

Source: dlpk\graphs\CT-figure51391-PI.png

Immunogenicity

Table 4.1.2-3: ADA Assessments Summary - All Nivolumab Treated Subjects With with Baseline and At Least One Post-Baseline Assessment in CA209649

	Nivo + Chemo		
Subject ADA Status (%)	Nivolumab + XELOX N = 320	Nivolumab + FOLFOX N = 361	Nivolumab + Chemo N = 681
BASELINE ADA POSITIVE	17 (5.3)	16 (4.4)	33 (4.8)
ADA POSITIVE	33 (10.3)	27 (7.5)	60 (8.8)
PERSISTENT POSITIVE (PP)	1 (0.3)	0	1 (0.1)
NOT PP - LAST SAMPLE POSITIVE	16 (5.0)	9 (2.5)	25 (3.7)
OTHER POSITIVE	16 (5.0)	18 (5.0)	34 (5.0)
NEUTRALIZING POSITIVE	1 (0.3)	1 (0.3)	2 (0.3)
ADA NEGATIVE	287 (89.7)	334 (92.5)	621 (91.2)

Baseline ADA Positive: A subject with baseline ADA-positive sample;

ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater [≥] than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart;
Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling timepoint;
Other Positive: Not persistent but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Post-baseline assessments are assessments reported after initiation of treatment.
Note: At the time of data generation, there were 8 nivolumab NAb samples pending analysis due to the impact of BMS site COVID-19 closure and assay method issues. All 8 NAb samples have since been analyzed and all antibodies were non-neutralizing.
Source: Refer to Table 11.1-1 in the CA209649 CSR

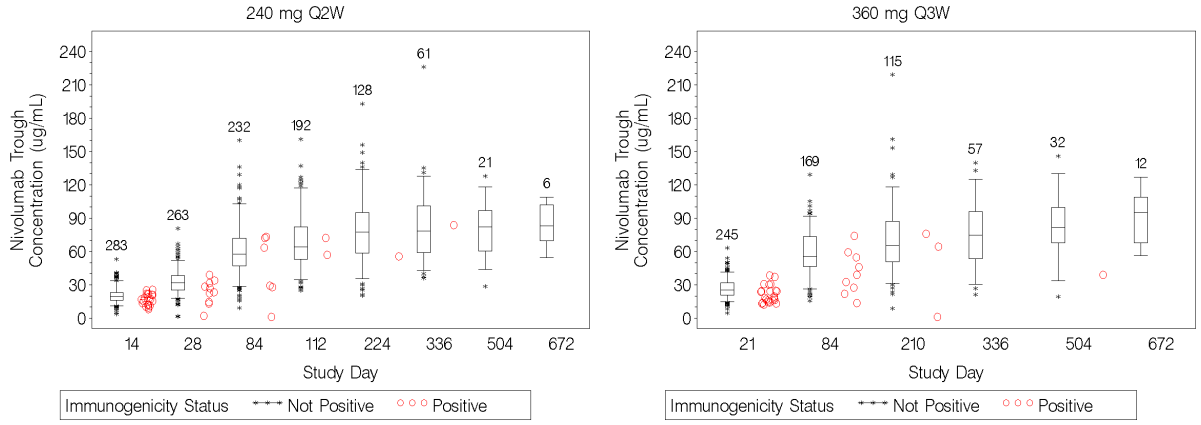
Table 4.1.3-4: Summary of Select Adverse Events of Hypersensitivity/Infusion Reaction by ADA Status (Positive, Negative) - All Nivolumab + Chemotherapy Treated 1L GC/GEJC/EAC Subjects with ADA Positive or ADA Negative

	Nivo + Chemo	
Preferred Term (%)	Nivolumab ADA Positive N = 60	Nivolumab ADA Negative N = 621
TOTAL SUBJECTS WITH AN EVENT	11 (18.3)	98 (15.8)
Anaphylactic reaction	2 (3.3)	3 (0.5)
Bronchospasm	0	1 (0.2)
Hypersensitivity	3 (5.0)	45 (7.2)
Infusion related hypersensitivity reaction	0	3 (0.5)
Infusion related reaction	6 (10.0)	57 (9.2)

MedDRA Version: 23.0
CTC Version 4.0
Includes events between first dose and within the last dose of therapy + 100 days.
Source: Refer to Table 11.1.2-1 in the CA209649 CSR

Figure 4.1.5-4: Time Course of Observed Nivolumab Trough Concentrations by Nivolumab ADA (A) and Neutralizing Antibody (B) Status in Study CA209649

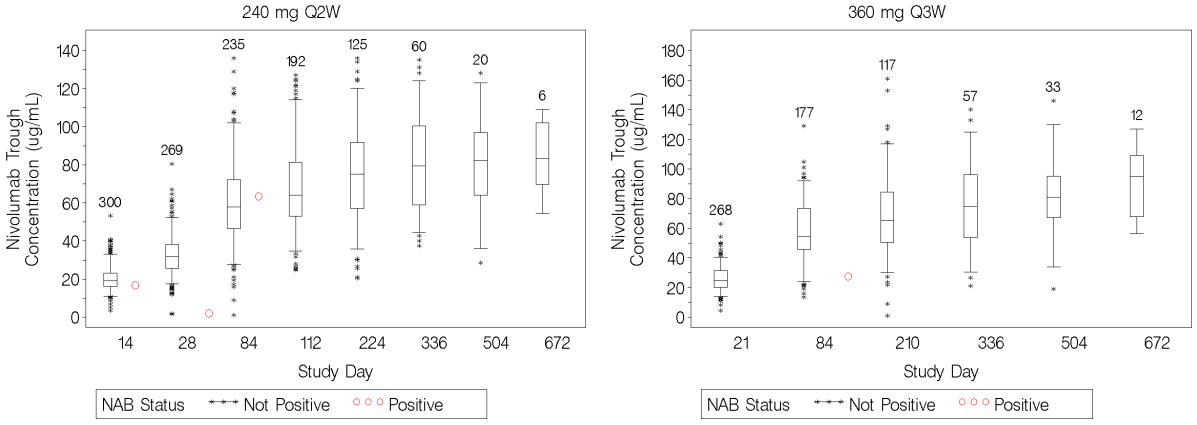
(A)



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

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

(B)



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

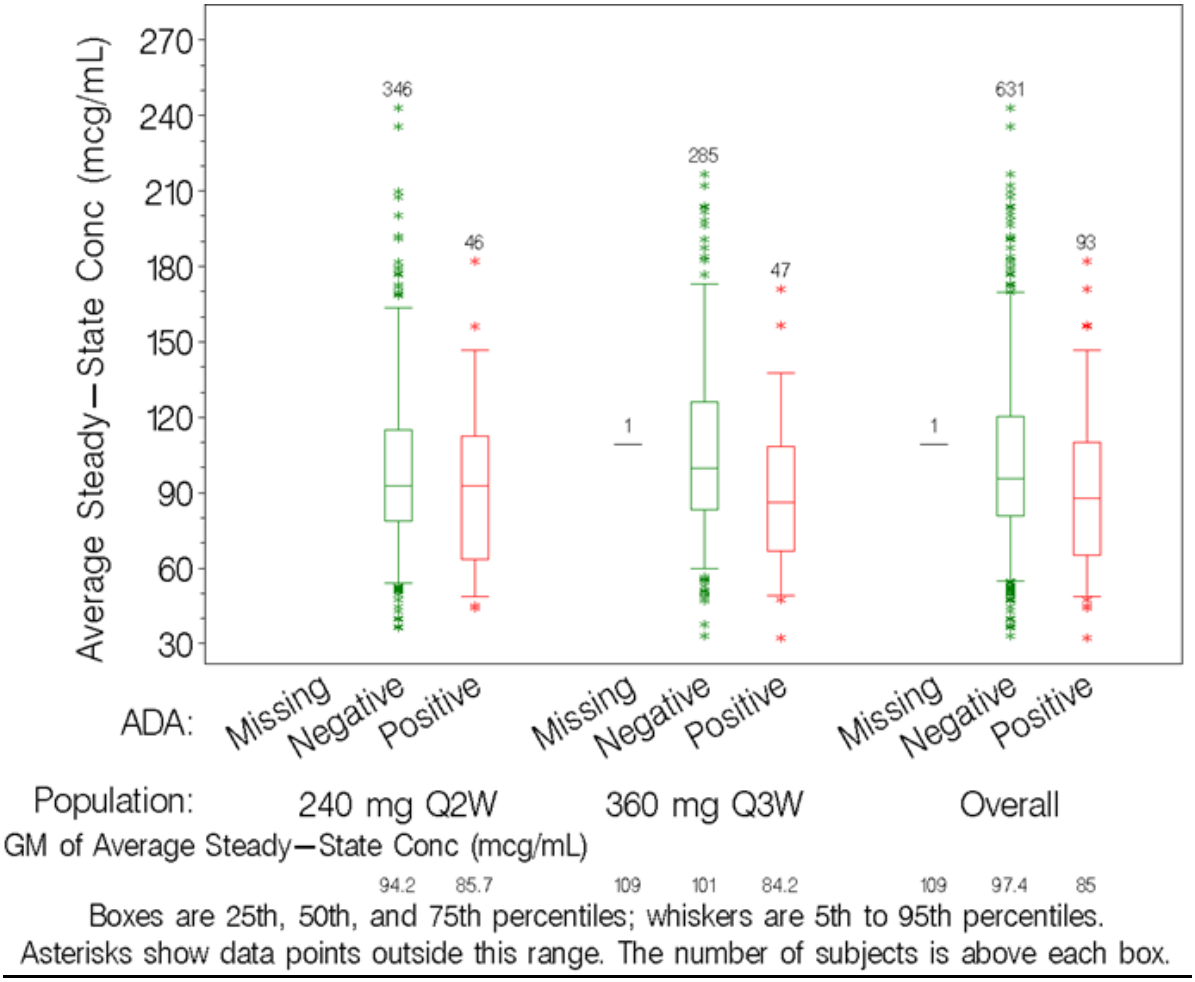
Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range. The number of samples is above each box.

Note: The number above each boxplot is the number of trough concentrations within a ± 3-day window by study day from subjects with (A) ADA negative status and (B) NAB negative status.

Abbreviations: ADA = anti-drug antibody; NAB = neutralizing antibody; Q2W = every 2 weeks; Q3W = every 3 weeks.

Source: Refer to Figure 3.2.1.5-2 and Figure 3.2.1.5-3 in the PPK Analysis Report

Figure 4.1.5-5: Distributions of Cavgss for Nivolumab + Chemotherapy in Study CA209649 in Relation to Immunogenicity Status (Positive or Negative)



Abbreviations: ADA = anti-drug antibody; Cavgss = time-averaged serum concentration at steady state; Conc = concentration; GM = geometric mean; Q2W = every 2 weeks; Q3W = every 3 weeks.

Source: Refer to Figure 5.1.3.4-2 in the PPK Analysis Report

2.3.3. Pharmacodynamics

2.3.4. PK/PD modelling

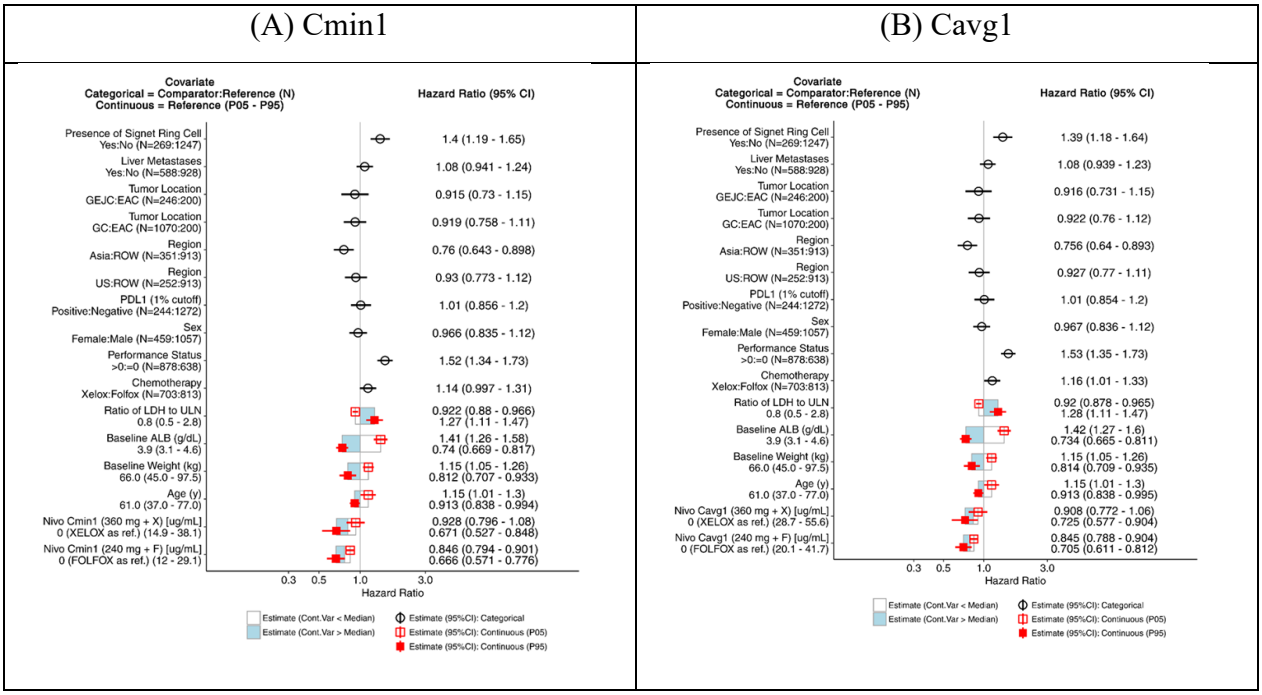
Exposure-efficacy relationship

A CPH model was developed to describe the relationship between nivolumab Cmin1 or Cavg1 and the hazard of death in all randomized subjects from the nivo + chemo (n= 725 [nivolumab 240 mg + FOLFOX n=392; nivolumab 360 mg + XELOX n=333]) and chemo (n=791 [FOLFOX n=421; XELOX n=370]) arms in CA209649.

Figure 3.2.1.1-1 is a graphical presentation of all the estimated effects in the Cmin1-OS (A) and Cavg1-OS (B) full models, showing the HR of OS across the covariate ranges and the associated 95% CIs, relative to the median value (for continuous covariates except exposure) or reference group (for categorical covariates). The effect of nivolumab exposure on HR of OS was calculated relative to the corresponding chemotherapy only arm (nivolumab 360 mg + XELOX Q3W versus XELOX; nivolumab

240 mg + FOLFOX Q2W versus FOLFOX). The findings from the Cmin1-OS and the Cavg1-OS models were generally consistent.

Figure 3.2.1.1-6: Estimated Covariate Effects on the Hazard Ratio of OS in All Randomized Subjects in CA209649 (Full Model)



Abbreviations: ALB = albumin; CI = confidence interval; Cmin1 = trough serum concentration after the first nivolumab dose; Cont. Var = continuous variable; EAC = esophageal adenocarcinoma cancer; Folfox = chemotherapy regimen of folinic acid, fluorouracil, and oxaliplatin; GC = gastric cancer; GEJC = gastroesophageal junction cancer; LDH = lactate dehydrogenase; N = number of subjects; Nivo = nivolumab; PD-L1 = programmed death-ligand 1; OS = overall survival; Q2W = every 2 weeks; Q3W = every 3 weeks; ROW = Rest of World; ULN = upper limit of normal; US = United States; Xelox = chemotherapy regimen of capecitabine plus oxaliplatin.

Source: Refer to Figure 5.2.1.1-1 and Figure 5.2.1.2-1 in the E-R Analysis Report

Table 3.2.1.1-5: Predicted OS HRs (95% CI) at 5th and 95th percentile of Nivolumab Exposure by Dosing Regimen in All Randomized Subjects in CA209649

Nivolumab exposure (µg/mL)	HR (95% CI)			
	Nivolumab 360 mg + XELOX vs. XELOX		Nivolumab 240 mg + FOLFOX vs. FOLFOX	
	5th percentile of exposure	95th percentile of exposure	5th percentile of exposure	95th percentile of exposure
Cmin1	0.928 (0.796, 1.08)	0.671 (0.527, 0.848)	0.846 (0.794, 0.901)	0.666 (0.571, 0.776)
Cavg1	0.908 (0.772, 1.06)	0.725 (0.577, 0.904)	0.845 (0.788, 0.904)	0.705 (0.611, 0.812)

Abbreviations: Cavg1 - Concentration following the 1st dose, Cmin1 - trough serum concentration after the first nivolumab dose

Source: Refer to Figure 5.2.1.1-1 and Figure 5.2.1.2-1 of the E-R Analysis Report

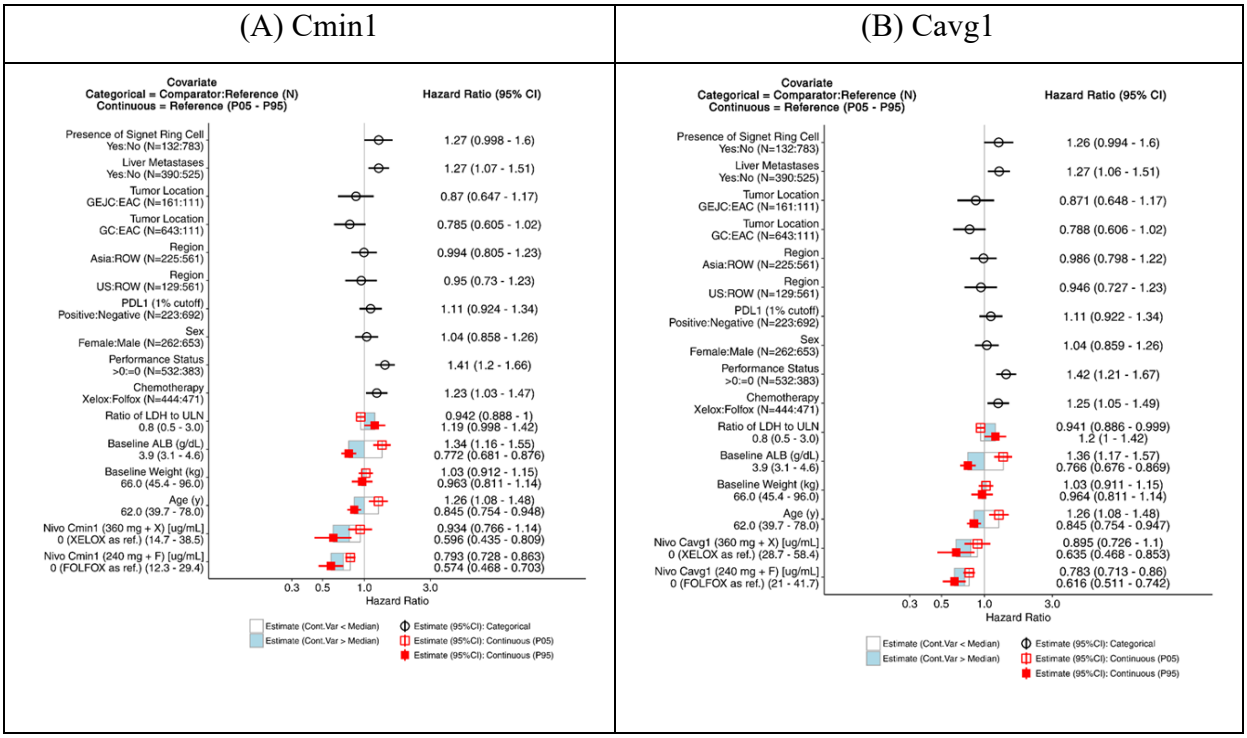
A CPH model was developed to describe the relationship between nivolumab Cmin1 or Cavg1 and the hazard of disease progression or death in all randomized subjects with PD-L1 CPS ≥ 5 from the nivo+chemo (n= 434 [nivolumab 240 mg + FOLFOX n=218; nivolumab 360 mg + XELOX n=216]) and chemo (n=481 [FOLFOX n=253; XELOX n=228]) arms in CA209649.

Figure 3.2.1.2-1 is a graphical presentation of all of the estimated effects in the Cmin1-PFS (A) and Cavg1-PFS (B) full models, showing the HR of PFS across the covariate ranges and the associated 95% CIs, relative to the median value (for continuous covariates except exposure) or reference group (for categorical covariates). The effect of nivolumab exposure on HR of PFS was calculated relative to the corresponding chemotherapy only arm (nivolumab 360 mg + XELOX Q3W versus XELOX; nivolumab 240 mg + FOLFOX Q2W versus FOLFOX). The findings from the Cmin1-PFS and the Cavg1-PFS models were generally consistent.

The effect of chemotherapy on PFS was evaluated in an E-R PFS model; XELOX was suggested to be a significant predictor (95% CI did not include 1) with a slightly higher risk than FOLFOX as backbone chemotherapy (Figure 3.2.1.2-1). The interaction term between chemotherapy and nivolumab exposure was also tested and was not kept in either full model, as it did not reduce BIC.

PFS HRs favored (HR < 1) nivo+chemo compared to chemo within the exposure range produced by the 2 nivolumab dosing regimens (Figure 3.2.1.2-1). Both Cmin1 and Cavg1 were identified as significant predictors (95% CI did not include 1) for PFS, because chemotherapy control arm data were included, and exposure in the model represented the nivolumab treatment effect. The effect of Cavg1 on the HR of OS (0.988) (refer to Table 5.1.1.2-1 in the E-R Analysis Report) was slightly flatter as compared to that of Cmin1 (0.981) (refer to Table 5.1.1.1-1 in the E-R Analysis Report). The magnitude of treatment effect on PFS was similar for the 2 nivolumab dosing regimens. Although increasing nivolumab exposure appeared to be associated with numerically smaller HRs of PFS (Figure 3.2.1.2-1),the predicted PFS HR (95% CI) for nivolumab 360 mg + XELOX Q3W overlapped between the 5th and 95th percentile of Cmin1 and Cavg1 (Table 3.2.1.2-1); the predicted OS HR (95% CI) for nivolumab 240 mg + FOLFOX Q2W overlapped between the 5th and 95th percentile of Cavg1 (Table 3.2.1.2-1).

Figure 3.2.1.2-7: Estimated Covariate Effects on the Hazard Ratio of PFS in All Randomized Subjects with PD-L1 CPS ≥ 5 in CA209649 (Full Model)



Abbreviations: ALB = albumin; CI = confidence interval; Cavg1 = average serum concentration after the first nivolumab dose; Cmin1 = trough serum concentration after the first nivolumab dose; Cont. Var = continuous variable; EAC = esophageal adenocarcinoma cancer; Folfox = chemotherapy regimen of folinic acid, fluorouracil, and oxaliplatin; GC = gastric cancer; GEJC = gastroesophageal junction cancer; LDH = lactate dehydrogenase; N = number of subjects; Nivo = nivolumab; PDL1 = programmed death-ligand 1; PFS = progression-free survival; Q2W = every 2 weeks; Q3W = every 3 weeks; ROW = Rest of World; ULN = upper limit of normal; US = United States; Xelox = chemotherapy regimen of capecitabine + oxaliplatin.

Source: Refer to Figure 5.1.1.1-1 and Figure 5.1.1.2-1 in the E-R Analysis Report

Table 3.2.1.2-6: Predicted PFS HRs (95% CI) at 5th and 95th percentile of Nivolumab Exposure by Dosing Regimen in All Randomized Subjects with PD-L1 CPS ≥ 5 in CA209649

	HR (95% CI)			
Nivolumab exposure (μg/mL)	Nivolumab 360 mg + XELOX vs. XELOX		Nivolumab 240 mg + FOLFOX vs. FOLFOX	
	5th percentile of exposure	95th percentile of exposure	5th percentile of exposure	95th percentile of exposure
Cmin1	0.934 (0.766, 1.14)	0.596 (0.435, 0.809)	0.793 (0.728, 0.863)	0.574 (0.468, 0.703)
Cavg1	0.895 (0.726, 1.10)	0.635 (0.468, 0.853)	0.783 (0.713, 0.860)	0.616 (0.511, 0.742)

Abbreviations: Cavg1 - Concentration following the 1st dose, Cmin1 - trough serum concentration after the first nivolumab dose
Source: Refer to Figure 5.1.1.1-1 and Figure 5.1.1.2-1 of the E-R Analysis Report

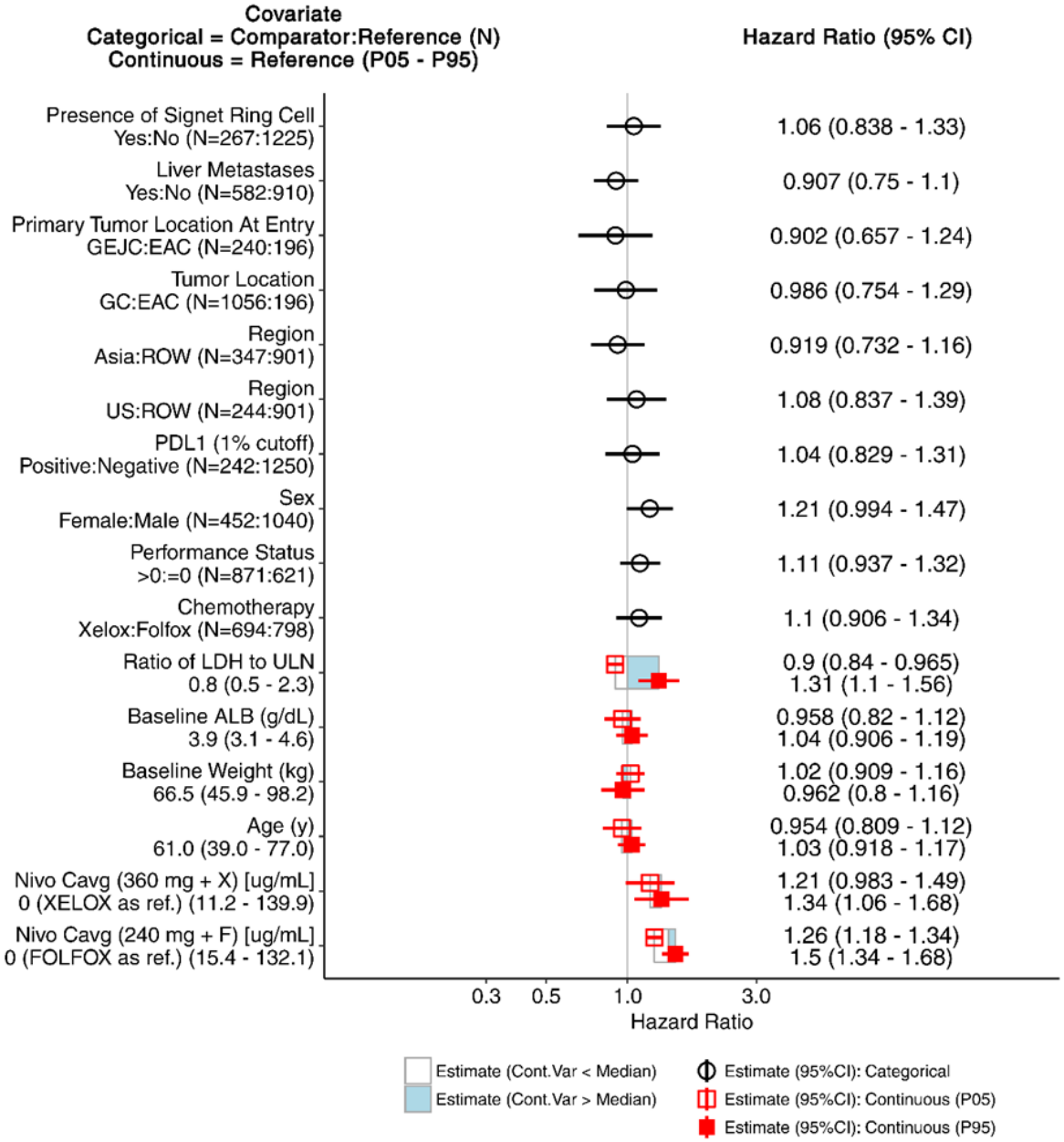
Exposure-safety

A CPH model was developed to describe the relationship between daily Cavg and time to first occurrence of Gr 2+ IMAEs in all treated subjects from the nivo+chemo (n= 725 [nivolumab 240 mg + FOLFOX n=392; nivolumab 360 mg + XELOX n=333]) and chemo (n=767 [FOLFOX n=406; XELOX n=361]) arms in CA209649.

Figure 3.2.2.1-1 is a graphical presentation of all the estimated effects in the full model, showing the HR of Gr 2+ IMAEs across the covariate ranges and the associated 95% CIs, relative to the median value (for continuous covariates except exposure) or reference group (for categorical covariates). The effect of nivolumab log daily Cavg on HR was calculated relative to the corresponding chemotherapy only arm (360 mg Q3W nivolumab + XELOX versus XELOX; 240 mg Q2W nivolumab + FOLFOX versus FOLFOX).

Log daily Cavg was identified as a significant predictor (95% CI did not include 1) in E-R safety modeling for Gr 2+ IMAE, because chemotherapy control arm data were included, and exposure in the model represented the nivolumab treatment effect.

Figure 3.2.2.1-8: Estimated Effects of Exposure-response Grade 2+ IMAE in CA209649 (Full Model)



Abbreviations: ALB = albumin; CI = confidence interval; Cavg = daily average nivolumab concentration Cont. Var = continuous variable; EAC = esophageal adenocarcinoma cancer; Folfox = chemotherapy regimen of folinic acid, fluorouracil, and oxaliplatin; GC = gastric cancer; GEJC = gastroesophageal junction cancer; Gr 2+ IMAEs = Grade ≥ 2 immune-mediated adverse events; LDH = lactate dehydrogenase; N = number of subjects; Nivo = nivolumab; PDL1 = programmed death-ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks; ROW = Rest of World; ULN = upper limit of normal; US = United States; Xelox = chemotherapy regimen of capecitabine plus oxaliplatin.Source: Source: Refer to Figure 5.3.1.1-1 in the E-R Analysis Report

Table 3.2.2.1-7: Predicted Grade 2+ IMAE HRs (95% CI) at 5th and 95th percentile of Nivolumab Daily Cavg by Dosing Regimen in All Randomized Subjects in CA209649

Nivolumab exposure (μg/mL)	HR (95% CI) of Grade 2+ IMAEs			
	Nivolumab 360 mg + XELOX vs. XELOX		Nivolumab 240 mg + FOLFOX vs. FOLFOX	
	5th percentile of exposure	95th percentile of exposure	5th percentile of exposure	95th percentile of exposure
Daily Cavg	1.21 (0.983, 1.49)	1.34 (1.06, 1.68)	1.26 (1.18, 1.34)	1.50 (1.34, 1.68)

Source: Refer to Figure 5.3.1.1-1 of the E-R Analysis Report

2.3.5. Discussion on clinical pharmacology

Both analytical methods used for the quantification of BMS-936558 in human serum samples in support of study CA209649 were previously assessed. Since the data were obtained within a study from two different laboratories comparison of those data was performed by a cross validation. The outcome of the cross validation show that the obtained data were reliable and they can be compared and used. All study samples analysed at both sites and reported for nivolumab (BMS-936558) were covered by 2373 days of long-term stability at nominal at -70 ºC.

Both in-study validations show acceptable calibration standards and QCs. The reasons for the re-analysis of samples are considered acceptable. For samples re-assayed inadvertently, the original values were reported. Incurred Sample Reproducibility was performed at both sites and the reanalysis confirms the validity and performance of the Analytical Method Procedure for all analytes.

The MAH has conducted a Phase 3 study (CA209649) to characterize the pharmacokinetics, immunogenicity, and exposure-response relationship of nivolumab in subjects with advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma (GC/GEJC/EAC) to support the administration of nivolumab 240 mg every 2 weeks (Q2W) or nivolumab 360 mg every 3 weeks (Q3W) intravenous (IV) in combination with fluoropyrimidine and platinum-containing chemotherapy (hereafter referred to as nivo+chemo) for first-line (1L) treatment.

The modelling strategy consisted in a pooled analysis of PK data in subjects with 1L GC/GEJC/EAC from Study CA209649 and data from other relevant nivolumab monotherapies, across multiple tumour types, which is endorsed. The pooled analysis offered the advantage of a solid, robust and precise estimation of the PK properties of nivolumab (parameters and covariate effects) and allowed to identify differences in PK elements due to disease type. The updated population PK model adequately characterized the time-course of nivolumab in patients with 1L GC/GEJC/EAC based on the GOF, pc-VPC and parameter estimates.

No covariates were found to have a clinically meaningful effect on nivolumab PK in the updated analysis. Graphical representations of the effect of categorical and continuous covariates on the typical value of the structural model parameters of CL, volume of central compartment (VC), and CLss/CL0 (EXP[EMAX]) are presented in Figure 3.1.1-1. All covariate effects were within ± 20% boundaries, except for the effect of baseline body weight on CL and VC and baseline albumin (ALB) on CL. Baseline body weight was associated with a 26% increase in CL and a 22% increase in VC in subjects with 95th percentile weight relative to subjects with median body weight. Nivolumab CL increased approximately 31% in subjects with 5th percentile baseline ALB relative to subjects with median baseline ALB value. However, the magnitudes of body weight, VC, and ALB effect on CL were consistent with findings of previous analyses. These findings were not considered to be clinically relevant, as the 95th percentile body weight or 5th percentile ALB only resulted in approximately 18.5% or 21.4% lower Cavgss,

respectively, relative to those observed in subjects with median body weight or median ALB at baseline in Study CA209649.

A forest plot (Figure 3.1.1-1 above) has been provided to assess the clinical relevance of the covariates selected based on the change on main PK parameters, suggesting differences in general less than 20% in PK values. Predicted exposure metrics were evaluated across different body weight stratified for each regimen, showing a slightly higher exposure for patients with low body weight and lower exposure levels in patients with higher body weight and no differences in exposure due to the schedule administered. Similar exposure was predicted between both regimens for each sub-group of body weight category.

The immunogenicity evaluation revealed the lack of any clinical concern in terms of differences in clearance or exposure. The incidence of immunogenicity is of minor relevance.

The exposure-efficacy relationship has been established to characterize the probability of OS and predict at the proposed dosing regimens. The forest plot analysis of the Hazard Ratio for the two exposure parameters Cave1 and Cmin1, suggested a better efficacy in subjects with higher nivolumab exposures although the point estimate of the Hazard ratio remained < 1 even for subjects with low nivolumab exposures (5^{th} percentile). Since only one dose level was evaluated, the confounding effect of disease/health condition on exposure cannot be distinguished, and hence the exposure-efficacy analyses should be cautiously interpreted.

The exposure-safety analysis characterized the probability of Gr2+ imAE for the proposed dosing regimens (nivolumab 240mg Q2W +FOLFOX and nivolumab 360 mg Q3W + XELOX). The results show higher probability (21-26%) of Gr2+ imAE and roughly no differences between the proposed dosing regimens.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of nivolumab for the adjuvant treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma (GC/GEJC/EAC) have been adequately characterized through a pooled analysis using previous clinical data together with experimental evidence from study CA209649. The population PK model, which shares the same structural elements as previous submissions, adequately describes the experimental data. The exposure-response analysis should be interpreted with caution, since only one dose level was evaluated and different populations were considered, where confounding factors (effect of disease/health conditions) may affect.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies were included in this application.

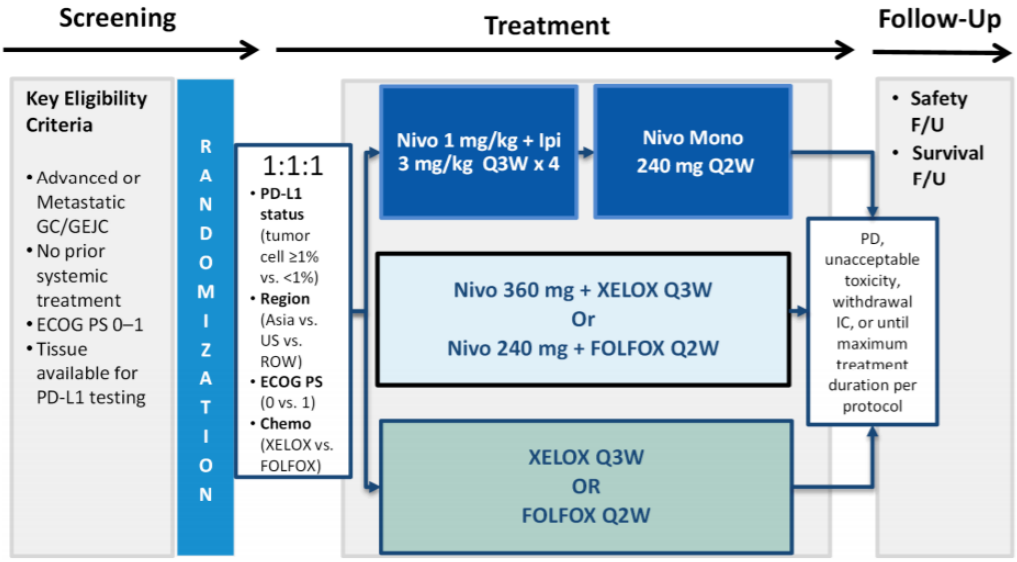
2.4.2. Main study

<u>Study CA209649</u> (CheckMate 649): A randomized, multicenter, open-label, phase 3 study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine versus oxaliplatin plus fluoropyrimidine in subjects with previously untreated advanced or metastatic gastric,

gastroesophageal junction cancer or oesophageal adenocarcinoma (GC/GEJC/OAC).

Methods

Figure 1. Study Design Schematic



Abbreviations: Chemo = chemotherapy, ECOG PS = Eastern Cooperative Oncology Group Performance Status, FOLFOX = leucovorin plus fluorouracil plus oxaliplatin, GC = gastric cancer, GEJC = gastroesophageal junction cancer, Ipi = ipilimumab, Mono = monotherapy, Nivo = nivolumab, Q2W = every 2 weeks, Q3W = every 3 weeks, PD = progressive disease, PD-L1 = programmed death-ligand 1, ROW = rest of world, XELOX = capecitabine plus oxaliplatin

Study participants

Main inclusion criteria

a) Males and Females, ≥ 18 years of age.

b) All subjects must have inoperable, advanced or metastatic GC or GEJ or distal esophageal carcinoma and have histologically confirmed predominant adenocarcinoma. The documentation of GEJ involvement can include biopsy, endoscopy, or imaging.

c) Subject must be previously untreated with systemic treatment (including HER 2 inhibitors) given as primary therapy for advanced or metastatic disease.

d) Allowed Prior Therapies: Prior adjuvant or neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy for GC or GEJ cancer are permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 6 months prior to randomization. Palliative radiotherapy is allowed and must be completed 2 weeks prior to randomization.

e) Subject must have at least one measurable lesion or evaluable disease by CT or MRI per RECIST 1.1 criteria; radiographic tumour assessment should be performed within 28 days prior to randomization.

f) ECOG performance status score of 0 or 1.

g) Tumour tissue must be provided for biomarker analyses. In order to be randomized, a subject must have an evaluable PD-L1 expression classification (≥ 1% or < 1%, or indeterminate) as determined by the central lab. Subjects with non-evaluable results will not be allowed to be

randomized. Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumour tissue sections, with an associated pathology report, must be submitted for biomarker evaluation prior to randomization. The tumour tissue sample may be fresh or archival if obtained within 6 months prior to randomization, and there can have been no systemic therapy (e.g. adjuvant) given after the sample was obtained. Tissue must be a core needle biopsy, excisional or incisional biopsy.

h) Subject re-enrolment: this study permits the re-enrolment of a subject who has discontinued the study as a pre-treatment failure (i.e. subject has not been randomized). If re-enrolled, the subject must be re-consented.

Main exclusion criteria

a) Known HER2 positive status.

b) Subjects with untreated known CNS metastases. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization.

c) Subjects with ascites which cannot be controlled with appropriate interventions.

d) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

e) Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enrol.

f) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

g) 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. e) All toxicities attributed to prior anti-cancer therapy other than hearing loss, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

h) Subjects with > Grade 1 peripheral neuropathy.

i) Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive study drug.

j) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated locally.

k) Subjects who have received a live/attenuated vaccine within 30 days of first treatment. (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]).

l) Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, e.g., hepatitis B surface antigen (HBsAg, Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV RNA negative).

Treatments

The treatments were

Nivo+chemo (XELOX or FOLFOX) Arm:

- Nivolumab plus XELOX:
  - Nivolumab 360 mg intravenous (IV) over 30 minutes on Day 1 of each treatment cycle, Q3W
  - Oxaliplatin 130 mg/m^2 IV on Day 1 of each treatment cycle + capecitabine 1000 mg/m^2 orally twice daily (BID) on Days 1 to 14 of each treatment cycle, Q3W
- Nivolumab plus FOLFOX:
  - Nivolumab 240 mg IV over 30 minutes on Day 1 of each treatment cycle, Q2W
  - Oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m2 IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours daily (QD) or per local standard on Days 1 and 2 of each treatment cycle, Q2W

The treatment of nivolumab could be given up to 24 months in the absence of disease progression or unacceptable toxicity. Nivolumab monotherapy (240 mg Q2W, 360 mg Q3W or 480 mg Q4W) was permitted in cases where all chemotherapy components were discontinued per standard of care or toxicity.

Chemo (XELOX or FOLFOX) Arm:

- XELOX: Oxaliplatin 130 mg/m^2 IV on Day 1 of each treatment cycle + capecitabine 1000 mg/m^2 orally (PO) BID on Days 1 to 14 of each treatment cycle, Q3W
- FOLFOX: Oxaliplatin 85 mg/m^2 + leucovorin 400 mg/m^2 + fluorouracil 400 mg/m^2 IV on Day 1 of each treatment cycle, and fluorouracil 1200 mg/m^2 IV continuous infusion over 24 hours QD or per local standard on Days 1 and 2 of each treatment cycle, Q2W.

Dose reductions for nivolumab were not permitted. Dose reductions for chemotherapy were permitted according to local standard or local package insert.

Objectives

Primary Objectives

- To compare OS in subjects with advanced or metastatic GC or GEJC with PD-L1 CPS ≥5.
- To compare PFS, as assessed by BICR in subjects with advanced or metastatic GC or GEJC with PD-L1 CPS ≥ 5.

Hierarchically Tested Secondary Objectives

- To compare OS in subjects with advanced or metastatic GC or GEJC with PD-L1 CPS ≥ 1 or all randomized subjects

Other Secondary Objectives

- To evaluate OS in subjects with advanced or metastatic GC or GEJC with PD-L1 CPS ≥10
- To evaluate PFS, as assessed by BICR, in subjects with advanced or metastatic GC or GEJC with PD-L1 CPS ≥ 10, CPS ≥ 1 or all randomized subjects
- To evaluate ORR, as assessed by BICR, in subjects with advanced or metastatic GC or GEJC with PD-L1 CPS ≥10, CPS ≥ 5, CPS ≥ 1, or all randomized subjects

Exploratory Objectives

- To assess time to symptom deterioration (TTSD) as assessed using Gastric Cancer Subscale (GaCS) of Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) in subjects with advanced or metastatic GC or GEJC with PD-L1 CPS ≥ 10, CPS ≥ 5, CPS ≥ 1, or all randomized subjects
- To assess PFS and ORR, as assessed by the investigator in subjects with advanced or metastatic GC or GEJC across CPS cut-offs
- To evaluate duration of response (DOR) as assessed by BICR and by investigator, in subjects with advanced or metastatic GC or GEJC
- To evaluate the durable response rate (DRR: objective response lasting continuously > 6 months) as assessed by BICR and by investigator, in subjects with advanced or metastatic GC or GEJC
- To evaluate second disease progression (PFS2) or time to second subsequent line therapy (TSST) in subjects with advanced or metastatic GC or GEJC
- To assess PFS, ORR as assessed by either BICR or investigator, OS in subjects with advanced or metastatic GC or GEJC across tumour cell PD-L1 cut-offs
- To assess the overall safety and tolerability of nivolumab in combination with oxaliplatin plus fluoropyrimidine vs. oxaliplatin plus fluoropyrimidine in subjects with advanced or metastatic GC or GEJC
- To explore potential biomarkers predictive of or associated with clinical efficacy (OS, PFS and ORR) including microsatellite instability (MSI) status in subjects with advanced or metastatic GC or GEJC
- To characterize the immunogenicity (IMG) of nivolumab in combination with oxaliplatin plus fluoropyrimidine when administered in combination to subjects with advanced or metastatic GC or GEJC
- To assess changes from baseline in the subject's overall health status using the 3-level version of the EQ-5D (EQ-5D-3L) index and visual analog scale (EQ-5D-3L VAS) of nivolumab in combination with oxaliplatin plus fluoropyrimidine vs. oxaliplatin plus fluoropyrimidine in subjects with advanced or metastatic GC or GEJC
- To assess the subject's cancer-related quality of life using the FACT-Ga questionnaire and selected components, including the GaCS and 7-item version of the FACT-General (FACT-G7) of nivolumab in combination with oxaliplatin plus fluoropyrimidine vs. oxaliplatin plus fluoropyrimidine in subjects with advanced or metastatic GC or GEJC

Outcomes/endpoints

Table 1. Key Objectives/Endpoints for Nivo+Chemo vs. Chemo (CA209649)

Primary Endpoints	• OS in randomized subjects with PD-L1 CPS ≥ 5 • PFS by BICR in randomized subjects with PD-L1 CPS ≥ 5
Secondary Endpoints (in hierarchical testing order)	• OS in randomized subjects with PD-L1 CPS ≥ 1 • OS in all randomized subjects.
Secondary Endpoints (descriptive)	• OS in randomized subjects with PD-L1 CPS ≥ 10 • PFS by BICR in randomized subjects with PD-L1 CPS ≥ 10, 1 or all randomized subjects • ORR by BICR in randomized subjects with PD-L1 CPS ≥ 10, 5, 1 or all randomized subjects
Exploratory Endpoints	• ORR,[a,b] PFS by investigator in randomized subjects with PD-L1 CPS ≥10, 5, 1 or all randomized subjects • OS, PFS,[a] ORR[a,b] in randomized subjects across TC PD-L1 cut-offs • PFS2 or TSST of next line treatment • DOR[a,b] • DRR: objective response lasting continuously > 6 months, only in subjects with PD-L1 CPS ≥ 5) [a,b] • PRO in randomized subjects with PD-L1 CPS ≥10, 5, 1, or all randomized subjects • Biomarkers, safety and tolerability, and immunogenicity

[a] by BICR and investigator

[b] ORR in all randomized subjects; ORR and DOR in subjects with measurable disease

Abbreviations: BICR - blinded independent central review, CPS - combined positive score, DOR - duration of response, DRR - durable response rate, ORR - objective response rate, OS – overall survival, PD-L1 – programmed death ligand 1, PFS - progression-free survival, PFS2 - PFS after next line of treatment, PRO - patient reported outcomes, TC - tumour cell, TSST - time to second subsequent line therapy

Biomarkers

Subjects were enrolled regardless of tumour cell PD-L1 expression. Per revised Protocol 07 (included Amendment 23 dated 14-Sep-2018, "Protocol amendments" below), the primary population was changed to subjects with PD-L1 CPS ≥ 5, however, stratification by tumour cell PD-L1 remained unchanged.

An archival (or fresh) formalin-fixed paraffin embedded (FFPE) tissue block or 20 unstained tumour tissue sections (with an associated pathology report) were required to be collected within 6 months prior to enrolment. No systemic therapy (e.g. adjuvant or neoadjuvant chemotherapy) was to be given after the sample was obtained. Tissue was required to be from a core needle, excisional or incisional biopsy. An optional fresh biopsy at the time of suspected tumour progression might also have been collected.

Tumour cell PD-L1

Tumour cell PD-L1 at 1% cut-off was one of the stratification factors. Tumour tissue specimens were sent to the central lab (LabCorp Center for Molecular Biology and Pathology [CMBP] in North Carolina, USA or Covance Shanghai) for PD-L1 testing during the screening period. Tumour cell PD-L1 expression was defined as the percent of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells per validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test according to the manufacturer's instructions with the DAKO Autostainer Link-48 system.

PD-L1 combined positive score (CPS):

CPS was generated centrally by rescoring the tumour cell PD-L1 stained slides using the central lab DAKO CPS algorithm. CPS is a scoring algorithm taking into account immunoreactivity for PDL1 in both tumour cells and tumour associated immune cells (restricted to lymphocytes and macrophages) within or directly associated with tumour cell strands. As such, CPS is the number of PD-L1 positive cells (tumour cells, lymphocytes and macrophages) divided by the total number of viable tumour cells within the evaluated tumour area, multiplied by 100. Although the calculation might have been greater than 100, the maximum CPS is defined as 100.

Microsatellite Instability (MSI)

MSI status was determined retrospectively on pre-treatment FFPE tissues using the Idylla™ MSI Test by a central laboratory. The Idylla™ MSI Test is an automated PCR based qualitative test and determines microsatellite stability/instability through mathematical scoring related to the detection of a novel panel of seven monomorphic biomarkers: ACVR2A, BTBD, DIDO1, MRE11, RYR3, SEC31A, and SULF2. The Idylla™ MSI Test reports results as microsatellite stable (MSS), microsatellite instability high (MSI-H), or invalid in cases where the MSI status of tested samples cannot be reliably determined.

Sample size

This section summarizes power calculation of the primary endpoints of PFS and OS per the last revised protocol before the database lock (DBL) (Revised Protocol 09 [Amendment 29]). The study enrolment was completed prior to Revised Protocol 09 based on the sample size as determined by the original design assumptions. This revision changed the final PFS and interim OS analyses to be conducted at a minimum follow-up time of 12 months and final OS analysis at a minimum follow-up time of 24 months after the last subject was randomized. Under the assumption that the prevalence of PD-L1 CPS ≥5 was 35%, it was estimated that the primary population would consist of 554 subjects concurrently randomized to the nivo+chemo and chemo arms. The hazard ratio (HR) for PFS was modelled as a 2-piece hazard ratio with a delayed effect (HR=1) of the first 3 or 6 months followed by a constant HR of 0.56 thereafter. With a type I error of 2% at 12 months minimum follow-up, the expected number of PFS events was estimated to be 497 for a 3-month delay and approximately 99% power; or 506 for a 6-month delay and approximately 60% power.

For OS, the HR was modelled as a 2-piece hazard ratio, a delayed effect with a HR of 1 vs. chemotherapy for the first 6 months followed by a constant HR of 0.65 thereafter. At 24 months minimum follow-up at final analysis, it was expected that 466 events would be observed providing an adequate power of approximately 85% with a type I error of 3% (two-sided).

The actual observed prevalence of PD-L1 CPS ≥ 5 was 60% in the locked database of 10-Jul-2020 among the randomized subjects pooled over the 3 treatments arms. Therefore, prior to the DMC efficacy review meeting and unblinding of BMS study team, the power for PFS and OS were updated using this actual prevalence of PD-L1 CPS ≥ 5 (reflected in statistical analysis plan [SAP] V4.0 Appendix 5). Based on randomization schema, the primary population would consist of 949 subjects concurrently randomized to nivo+chemo and chemo. Using the same PFS model as in the design, with 3 months or 6 months delayed treatment effect, the expected number of PFS events would be 841 and 857, with corresponding power of 99.9% and 84%, respectively. For OS, the expected number of events, using the same model as in the design, was 800 events providing a power of 97.9%.

Randomisation

Once enrolled in Interactive Web Response System (IWRS), subjects who had met all eligibility were randomized 1:1 to treatment with either nivo+ipi or chemo per original study design, with stratification by tumour cell PD-L1 expression level (≥1% vs. < 1% or indeterminate), region (Asia vs. North America [US and Canada] vs. rest of the world) and ECOG performance status (0 vs. 1). After implementation of Revised Protocol 02 (Amendment 08), subjects were randomized 1:1:1 to treatment with either nivo+ipi, nivo+chemo, or chemo, with the above 3 original stratification factors and the choice of chemotherapy regimen (XELOX vs. FOLFOX) as an additional stratification factor. As of 05-Jun-2018, the nivo+ipi arm was closed to enrolment per DMC recommendation and, following implementation of Revised Protocol 06 (Amendment 20), subjects were then randomized 1:1 to treatment with either nivo+chemo or chemo.

Table 2. Randomisation allocation

Protocol Periods	Randomization allocation	Number of Randomized Subjects Current / Cumulative
First patient randomized - Amendment 8	1:1 (Nivolumab +Ipilimumab: Chemotherapy)	83/83
Amendment 08 - Amendment 20	1:1:1 (Nivolumab + Ipilimumab: Chemotherapy: Nivolumab + Chemotherapy)	1098/1181
Amendment 20 to amendment 26	1:1 (Chemotherapy: Nivolumab + Chemotherapy)	468/1649
Amendment 26 to the end of enrollment	1:1 (Chemotherapy: Nivolumab + Chemotherapy)	382/2031

Blinding (masking)

The trial is open-label.

Statistical methods

The initial study SAP version 1.0 was finalized on 25-Apr-2017. Version 2.0 of the SAP reflected the changes according to the Revised Protocol 09 (Amendment 29) and was issued on 02-Dec-2019. Version 3.0 was finalized on 03-Jun-2020, prior to the CSR DBL (10-Jul-2020) and introduced additional sensitivity analyses for PFS and OS. The final version 4.0 was issued on 05-Aug-2020, this version introduced one additional Appendix 5 to the SAP reflecting the expected number of events for PFS and OS in the primary population based on the actual prevalence of PD-L1 CPS ≥ 5 rather than the assumed prevalence used in previous versions of the SAP.

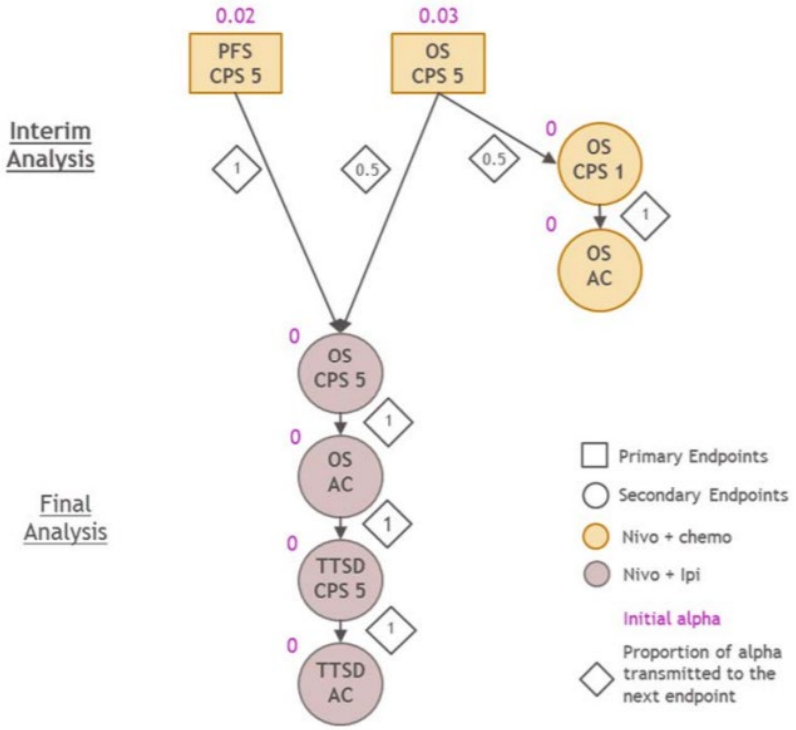
Type I error control

The hierarchical testing strategy as per the last SAP described in Figure 2 ensures control of family-wise error rate (FWER) at a 2-sided significance (alpha) level of 5 % for the primary and key secondary endpoints.

For the dual primary endpoints of PFS and OS in the comparison of nivo+chemo vs. chemo in randomized subjects with PD-L1 CPS ≥ 5, a 2-sided significance level of 2% was allocated to PFS and 3% was allocated to OS. If the OS comparison in subjects with PD-L1 CPS ≥ 5 between nivo+chemo vs. chemo was significant, then OS in subjects with PD-L1 CPS ≥ 1 and OS in all randomized were planned to be sequentially tested at a 2-sided 1.5% significance level.

For OS in PD-L1 CPS ≥ 5, 1 and all randomized subjects, the significance levels at the interim and final analyses were obtained following group sequential design using the Lan-DeMets alpha spending function with O'Brien-Fleming type boundary. At the time of the interim analysis, the significance level was based on actual OS events observed and the estimated final number of events. At the final analysis, the significance level will be calculated using the number of events in the database at the time of database lock (DBL) with consideration of the alpha already spent at the interim analysis. For the interim analysis of OS in randomized subjects with PD-L1 CPS ≥ 1 and all randomized subjects, the significance levels were obtained using the same information fraction as the randomized subjects with PD-L1 CPS ≥ 5.

Figure 2. Testing Procedure for Primary and Secondary Endpoints



Abbreviations: AC: all comers; chemo: chemotherapy; CPS: combined positive score; ipi: ipilimumab; nivo: nivolumab; OS: overall survival; PFS: progression-free survival; TTSD: time to symptom deterioration.

Key statistical analyses methods

The dual primary endpoints of PFS by BICR and OS for subjects with PD-L1 CPS ≥ 5 were compared between nivo+chemo and chemo arms using a 2-sided stratified log rank test. The estimate of the hazard ratio between treatment groups was calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate. Ties were handled using the exact method. Confidence intervals (CIs) adjusted for the corresponding significance level for the hazard ratio were provided.

The PFS and OS function for each treatment group was estimated using the KM product limit method and displayed graphically. Two-sided 95% CI for the median in each treatment group were obtained via the log-log transformation method. PFS and OS rates at fixed time points (depending on the minimum follow-up) were presented along with their associated 95% CIs. These estimates were derived from the Kaplan Meier estimate and corresponding CIs were derived based on the Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. Stratification factors for stratified analyses were region (Asia vs. North America [US and Canada] vs. ROW), ECOG PS status (0 vs. 1), chemotherapy regimen (XELOX vs. FOLFOX), and TC PD-L1 (≥ 1% vs. < 1% or indeterminate) as recorded in the interactive response technology (IRT).

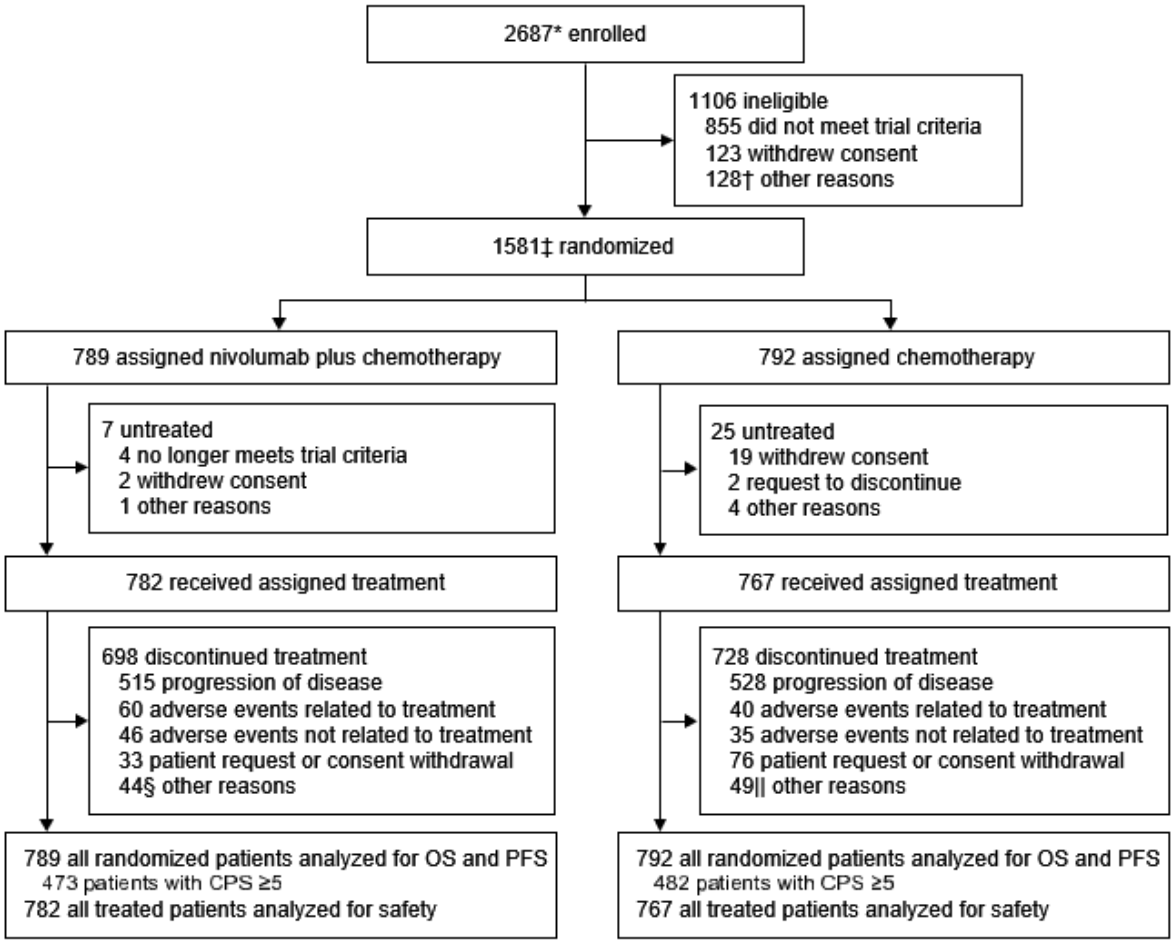
Results

Participant flow

The clinical cut-off occurred on 27-May-2020 (last patient last visit [LPLV]) and database lock occurred on 10-Jul-2020. Minimum follow-up (date of the last subject randomized to LPLV) for all randomized subjects in the nivo+chemo and chemo arms was 12.1 months.

A total of 1581 subjects were concurrently randomized in the nivo+chemo and chemo arms: 789 to the nivo+chemo arm and 792 to the chemo arm; see figure below. 1549 subjects were treated: 782 with nivo+chemo and 767 with chemo. 32 subjects were randomized but not treated (7 in the nivo+chemo arm and 25 in the chemo arm). Of the 1549 treated subjects, 123 (7.9%) subjects were continuing in the treatment period at the time of database lock: 84 (10.7%) nivo+chemo subjects and 39 (5.1%) chemo subjects.

Participant Flow Chart - Concurrently Randomized Subjects in the Nivo+Chemo and Chemo Arms in CA209649



The overall rates of treatment discontinuation were 89.3% and 94.9% in the nivo+chemo and chemo arms, respectively.

- The primary reason for not continuing the treatment period was disease progression in both treatment arms (1043 subjects, 67.3%): 515 (65.9%) nivo+chemo-treated subjects and 528 (68.8%) chemo-treated subjects.
- Subjects who discontinued due to study drug toxicity were 60 (7.7%) and 40 (5.2%) subjects in the nivo+chemo and chemo arms, respectively.

- 61 (3.9%) subjects overall withdrew consent and did not complete the treatment period: 20 (2.6%) in the nivo+chemo arm and 41 (5.3%) in the chemo arm.

Table 3. End of Treatment Period Status Summary - All Enrolled, Randomized and Treated Subjects

	Nivo + Chemo	Chemo	Total
ENROLLED[a]			2687
RANDOMIZED	789	792	1581
TREATED[b] (%)	782 (99.1)	767 (96.8)	1549 (98.0)
NOT TREATED[b] (%)	7 (0.9)	25 (3.2)	32 (2.0)
REASON FOR NOT BEING TREATED[b] (%)			
DISEASE PROGRESSION	0	1 (0.1)	1 (<0.1)
ADVERSE EVENT UNRELATED TO STUDY DRUG	0	2 (0.3)	2 (0.1)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	2 (0.3)	2 (0.1)
SUBJECT WITHDREW CONSENT	2 (0.3)	19 (2.4)	21 (1.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	4 (0.5)	1 (0.1)	5 (0.3)
OTHER	1 (0.1)	0	1 (<0.1)
CONTINUING IN THE TREATMENT PERIOD[c]	84 (10.7)	39 (5.1)	123 (7.9)
NOT CONTINUING IN THE TREATMENT PERIOD[c]	698 (89.3)	728 (94.9)	1426 (92.1)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD[c]			
DISEASE PROGRESSION	515 (65.9)	528 (68.8)	1043 (67.3)
STUDY DRUG TOXICITY	60 (7.7)	40 (5.2)	100 (6.5)
DEATH	0	1 (0.1)	1 (<0.1)
ADVERSE EVENT UNRELATED TO STUDY DRUG	46 (5.9)	35 (4.6)	81 (5.2)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	13 (1.7)	35 (4.6)	48 (3.1)
SUBJECT WITHDREW CONSENT	20 (2.6)	41 (5.3)	61 (3.9)
LOST TO FOLLOW-UP	2 (0.3)	2 (0.3)	4 (0.3)
MAXIMUM CLINICAL BENEFIT	10 (1.3)	25 (3.3)	35 (2.3)
POOR/NON-COMPLIANCE	1 (0.1)	4 (0.5)	5 (0.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.1)	3 (0.4)	4 (0.3)
COMPLETED TREATMENT AS PER PROTOCOL	20 (2.6)	0	20 (1.3)
OTHER	10 (1.3)	14 (1.8)	24 (1.5)
CONTINUING IN THE STUDY[c,d,e]	624 (79.8)	625 (81.5)	1249 (80.6)
NOT CONTINUING IN THE STUDY[c,d]	158 (20.2)	142 (18.5)	300 (19.4)
REASON FOR NOT CONTINUING IN THE STUDY[c,d]			
DEATH	121 (15.5)	88 (11.5)	209 (13.5)
SUBJECT WITHDREW CONSENT	20 (2.6)	36 (4.7)	56 (3.6)
LOST TO FOLLOW-UP	5 (0.6)	6 (0.8)	11 (0.7)
OTHER	12 (1.5)	12 (1.6)	24 (1.5)

[a] Enrolled population contains all concurrently randomized subjects to nivo+chemo and chemo as well as subjects enrolled as of the start of the 1:1:1 randomization and not randomized to any of the treatment arms

[b] Percentages based on subjects randomized.

[c] Percentages based on subjects treated.

[d] Subject status at end of treatment

[e] Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period.

Recruitment

This study was conducted at 175 sites in 29 countries (Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Japan, Mexico, Peru, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Singapore, Spain, Taiwan, Turkey, United Kingdom, and United States [US]).

Enrollment in CA209649 started in Oct-2016 for the nivo+ipi and chemo arms and enrollment in the additional nivo+chemo arm started in Mar-2017. Enrollment to the nivo+ipi arm was closed in Jun-2018 (per Revised Protocol 06/Amendment 20) as recommended by the DMC; however, enrollment continued in the nivo+chemo and chemo arms.

The CSR includes data for 1581 subjects concurrently randomized to the nivo+chemo or chemo arms from 17-Apr-2017 (first subject randomized) to 27-May-2019 (last subject randomized). The analysis for concurrently randomized subjects in the nivo+ipi vs. chemo arms is planned for 2021 and is not included in the CSR.

Conduct of the study

Protocol amendments

The original protocol for this study was dated 04-May-2016. The original study design compared nivo+ipi vs. chemo (XELOX or FOLFOX) with OS in subjects with tumour cell PD-L1 ≥ 1% as the primary endpoint. As of the 10-Jul-2020 DBL, there were 29 amendments to the protocol (including 9 global amendments and 20 country specific amendments), many of which were based on emerging data external to the CA209649 study. A description of the 9 global protocol amendments and the key study design changes are provided in Table 4.

Table 4. Summary of the 9 Global Protocol Revisions for CA209649

Document (Amendment) Date	Key Changes in Study Design	Planned Sample Size	Rationale	Total Subjects Randomized at Time of Amendment
Original Protocol 04-May-2016	**Original study design:** nivo+ipi vs. chemo (XELOX or FOLFOX); the primary endpoint was OS in subjects with TC PD-L1 ≥ 1%.	750	Not applicable	0
Revised Protocol 01 (Amendment 07) 20-Oct-2016	No impact on study design	750	Updated study procedures	0
Revised Protocol 02 (Amendment 08) 07-Dec-2016	Added a new arm nivo+chemo (XELOX or FOLFOX) and randomization changed to 1:1:1. Primary endpoint for nivo+chemo vs. chemo was OS in subjects with TC PD-L1 ≥ 1.	1349	CA209012[1] (data available: Jun-2016 in JCO)* and KEYNOTE 059[2] (data available: Jun-2016 at ASCO)* data supported the clinical activity of immunotherapy + chemo. The primary endpoint was changed to be consistent for nivo+ipi vs. chemo and nivo+chemo vs. chemo. TC PD-L1 ≥ 1% was considered a promising biomarker for immuno-oncology therapy in 2016.	3[a]
Revised Protocol 03 (Amendment 13) 10-May-2017	No impact on study design	1349	Updated study procedures	97
Revised Protocol 04 (Amendment 17) 05-Jan-2018	Changed the primary population to all randomized subjects, and endpoints to OS, PFS and ORR for nivo+chemo vs. chemo comparison	1349	Attraction-4 (ONO-4538-37; data available Sep-2017 at ESMO)* Part 1[3] data supported the clinical activity of nivo+chemo in all randomized subjects with promising ORR and PFS results.	679
Revised Protocol 05 (Amendment 19) 29-May-2018	Increased sample size to 1649	1649	Increased interest in PD-L1 CPS as new biomarker. Data from KEYNOTE-61[4] (data available from ASCO abstract: May-2018)* and CA209032 (internal data available: Mar-2018)* suggested CPS ≥ 10 (prevalence less	1158

Document (Amendment) Date	Key Changes in Study Design	Planned Sample Size	Rationale	Total Subjects Randomized at Time of Amendment
			than 20%) is a better predictor of efficacy. Increased sample size in order to have sufficient robust analyses at different PD-L1 cutoffs.	
Revised Protocol 06 (Amendment 20) 11-Jun-2018	Closed nivo+ipi enrollment	1649	Accepted the following DMC recommendation: "Due to the concern of the observed increased early death rate in nivolumab plus ipilimumab arm as well as the increased toxicity rate, the DMC recommends to stop the future enrollment of the nivolumab plus ipilimumab arm. The current patients who are already in the nivolumab plus ipilimumab arm should continue as planned, as should the other two arms."	1205
Revised Protocol 07 (Amendment 23) 14-Sep-2018	Changed the primary population to subjects with PD-L1 CPS ≥ 5 for both comparisons, assumed the prevalence of PD-L1 CPS ≥ 5 as 35% Moved OS to a secondary endpoint for nivo+ipi vs. chemo Maintained the primary endpoints of OS and PFS, and moved ORR to secondary endpoint for nivo+chemo vs. chemo	1649	CA209032 (internal data available: Mar-2018),* KEYNOTE-059[5,] (data available: Jun-2018 at ASCO)* and KEYNOTE-061 (data available: Jun-2018 at ASCO)* data suggested PD-L1 CPS as a better predictor for efficacy than TC PD-L1. The number of subjects in the nivo+ipi arm was less than targeted due to the early closure of enrollment. Moving the OS endpoint for nivo+ipi vs. chemo to a secondary endpoint allocated more alpha to the primary endpoints for nivo+chemo vs. chemo. Limited the primary endpoints to PFS and OS for nivo+chemo vs. chemo in order to have robust analyses for the primary endpoints.	1449
Revised Protocol 08 (Amendment 26) 15-Nov-2018	Increased sample size to 2005	2005	Initial monitoring of PD-L1 CPS ≥ 5 prevalence in a pooled blinded fashion indicated that the prevalence was lower than the assumed 35% (internal data from CA209649 available for the first 203 subjects: Nov-2018).* Increased the total sample size in order to maintain the planned sample size for primary PFS and OS analyses in the primary population	1646

Document (Amendment) Date	Key Changes in Study Design	Planned Sample Size	Rationale	Total Subjects Randomized at Time of Amendment
Revised Protocol 09 (Amendment 29) 16-Sep-2019	Changed the primary analyses of nivo+chemo vs. chemo from event driven to time-driven with a minimum follow-up of 12 months (interim OS analysis and final PFS analysis), and 24 months for final OS analysis	2005	KEYNOTE-062 (data available: Jun-2019 at ASCO)* study suggested sufficient follow up was needed in order to capture the full treatment effects	2031 (accrual was completed in May 2019)

[a] There was a lag time between protocol amendment and the randomisation system update, 83 patients were already randomized when the randomization changed to 1:1:1

Table 5. Changes in the statistical analysis plan through the protocol amendments (summary made by the assessor)

Protocol Amend-ment date	Multiple testing procedure **regarding OS in AC (N+C vs. C)**: order, alpha (α) allocation, timing of analyses including interims)	Planned sample size (since the 1:1:1 randomisation started)
Prot.02 Amend.08 07Dec2016	*(nivolumab + chemotherapy arm added)* *(stratification on type of chemo added)* **when** 149 events in chemo patients with PD-L1 ≥1%: OS in PD-L1 ≥1% (α=0.025) ⇓ OS in AC (**α =0.025**)	507 patients with PD-L1 ≥1% across three arms (1266)
Prot.04 Amend.17 05Jan2018	In **AC:** ORR (α =0.001); PFS (α =0.009); OS (**α =0.015** in total) • IA at 488 events (α =0.006), • FA at 610 (α =0.013) (O'Brien-Fleming boundaries)	844 AC patients in N+C vs. C (1266)
Prot.05 Amend.17 29May2018		**+ 300** subjects (1566)
(Prot.06 11Jun2018)	*(N+I arm stopped)*	
Prot.07 Amend.23 14Sep2018	*(PD-L1 CPS added)* PFS in CPS≥5 (α =0.02); OS in CPS≥5 (α=0.03 or **0.05 if PFS stat.sign**): • IA1 at 248 events • IA2 at 301 event • FA at 354 events (O'Brien-Fleming boundaries) ⇓ OS in CPS≥1 (half α, so =0.015 or 0.025) ⇓ OS in AC (half so =0.015 or 0.025)	
Prot.08 Amend.26 15Nov2018		**+ 356** subjects (1922)
Prot.09	OS in CPS≥5 (**α=0.03**):	

Amend.29 16Sep2019	• IA **at 12 months** since last patient randomized to N+C vs. C • FA **at 24 months** since last patient randomized to N+C vs. C (O'Brien-Fleming boundaries on actual number of events) ⇓ OS in CPS≥1 (half α, so =0.015) ⇓ OS in AC (half α so =0.015)	

N=nivolumab, C=chemotherapy, AC=all comers, ⇓ hierarchical testing: the endpoint below the arrow is only tested if the endpoint above the arrow is statistically significant, IA=interim analysis, FA=final analysis, CPS=combined positivity score.

Protocol deviations

Relevant protocol deviations are those that are related to inclusion or exclusion criteria, study conduct, study management, or subject assessment that were programmable and could potentially affect the interpretability of study results.

Overall, relevant protocol deviations (at study entry and on-treatment) were reported in a total of 21 (1.3%) randomized subjects: 10 (1.3%) in the nivo+chemo arm and 11 (1.4%) in the chemo arm. The most common relevant protocol deviation in the nivo+chemo arm was prohibited anti-cancer therapy while on-treatment reported in 8 (1.0%) of subjects. The most common relevant protocol deviations in the chemo arm were baseline ECOG > 1 at study entry and prohibited anti-cancer therapy while on treatment, both reported in 4 (0.5%) of subjects.

Table 6. Relevant Protocol Deviations Summary - All Randomized Subjects

	Number of Subjects (%)		
	Nivo + Chemo N = 789	Chemo N = 792	Total N = 1581
SUBJECTS WITH AT LEAST ONE DEVIATION	10 (1.3)	11 (1.4)	21 (1.3)
AT ENTRANCE			
WRONG CANCER DIAGNOSIS (A)*	0	2 (0.3)	2 (0.1)
PROHIBITED PRIOR ANTI-CANCER THERAPY (B)	1 (0.1)	0	1 (<0.1)
BASELINE ECOG > 1	1 (0.1)	4 (0.5)	5 (0.3)
NO DISEASE AT BASELINE (C)	0	1 (0.1)	1 (<0.1)
NO PD-L1 RESULT (D)	0	0	0
ON-TREATMENT DEVIATIONS			
PROHIBITED ANTI-CANCER THERAPY (E)**	8 (1.0)	4 (0.5)	12 (0.8)
NOT TREATED AS RANDOMIZED	0	0	0

(A) Subjects without inoperable, advanced or metastatic GC or GEJ or distal esophageal carcinoma or without histologically confirmed predominant adenocarcinoma
(B) Prior neo-adjuvant and/or adjuvant treatment is allowed.
(C) No disease at baseline is assessed based on investigator tumor assessments.
(D) Per tumor cells score.
(E) Palliative radiotherapy is not counted as a deviation.
*Of the 2 subjects with a wrong cancer diagnosis, 1 subject was diagnosed after randomization and was immediately discontinued from the study when corrected and 1 subject's corrected diagnosis was multiple myeloma which was found after the subject discontinued study treatment.
**One subject with prohibited therapy listed in the table received Human Granulocyte Colony Stimulating Factor which was allowed.

Baseline data

Demographic and baseline characteristics

Table 7. Demographic and Baseline Characteristics in All Randomized Subjects

	Nivo + Chemo N = 789	Chemo N = 792	Total N = 1581
AGE (YEARS)			
MEAN	60.3	59.9	60.1
MEDIAN	62.0	61.0	61.0
MIN , MAX	18 , 88	21 , 90	18 , 90
AGE CATEGORIZATION (%)			
< 65	473 (59.9)	488 (61.6)	961 (60.8)
>= 65 AND < 75	237 (30.0)	229 (28.9)	466 (29.5)
>= 75 AND < 85	77 (9.8)	69 (8.7)	146 (9.2)
>= 85	2 (0.3)	6 (0.8)	8 (0.5)
>= 75	79 (10.0)	75 (9.5)	154 (9.7)
>= 65	316 (40.1)	304 (38.4)	620 (39.2)
SEX (%)			
MALE	540 (68.4)	560 (70.7)	1100 (69.6)
FEMALE	249 (31.6)	232 (29.3)	481 (30.4)
RACE (%)			
WHITE	556 (70.5)	541 (68.3)	1097 (69.4)
BLACK OR AFRICAN AMERICAN	7 (0.9)	11 (1.4)	18 (1.1)
AMERICAN INDIAN OR ALASKA NATIVE	12 (1.5)	14 (1.8)	26 (1.6)
ASIAN	186 (23.6)	189 (23.9)	375 (23.7)
ASIAN INDIAN	4 (0.5)	4 (0.5)	8 (0.5)
CHINESE	116 (14.7)	121 (15.3)	237 (15.0)
JAPANESE	57 (7.2)	54 (6.8)	111 (7.0)
ASIAN OTHER	9 (1.1)	10 (1.3)	19 (1.2)
OTHER	28 (3.5)	36 (4.5)	64 (4.0)
NOT REPORTED	0	1 (0.1)	1 (<0.1)
REGION (%)			
ASIA [INCLUDING CHINA]	178 (22.6)	178 (22.5)	356 (22.5)
ASIA [EXCLUDING CHINA]	79 (10.0)	69 (8.7)	148 (9.4)
CHINA	99 (12.5)	109 (13.8)	208 (13.2)
US	131 (16.6)	132 (16.7)	263 (16.6)
REST OF WORLD	480 (60.8)	482 (60.9)	962 (60.8)
INITIAL DIAGNOSIS			
GASTROESOPHAGEAL JUNCTION CANCER (A)	132 (16.7)	128 (16.2)	260 (16.4)
GASTRIC CANCER	554 (70.2)	556 (70.2)	1110 (70.2)
ESOPHAGEAL ADENOCARCINOMA (B)	103 (13.1)	108 (13.6)	211 (13.3)
DISEASE STAGE AT INITIAL DIAGNOSIS			
STAGE I	7 (0.9)	4 (0.5)	11 (0.7)
STAGE II	25 (3.2)	40 (5.1)	65 (4.1)
STAGE III	108 (13.7)	118 (14.9)	226 (14.3)
STAGE IV	646 (81.9)	628 (79.3)	1274 (80.6)
NOT REPORTED	3 (0.4)	2 (0.3)	5 (0.3)
DISEASE STATUS CLASSIFICATION			
LOCALLY RECURRENT	5 (0.6)	2 (0.3)	7 (0.4)
METASTATIC	757 (95.9)	756 (95.5)	1513 (95.7)
LOCALLY ADVANCED	27 (3.4)	34 (4.3)	61 (3.9)
LAUREN CLASSIFICATION			
INTESTINAL TYPE	272 (34.5)	267 (33.7)	539 (34.1)
DIFFUSE TYPE	254 (32.2)	273 (34.5)	527 (33.3)
MIXED	58 (7.4)	48 (6.1)	106 (6.7)
UNKNOWN	205 (26.0)	204 (25.8)	409 (27.9)

	Nivo + Chemo N = 789	Chemo N = 792	Total N = 1581
WHO HISTOLOGIC CLASSIFICATION (CELL TYPE)			
ADENOSQUAMOUS CARCINOMA	107 (13.6)	113 (14.3)	220 (13.9)
MUCINOUS ADENOCARCINOMA	50 (6.3)	49 (6.2)	99 (6.3)
PAPILLARY SEROUS ADENOCARCINOMA	7 (0.9)	5 (0.6)	12 (0.8)
SIGNET RING CELL	145 (18.4)	136 (17.2)	281 (17.8)
TUBULAR ADENOCARCINOMA	128 (16.2)	130 (16.4)	258 (16.3)
OTHER	352 (44.6)	357 (45.1)	709 (44.8)
NOT REPORTED	0	2 (0.3)	2 (0.1)
TNM CLASSIFICATION			
TUMORS			
TX	248 (31.4)	233 (29.4)	481 (30.4)
T0	6 (0.8)	4 (0.5)	10 (0.6)
TIS	0	0	0
T1	7 (0.9)	11 (1.4)	18 (1.1)
T2	27 (3.4)	29 (3.7)	56 (3.5)
T3	184 (23.3)	192 (24.2)	376 (23.8)
T4	205 (26.0)	212 (26.8)	417 (26.4)
UNKNOWN	76 (9.6)	73 (9.2)	149 (9.4)
NOT REPORTED	36 (4.6)	38 (4.8)	74 (4.7)
NODES			
NX	251 (31.8)	226 (28.5)	477 (30.2)
N0	58 (7.4)	69 (8.7)	127 (8.0)
N1	117 (14.8)	126 (15.9)	243 (15.4)
N2	100 (12.7)	125 (15.8)	225 (14.2)
N3	146 (18.5)	135 (17.0)	281 (17.8)
UNKNOWN	81 (10.3)	73 (9.2)	154 (9.7)
NOT REPORTED	36 (4.6)	38 (4.8)	74 (4.7)
METASTASES			
MX	7 (0.9)	9 (1.1)	16 (1.0)
M0	30 (3.8)	31 (3.9)	61 (3.9)
M1	715 (90.6)	713 (90.0)	1428 (90.3)
UNKNOWN	5 (0.6)	1 (0.1)	6 (0.4)
NOT REPORTED	32 (4.1)	38 (4.8)	70 (4.4)
SMOKING STATUS			
CURRENT/FORMER	376 (47.7)	385 (48.6)	761 (48.1)
NEVER SMOKED	395 (50.1)	378 (47.7)	773 (48.9)
UNKNOWN	18 (2.3)	29 (3.7)	47 (3.0)
CNS METASTASES (C)			
YES	1 (0.1)	0	1 (<0.1)
NO	765 (97.0)	766 (96.7)	1531 (96.8)
NOT REPORTED	23 (2.9)	26 (3.3)	49 (3.1)
LIVER METASTASES (C)			
YES	301 (38.1)	314 (39.6)	615 (38.9)
NO	465 (58.9)	452 (57.1)	917 (58.0)
NOT REPORTED	23 (2.9)	26 (3.3)	49 (3.1)
PERITONEAL METASTASES (C)			
YES	188 (23.8)	188 (23.7)	376 (23.8)
NO	578 (73.3)	578 (73.0)	1156 (73.1)
NOT REPORTED	23 (2.9)	26 (3.3)	49 (3.1)
MICROSATELLITE INSTABILITY			
MSI-H	23 (2.9)	21 (2.7)	44 (2.8)
MSS	695 (88.1)	682 (86.1)	1377 (87.1)
INVALID	11 (1.4)	17 (2.1)	28 (1.8)
NOT REPORTED	60 (7.60)	72 (9.1)	132 (8.3)
HER-2 STATUS			
POSITIVE	3 (0.4)	4 (0.5)	7 (0.4)
NEGATIVE	459 (58.2)	472 (59.6)	931 (58.9)
UNKNOWN	5 (0.6)	4 (0.5)	9 (0.6)
NOT REPORTED	322 (40.8)	312 (39.4)	634 (40.1)
ECOG PS (based on IRT)			
0	349 (44.2)	349 (44.1)	698 (44.1)
1	440 (55.8)	443 (55.9)	883 (55.9)

Percentages based on all randomized subjects.
US: United States of America and Canada
(A) Gastroesophageal Junction Cancer represents patients with diagnosis GEJ and Siewert-Stein Type II or III or unknown
(B) Esophageal Adenocarcinoma represents patients with diagnosis EAC or Gastroesophageal Junction Cancer with Siewert-Stein Type I
(C) Presence of metastases per BICR assessment.

Previous Cancer Therapy - All Randomized Subjects

105 (13.3%) subjects in the nivo+chemo arm and 112 (14.1%) subjects in the chemo arm received prior systemic anticancer therapy (platinum-based agent or other chemotherapy) in the adjuvant, neo-

adjuvant, or definitive chemoradiation setting. 160 (20.3%) subjects in the nivo+chemo arm and 176 (22.2%) subjects in the chemo arm received prior surgery related to cancer. 75 (9.5%) subjects in the nivo+chemo arm and 77 (9.7%) subjects in the chemo arm received prior radiotherapy.

Table 8. Prior Cancer Therapy Summary All Randomized Subjects

	Number of Subjects (%)		
	Nivo + Chemo N = 789	Chemo N = 792	Total N = 1581
SUBJECTS WITH PRIOR SYSTEMIC THERAPY	105 (13.3)	112 (14.1)	217 (13.7)
NUMBER OF SYSTEMIC CANCER THERAPY REGIMEN RECEIVED			
0	684 (86.7)	680 (85.9)	1364 (86.3)
1	99 (12.5)	108 (13.6)	207 (13.1)
2	5 (0.6)	4 (0.5)	9 (0.6)
>=3	1 (0.1)	0	1 (<0.1)
SETTING OF PRIOR SYSTEMIC THERAPY			
ADJUVANT THERAPY	63 (8.0)	56 (7.1)	119 (7.5)
METASTATIC DISEASE	1 (0.1)	0	1 (<0.1)
NEO-ADJUVANT THERAPY	48 (6.1)	61 (7.7)	109 (6.9)
TIME FROM COMPLETION OF MOST RECENT PRIOR ADJUVANT/ NEO-ADJUVANT THERAPY TO RANDOMIZATION (A)			
< 6 MONTHS	1 (1.0)	3 (2.7)	4 (1.9)
6-12 MONTHS	37 (35.6)	39 (34.8)	76 (35.2)
>= 12 MONTHS	66 (63.5)	70 (62.5)	136 (63.0)
PRIOR SURGERY RELATED TO CANCER			
YES	160 (20.3)	176 (22.2)	336 (21.3)
NO	629 (79.7)	616 (77.8)	1245 (78.7)
PRIOR RADIOTHERAPY			
YES	75 (9.5)	77 (9.7)	152 (9.6)
NO	714 (90.5)	715 (90.3)	1429 (90.4)

(A) Percentages are based on subjects with prior adjuvant/neo-adjuvant therapy.

Subsequent Anti-Cancer Therapy - All Randomized Subjects

Among all randomized subjects, subsequent cancer therapy (radiotherapy, surgery, and/or systemic therapy) was received by 297 (37.6%) subjects in the nivo+chemo arm compared to 326 (41.2%) subjects in the chemo arm (Table 9). Subsequent systemic therapy was received by 268 (34.0%) subjects in the nivo+chemo arm and 311 (39.3%) subjects in the chemo arm. Subsequent immunotherapy was received by a lower percentage of subjects in the nivo+chemo arm compared with the chemo arm (1.5% vs 8.1%). A similar percentage of subjects in the nivo+chemo arm and chemo arm received subsequent chemotherapy (32.7% vs 36.6%).

Table 9. Subsequent Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)	
	Nivo + Chemo N = 789	Chemo N = 792
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	297 (37.6)	326 (41.2)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY* (%)	37 (4.7)	44 (5.6)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	17 (2.2)	23 (2.9)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	268 (34.0)	311 (39.3)
IMMUNOTHERAPY	12 (1.5)	64 (8.1)
ANTI-PD1	9 (1.1)	58 (7.3)
NIVOLUMAB	6 (0.8)	28 (3.5)
PEMBROLIZUMAB	2 (0.3)	27 (3.4)
TORIPALIMAB	1 (0.1)	3 (0.4)
ANTI-PD-L1	0	4 (0.5)
ATEZOLIZUMAB	0	4 (0.5)
ANTI-CTLA4	1 (0.1)	2 (0.3)
IPILIMUMAB	1 (0.1)	2 (0.3)
OTHER IMMUNOTHERAPY	3 (0.4)	2 (0.3)
INVESTIGATIONAL IMMUNOMODULATING AGENT	1 (0.1)	0
INVESTIGATIONAL IMMUNOTHERAPY	2 (0.3)	1 (0.1)
TUMOR NECROSIS FACTOR	0	1 (0.1)
TARGETED THERAPY	113 (14.3)	116 (14.6)
AFLIBERCEPT	1 (0.1)	0
APATINIB	12 (1.5)	19 (2.4)
BEVACIZUMAB	0	2 (0.3)
CABOZANTINIB	0	1 (0.1)
CRENOLANIB	2 (0.3)	1 (0.1)
ENDOSTAR	1 (0.1)	1 (0.1)
IBRUTINIB	1 (0.1)	1 (0.1)
LAPATINIB	2 (0.3)	0
LENVATINIB	0	1 (0.1)
MONOCLONAL ANTIBODY	0	1 (0.1)
OLAPARIB	1 (0.1)	0
RAMUCIRUMAB	91 (11.5)	85 (10.7)
REGORAFENIB	2 (0.3)	2 (0.3)
SELUMETINIB	0	1 (0.1)
TRASTUZUMAB	7 (0.9)	8 (1.0)
OTHER SYSTEMIC CANCER THERAPY - EXPERIMENTAL DRUGS	28 (3.5)	35 (4.4)
INVESTIGATIONAL ANTINEOPLASTIC	28 (3.5)	35 (4.4)
OTHER SYSTEMIC CANCER THERAPY - CHEMOTHERAPY	258 (32.7)	290 (36.6)
ANTINEOPLASTIC	2 (0.3)	0
CAPECITABINE	21 (2.7)	22 (2.8)
CARBOPLATIN	7 (0.9)	9 (1.1)
CISPLATIN	14 (1.8)	15 (1.9)
DOCETAXEL	18 (2.3)	22 (2.8)
DOXORUBICIN	0	1 (0.1)
EPIRUBICIN	0	3 (0.4)
ETOPOSIDE	1 (0.1)	1 (0.1)
FLOXURIDINE	0	1 (0.1)
FLUOROPYRIMIDINE	0	1 (0.1)
FLUOROURACIL	68 (8.6)	106 (13.4)
FLUR/IRINOT/LEUCO	1 (0.1)	0
GIMER/OTERA/TEGFUR	14 (1.8)	17 (2.1)
HERBAL ANTICANCER REMEDIES	0	1 (0.1)
IRINOTECAN	91 (11.5)	118 (14.9)
METHOTREXATE	1 (0.1)	1 (0.1)
MITOMYCIN	0	1 (0.1)
OXALIPLATIN	27 (3.4)	43 (5.4)
PACLITAXEL	154 (19.5)	170 (21.5)
PIRARUBICIN	0	1 (0.1)
RALTITREXED	4 (0.5)	7 (0.9)

(1) Subject may have received more than one type of subsequent therapy.
* Includes palliative radiotherapy

Baseline Tumour Specimen Characteristics

Tumour Cell PD-L1 (TC PD-L1)

Overall, 789/789 (100.0%) randomized subjects in the nivo+chemo arm and 787/792 (99.4%) randomized subjects in the chemo arm had quantifiable TC PD-L1 expression at baseline. TC PD-L1

expression was well balanced across treatment arms in all randomized subjects with PD-L1 quantifiable at baseline:

- In all randomized subjects with PD-L1 quantifiable at baseline, 11.5% (91/789) and 11.7% (92/787) had a baseline TC PD-L1 ≥ 5% in the nivo+chemo and chemo arms, respectively.
- In all randomized subjects with PD-L1 quantifiable at baseline, 16.0% (126/789) and 16.1% (127/787) had a baseline TC PD-L1 ≥ 1% in the nivo+chemo and chemo arms, respectively.

Table 10. Frequency of TC PD-L1 Expression Status - All Randomized Subjects

Population PD-L1 Expression Category	Nivo + Chemo N = 789	Chemo N = 792	Total N = 1581
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE (N(%))	0	1 (0.1)	1 (<0.1)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	789 (100.0)	787 (99.4)	1576 (99.7)
PD-L1 EXPRESSION (%)			
MEAN	3.7	4.4	4.0
MEDIAN	0.0	0.0	0.0
MIN , MAX	0 , 95	0 , 100	0 , 100
Q1 , Q3	0.0 , 0.0	0.0 , 0.0	0.0 , 0.0
STANDARD DEVIATION	13.3	15.3	14.4
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	126/ 789 (16.0)	127/ 787 (16.1)	253/ 1576 (16.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	663/ 789 (84.0)	660/ 787 (83.9)	1323/ 1576 (83.9)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	91/ 789 (11.5)	92/ 787 (11.7)	183/ 1576 (11.6)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	698/ 789 (88.5)	695/ 787 (88.3)	1393/ 1576 (88.4)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 10%	76/ 789 (9.6)	75/ 787 (9.5)	151/ 1576 (9.6)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 10%	713/ 789 (90.4)	712/ 787 (90.5)	1425/ 1576 (90.4)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE (N(%))	0	4 (0.5)	4 (0.3)
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	0	0	0

PD-L1 CPS

Among the 1581 subjects concurrently randomized to the nivo+chemo and chemo arms, 781/789 (99.0%) and 780/792 (98.5%) subjects had quantifiable PD-L1 CPS expression at baseline, respectively. PD-L1 CPS expression was well balanced across treatment arms in all randomized subjects with PD-L1 quantifiable at baseline:

- In all randomized subjects with PD-L1 CPS quantifiable at baseline, 60.6% (473/781) and 61.8% (482/780) had a baseline PD-L1 CPS ≥ 5 in the nivo+chemo and chemo arms, respectively.
- In all randomized subjects with PD-L1 CPS quantifiable at baseline, 82.1% (641/781) and 84.0% (655/780) had a baseline PD-L1 CPS ≥ 1 in the nivo+chemo and chemo arms, respectively.

Table 11. Frequency of PD-L1 CPS Expression Status - All Randomized Subjects

Population PD-L1 Expression Category	Nivo + Chemo N = 789	Chemo N = 792	Total N = 1581
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE (N(%))	0	1 (0.1)	1 (<0.1)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	781 (99.0)	780 (98.5)	1561 (98.7)
PD-L1 EXPRESSION			
MEAN	18.2	19.9	19.1
MEDIAN	5.0	10.0	8.0
MIN , MAX	0 , 100	0 , 100	0 , 100
Q1 , Q3	1.0 , 25.0	1.0 , 30.0	1.0 , 30.0
STANDARD DEVIATION	25.0	26.6	25.8
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1	641/ 781 (82.1)	655/ 780 (84.0)	1296/ 1561 (83.0)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1	140/ 781 (17.9)	125/ 780 (16.0)	265/ 1561 (17.0)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5	473/ 781 (60.6)	482/ 780 (61.8)	955/ 1561 (61.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5	308/ 781 (39.4)	298/ 780 (38.2)	606/ 1561 (38.8)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 10	375/ 781 (48.0)	393/ 780 (50.4)	768/ 1561 (49.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 10	406/ 781 (52.0)	387/ 780 (49.6)	793/ 1561 (50.8)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE (N(%))	0	4 (0.5)	4 (0.3)
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	8 (1.0)	7 (0.9)	15 (0.9)

Cross-tabulation of TC PD-L1 and PD-L1 CPS

TC PD-L1 at the 1% cut-off was one of the stratification factors; the percentage of subjects with TC PD-L1 ≥ 1% was balanced across the treatment arms in the pre-specified primary efficacy population (subjects with PD-L1 CPS ≥ 5) and in the pre-specified secondary efficacy populations (subjects with PD-L1 CPS ≥ 1 and all randomized subjects).

Table 12. Frequency of Subjects with TC PD-L1 ≥ 1% Among Pre-Specified PD-L1 CPS Populations

Efficacy Population	Subjects with TC PD-L1 ≥ 1% / All Randomized Subjects (n/N, %)		
	Nivo+Chemo	Chemo	Total
PD-L1 CPS ≥ 5	110/473 (23.3)	120/482 (24.9)	230/955 (24.1)
PD-L1 CPS ≥ 1	122/641 (19.0)	123/655 (18.8)	245/1296 (18.9)
All Randomized	127/789 (16.1)	127/792 (16.0)	254/1581 (16.1)

Abbreviations: CPS - combined positive score, PD L1 - programmed death-ligand 1

MSI Status in All Randomized Subjects

MSI status was determined retrospectively on pre-treatment FFPE tissues using the Idylla™ MSI Test by central laboratories. The Idylla™ MSI Test reported results as MSS, MSI-H, or invalid in cases where the MSI status of tested samples could not be reliably determined. Of the 1581 randomized subjects, 44 (2.8%) subjects were MSI-H, 1377 (87.1%) subjects were MSS, 132 (8.3%) subjects had no tumour tissue for MSI testing, and 28 (1.8%) subjects had invalid results.

Numbers analysed

Table 13. Analysis Populations in CA209649

Population	Nivo+Chemo	Chemo	Total
Randomized: subjects randomized concurrently to nivo+chemo or chemo from 17-Apr-2017 (included, the start date of randomization)	789	792	1581
Randomized with measurable disease (BICR): randomized subjects who have at least one target/measurable or non-measurable lesion at baseline (per BICR)	603	608	1211
Randomized, CPS ≥ 5: randomized subjects with CPS ≥ 5	473	482	955
Randomized, CPS ≥ 1: randomized subjects with CPS ≥ 1	641	655	1296
All Treated: all randomized subjects who received at least one dose of study drug	782	767	1549
All TC PD-L1 Quantifiable: all PD-L1 tested subjects with quantifiable TC PD-L1 expression at baseline	789	787	1576
All PD-L1 CPS Quantifiable: all PD-L1 tested subjects with quantifiable PD-L1 CPS expression at baseline	781	780	1561

Abbreviations: BICR - blinded independent central review, chemo - chemotherapy, CPS - combined positive score, MSI - microsatellite instability, nivo - nivolumab, TC PD-L1 - tumor cell programmed death ligand 1

Outcomes and estimation

Efficacy analyses were performed on the population of all subjects concurrently randomized (using the interactive response technology [IRT]) to either the nivo+chemo or chemo arms from 17-Apr-2017 to 27-May-2019.

Table 14. Summary of Key Efficacy Results

	All Randomized Subjects with PD-L1 CPS ≥ 5		All Randomized Subjects with PD-L1 CPS ≥ 1		All Randomized Subjects	
Efficacy Parameter	**Nivo+Chemo (N = 473)**	**Chemo (N = 482)**	**Nivo+Chemo (N = 641)**	**Chemo (n = 655)**	**Nivo+Chemo (N = 789)**	**Chemo (N = 792)**
OS						
Events, n (%)	309 (65.3)	362 (75.1)	434 (67.7)	492 (75.1)	544 (68.9)	591 (74.6)
Median OS (95% CI)[a], months	14.39 (13.11, 16.23)	11.10 (10.02, 12.09)	13.96 (12.55, 14.98)	11.33 (10.64, 12.25)	13.83 (12.55, 14.55)	11.56 (10.87, 12.48)
HR (CI)[b]	0.71 (98.4% CI: 0.59, 0.86)		0.77 (99.3% CI: 0.64, 0.92)		0.80 (99.3% CI: 0.68, 0.94)	
p-value[c]	< 0.0001		< 0.0001		0.0002	
12 month OS Rates (95% CI)[a], %	57.3 (52.6, 61.6)	46.4 (41.8, 50.8)	55.5 (51.5, 59.3)	47.0 (43.1, 50.9)	55.0 (51.4, 58.4)	47.9 (44.4, 51.4)
PFS per BICR (1° Definition)						
Events, n (%)	328 (69.3)	350 (72.6)	454 (70.8)	472 (72.1)	559 (70.8)	557 (70.3)
Median PFS (95% CI)[a], months	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)	7.49 (7.03, 8.41)	6.90 (6.08, 7.03)	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)
HR (CI)[b]	0.68 (98% CI: 0.56, 0.81)		0.74 (95% CI: 0.65, 0.85)		0.77 (95% CI: 0.68, 0.87)	
p-value[c]	< 0.0001		Not tested		Not tested	
12 month OS Rates (95% CI)[a], %	36.3 (31.7, 41.0)	21.9 (17.8, 26.1)	34.2 (30.3, 38.2)	22.4 (18.8, 26.1)	33.4 (29.9, 37.0)	23.2 (19.9, 26.7)
ORR per BICR (CR + PR) in All Randomized Subjects						
N responders/N (%)	237/473 (50.1)	184/482 (38.2)	314/641 (49.0)	249/655 (38.0)	370/789 (46.9)	293/792 (37.0)
95% CI[d]	(45.5, 54.7)	(33.8, 42.7)	(45.1, 52.9)	(34.3, 41.9)	(43.4, 50.4)	(33.6, 40.5)
Difference of ORR (95% CI)[e]	12.7 (6.7, 18.8)		12.4 (7.3, 17.6)		12.2 (7.5, 16.8)	
ORR per BICR (CR + PR) in Subjects with Measurable Disease						
N responders/N (%)	226/378 (59.8)	177/391 (45.3)	300/504 (59.5)	239/515 (46.4)	350/603 (58.0)	280/608 (46.1)
95% CI[d]	(54.7, 64.8)	(40.3, 50.4)	(55.1, 63.8)	(42.0, 50.8)	(54.0, 62.0)	(42.0, 50.1)
Difference of ORR (95% CI)[e]	16.1 (9.4, 22.8)		14.2 (8.3, 20.1)		12.8 (7.3, 18.2)	

DOR per BICR in Subjects with Measurable Disease						
N events/N responders (%)	143/226 (63.3)	125/177 (70.6)	194/300 (64.7)	177/239 (74.1)	231/350 (66.0)	206/280 (73.6)
Median (95% CI)[a], months	9.49 (7.98, 11.37)	6.97 (5.65, 7.85)	8.54 (7.69, 10.22)	6.93 (5.78, 7.56)	8.51 (7.23, 9.92)	6.93 (5.82, 7.16)
Min, Max, months	1.1+, 29.6+	1.2+, 30.8+	1.1+, 29.6+	1.2+, 30.8+	1.0+, 29.6+	1.2+, 30.8+
% with DOR (95% CI)[a] ≥ 12 months	42.5 (35.6, 49.2)	29.9 (22.8, 37.3)	41.2 (35.3, 47.0)	28.2 (22.2, 34.5)	40.4 (34.9, 45.8)	27.9 (22.3, 33.7)

[a] Based on Kaplan-Meier estimates.

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

[c] 2-sided p-value using a stratified log-rank test. Stratified by region (Asia vs. US vs ROW), ECOG (0 vs 1), Tumor Cell PD-L1 (≥ 1% vs <1% [including indeterminate]) and chemotherapy (XELOX vs FOLFOX).

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

[e] The difference in response rate (Nivo + Chemo vs Chemo) is not the simple difference between the rates but is adjusted for the stratification factors based on the DerSimonian and Laird methodology

Symbol + indicates a censored value.

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months.

Abbreviations: BICR - blinded independent central review, chemo - chemotherapy, CI - confidence interval, CPS - combined positive score, CR - complete response, DOR - duration of response, HR - hazard ratio, Nivo - nivolumab, ORR - objective response rate, OS - overall survival, PD-L1 - programmed death-ligand 1, PFS - progression-free survival, PR - partial response

Primary endpoints

OS in subjects with PD-L1 CPS ≥ 5

In all randomized subjects with PD-L1 CPS ≥ 5, nivo+chemo demonstrated a statistically significant improvement in OS compared with chemo: HR = 0.71 (98.4% CI: 0.59, 0.86); stratified log-rank test p-value < 0.0001. Median OS (95% CI) was longer in the nivo+chemo arm compared with the chemo arm: 14.39 (13.11, 16.23) vs. 11.10 (10.02, 12.09) months.

OS rates (95% CI) were higher in the nivo+chemo arm compared with the chemo arm: 81.4% (77.5, 84.6) vs. 74.8% (70.6, 78.5) at 6 months and 57.3% (52.6, 61.6) and 46.4% (41.8, 50.8) at 12 months. At database lock (minimum follow-up 12.1 months), 34.7% and 24.9% of all randomized subjects with PD-L1 CPS ≥ 5 in the nivo+chemo and chemo arms, respectively, were censored for OS. 147/473 (31.1%) and 90/482 (18.7%) subjects are either continuing on-treatment or in follow-up in the nivo+chemo and chemo arms, respectively.

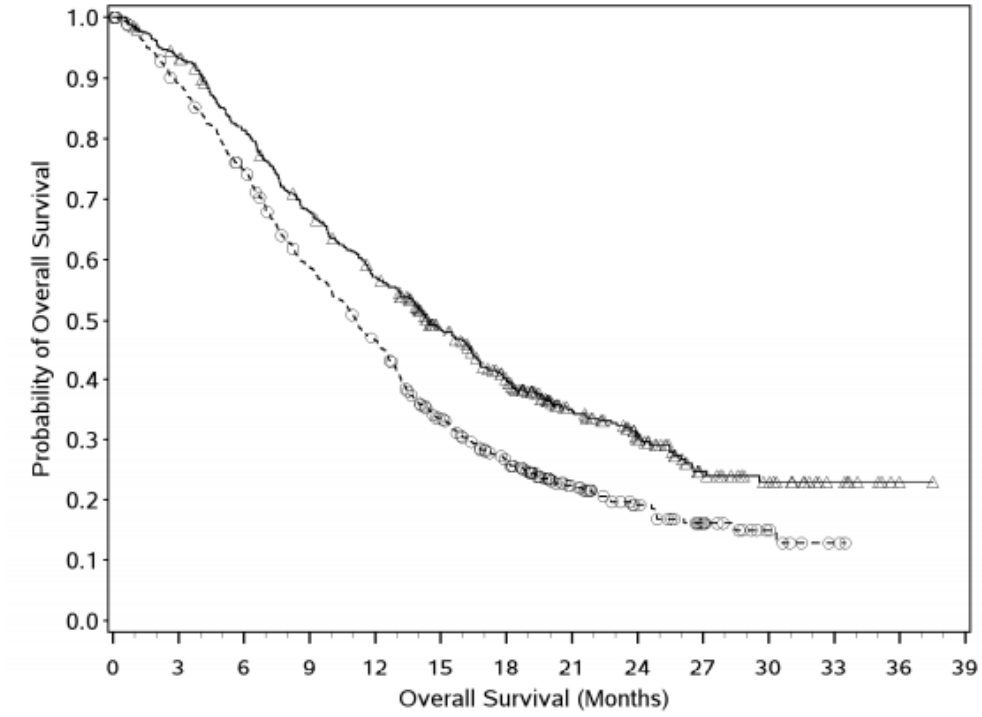
Table 15. Status of censored subjects, overall survival – All randomised subjects with PD-L1 CPS≥5

	Number of Subjects (%)	
	Nivo + Chemo N = 473	Chemo N = 482
NUMBER OF DEATHS (%)	309 (65.3)	362 (75.1)
NUMBER OF SUBJECTS CENSORED (%)	164 (34.7)	120 (24.9)
STATUS OF CENSORED SUBJECTS (%)		
STILL ON TREATMENT	62 (13.1)	25 (5.2)
NOT PROGRESSED	57 (12.1)	25 (5.2)
PROGRESSED (1)	5 (1.1)	0
IN FOLLOW-UP	85 (18.0)	65 (13.5)
OFF STUDY	17 (3.6)	30 (6.2)
SUBJECT WITHDREW CONSENT	10 (2.1)	19 (3.9)
LOST TO FOLLOW-UP	7 (1.5)	10 (2.1)
OTHER	0	1 (0.2)

(1) Radiographic or Clinical Progression

Separation of the Kaplan-Meier curves favouring nivo+chemo over chemo occurred early (at < 1 month), with increased separation over time.

Figure 3. Kaplan Meier Plot of Overall Survival - All Randomized Subjects with PD-L1 ≥ 5



Number of Subjects at Risk

Nivo + Chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

Nivo + Chemo (events : 309/473), median and 95% CI : 14.39 (13.11, 16.23)

Chemo (events : 362/482), median and 95% CI : 11.10 (10.02, 12.09)

Nivo + Chemo vs Chemo - hazard ratio (98.4% CI): 0.71 (0.59, 0.86), p-value: <0.0001

Symbols represent censored observations.

Stratified Cox proportional hazard model for hazard ratio.

Stratified log-rank test for p-value.

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

- unstratified analysis: HR = 0.70 (98.4% CI: 0.58, 0.84)
- unstratified analysis with the stratification factors as covariates: HR = 0.68 (98.4% CI: 0.57, 0.83)
- stratified analysis based on the first 420 randomized subjects with PD-L1 CPS ≥ 5: HR = 0.70 (98.4% CI: 0.53, 0.92). Stratified analysis based on the population with the first 354 events among all randomized subjects with PD-L1 CPS ≥ 5: HR = 0.64 (98.4% CI: 0.49, 0.83). These analyses were conducted to reflect the OS analysis planned under Revised Protocol 07.

In a multivariate analysis of OS, the treatment effect of nivo+chemo vs. chemo was consistent with the primary OS analysis when adjusted for the baseline factors listed below (HR = 0.71; 95% CI: 0.61, 0.84; multivariate Cox model p value < 0.0001): age (< 65 vs. ≥ 65), sex (male vs. female), primary tumour location (GC vs. EAC and EAC vs. GEJC), disease status (locally recurrent/advanced vs. metastatic), Lauren classification (intestinal type vs. diffuse type, mixed vs. diffuse type, and unknown vs. diffuse type), peritoneal metastases (no vs. yes), prior surgery or radiotherapy (yes vs. no), number of organs with baseline lesion (≤ 1 vs. ≥ 2), and presence of signet ring cells (no vs. yes).

Overall in subjects with PD-L1 CPS ≥ 5, 37.2% and 40.2% of subjects in the nivo+chemo and chemo arms, respectively, received subsequent cancer therapy. In the nivo+chemo arm, 33.4% received subsequent systemic therapy; this included 1.3% who received subsequent immunotherapy, 13.1% who received targeted therapy, and 31.9% who received subsequent chemotherapy. In the chemo arm, 38.6% received subsequent systemic therapy; this included 8.7% who received subsequent immunotherapy (7.7% who received subsequent anti-PD-1 therapy), 14.1% who received targeted therapy, and 36.7% who received subsequent chemotherapy.

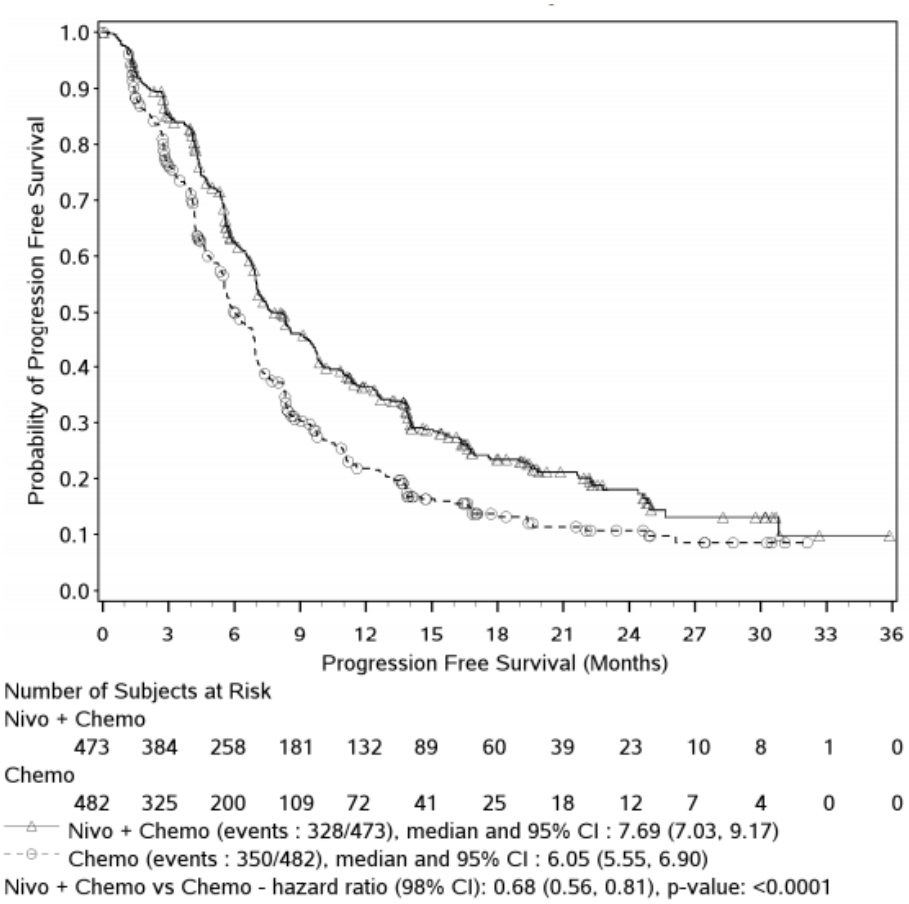
PFS per BICR (Primary Definition) in subjects with PD-L1 CPS ≥ 5

In all randomized subjects with PD-L1 CPS ≥ 5, nivo+chemo demonstrated a statistically significant improvement in PFS per BICR (primary definition) compared with chemo: HR = 0.68 (98% CI: 0.56, 0.81); stratified log-rank test p-value < 0.0001. Median PFS (95% CI) was longer with nivo+chemo compared with chemo: 7.69 (7.03, 9.17) vs. 6.05 (5.55, 6.90) months, respectively.

PFS rates were higher with nivo+chemo compared with chemo: 62.4% vs. 50.1% at 6 months, respectively, and 36.3% vs. 21.9% at 12 months, respectively. At database lock, 30.7% and 27.4% of randomized subjects in the nivo+chemo and chemo arms, respectively, were censored for PFS (see Table S.5.24.1 for the reasons for censoring).

Separation of the Kaplan-Meier curves favouring nivo+chemo over chemo occurred at approximately 2 months, with increased separation over time.

Figure 4. Kaplan Meier Plot of Progression-Free Survival per BICR, Primary Definition - All Randomized Sujects with PD-L1 CPS ≥ 5



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

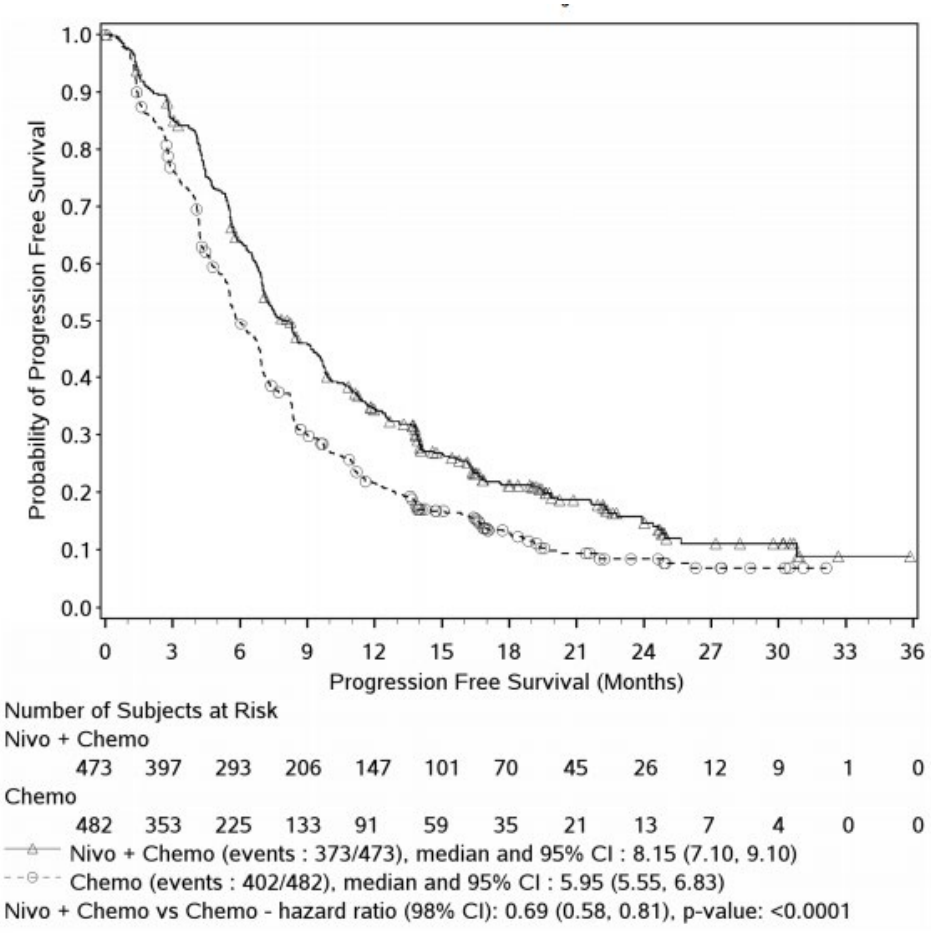
Results for the following sensitivity analyses were consistent with the primary PFS analysis per BICR:

- unstratified analysis: HR = 0.69 (98% CI: 0.58, 0.83)
- unstratified analysis with the stratification factors as covariates: HR = 0.68 (98% CI: 0.57, 0.81)
- stratified analysis based on subjects with the first 228 events among the first 298 randomized subjects with PD-L1 CPS ≥ 5: HR = 0.69 (98% CI: 0.49, 0.97) This sensitivity analysis was conducted to reflect the design per Revised Protocol 07.

In a multivariate analysis of PFS, the treatment effect of nivo+chemo vs. chemo was consistent with the primary PFS analysis when adjusted for the baseline factors listed below (HR = 0.66; 95% CI: 0.56, 0.77; multivariate Cox model p value < 0.0001): age (< 65 vs. ≥ 65), sex (male vs. female), primary tumour location (GC vs. EAC and EAC vs. GEJC), disease status (locally recurrent/advanced vs. metastatic), Lauren classification (intestinal type vs. diffuse type, mixed vs. diffuse type, and unknown vs. diffuse type), peritoneal metastases (no vs. yes), prior surgery or radiotherapy (yes vs. no), number of organs with baseline lesion (≤ 1 vs. ≥ 2), and presence of signet ring cells (no vs. yes).

Analysis of PFS per BICR using the secondary PFS definition, which accounts for the tumour scans post subsequent therapies (HR = 0.69; 98% CI: 0.58, 0.81; p-value < 0.0001), was consistent with the analysis using the primary PFS definition.

Figure 5. Kaplan-Meier Plot of Progression-free Survival per BICR, Secondary Definition - All Randomized Subjects with PD-L1 CPS ≥ 5



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

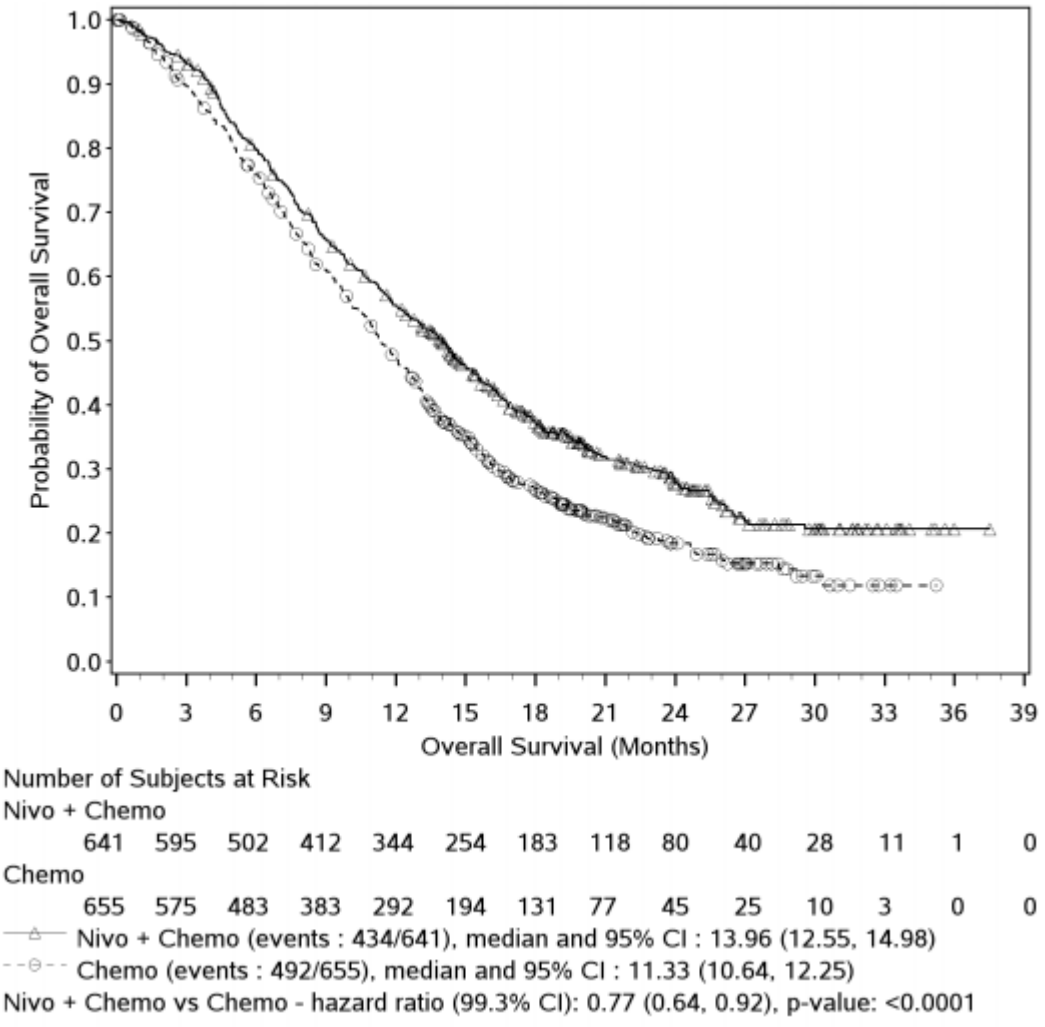
The concordance between BICR and investigator PFS (primary definition) assessments of events and censoring was high: 87.9% for nivo+chemo and 88.4% for chemo.

Secondary endpoints (hierarchically tested)

OS in subjects with PD-L1 CPS ≥1

The OS HR was 0.77 (99.3% CI: 0.64, 0.92) for nivo+chemo vs. chemo with a stratified log rank test p-value <0.0001. Median OS was 13.96 (95% CI: 12.55, 14.98) vs. 11.33 (95% CI: 10.64, 12.25) months, respectively.

Figure 6. Kaplan-Meier Plot of Overall Survival - All Randomized Subjects with PD-L1 CPS ≥1



OS in All Randomized Subjects

Median follow up for survival (date of randomization to the last known date alive or death date) was 13.08 months for subjects in the nivo+chemo arm and 11.06 months for subjects in the chemo arm.

In all randomized subjects, nivo+chemo demonstrated a statistically significant improvement in OS compared with chemo: HR = 0.80 (99.3% CI: 0.68, 0.94); stratified log-rank test p-value = 0.0002. Median OS (95% CI) was longer in the nivo+chemo arm compared with the chemo arm: 13.83 (12.55, 14.55) vs. 11.56 (10.87, 12.48) months.

OS rates (95% CI) were higher in the nivo+chemo arm compared with the chemo arm: 80.1% (77.2, 82.8) vs. 76.3% (73.1, 79.1) at 6 months and 55.0% (51.4, 58.4) and 47.9% (44.4, 51.4) at 12 months. At database lock (minimum follow-up 12.1 months), 31.1% and 25.4% of all randomized subjects in the nivo+chemo and chemo arms, respectively, were censored for OS. 10.6% and 4.9% subjects in the nivo+chemo and chemo arms respectively were still on treatment, and 17.1% and 14.9% subjects in the 2 arms respectively were in follow-up.

Separation of the Kaplan-Meier curves favouring nivo+chemo over chemo occurred at approximately 2 months, with increased separation over time.

Table 16. Overall Survival of Nivo+Chemo vs. Chemo in All Randomized Subjects (CA209649)

Efficacy Parameter	All Randomized Subjects	
	Nivo+Chemo (N = 789)	Chemo (N = 792)
OS (formally tested endpoint)		
Events, n (%)	544 (68.9)	591 (74.6)
Median OS (95% CI)[a], months	13.83 (12.55, 14.55)	11.56 (10.87, 12.48)
HR (CI) [b]	0.80 (99.3% CI: 0.68, 0.94)	
p-value[c]	0.0002	
12 month OS rates (95% CI)[a], %	55.0 (51.4, 58.4)	47.9 (44.4, 51.4)

[a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model. HR is Nivo+Chemo over Chemo.
[c] 2-sided p-value using a stratified log-rank test. Stratified by region (Asia [China, Japan, Korea, Taiwan, Hong Kong, and Singapore] vs. US [US and Canada] vs. ROW [Europe, Australia, Latin America, Israel, Russian Federation, and Turkey]), ECOG PS (0 vs. 1), TC PD-L1 (≥ 1% vs. <1%/indeterminate) and chemotherapy (XELOX vs. FOLFOX).

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months.

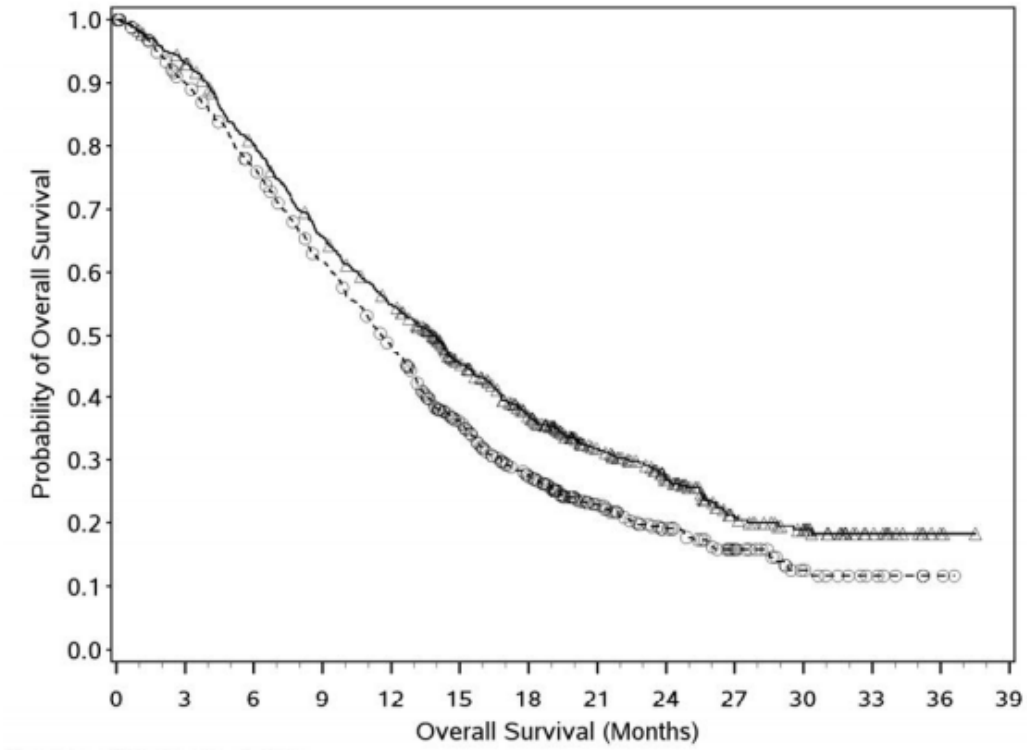
Abbreviations: CI - confidence interval, ECOG - Eastern Cooperative Oncology Group, FOLFOX - folinic acid (leucovorin) "FOL", (fluorouracil [5-FU]) "F", and oxaliplatin (eloxatin) "OX", HR - hazard ratio, Nivo - nivolumab, OS - overall survival, PS - performance status, ROW - rest of world, XELOX - Xeloda (capecitabine)"XEL" and oxaliplatin "OX"

Table 17. Status of Censored Subjects, Overall Survival All Randomized Subjects

	Number of Subjects (%)	
	Nivo + Chemo N = 789	Chemo N = 792
NUMBER OF DEATHS (%)	544 (68.9)	591 (74.6)
NUMBER OF SUBJECTS CENSORED (%)	245 (31.1)	201 (25.4)
STATUS OF CENSORED SUBJECTS (%)		
STILL ON TREATMENT	84 (10.6)	39 (4.9)
NOT PROGRESSED	77 (9.8)	39 (4.9)
PROGRESSED (1)	7 (0.9)	0
IN FOLLOW-UP	135 (17.1)	118 (14.9)
OFF STUDY	26 (3.3)	44 (5.6)
SUBJECT WITHDREW CONSENT	15 (1.9)	31 (3.9)
LOST TO FOLLOW-UP	11 (1.4)	10 (1.3)
OTHER	0	3 (0.4)

(1) Radiographic or Clinical Progression

Figure 7. Kaplan Meier Plot of Overall Survival - All Randomized Subjects



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

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

- unstratified analysis: HR = 0.79 (99.3% CI: 0.67, 0.93)
- unstratified analysis with stratification factors as covariates: HR = 0.78 (99.3% CI: 0.67, 0.92)

In a multivariate analysis of OS, the treatment effect of nivo+chemo vs. chemo was consistent with the primary OS analysis when adjusted for the baseline factors listed below (HR = 0.82; 95% CI: 0.73, 0.92; multivariate Cox model p-value = 0.0011). age (< 65 vs. ≥ 65), sex (male vs. female), primary tumour location (GC vs. EAC and EAC vs. GEJC), disease status (locally recurrent/advanced vs. metastatic), Lauren classification (intestinal type vs. diffuse type, mixed vs. diffuse type, and unknown vs. diffuse type), peritoneal metastases (no vs. yes), prior surgery or radiotherapy (yes vs. no), number of organs with baseline lesion (≤ 1 vs. ≥ 2), and presence of Signet Ring Cells (no vs. yes).

Subsequent cancer therapy was reported in 37.6% and 41.2% of subjects in the nivo+chemo and chemo arms, respectively. In the nivo+chemo arm, 34.0% received subsequent systemic therapy; this included 32.7% and 1.5% who received subsequent chemotherapy and immunotherapy respectively.

In the chemo arm, 39.3% received subsequent systemic therapy; this included 36.6% and 8.1% who received subsequent chemotherapy and immunotherapy respectively.

Other secondary endpoints

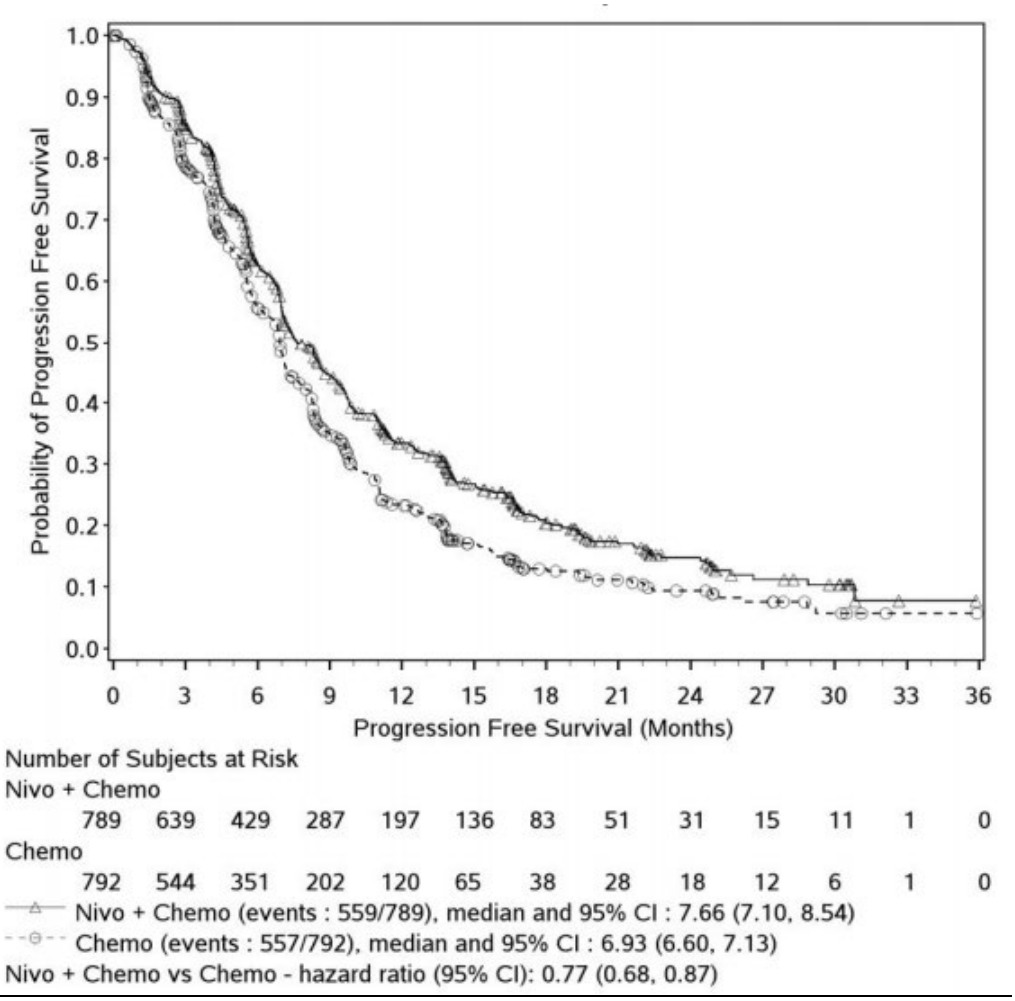
PFS per BICR in All Randomized Subjects

In all randomized subjects, an improvement of PFS per BICR (primary definition) was observed with nivo+chemo compared with chemo (pre-specified but not formally tested): HR = 0.77 (95% CI: 0.68, 0.87). Median PFS (95% CI) was longer with nivo+chemo compared with chemo: 7.66 (7.10, 8.54) vs. 6.93 (6.60, 7.13) months, respectively. 559 (70.8%) and 557 (70.3%) subjects in the nivo+chemo vs. chemo arms respectively had an event. PFS rates were higher with nivo+chemo compared with chemo: 62.6% vs. 55.7% at 6 months, respectively, and 33.4% vs. 23.2% at 12 months, respectively.

Separation of the Kaplan-Meier curves favouring nivo+chemo over chemo occurred at approximately 2 months, with increased separation over time.

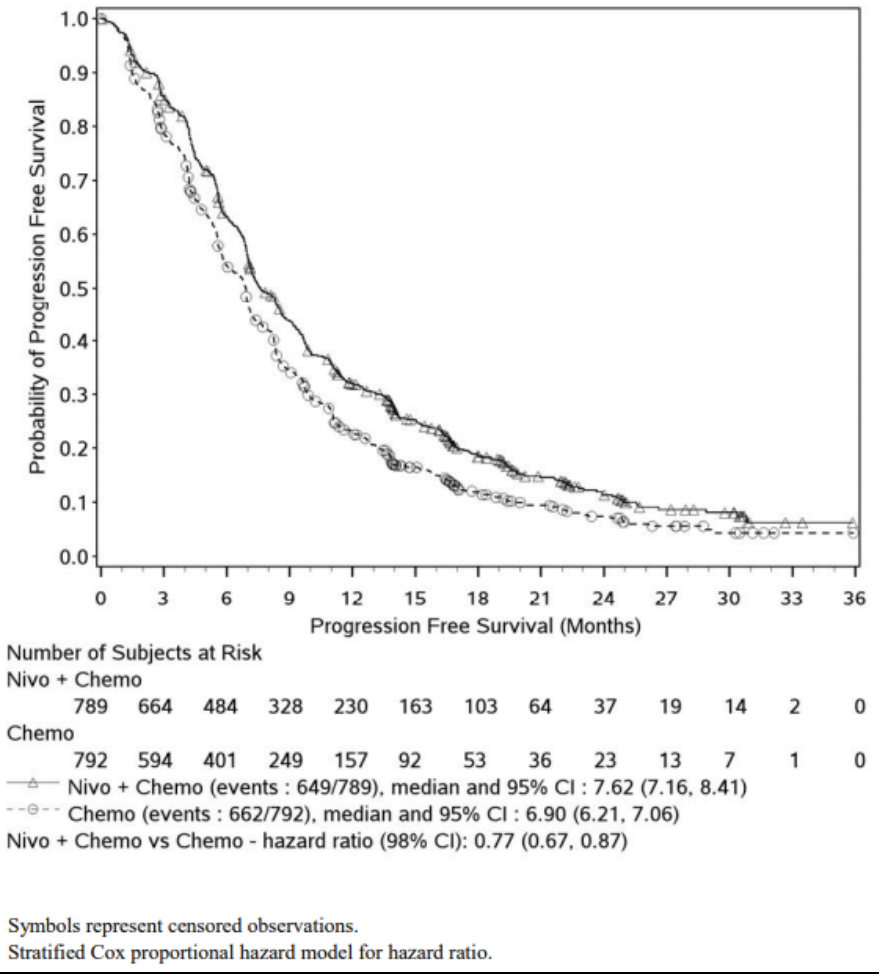
Analysis of PFS per BICR using the secondary PFS definition (HR = 0.77; 98% CI: 0.67, 0.87), was consistent with the analysis using the primary PFS definition.

Figure 8. Kaplan-Meier plot of Progression-free Survival per BICR, Primary Definition - All Randomized Subjects



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

Figure 9. Kaplan-Meier Plot of Progression-free Survival per BICR, Secondary Definition - All Randomized Subjects



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

Results for PFS per investigator assessment were consistent with those for PFS per BICR. Median PFS by investigator (primary definition) was consistent with that reported by BICR, with median (95% CI) PFS of 7.52 (6.97, 8.34) months for nivo+chemo and 6.31 (5.68, 6.93) months for chemo (HR = 0.75, 95% CI: 0.67, 0.84)

ORR in All Randomized Subjects

At baseline, 603 subjects in the nivo+chemo arm and 608 subjects in the chemo arm had **measurable disease** per BICR. In all randomized subjects with measurable disease, an improvement in BICR-assessed ORR was observed in nivo+chemo over chemo: 58.0% (95% CI: 54.0, 62.0) vs. 46.1% (95% CI: 42.0, 50.1); odds ratio = 1.61 (95% CI: 1.28, 2.02).

The magnitude of benefit in ORR was consistent per Investigator assessment (ORR difference of 10.9% [95% CI: 5.9, 16.0]), though ORR rates were lower (52.2% [95% CI: 48.4, 55.9] for nivo+chemo vs. 41.1% [95% CI: 37.4, 44.8] for chemo), driven by lower CR rates (4.5% vs. 1.3%). PR rates were consistent with BICR assessment.

Table 18. Best Overall Response per BICR - All Randomized Subjects with Measurable Disease at Baseline

	Nivo + Chemo N = 603	Chemo N = 608
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	59 (9.8)	39 (6.4)
PARTIAL RESPONSE (PR)	291 (48.3)	241 (39.6)
STABLE DISEASE (SD)	171 (28.4)	200 (32.9)
PROGRESSIVE DISEASE (PD)	41 (6.8)	61 (10.0)
UNABLE TO DETERMINE (UTD)	41 (6.8)	67 (11.0)
OBJECTIVE RESPONSE RATE (1) (95% CI)	350/603 (58.0%) (54.0, 62.0)	280/608 (46.1%) (42.0, 50.1)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3) (95% CI)	12.8% (7.3, 18.2)	
ESTIMATE OF ODDS RATIO (3, 4) (95% CI)	1.61 (1.28, 2.02)	
P-VALUE (3, 5)	<0.0001	

(1) Confirmed CR or PR per RECIST 1.1. Confidence interval based on Clopper-Pearson method.
(2) Strata adjusted difference in response rate (Nivo + Chemo - Chemo) based on DerSimonian and Laird method of weighting.
(3) Stratified by region (Asia vs US vs. RoW), ECOG (0 vs 1), Tumor Cell PD-L1 (≥ 1% vs < 1%/indeterminate) and chemotherapy (XELOX vs. FOLFOX).
(4) Strata adjusted odds ratio (Nivo + Chemo over Chemo) using Mantel-Haenszel method.
(5) Two-sided p-value from stratified CMH Test.

Table 19 (bis). Best Overall Response per BICR - All Randomized Subjects

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Best Overall Response per BICR
All Randomized Subjects

	Nivo + Chemo N = 789	Chemo N = 792
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	78 (9.9)	52 (6.6)
PARTIAL RESPONSE (PR)	292 (37.0)	241 (30.4)
STABLE DISEASE (SD)	301 (38.1)	326 (41.2)
PROGRESSIVE DISEASE (PD)	53 (6.7)	66 (8.3)
UNABLE TO DETERMINE (UTD)	64 (8.1)	102 (12.9)
NOT REPORTED	1 (0.1)	5 (0.6)
OBJECTIVE RESPONSE RATE (1) (95% CI)	370/789 (46.9%) (43.4, 50.4)	293/792 (37.0%) (33.6, 40.5)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3) (95% CI)	12.2% (7.5, 16.8)	
ESTIMATE OF ODDS RATIO (3, 4) (95% CI)	1.50 (1.23, 1.83)	
P-VALUE (3, 5)	<0.0001	

(1) Confirmed CR or PR per RECIST 1.1. Confidence interval based on Clopper-Pearson method.
(2) Strata adjusted difference in response rate (Nivo + Chemo - Chemo) based on DerSimonian and Laird method of weighting.
(3) Stratified by region (Asia vs. US vs. RoW), ECOG (0 vs. 1), Tumor Cell PD-L1 (>=1% vs. <1%/indeterminate) and chemotherapy (XELOX vs. FOLFOX).
(4) Strata adjusted odds ratio (Nivo + Chemo over Chemo) using Mantel-Haenszel method.
(5) Two-sided p-value from stratified CMH Test.
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ORR in subjects with PD-L1 CPS≥5

In all randomized subjects with **measurable disease** and PD-L1 CPS ≥ 5, an improvement in BICRassessed ORR was observed with nivo+chemo over chemo, 59.8% (95% CI: 54.7, 64.8) vs. 45.3% (95% CI: 40.3, 50.4); odds ratio = 1.80 (95% CI: 1.34, 2.41).

Table 20. Best Overall Response per BICR - All Measurable Subjects with PD-L1 CPS ≥ 5

	Nivo + Chemo N = 378	Chemo N = 391
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	44 (11.6)	27 (6.9)
PARTIAL RESPONSE (PR)	182 (48.1)	150 (38.4)
STABLE DISEASE (SD)	104 (27.5)	132 (33.8)
PROGRESSIVE DISEASE (PD)	26 (6.9)	42 (10.7)
UNABLE TO DETERMINE (UTD)	22 (5.8)	40 (10.2)
OBJECTIVE RESPONSE RATE (1)	226/378 (59.8%)	177/391 (45.3%)
(95% CI)	(54.7, 64.8)	(40.3, 50.4)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (2, 3)	16.1%	
(95% CI)	(9.4, 22.8)	
ESTIMATE OF ODDS RATIO (3, 4)	1.80	
(95% CI)	(1.34, 2.41)	
P-VALUE (3, 5)	<0.0001	
DURABLE (>=6 MONTHS) RESPONSE RATE (1)	133/378 (35.2%)	86/391 (22.0%)
(95% CI)	(30.4, 40.2)	(18.0, 26.4)
DIFFERENCE OF DURABLE RESPONSE RATES (2, 3)	11.8%	
(95% CI)	(5.6, 18.0)	
ESTIMATE OF ODDS RATIO FOR DURABLE RESPONSE (3, 4) (95% CI)	1.89 (1.37, 2.61)	

(1) Confirmed CR or PR per RECIST 1.1. Confidence interval based on Clopper-Pearson method.
(2) Strata adjusted difference in response rate (Nivo + Chemo - Chemo) based on DerSimonian and Laird method of weighting.
(3) Stratified by region (Asia vs US vs. RoW), ECOG (0 vs 1), Tumor Cell PD-L1 (≥ 1% vs < 1%/indeterminate) and chemotherapy (XELOX vs. FOLFOX).
(4) Strata adjusted odds ratio (Nivo + Chemo over Chemo) using using Mantel-Haenszel method.
(5) 2-sided p value from CMH test.

Exploratory endpoints

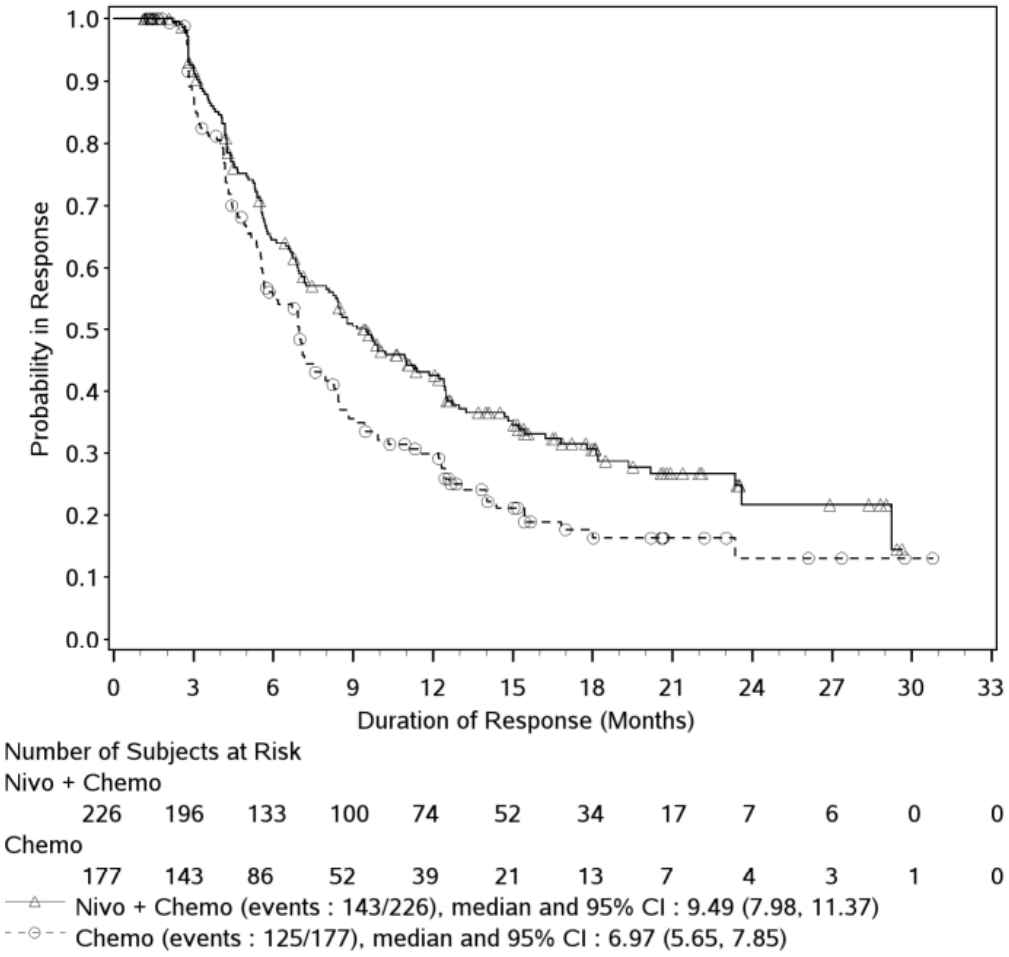
Time to response and duration of response in subjects with PD-L1 CPS≥5

Table 21. Time to Response and Duration of Response per BICR - All Measurable Responders with PD-L1 CPS ≥ 5

	Nivo + Chemo N = 226	Chemo N = 177
TIME TO OBJECTIVE RESPONSE (MONTHS)		
MEAN	2.16	1.96
MEDIAN	1.48	1.45
MIN, MAX	0.8, 10.2	1.0, 7.1
Q1, Q3	1.38, 2.76	1.38, 2.69
STANDARD DEVIATION	1.35	0.96
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.1+, 29.6+	1.2+, 30.8+
MEDIAN (95% CI) (B)	9.49 (7.98, 11.37)	6.97 (5.65, 7.85)
N EVENT/N RESP (%)	143/226 (63.3)	125/177 (70.6)
PROPORTION OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (95% CI) (C)		
3 MONTHS	91.7 (87.1, 94.7)	87.3 (81.2, 91.5)
6 MONTHS	64.5 (57.6, 70.6)	55.5 (47.5, 62.8)
9 MONTHS	50.6 (43.6, 57.2)	35.6 (28.1, 43.1)
12 MONTHS	42.5 (35.6, 49.2)	29.9 (22.8, 37.3)

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

Figure 10. Kaplan-Meier Plot of Duration of Response per BICR - All Responders with PD-L1 CPS ≥ 5



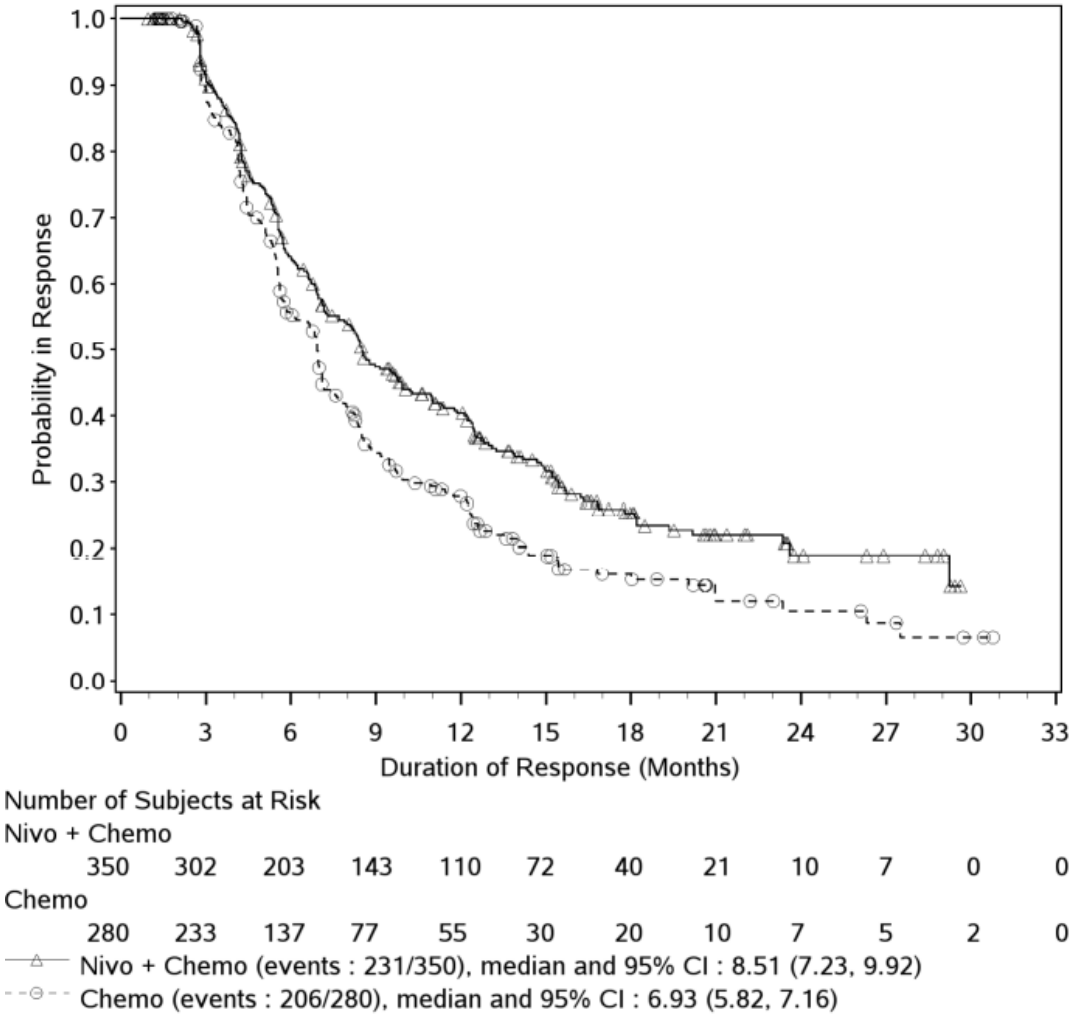
Time to response and duration of response in all randomised subjects

Table 22. Time to Response and Duration of Response per BICR - All Measurable Responders

	Nivo + Chemo N = 350	Chemo N = 280
TIME TO OBJECTIVE RESPONSE (MONTHS)		
MEAN	2.20	2.11
MEDIAN	1.51	1.48
MIN, MAX	0.8, 10.9	0.6, 7.1
Q1, Q3	1.38, 2.79	1.40, 2.79
STANDARD DEVIATION	1.40	1.17
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.0+, 29.6+	1.2+, 30.8+
MEDIAN (95% CI) (B)	8.51 (7.23, 9.92)	6.93 (5.82, 7.16)
N EVENT/N RESP (%)	231/350 (66.0)	206/280 (73.6)
PROPORTION OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (95% CI) (C)		
3 MONTHS	91.0 (87.4, 93.6)	89.4 (85.0, 92.5)
6 MONTHS	64.2 (58.7, 69.1)	55.4 (49.1, 61.2)
9 MONTHS	47.4 (41.8, 52.7)	34.3 (28.4, 40.3)
12 MONTHS	40.4 (34.9, 45.8)	27.9 (22.3, 33.7)

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

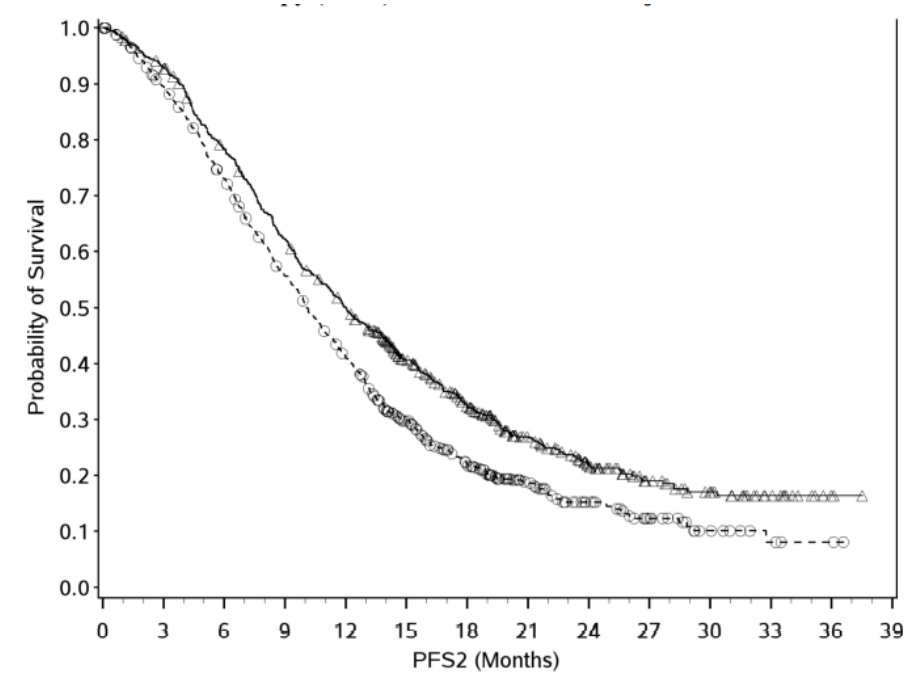
Figure 11. Kaplan-Meier Plot of Duration of Response per BICR - All Measurable Responders



Progression-Free Survival Including Next Line of Therapy (PFS2) per Investigator - All Randomized Subjects

In all randomized subjects, median PFS2 (95% CI) per investigator was 11.99 (11.14, 13.1) and 10.05 (9.53, 10.81) months for nivo+chemo vs. chemo, respectively; HR = 0.77 (95% CI: 0.69, 0.86). PFS2 is defined as the time from randomization to objectively documented progression after the next line of therapy, per investigator assessment, or to death from any cause, whichever occurred first. Subjects who were alive and without progression after the next line of therapy were censored at their last known alive date.

Figure 12. Kaplan-Meier Plot of Progression-free Survival Including Next Line of Therapy (PFS2) - All Randomized Subjects



Number of Subjects at Risk

Nivo + Chemo	789	729	608	482	383	275	199	123	78	43	29	13	2	0
Chemo	792	693	561	423	306	193	123	72	42	23	10	4	2	0

Nivo + Chemo (events : 574/789), median and 95% CI : 11.99 (11.14, 13.11)

Chemo (events : 620/792), median and 95% CI : 10.05 (9.53, 10.81)

Nivo + Chemo vs Chemo - hazard ratio (95% CI): 0.77 (0.69, 0.86)

Efficacy by tumour cell PD-L1 expression

Table 23. Efficacy of Nivolumab + Chemotherapy 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+ Chemo N = 663	Chemo N = 660	Nivo+ Chemo N = 126	Chemo N = 127	Nivo+ Chemo N = 698	Chemo N = 695	Nivo+ Chemo N = 91	Chemo N = 92	Nivo+ Chemo N = 713	Chemo N = 712	Nivo+ Chemo N = 76	Chemo N = 75
OS												
HR (95% CI)[a]	0.85 (0.75, 0.96)		0.57 (0.42, 0.77)		0.83 (0.73, 0.94)		0.59 (0.41, 0.84)		0.83 (0.73, 0.93)		0.57 (0.38, 0.84)	
Events, n (%)	469 (70.7)	489 (74.1)	75 (59.5)	97 (76.4)	489 (70.1)	515 (74.1)	55 (60.4)	71 (77.2)	500 (70.1)	529 (74.3)	44 (57.9)	57 (76.0)
Median OS, mo (95% CI)[b]	13.60 (12.09, 14.39)	11.99 (11.14, 12.78)	15.64 (11.76, 23.06)	9.66 (7.20, 11.24)	13.7 (12.39, 14.42)	11.96 (11.10, 12.71)	16.13 (10.15, 23.06)	9.23 (6.28, 11.63)	13.60 (12.29, 14.39)	11.76 (10.97, 12.58)	16.23 (10.15, 23.92)	9.82 (6.21, 13.21)
PFS per BICR (primary definition)												
HR (95% CI)[a,]	0.84 (0.74, 0.96)		0.52 (0.39, 0.71)		0.81 (0.72, 0.92)		0.56 (0.40, 0.80)		0.80 (0.70, 0.90)		0.60 (0.41, 0.89)	
Events, n (%)	478 (72.1)	461 (69.8)	81 (64.3)	91 (71.7)	499 (71.5)	482 (69.4)	60 (65.9)	70 (76.1)	507 (71.1)	498 (69.9)	52 (68.4)	54 (72.0)
Median PFS, mo. (95% CI)[b]	7.52 (7.03, 8.44)	7.03 (6.90, 7.72)	9.66 (6.97, 12.35)	5.26 (4.17, 6.05)	7.62 (7.06, 8.54)	7.03 (6.87, 7.59)	8.31 (5.45, 11.37)	5.29 (3.55, 6.21)	7.66 (7.06, 8.57)	6.97 (6.83, 7.29)	7.29 (4.73, 11.43)	5.29 (3.55, 6.77)
ORR per BICR (CR + PR)[c]												
ORR (95% CI)	58.5 (54, 63)	48.2 (44, 53)	55.8 (46, 66)	36.2 (27, 46)	58.1 (54, 62)	47.8 (44, 52)	57.5 (45, 69)	34.6 (24, 46)	58.0 (54, 62)	47.6 (43, 52)	58.1 (45, 71)	33.3 (22, 46)

[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, CI - confidence interval, CR - complete response, HR - hazard ratio, ORR - objective response rate, OS - overall survival, PD-L1 - programmed death-ligand 1, PFS - progression-free survival, PR - partial response

Efficacy by CPS PD-L1 Status

Table 24. Efficacy of Nivolumab + Chemotherapy vs. Chemotherapy by Baseline CPS PD-L1 Status - All Randomized Subjects

	CPS < 1		CPS ≥ 1		CPS < 5		CPS ≥ 5		CPS < 10		CPS ≥ 10	
	Nivo+ Chemo N = 140	Chemo N = 125	Nivo+ Chemo N = 641	Chemo N = 655	Nivo+ Chemo N = 308	Chemo N = 298	Nivo+ Chemo N = 473	Chemo N = 482	Nivo+ Chemo N = 406	Chemo N = 387	Nivo+ Chemo N = 375	Chemo N = 393
OS												
HR (95% CI)[a]	0.92 (0.70, 1.23)		0.76 (0.67, 0.87)		0.94 (0.78, 1.13)		0.70 (0.60, 0.81)		0.94 (0.80, 1.10)		0.65 (0.55, 0.78)	
Events, n (%)	103 (73.6)	91 (72.8)	434 (67.7)	492 (75.1)	228 (74.0)	221 (74.2)	309 (65.3)	362 (75.1)	302 (74.4)	288 (74.4)	235 (62.7)	295 (75.1)
Median OS, mo (95% CI)[b]	13.08 (9.82, 16.66)	12.48 (10.12, 13.83)	13.96 (12.55, 14.98)	11.33 (10.64, 12.25)	12.42 (10.61, 14.26)	12.25 (10.97, 13.24)	14.39 (13.11, 16.23)	11.10 (10.02, 12.09)	12.55 (11.07, 14.19)	12.52 (11.24, 13.27)	15.01 (13.77, 16.79)	10.87 (9.82, 11.83)
PFS per BICR (primary definition)												
HR (95% CI)[a,]	0.93 (0.69, 1.26)		0.75 (0.65, 0.85)		0.93 (0.76, 1.12)		0.69 (0.59, 0.80)		0.91 (0.77, 1.08)		0.65 (0.55, 0.77)	
Events, n (%)	99 (70.7)	77 (61.6)	454 (70.8)	472 (72.1)	225 (73.1)	199 (66.8)	328 (69.3)	350 (72.6)	301 (74.1)	260 (67.2)	252 (67.2)	289 (73.5)
Median PFS, mo. (95% CI)[b]	8.67 (6.93, 9.69)	8.11 (6.87, 9.82)	7.49 (7.03, 8.41)	6.90 (6.08, 7.03)	7.49 (6.97, 8.67)	8.15 (7.06, 8.67)	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)	7.49 (7.03, 8.44)	7.72 (6.97, 8.31)	8.31 (6.97, 9.69)	5.78 (5.45, 6.87)
ORR per BICR (CR + PR)[c]												
Subjects with measurable disease, N	93	85	504	515	219	209	378	391	297	281	300	319
ORR (95% CI)	50.5 (40, 61)	41.2 (31, 52)	59.5 (55, 64)	46.4 (42, 51)	55.3 (48, 62)	46.4 (40, 53)	59.8 (55, 65)	45.3 (40, 50)	57.9 (52, 64)	47.3 (41, 53)	58.3 (53, 64)	44.2 (39, 50)
CR, n/N (%)	7/93 (7.5)	4/85 (4.7)	51/504 (10.1)	32/515 (6.2)	14/219 (6.4)	9/209 (4.3)	44/378 (11.6)	27/391 (6.9)	27/297 (9.1)	15/281 (5.3)	31/300 (10.3)	21/319 (6.6)
PR, n/N (%)	40/93 (43.0)	31/85 (36.5)	249/504 (49.4)	207/515 (40.2)	107/219 (48.9)	88/209 (42.1)	182/378 (48.1)	150/391 (38.4)	145 (48.8)	118 (42.0)	144 (48.0)	120 (37.6)

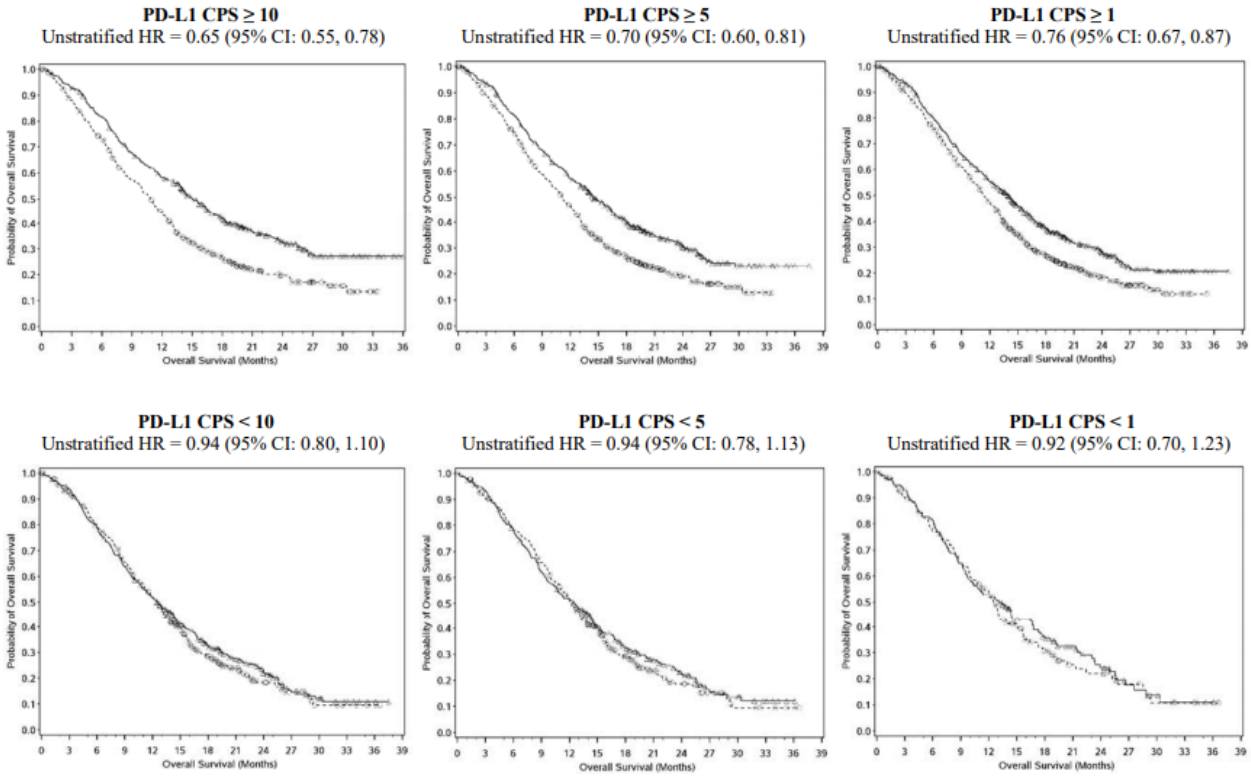
[a] Unstratified Cox proportional hazards model.

[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, BOR - best overall response, CI - confidence interval, CPS - combined positive score, CR - complete response, HR - hazard ratio, ORR - objective response rate, OS - overall survival, PD-L1 - programmed death-ligand 1, PFS - progression-free survival, PR - partial response

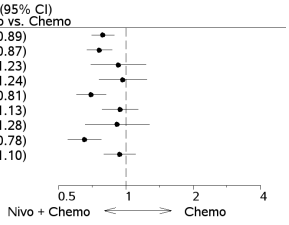
Figure 13. Pre-specified Subgroup Analyses of OS by PD-L1 CPS cut-offs - All Randomized Subjects



Only OS by PD-L1 CPS ≥ 5 and PD-L1 CPS ≥1 were formally tested.

Figure 14. Forest Plot of Treatment Effect on OS by PD-L1 CPS Status - All randomised Subjects

		Nivo + Chemo		Chemo		Unstratified
	N	N of Events (N of Subjects)	mOS (95% CI)	N of Events (N of Subjects)	mOS (95% CI)	Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Overall	1581	544 (789)	13.83 (12.55, 14.55)	591 (792)	11.56 (10.87, 12.48)	0.79 (0.70, 0.89)
CPS PD-L1 Expression >= 1	1296	434 (641)	13.96 (12.55, 14.98)	492 (655)	11.33 (10.64, 12.25)	0.76 (0.67, 0.87)
CPS PD-L1 Expression < 1	265	103 (140)	13.08 (9.82, 16.66)	91 (125)	12.48 (10.12, 13.83)	0.92 (0.70, 1.23)
CPS PD-L1 Expression >= 1 and < 5	341	125 (168)	12.29 (9.63, 14.26)	130 (173)	11.99 (10.87, 13.90)	0.97 (0.76, 1.24)
CPS PD-L1 Expression >= 5	955	309 (473)	14.39 (13.11, 16.23)	362 (482)	11.10 (10.02, 12.09)	0.70 (0.60, 0.81)
CPS PD-L1 Expression < 5	606	228 (308)	12.42 (10.61, 14.26)	221 (298)	12.25 (10.97, 13.24)	0.94 (0.78, 1.13)
CPS PD-L1 Expression >= 5 and < 10	187	74 (98)	12.62 (10.71, 16.23)	67 (89)	12.94 (9.40, 14.42)	0.92 (0.66, 1.28)
CPS PD-L1 Expression >= 10	768	235 (375)	15.01 (13.77, 16.79)	295 (393)	10.87 (9.82, 11.83)	0.65 (0.55, 0.78)
CPS PD-L1 Expression < 10	793	302 (406)	12.55 (11.07, 14.19)	288 (387)	12.52 (11.24, 13.27)	0.94 (0.80, 1.10)
CPS PD-L1 Expression Indeterminate/Not Evaluable/Not Reported	20	7 (8)	13.19 (1.22, 19.25)	8 (12)	12.14 (6.97, N.A.)	



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

Efficacy by MSI Status

The MSI prevalence by category was calculated based on the number of subjects for whom MSI data were available. Of the 1581 randomized subjects 1449 (91.7%) subjects had tumour tissue available for MSI testing; 132 (8.3%) subjects had no tumour tissue for MSI testing, 44 (2.8%) subjects were MSI-H and 1377 (87.1%) subjects were MSS.

Table 25. Efficacy of Nivolumab + Chemotherapy vs. Chemotherapy by Baseline MSI status - All Randomized Subjects

	MSI-H		MSS		Invalid/Not Reported	
	Nivo+Chemo N = 23	Chemo N = 21	Nivo+Chemo N = 695	Chemo N = 682	Nivo+Chemo N = 71	Chemo N = 89
OS						
HR (95% CI)[a]	0.37 (0.16, 0.87)		0.80 (0.71, 0.91)		0.83 (0.58, 1.20)	
Events, n (%)	9 (39.1)	15 (71.4)	483 (69.5)	507 (74.3)	52 (73.2)	69 (77.5)
Median OS, mo. (95% CI)[b]	NA (8.38, NA)	12.25 (4.11, 21.55)	13.83 (12.42, 14.62)	11.37 (10.74, 12.48)	11.79 (8.87, 16.66)	11.76 (10.48, 13.54)
PFS per BICR (Primary Definition)						
HR (95% CI)[a]	0.37 (0.17, 0.81)		0.77 (0.68, 0.87)		1.03 (0.71, 1.48)	
Events, n (%)	11 (47.8)	16 (76.2)	493 (70.9)	478 (70.1)	55 (77.5)	63 (70.8)
Median PFS, mo. (95% CI)[b]	14.00 (4.21, NA)	4.27 (2.76, 8.34)	7.75 (7.13, 8.57)	6.93 (6.28, 7.06)	6.93 (5.75, 8.67)	7.85 (5.78, 9.56)
ORR per BICR (CR + PR)[c]						
ORR (95% CI), %	52.6 (28.9, 75.6)	38.9 (17.3, 64.3)	59.1 (54.8, 63.3)	46.4 (42.1, 50.8)	49.0 (34.4, 63.7)	44.6 (31.3, 58.5)

[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.

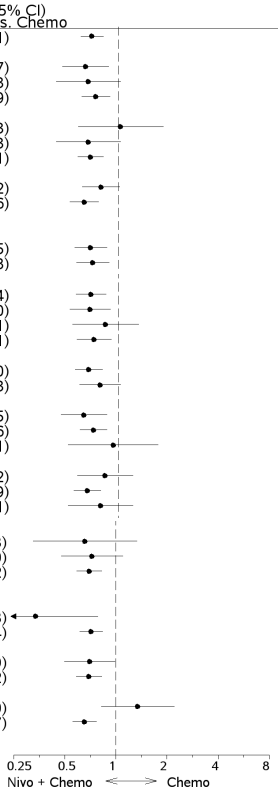
Abbreviations: BICR - blinded independent central review, CI - confidence interval, CR - complete response; HR - hazard ratio, MSI - microsomal instability, ORR - objective response rate, OS - overall survival, PD-L1 - programmed death-ligand 1, PFS - progression-free survival, PR - partial response

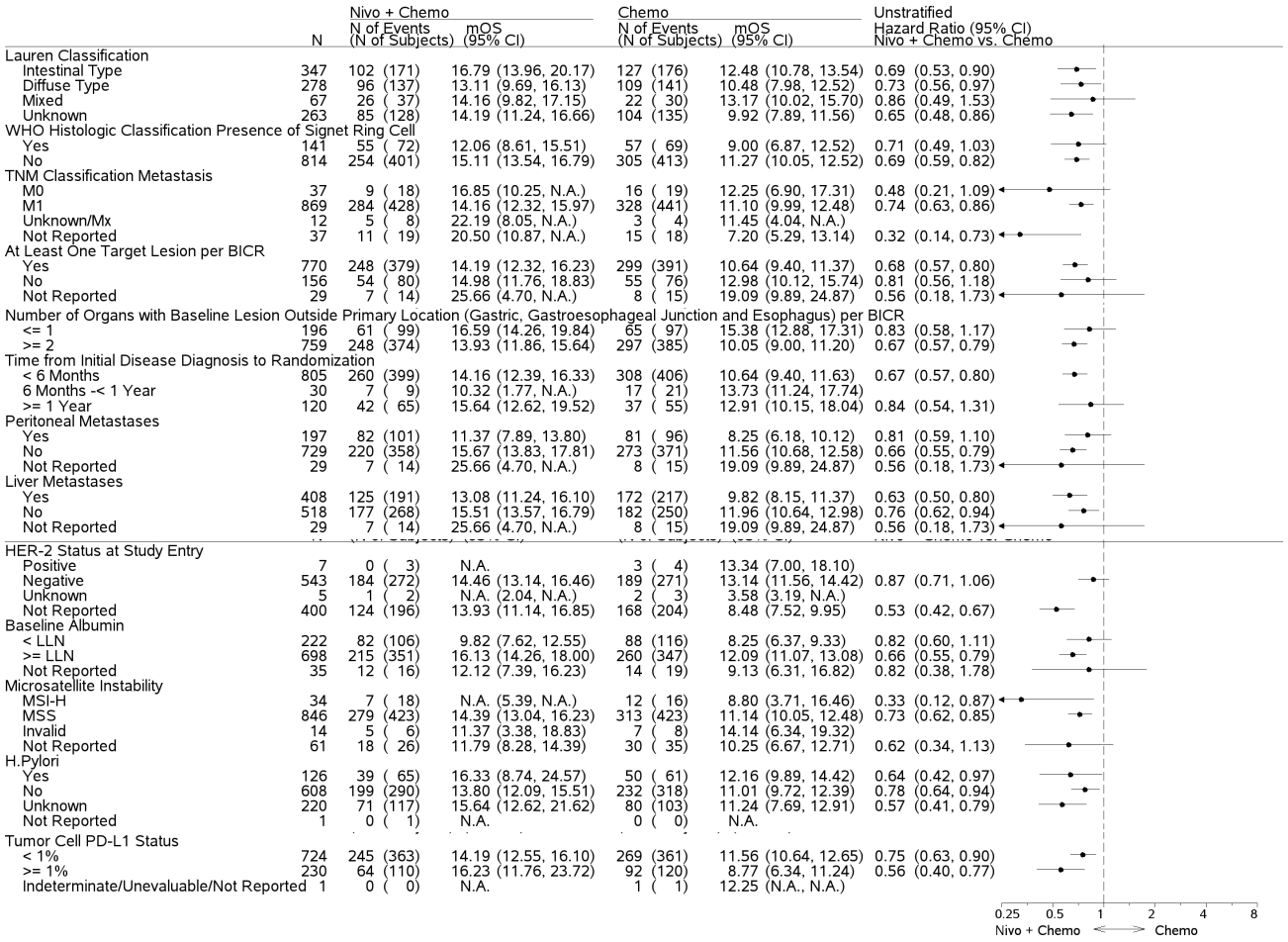
Ancillary analyses

Subgroup analyses

Figure 15. Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomized Subjects with PD-L1 CPS ≥ 5

	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Overall	955	309 (473)	14.39 (13.11, 16.23)	362 (482)	11.10 (10.02, 12.09)	0.70 (0.60, 0.81)
Region 1						
Asia	228	74 (117)	15.64 (12.94, 21.09)	86 (111)	11.79 (9.00, 13.93)	0.64 (0.47, 0.87)
US	137	37 (67)	16.79 (11.79, 25.99)	47 (70)	12.55 (11.24, 15.15)	0.67 (0.43, 1.03)
Rest of World	590	198 (289)	13.57 (11.37, 15.67)	229 (301)	10.38 (9.13, 11.56)	0.74 (0.61, 0.89)
Region 2						
Asia [without China]	72	28 (42)	16.30 (11.56, 23.95)	20 (30)	16.82 (12.52, 24.77)	1.03 (0.58, 1.83)
US	137	37 (67)	16.79 (11.79, 25.99)	47 (70)	12.55 (11.24, 15.15)	0.67 (0.43, 1.03)
RoW [including China]	746	244 (364)	13.83 (12.09, 15.64)	295 (382)	10.15 (9.00, 11.33)	0.69 (0.58, 0.81)
ECOG Performance Status						
0	397	114 (194)	17.64 (14.98, 20.50)	131 (203)	13.77 (12.48, 16.23)	0.79 (0.61, 1.02)
1	557	195 (279)	12.62 (11.14, 14.26)	230 (278)	8.77 (7.82, 10.12)	0.63 (0.52, 0.76)
Not Reported	1	0 (0)	N.A.	1 (1)	7.00 (N.A., N.A.)	
Chemotherapy Regimen						
XELOX	454	158 (231)	15.01 (12.94, 16.46)	172 (223)	11.01 (9.23, 12.58)	0.69 (0.55, 0.85)
FOLFOX	479	147 (237)	14.32 (12.06, 16.79)	178 (242)	11.27 (10.05, 12.62)	0.71 (0.57, 0.88)
Age Categorization						
< 65	552	170 (266)	14.82 (12.39, 16.46)	215 (286)	11.04 (9.92, 12.52)	0.69 (0.56, 0.84)
>= 65 and < 75	298	100 (151)	14.16 (11.86, 17.54)	109 (147)	11.24 (8.77, 13.17)	0.68 (0.52, 0.90)
>= 75	105	39 (56)	14.26 (9.86, 16.59)	38 (49)	11.02 (6.90, 13.77)	0.84 (0.54, 1.31)
>= 65	403	139 (207)	14.26 (12.19, 16.79)	147 (196)	11.24 (9.33, 12.71)	0.72 (0.57, 0.91)
Sex						
Male	680	210 (331)	14.42 (13.11, 16.79)	261 (349)	10.78 (9.72, 11.96)	0.67 (0.56, 0.80)
Female	275	99 (142)	14.39 (11.24, 16.43)	101 (133)	12.09 (9.82, 13.08)	0.78 (0.59, 1.03)
Race						
Asian	236	75 (119)	16.10 (13.77, 23.06)	90 (117)	11.48 (8.48, 13.93)	0.63 (0.46, 0.85)
White	655	216 (328)	14.00 (12.19, 16.23)	246 (327)	11.07 (9.95, 12.39)	0.71 (0.59, 0.86)
Other	64	18 (26)	9.79 (5.36, 23.92)	26 (38)	10.55 (7.56, 13.73)	0.93 (0.51, 1.71)
Primary Tumor Location at Initial Diagnosis						
GEJ Cancer (A)	170	53 (84)	14.19 (11.76, 20.50)	57 (86)	13.08 (10.84, 16.23)	0.84 (0.57, 1.22)
Gastric Cancer	667	219 (333)	14.98 (13.14, 16.59)	259 (334)	10.48 (9.00, 11.96)	0.66 (0.55, 0.79)
Esophageal Adenocarcinoma (B)	118	37 (56)	11.24 (8.38, 16.79)	46 (62)	11.27 (8.48, 12.91)	0.78 (0.51, 1.21)
Disease Stage at Initial Diagnosis						
Stage I-II	46	12 (19)	14.46 (7.13, N.A.)	22 (27)	12.58 (7.00, 17.05)	0.66 (0.33, 1.33)
Stage III	131	43 (66)	15.67 (11.76, 20.04)	46 (65)	12.09 (10.78, 15.74)	0.72 (0.48, 1.10)
Stage IV	776	254 (387)	14.16 (12.39, 16.30)	294 (389)	10.81 (9.66, 11.96)	0.70 (0.59, 0.82)
Not Reported	2	0 (1)	N.A.	0 (1)	N.A.	
Disease Status						
Locally Recurrent/Advanced	40	9 (19)	23.92 (12.09, N.A.)	17 (21)	11.56 (6.90, 16.23)	0.34 (0.14, 0.78)
Metastatic	915	300 (454)	14.26 (12.94, 15.97)	345 (461)	11.07 (9.92, 12.09)	0.72 (0.61, 0.84)
Prior Surgery Related to Current Cancer						
Yes	202	59 (97)	16.23 (14.29, 20.17)	74 (105)	12.65 (11.10, 15.74)	0.70 (0.50, 0.99)
No	753	250 (376)	13.83 (11.86, 15.97)	288 (377)	10.48 (9.30, 11.63)	0.69 (0.59, 0.82)
Prior Radiotherapy						
Yes	86	34 (44)	9.79 (5.62, 13.96)	30 (42)	12.25 (10.94, 16.46)	1.34 (0.82, 2.20)
No	869	275 (429)	15.51 (13.57, 16.72)	332 (440)	10.84 (9.76, 12.09)	0.65 (0.56, 0.77)

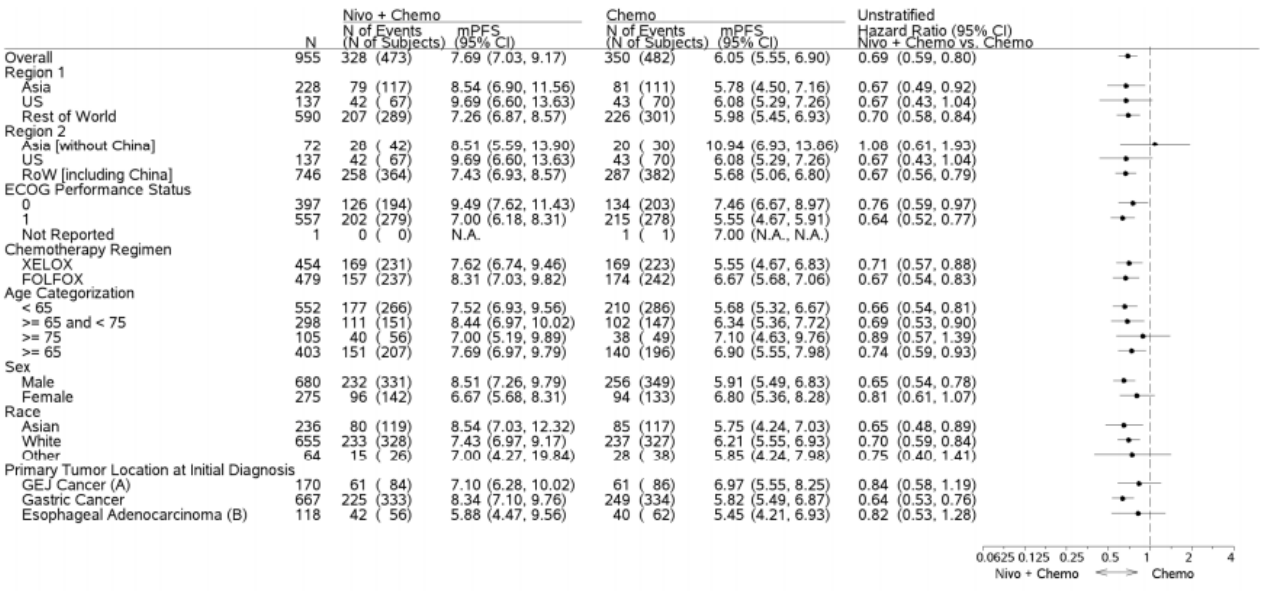




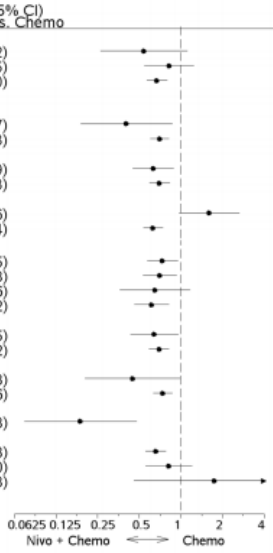
HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.

(A) Gastroesophageal Junction Cancer represents patients with diagnosis GEJ and Siewert-Stein Type II or III or unknown
(B) Esophageal Adenocarcinoma represents patients with diagnosis EAC or Gastroesophageal Junction Cancer with Siewert-Stein Type I
(C) Stratification factors are based on CRF source, not IRT.

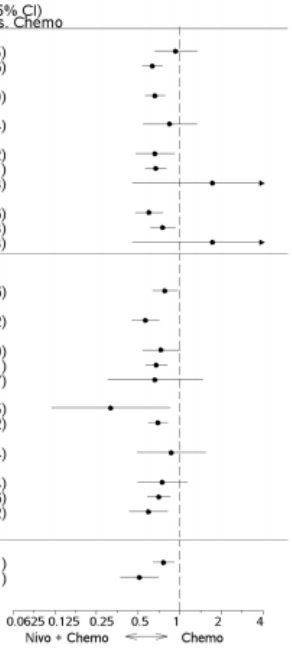
Figure 16. Forest Plot of Treatment Effect on PFS per BICR, Primary Definition in Predefined Subsets - All Randomized Subjects with PD-L1 CPS ≥ 5



	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mPFS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mPFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Disease Stage at Initial Diagnosis						
Stage I-II	46	12 (19)	9.69 (5.55, 24.64)	20 (27)	7.13 (5.32, 9.72)	0.54 (0.26, 1.12)
Stage III	131	48 (66)	6.97 (5.68, 9.92)	45 (65)	6.93 (5.06, 8.41)	0.83 (0.55, 1.25)
Stage IV	776	267 (387)	7.69 (7.03, 9.40)	285 (389)	5.75 (5.45, 6.54)	0.67 (0.57, 0.80)
Not Reported	2	1 (1)	2.89 (N.A., N.A.)	0 (1)	N.A.	
Disease Status						
Locally Recurrent/Advanced	40	11 (19)	10.02 (5.45, N.A.)	18 (21)	6.93 (3.02, 9.72)	0.41 (0.19, 0.87)
Metastatic	915	317 (454)	7.56 (6.97, 9.00)	332 (461)	5.95 (5.55, 6.83)	0.71 (0.61, 0.83)
Prior Surgery Related to Current Cancer						
Yes	202	65 (97)	9.63 (6.77, 11.30)	71 (105)	6.67 (4.53, 7.03)	0.64 (0.45, 0.89)
No	753	263 (376)	7.52 (6.97, 8.54)	279 (377)	5.98 (5.55, 6.90)	0.70 (0.59, 0.83)
Prior Radiotherapy						
Yes	86	37 (44)	6.28 (4.11, 6.93)	27 (42)	8.25 (6.93, 11.37)	1.61 (0.98, 2.66)
No	869	291 (429)	8.34 (7.26, 9.72)	323 (440)	5.78 (5.52, 6.67)	0.63 (0.54, 0.74)
Lauren Classification						
Intestinal Type	347	115 (171)	8.57 (7.03, 10.94)	124 (176)	6.80 (5.65, 8.25)	0.74 (0.57, 0.95)
Diffuse Type	278	96 (137)	7.62 (6.67, 9.69)	103 (141)	6.34 (5.06, 7.59)	0.70 (0.53, 0.93)
Mixed	67	22 (37)	9.63 (5.62, 19.48)	24 (30)	6.93 (5.26, 10.41)	0.65 (0.36, 1.16)
Unknown	263	95 (128)	6.97 (5.82, 8.34)	99 (135)	4.76 (4.17, 6.14)	0.61 (0.46, 0.82)
WHO Histologic Classification Presence of Signet Ring Cell						
Yes	141	50 (72)	7.49 (5.75, 10.94)	51 (69)	6.14 (4.86, 7.03)	0.64 (0.43, 0.95)
No	814	278 (401)	8.31 (7.03, 9.46)	299 (413)	6.05 (5.55, 6.93)	0.70 (0.59, 0.82)
TNM Classification Metastasis						
M0	37	11 (18)	10.02 (4.70, N.A.)	15 (19)	6.98 (2.86, 9.76)	0.45 (0.20, 0.98)
M1	869	303 (428)	7.33 (6.93, 8.51)	318 (441)	6.05 (5.55, 6.87)	0.74 (0.63, 0.86)
Unknown/Mx	12	6 (8)	8.57 (4.21, 19.84)	2 (4)	7.11 (4.67, 9.56)	
Not Reported	37	8 (19)	13.11 (7.52, 22.31)	15 (18)	5.03 (1.74, 7.20)	0.19 (0.07, 0.48)
At Least One Target Lesion per BICR						
Yes	770	266 (379)	7.10 (6.83, 8.44)	296 (391)	5.59 (5.03, 6.28)	0.66 (0.56, 0.78)
No	156	53 (80)	9.69 (7.69, 11.37)	51 (76)	7.33 (5.78, 10.94)	0.82 (0.56, 1.20)
Not Reported	29	9 (14)	13.16 (4.70, 25.66)	3 (15)	24.87 (6.28, 24.87)	1.74 (0.46, 6.63)



	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mPFS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mPFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Number of Organs with Baseline Lesion Outside Primary Location (Gastric, Gastroesophageal Junction and Esophagus) per BICR						
<= 1	196	70 (99)	9.17 (7.10, 11.20)	55 (97)	8.57 (6.93, 11.10)	0.94 (0.66, 1.35)
>= 2	759	258 (374)	7.33 (6.93, 8.54)	295 (385)	5.55 (4.93, 6.14)	0.64 (0.54, 0.76)
Time from Initial Disease Diagnosis to Randomization						
< 6 Months	805	273 (399)	8.31 (7.03, 9.49)	299 (406)	5.78 (5.49, 6.54)	0.67 (0.57, 0.79)
6 Months -< 1 Year	30	6 (9)	6.97 (1.77, 13.93)	18 (21)	5.65 (4.24, 16.76)	
>= 1 Year	120	49 (65)	7.10 (5.98, 9.72)	33 (55)	7.26 (6.93, 8.38)	0.86 (0.55, 1.34)
Peritoneal Metastases						
Yes	197	74 (101)	6.08 (5.39, 8.34)	77 (96)	5.32 (4.17, 6.83)	0.67 (0.48, 0.92)
No	729	245 (358)	8.31 (7.10, 9.59)	270 (371)	6.24 (5.59, 6.93)	0.68 (0.57, 0.81)
Not Reported	29	9 (14)	13.16 (4.70, 25.66)	3 (15)	24.87 (6.28, 24.87)	1.74 (0.46, 6.63)
Liver Metastases						
Yes	408	131 (191)	6.97 (6.28, 8.31)	172 (217)	5.26 (4.21, 5.75)	0.61 (0.48, 0.76)
No	518	188 (268)	8.41 (7.43, 9.79)	175 (250)	6.93 (5.82, 7.59)	0.76 (0.62, 0.93)
Not Reported	29	9 (14)	13.16 (4.70, 25.66)	3 (15)	24.87 (6.28, 24.87)	1.74 (0.46, 6.63)
HER-2 Status at Study Entry						
Positive	7	1 (3)	N.A. (2.83, N.A.)	1 (4)	6.93 (N.A., N.A.)	
Negative	543	184 (272)	8.28 (6.80, 9.56)	186 (271)	6.93 (5.68, 7.33)	0.78 (0.64, 0.96)
Unknown	5	2 (2)	1.69 (0.49, 2.89)	2 (3)	9.71 (2.66, 16.76)	
Not Reported	400	141 (196)	7.69 (6.97, 9.79)	161 (204)	5.55 (4.50, 6.24)	0.57 (0.45, 0.72)
Baseline Albumin						
< LLN	222	82 (106)	5.88 (4.47, 7.69)	88 (116)	5.06 (3.78, 6.34)	0.74 (0.54, 1.00)
>= LLN	698	234 (351)	8.44 (7.23, 9.79)	249 (347)	6.67 (5.75, 6.97)	0.68 (0.57, 0.81)
Not Reported	35	12 (16)	7.62 (5.55, 13.83)	13 (19)	6.28 (3.38, 11.37)	0.66 (0.30, 1.47)
Microsatellite Instability						
MSI-H	34	9 (18)	12.48 (2.89, N.A.)	12 (16)	4.27 (1.97, 7.13)	0.32 (0.12, 0.85)
MSS	846	294 (423)	8.31 (7.06, 9.46)	303 (423)	6.21 (5.59, 6.93)	0.70 (0.59, 0.82)
Invalid	14	5 (6)	4.24 (0.30, 9.99)	6 (8)	5.55 (1.41, 13.83)	
Not Reported	61	20 (26)	6.54 (4.24, 8.28)	29 (35)	5.78 (3.55, 8.97)	0.87 (0.49, 1.54)
H.Pylori						
Yes	126	46 (65)	7.00 (5.59, 13.83)	45 (61)	5.91 (4.24, 8.54)	0.75 (0.50, 1.14)
No	608	194 (290)	8.31 (6.97, 9.40)	230 (318)	6.34 (5.55, 6.93)	0.71 (0.58, 0.86)
Unknown	220	88 (117)	7.69 (6.51, 10.84)	75 (103)	5.55 (4.34, 6.93)	0.59 (0.43, 0.82)
Not Reported	1	0 (1)	N.A.	0 (0)	N.A.	
Tumor Cell PD-L1 Status						
< 1%	724	258 (363)	7.52 (6.97, 8.57)	261 (361)	6.67 (5.78, 6.97)	0.76 (0.64, 0.91)
>= 1%	230	70 (110)	9.89 (6.97, 13.83)	88 (120)	4.76 (4.04, 5.68)	0.51 (0.37, 0.71)
Indeterminate/Unevaluable/Not Reported	1	0 (0)	N.A.	1 (1)	7.13 (N.A., N.A.)	



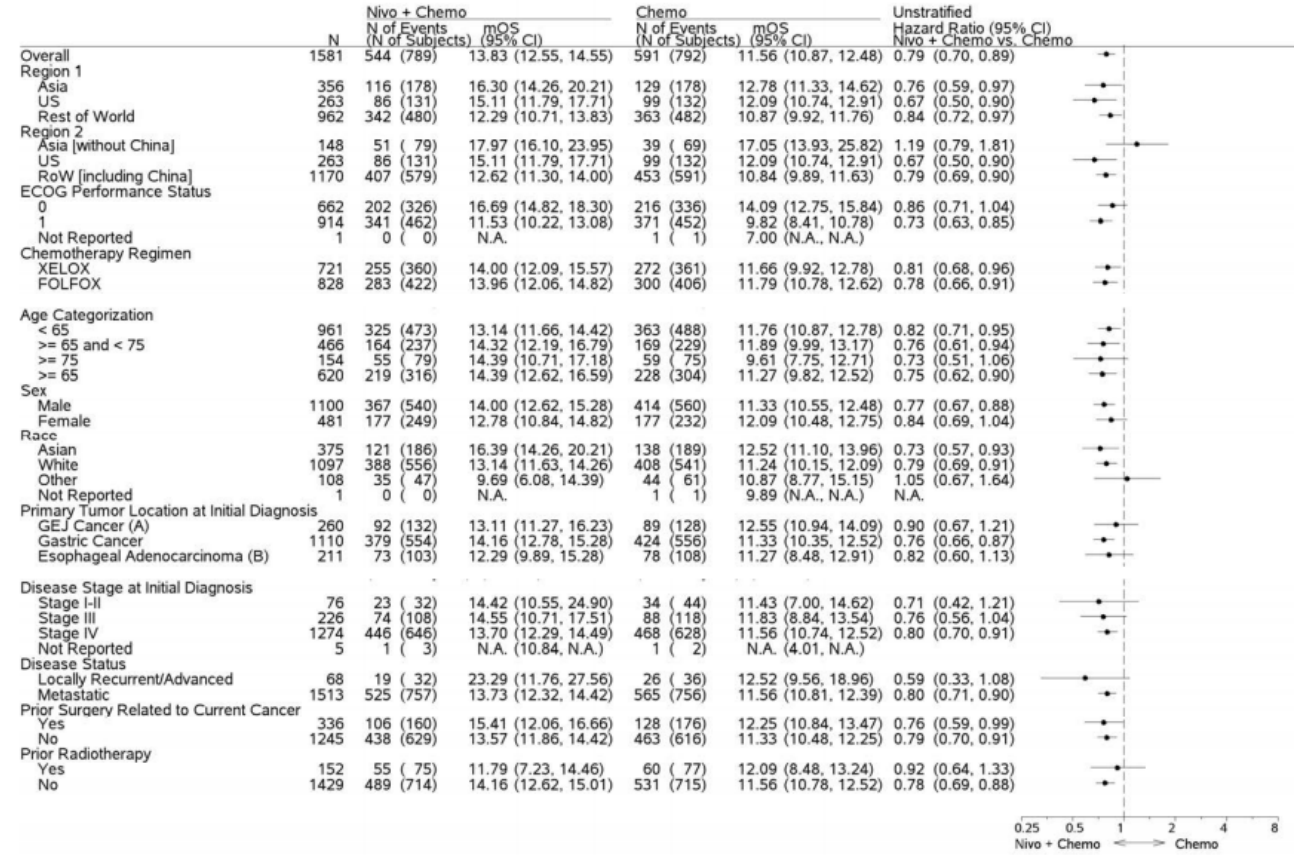
HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.

(A) Gastroesophageal Junction Cancer represents patients with diagnosis GEJ and Siewert-Stein Type II or III or unknown

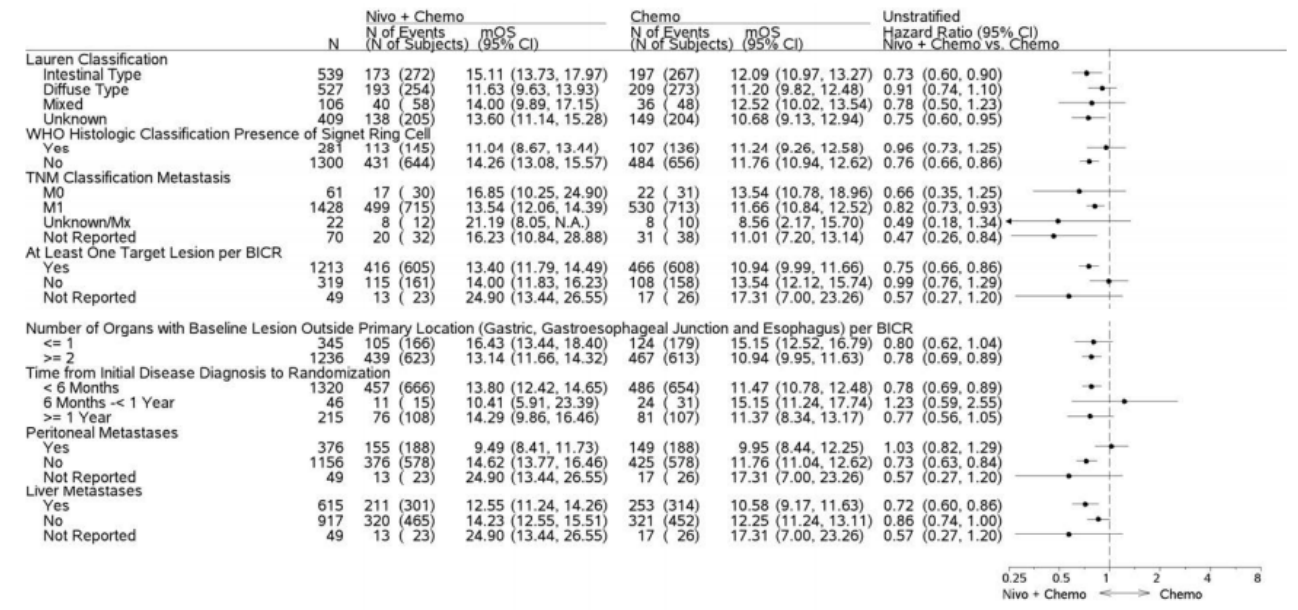
(B) Esophageal Adenocarcinoma represents patients with diagnosis EAC or Gastroesophageal Junction Cancer with Siewert-Stein Type I

(C) Stratification factors are based on CRF source, not IRT.

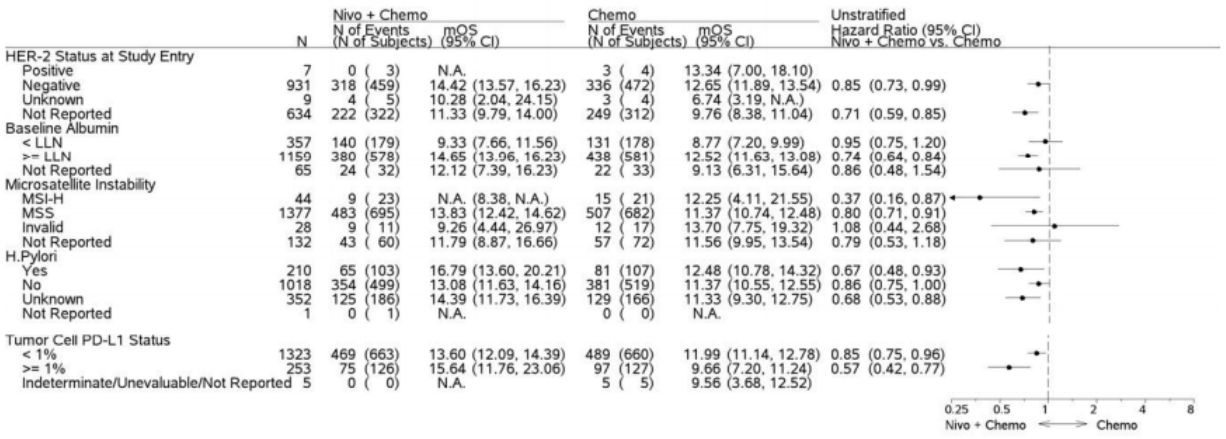
Figure 17. Forest Plot of Treatment Effect on Overall Survival in Predefined Subsets - All Randomized Subjects



	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Overall	1581	544 (789)	13.83 (12.55, 14.55)	591 (792)	11.56 (10.87, 12.48)	0.79 (0.70, 0.89)
Region 1						
Asia	356	116 (178)	16.30 (14.26, 20.21)	129 (178)	12.78 (11.33, 14.62)	0.76 (0.59, 0.97)
US	263	86 (131)	15.11 (11.79, 17.71)	99 (132)	12.09 (10.74, 12.91)	0.67 (0.50, 0.90)
Rest of World	962	342 (480)	12.29 (10.71, 13.83)	363 (482)	10.87 (9.92, 11.76)	0.84 (0.72, 0.97)
Region 2						
Asia [without China]	148	51 (79)	17.97 (16.10, 23.95)	39 (69)	17.05 (13.93, 25.82)	1.19 (0.79, 1.81)
US	263	86 (131)	15.11 (11.79, 17.71)	99 (132)	12.09 (10.74, 12.91)	0.67 (0.50, 0.90)
RoW [including China]	1170	407 (579)	12.62 (11.30, 14.00)	453 (591)	10.84 (9.89, 11.63)	0.79 (0.69, 0.90)
ECOG Performance Status						
0	662	202 (326)	16.69 (14.82, 18.30)	216 (336)	14.09 (12.75, 15.84)	0.86 (0.71, 1.04)
1	914	341 (462)	11.53 (10.22, 13.08)	371 (452)	9.82 (8.41, 10.78)	0.73 (0.63, 0.85)
Not Reported	1	0 (0)	N.A.	1 (1)	7.00 (N.A., N.A.)	
Chemotherapy Regimen						
XELOX	721	255 (360)	14.00 (12.09, 15.57)	272 (361)	11.66 (9.92, 12.78)	0.81 (0.68, 0.96)
FOLFOX	828	283 (422)	13.96 (12.06, 14.82)	300 (406)	11.79 (10.78, 12.62)	0.78 (0.66, 0.91)
Age Categorization						
< 65	961	325 (473)	13.14 (11.66, 14.42)	363 (488)	11.76 (10.87, 12.78)	0.82 (0.71, 0.95)
>= 65 and < 75	466	164 (237)	14.32 (12.19, 16.79)	169 (229)	11.89 (9.99, 13.17)	0.76 (0.61, 0.94)
>= 75	154	55 (79)	14.39 (10.71, 17.18)	59 (75)	9.61 (7.75, 12.71)	0.73 (0.51, 1.06)
>= 65	620	219 (316)	14.39 (12.62, 16.59)	228 (304)	11.27 (9.82, 12.52)	0.75 (0.62, 0.90)
Sex						
Male	1100	367 (540)	14.00 (12.62, 15.28)	414 (560)	11.33 (10.55, 12.48)	0.77 (0.67, 0.88)
Female	481	177 (249)	12.78 (10.84, 14.82)	177 (232)	12.09 (10.48, 12.75)	0.84 (0.69, 1.04)
Race						
Asian	375	121 (186)	16.39 (14.26, 20.21)	138 (189)	12.52 (11.10, 13.96)	0.73 (0.57, 0.93)
White	1097	388 (556)	13.14 (11.63, 14.26)	408 (541)	11.24 (10.15, 12.09)	0.79 (0.69, 0.91)
Other	108	35 (47)	9.69 (6.08, 14.39)	44 (61)	10.87 (8.77, 15.15)	1.05 (0.67, 1.64)
Not Reported	1	0 (0)	N.A.	1 (1)	9.89 (N.A., N.A.)	N.A.
Primary Tumor Location at Initial Diagnosis						
GEJ Cancer (A)	260	92 (132)	13.11 (11.27, 16.23)	89 (128)	12.55 (10.94, 14.09)	0.90 (0.67, 1.21)
Gastric Cancer	1110	379 (554)	14.16 (12.78, 15.28)	424 (556)	11.33 (10.35, 12.52)	0.76 (0.66, 0.87)
Esophageal Adenocarcinoma (B)	211	73 (103)	12.29 (9.89, 15.28)	78 (108)	11.27 (8.48, 12.91)	0.82 (0.60, 1.13)
Disease Stage at Initial Diagnosis						
Stage I-II	76	23 (32)	14.42 (10.55, 24.90)	34 (44)	11.43 (7.00, 14.62)	0.71 (0.42, 1.21)
Stage III	226	74 (108)	14.55 (10.71, 17.51)	88 (118)	11.83 (8.84, 13.54)	0.76 (0.56, 1.04)
Stage IV	1274	446 (646)	13.70 (12.29, 14.49)	468 (628)	11.56 (10.74, 12.52)	0.80 (0.70, 0.91)
Not Reported	5	1 (3)	N.A. (10.84, N.A.)	1 (2)	N.A. (4.01, N.A.)	
Disease Status						
Locally Recurrent/Advanced	68	19 (32)	23.29 (11.76, 27.56)	26 (36)	12.52 (9.56, 18.96)	0.59 (0.33, 1.08)
Metastatic	1513	525 (757)	13.73 (12.32, 14.42)	565 (756)	11.56 (10.81, 12.39)	0.80 (0.71, 0.90)
Prior Surgery Related to Current Cancer						
Yes	336	106 (160)	15.41 (12.06, 16.66)	128 (176)	12.25 (10.84, 13.47)	0.76 (0.59, 0.99)
No	1245	438 (629)	13.57 (11.86, 14.42)	463 (616)	11.33 (10.48, 12.25)	0.79 (0.70, 0.91)
Prior Radiotherapy						
Yes	152	55 (75)	11.79 (7.23, 14.46)	60 (77)	12.09 (8.48, 13.24)	0.92 (0.64, 1.33)
No	1429	489 (714)	14.16 (12.62, 15.01)	531 (715)	11.56 (10.78, 12.52)	0.78 (0.69, 0.88)



	N	Nivo + Chemo N of Events (N of Subjects)	Nivo + Chemo mOS (95% CI)	Chemo N of Events (N of Subjects)	Chemo mOS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivo + Chemo vs. Chemo
Lauren Classification						
Intestinal Type	539	173 (272)	15.11 (13.73, 17.97)	197 (267)	12.09 (10.97, 13.27)	0.73 (0.60, 0.90)
Diffuse Type	527	193 (254)	11.63 (9.63, 13.93)	209 (273)	11.20 (9.82, 12.48)	0.91 (0.74, 1.10)
Mixed	106	40 (58)	14.00 (9.89, 17.15)	36 (48)	12.52 (10.02, 13.54)	0.78 (0.50, 1.23)
Unknown	409	138 (205)	13.60 (11.14, 15.28)	149 (204)	10.68 (9.13, 12.94)	0.75 (0.60, 0.95)
WHO Histologic Classification Presence of Signet Ring Cell						
Yes	281	113 (145)	11.04 (8.67, 13.44)	107 (136)	11.24 (9.26, 12.58)	0.96 (0.73, 1.25)
No	1300	431 (644)	14.26 (13.08, 15.57)	484 (656)	11.76 (10.94, 12.62)	0.76 (0.66, 0.86)
TNM Classification Metastasis						
M0	61	17 (30)	16.85 (10.25, 24.90)	22 (31)	13.54 (10.78, 18.96)	0.66 (0.35, 1.25)
M1	1428	499 (715)	13.54 (12.06, 14.39)	530 (713)	11.66 (10.84, 12.52)	0.82 (0.73, 0.93)
Unknown/Mx	22	8 (12)	21.19 (8.05, N.A.)	8 (10)	8.56 (2.17, 15.70)	0.49 (0.18, 1.34)
Not Reported	70	20 (32)	16.23 (10.84, 28.88)	31 (38)	11.01 (7.20, 13.14)	0.47 (0.26, 0.84)
At Least One Target Lesion per BICR						
Yes	1213	416 (605)	13.40 (11.79, 14.49)	466 (608)	10.94 (9.99, 11.66)	0.75 (0.66, 0.86)
No	319	115 (161)	14.00 (11.83, 16.23)	108 (158)	13.54 (12.12, 15.74)	0.99 (0.76, 1.29)
Not Reported	49	13 (23)	24.90 (13.44, 26.55)	17 (26)	17.31 (7.00, 23.26)	0.57 (0.27, 1.20)
Number of Organs with Baseline Lesion Outside Primary Location (Gastric, Gastroesophageal Junction and Esophagus) per BICR						
<= 1	345	105 (166)	16.43 (13.44, 18.40)	124 (179)	15.15 (12.52, 16.79)	0.80 (0.62, 1.04)
>= 2	1236	439 (623)	13.14 (11.66, 14.32)	467 (613)	10.94 (9.95, 11.63)	0.78 (0.69, 0.89)
Time from Initial Disease Diagnosis to Randomization						
< 6 Months	1320	457 (666)	13.80 (12.42, 14.65)	486 (654)	11.47 (10.78, 12.48)	0.78 (0.69, 0.89)
6 Months -< 1 Year	46	11 (15)	10.41 (5.91, 23.39)	24 (31)	15.15 (11.24, 17.74)	1.23 (0.59, 2.55)
>= 1 Year	215	76 (108)	14.29 (9.86, 16.46)	81 (107)	11.37 (8.34, 13.17)	0.77 (0.56, 1.05)
Peritoneal Metastases						
Yes	376	155 (188)	9.49 (8.41, 11.73)	149 (188)	9.95 (8.44, 12.25)	1.03 (0.82, 1.29)
No	1156	376 (578)	14.62 (13.77, 16.46)	425 (578)	11.76 (11.04, 12.62)	0.73 (0.63, 0.84)
Not Reported	49	13 (23)	24.90 (13.44, 26.55)	17 (26)	17.31 (7.00, 23.26)	0.57 (0.27, 1.20)
Liver Metastases						
Yes	615	211 (301)	12.55 (11.24, 14.26)	253 (314)	10.58 (9.17, 11.63)	0.72 (0.60, 0.86)
No	917	320 (465)	14.23 (12.55, 15.51)	321 (452)	12.25 (11.24, 13.11)	0.86 (0.74, 1.00)
Not Reported	49	13 (23)	24.90 (13.44, 26.55)	17 (26)	17.31 (7.00, 23.26)	0.57 (0.27, 1.20)



HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.
(A) Gastroesophageal Junction Cancer represents patients with diagnosis GEJ and Siewert-Stein Type II or III or unknown
(B) Esophageal Adenocarcinoma represents patients with diagnosis EAC or Gastroesophageal Junction Cancer with Siewert-Stein Type I
(C) Stratification factors are based on CRF source, not IRT.

Patient-Reported Outcomes (PRO) – All randomised subjects (Exploratory endpoints)

Questionnaire completion rates were acceptable, with ≥ 90% of subjects completing assessments at baseline and ≥ 80% at most time points during the treatment period.

Time to Disease-Related Symptom Deterioration - All Randomized Subjects

Symptom deterioration was defined as a clinically meaningful decline in GaCS score (worsening from baseline ≥ 8.2 points) during the treatment period. Subjects without deterioration while on treatment were censored at the last GaCS assessment.

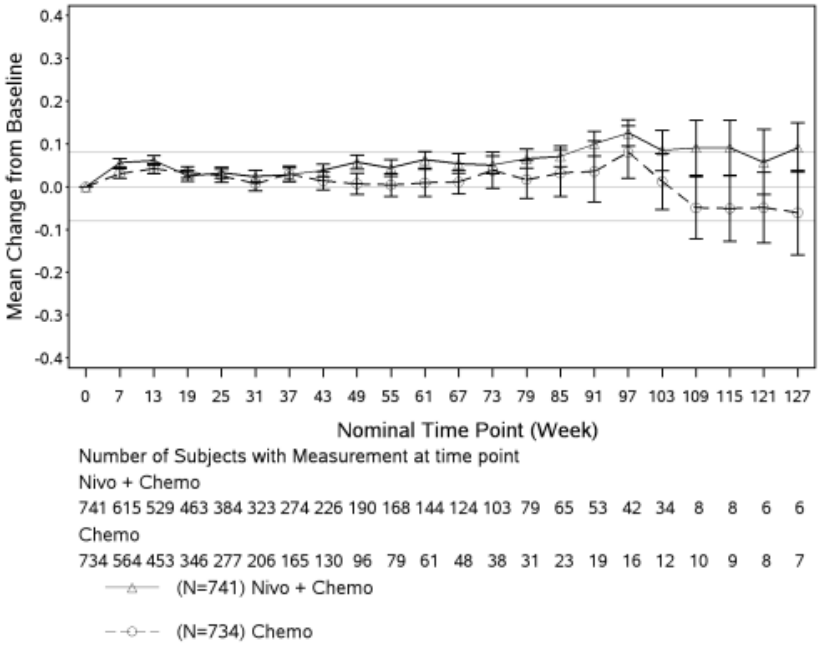
A total of 194/789 subjects in the nivo+chemo arm and 193/792 subjects in the chemo arm experienced a disease-related symptom deterioration event. Median time to symptom deterioration (TTSD) in all randomized subjects was not reached (95% CI: 22.64, N.A.) in the nivo+chemo arm and was 21.03 months (95% CI: 12.45, N.A.) in the chemo arm. Subjects in the nivo+chemo arm had a decreased risk (HR: 0.77, 95% CI: 0.63, 0.95) of deterioration compared to subjects in the chemo arm.

EQ-5D-3L Descriptive System and Utility Index

Mean baseline EQ-5D-3L UI scores in all randomized subjects were similar in the nivo+chemo (0.7339, SD: 0.2611) and chemo (0.7404, SD: 0.2398) arms. Subjects in the nivo+chemo arm had improvement in mean UI scores at all on-treatment assessments after baseline through Week 103 (last time point with N ≥ 10). The mean change from baseline met or exceeded the minimum important difference (MID) (≥ 0.08 points) at Weeks 91, 97, and 103. Subjects in the chemo arm had improvement in mean UI scores at most on-treatment assessments, with the mean change from baseline exceeding the MID at Week 97.

There was a decrease from baseline (worsening) that approached or exceeded the MID for both arms at most follow-up visits.

Figure 18. Mean Changes in EQ-5D-3L Utility Index Score from Baseline - All Randomized Subjects - with Baseline and at Least One Post-Baseline Assessment



EQ Visual Analogue Scale

Mean baseline EQ-5D-3L VAS scores in all randomized subjects were similar in the nivo+chemo (71.8, SD: 17.9) and chemo (71.8, SD: 18.2) arms. Overall, the mean EQ-5D-3L VAS scores in all randomized subjects increased (improved) over time in both arms. The mean change from baseline in the nivo+chemo arm met or exceeded the MID (≥ 7 points) at all the time points where there were ≥ 10 subjects eligible to respond, starting at Week 85. The mean change from baseline did not meet or exceed the MID for the chemo arm.

Updated analysis (DBL 16-Feb-2021; minimum follow-up: 19.4 months)

Updated overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) per blinded independent central review (BICR) data with nivolumab+chemotherapy (nivo+chemo) over chemotherapy (chemo) for CA209649 were provided during the procedure from an updated database lock (DBL) of 16-Feb-2021. The clinical cut-off (last patient last visit [LPLV]) was 04-Jan-2021. These update analyses are descriptive in nature.

Table 25. Summary of Overall Survival in CA209649 - Updated Analysis vs Primary CSR Analysis

	Primary CSR Analysis 10-Jul-2020 Database Lock (Minimum Follow-up: 12.1 mo.)		**Updated Analysis 16-Feb-2021 Database Lock (Minimum Follow-up: 19.4 mo.)**	
Overall Survival	**Nivo+Chemo**	**Chemo**	**Nivo+Chemo**	**Chemo**
All Randomized Subjects with PD-L1 CPS ≥ 5				
Events, n/N (%)	309/473 (65.3)	362/482 (75.1)	344/473 (72.7)	397/482 (82.4)
Median OS (95% CI)[a], mo.	14.39 (13.11, 16.23)	11.10 (10.02, 12.09)	14.42 (13.14, 16.26)	11.10 (10.02, 12.09)
Stratified HR (95% CI)[b]	0.71 (0.61, 0.83)		0.69 (0.60, 0.81)	

All Randomized Subjects with PD-L1 CPS ≥ 1				
Events, n/N (%)	434/641 (67.7)	492/655 (75.1)	478/641 (74.6)	540/656* (82.3)
Median OS (95% CI)[a], mo.	13.96 (12.55, 14.98)	11.33 (10.64, 12.25)	14.00 (12.55, 15.11)	11.33 (10.58, 12.12)
Stratified HR (95% CI)[b]	0.77 (0.68, 0.88)		0.75 (0.66, 0.85)	
All Randomized Subjects				
Events, n/N (%)	544/789 (68.9)	591/792 (74.6)	603/789 (76.4)	647/792 (81.7)
Median OS (95% CI)[a], mo.	13.83 (12.55, 14.55)	11.56 (10.87, 12.48)	13.93 (12.55, 14.65)	11.56 (10.87, 12.48)
Stratified HR (95% CI)[b]	0.80 (0.71, 0.90)		0.79 (0.70, 0.88)	

[a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model. HR is Nivo+Chemo over Chemo.
Abbreviations: chemo - chemotherapy, CI - confidence interval, CPS - combined positive score, CSR - clinical study report, DBL - database lock, HR - hazard ratio, Nivo - nivolumab, OS - overall survival, PD-L1 - programmed death-ligand 1

* One subject has CPS status changed for the updated DBL comparing with the previous DBL.

Source: Table S.5.22.A.1, Table S.5.222.A.1, Table S.5.222.A.2, Table S.5.22.EU.1, Table S.5.23.EU.1, and Table S.5.22.EU.3 of Appendix 2

Table 26. Summary of Other Key Efficacy Results - Updated Analysis from CA209649 (16-Feb-2021 Database Lock)

Minimum Follow-up: 19.4 mo.	**All Randomized Subjects with PD-L1 CPS ≥ 5**		**All Randomized Subjects**	
Efficacy Parameter	**Nivo+Chemo**	**Chemo**	**Nivo+Chemo**	**Chemo**
PFS per BICR (1ºDefinition)				
Events, n/N (%)	342/473 (72.3)	366/482 (75.9)	581/789 (73.6)	579/792 (73.1)
Median PFS (95% CI)[a], months	8.31 (7.03, 9.26)	6.05 (5.55, 6.90)	7.75 (7.13, 8.57)	6.93 (6.67, 7.13)
HR (95% CI)[b]	0.68 (0.59, 0.79)		0.78 (0.69, 0.88)	
ORR per BICR (CR + PR) in All Randomized Subjects				
N responders/N (%)	238/473 (50.3)	183/482 (38.0)	371/789 (47.0)	293/792 (37.0)
95% CI[c]	(45.7, 54.9)	(33.6, 42.5)	(43.5, 50.6)	(33.6, 40.5)
Difference of ORR (95% CI)[d]	13.3 (7.2, 19.3)		12.3 (7.7, 17.0)	
ORR per BICR (CR + PR) in Subjects with Measurable Disease				
N responders/N (%)	227/378 (60.1)	176/390 (45.1)	352/604 (58.3)	279/607 (46.0)
95% CI[c]	(54.9, 65.0)	(40.1, 50.2)	(54.2, 62.2)	(41.9, 50.0)
Difference of ORR (95% CI)[d]	16.4 (9.7, 23.1)		13.1 (7.6, 18.5)	
DoR per BICR in Subjects with Measurable Disease				
N events/N responders (%)	153/227 (67.4)	133/176 (75.6)	247/352 (70.2)	216/279 (77.4)
Median (95% CI)[a], months	9.69 (8.25, 12.22)	6.97 (5.62, 7.85)	8.54 (7.69, 10.22)	6.93 (5.82, 7.16)

[a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model. HR is Nivo+Chemo over Chemo.
[c] Confirmed CR or PR per RECIST 1.1. CI based on the Clopper and Pearson method.

[d] The difference in response rate (Nivo+Chemo vs Chemo) is not the simple difference between the rates but is adjusted for the stratification factors based on the DerSimonian and Laird methodology

Abbreviations: BICR - blinded independent central review, chemo - chemotherapy, CI - confidence interval, CPS - combined positive score, CR - complete response, DoR - duration of response, HR - hazard ratio, Nivo - nivolumab, ORR - objective response rate, PD-L1 - programmed death-ligand 1, PFS - progression-free survival, PR - partial response, RECIST - Response Evaluation Criteria in Solid Tumors

Source: Table S.5.22.EU.2, Table S.5.22.EU.4, Table S.5.9.EU.1, Table S.5.9.EU.2, Table S.5.9.EU.3, Table S.5.9.EU.4, Figure S.5.11.EU.1 and Figure S.5.11.EU.2 of Appendix 2

Further to the above updated analysis were submitted by PD-L1 CPS categorie.

Table 27. Efficacy of Nivolumab + Chemotherapy vs Chemotherapy by Baseline PD-L1 CPS Status - Updated Analysis from CA209649 (16-Feb-2021 Database Lock)

All Randomized Subjects	CPS < 1		CPS ≥ 1		CPS < 5		CPS ≥ 5		CPS < 10		CPS ≥ 10	
Minimum Follow-up: 19.4 mo.	Nivo+ Chemo N = 140	Chemo N = 123	Nivo+ Chemo N = 641	Chemo N = 656	Nivo+ Chemo N = 308	Chemo N = 297	Nivo+ Chemo N = 473	Chemo N = 482	Nivo+ Chemo N = 406	Chemo N = 386	Nivo+ Chemo N = 375	Chemo N = 393
OS												
HR (95% CI)[a]	0.96 (0.73, 1.25)		0.74 (0.66, 0.84)		0.94 (0.79, 1.13)		0.69 (0.59, 0.79)		0.91 (0.78, 1.07)		0.66 (0.56, 0.77)	
Events, n (%)	117 (83.6)	99 (80.5)	478 (74.6)	540 (82.3)	251 (81.5)	242 (81.5)	344 (72.7)	397 (82.4)	330 (81.3)	319 (82.6)	265 (70.7)	320 (81.4)
Median OS, mo (95% CI)[b]	13.08 (9.82, 16.46)	12.48 (9.99, 13.83)	14.00 (12.55, 15.11)	11.33 (10.58, 12.12)	12.42 (10.61, 14.26)	12.09 (10.97, 13.24)	14.42 (13.14, 16.26)	11.10 (10.02, 12.09)	12.55 (11.07, 14.19)	12.48 (11.14, 13.17)	15.11 (13.77, 16.79)	10.87 (9.82, 11.89)
PFS per BICR (primary definition)												
HR (95% CI)[a]	0.91 (0.68, 1.22)		0.75 (0.66, 0.85)		0.95 (0.78, 1.14)		0.68 (0.59, 0.79)		0.92 (0.78, 1.08)		0.65 (0.55, 0.77)	
Events, n (%)	100 (71.4)	78 (63.4)	475 (74.1)	493 (75.2)	233 (75.6)	205 (69.0)	342 (72.3)	366 (75.9)	310 (76.4)	271 (70.2)	265 (67.2)	300 (73.5)
Median PFS, mo. (95% CI)[b]	8.67 (6.93, 9.69)	8.11 (6.87, 9.82)	7.52 (7.03, 8.51)	6.90 (6.08, 7.03)	7.46 (6.97, 8.64)	8.15 (7.06, 8.67)	8.31 (7.03, 9.26)	6.05 (5.55, 6.90)	7.49 (7.03, 8.44)	7.72 (6.97, 8.31)	8.34 (7.00, 9.76)	5.78 (5.45, 6.87)
ORR per BICR (CR + PR)[c]												
Subjects with measurable disease, N	94	84	504	514	220	208	378	390	299	280	299	318
ORR, % (95% CI)	51.1 (41, 62)	40.5 (30, 52)	59.7 (55, 64)	46.3 (42, 51)	55.5 (49, 62)	46.2 (39, 53)	60.1 (55, 65)	45.1 (40, 50)	57.9 (52, 64)	46.8 (41, 53)	58.9 (53, 65)	44.3 (39, 50)
CR, n/N (%)	7/94 (7.4)	4/84 (4.8)	54/504 (10.7)	31/514 (6.0)	15/220 (6.8)	9/208 (4.3)	46/378 (12.2)	26/390 (6.7)	28/299 (9.4)	15/280 (5.4)	33/299 (11.0)	20/318 (6.3)
PR, n/N (%)	41/94 (43.6)	30/84 (35.7)	247/504 (49.0)	207/514 (40.3)	107/220 (48.6)	87/208 (41.8)	181/378 (47.9)	150/390 (38.5)	145/299 (48.5)	116/280 (41.4)	143/299 (47.8)	121/318 (38.1)
Difference in ORR, %[d] (95% CI)	10.6 (-4.0, 24.5)		13.4 (7.3, 19.4)		9.3 (-0.2, 18.5)		14.9 (7.9, 21.8)		11.1 (2.9, 19.0)		14.5 (6.6, 22.2)	

All Randomized Subjects	CPS < 1		CPS ≥ 1		CPS < 5		CPS ≥ 5		CPS < 10		CPS ≥ 10	
Minimum Follow-up: 19.4 mo.	Nivo+ Chemo N = 140	Chemo N = 123	Nivo+ Chemo N = 641	Chemo N = 656	Nivo+ Chemo N = 308	Chemo N = 297	Nivo+ Chemo N = 473	Chemo N = 482	Nivo+ Chemo N = 406	Chemo N = 386	Nivo+ Chemo N = 375	Chemo N = 393
DoR per BICR in all measurable responders												
Median DoR[b], mo. (95% CI)	6.97 (5.16, 12.12)	6.97 (5.45, 9.49)	8.64 (7.89, 10.94)	6.93 (5.78, 7.56)	7.69 (6.24, 9.92)	6.90 (5.65, 8.05)	9.69 (8.25, 12.22)	6.97 (5.62, 7.85)	7.69 (6.57, 9.69)	6.83 (5.55, 7.10)	9.92 (8.44, 12.71)	7.03 (5.65, 8.44)

[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.
[d] Unweighted difference in objective response rate (Nivo+Chemo - Chemo). Two-sided 95% confidence interval for unweighted difference was calculated using Newcombe method.

Abbreviations: BICR - blinded independent central review, chemo - chemotherapy, CI - confidence interval, CPS - combined positive score, CR - complete response, DoR - duration of response, HR - hazard ratio, nivo - nivolumab, ORR - objective response rate, OS - overall survival, PD-L1 - programmed death-ligand 1, PFS - progression-free survival, PR - partial response

Source: Figure S.9.3.EU.1, Figure S.9.3.EU.2, Table S.9.4.EU.1, Figure 5.12.EU.1 and Figure S.9.5.EU.1 of Appendix 2

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present

application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 268. Summary of Efficacy for trial CA209649 (CheckMate 649)

Title: Study CA209649 Phase 3, randomised, multicenter, open-label study in subjects with previously untreated advanced or metastatic gastric, gastroesophageal junction cancer or oesophageal adenocarcinoma			
Study identifier	Study CA209649 (EUDRACT Number 2016-001018-76)		
Design	Phase 3, randomized, multicenter, open-label study of nivolumab plus ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine		
	Duration of enrolment period:	From 17-Apr-2017 to 27-May-2019 subjects were concurrently randomised to the nivo+chemo and chemo arms	
Hypothesis	Superiority		
Treatments groups	Nivolumab + chemotherapy (XELOX or FOLFOX)		**<u>Nivolumab + XELOX</u>:** Nivolumab 360 mg IV on Day 1, Q3W Oxaliplatin 130 mg/m^2 IV on Day 1, Q3W Capecitabine 1000 mg/m^2 orally BID on Days 1 to 14 of each treatment cycle, Q3W **<u>Nivolumab + FOLFOX</u>**: Nivolumab 240 mg IV on Day 1, Q2W Oxaliplatin 85 mg/m^2 IV on Day 1, Q2W Leucovorin 400 mg/m^2 IV on Day 1, Q2W Fluorouracil 400 mg/m^2 IV on Day 1, Q2W Fluorouracil 1200 mg/ m^2 IV continuous infusion over 24 hours daily on Days 1 and 2, Q2W Treatment was given until disease progression, unacceptable toxicity, maximum 24 months treatment (for nivo) or subject withdrawal of consent. **N=789**
	Chemotherapy (XELOX or FOLFOX)		**<u>XELOX</u>:** Oxaliplatin 130 mg/m^2 IV on Day 1, Q3W Capecitabine 1000 mg/m^2 orally BID on Days 1 to 14 of each treatment cycle, Q3W **<u>FOLFOX</u>**: Oxaliplatin 85 mg/m^2 IV on Day 1, Q2W Leucovorin 400 mg/m^2 IV on Day 1, Q2W Fluorouracil 400 mg/m^2 IV on Day 1, Q2W Fluorouracil 1200 mg/ m^2 IV continuous infusion over 24 hours daily on Days 1 and 2, Q2W Treatment was given until disease progression, unacceptable toxicity or subject withdrawal of consent. **N=792**
Endpoints and definitions	Primary endpoint	Progression free survival (**PFS**) in subjects PD-L1 **CPS≥5**	Time from randomisation to the date of the first progressive disease or death due to anay cause as assessed by BIRC per RECIST 1.1. The primary population was all randomised subjects with PD-L1 CPS≥5
	Primary endpoint	Overall survival (**OS**) in subjects PD-L1 **CPS≥5**	Time from randomisation to the date of death from any cause. The primary population was all randomised subjects with PD-L1 CPS≥5

	Secondary endpoint	**OS** in subjects PD-L1 **CPS≥1**	See definition above
	Secondary endpoint	**OS** in all randomised subjects	See definition above
	Secondary endpoint	**PFS** in all randomised subjects	See definition above
	Secondary endpoint	Objective response rate (**ORR**) in all randomised subjects	Number of randomised subjects with a best overal response of complete response or partial response based on BIRC assessment (using RECIST v1.1 criteria), divided by the number of randomised subjects
Database lock	10-Jul-2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) for OS and PFS The primary population was all randomised subjects with PD-L1 CPS≥5 Clinical cut-off date: 27 May 2020 Minimum follow-up: 12.1 months		
Descriptive statistics and estimate variability	Treatment group	**Nivolumab + chemotherapy**	**Chemotherapy**
	Number of subject	**473**	**482**
	Median **OS** in PD-L1 **CPS≥5** (months)	14.39	11.10
	95% confidence interval (CI)	13.11, 16.23	10.02, 12.09
	Median **PFS** in PD-L1 **CPS≥5** (months)	7.69	6.05
	95% CI	7.03, 9.1	5.55, 6.90
	Number of subject	**789**	**792**
	Median **OS** (months)	13.83	11.56
	95% CI	12.55, 14.55	10.87, 12.48
	Median **PFS** (months)	7.66	6.93
	95% CI	7.10, 8.54	6.60, 7.13
	ORR (%)	59.8	45.3
	95% CI	54.7, 64.8	40.3, 50.4
Effect estimate per comparison	Primary endpoint **OS** in subjects with PD-L1 CPS≥5	Comparison groups	Nivo+chemo vs chemo
		Hazard ratio (HR)	0.71
		98.4% CI	0.59, 0.86
		P-value	<0.0001
	Primary endpoint **PFS** in subjects with PD-L1 CPS≥5	Comparison groups	Nivo+chemo vs chemo
		Hazard ratio (HR)	0.68
		98% CI	0.56, 0.81
		P-value	<0.0001

	Secondary endpoint **OS** in the all-randomised population	Comparison groups	Nivo+chemo vs chemo
		Hazard ratio (HR)	0.80
		99.3% CI	0.68, 0.94
		P-value	0.0002
	Secondary endpoint **PFS** in the all-randomised population	Comparison groups	Nivo+chemo vs chemo
		Hazard ratio (HR)	0.77
		95% CI	0.68, 0.87
		P-value	Not tested
	Secondary endpoint ORR in the all randomised population	Comparison groups	Nivo+chemo vs chemo
		Difference	12.8
		95% CI	7.3, 18.2
		P-value	Not tested
Notes	Enrollment in CA209649 started in Oct-2016 for the nivo+ipi and chemo arms. The nivo+chemo arm was added in Mar-2017 based on Revised Protocol 02 (Amendment 08). Enrollment to the nivo+ipi arm was closed on 05Jun2018. Data from the nivo+ipi arm have not been provided so far.		

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

Not applicable

Clinical studies in special populations

Not applicable

Supportive study(ies)

Not applicable

2.4.3. Discussion on clinical efficacy

Through the current variation application, the MAH is seeking approval for a new indication for OPDIVO, for the first-line treatment of adult patients with advanced or metastatic gastric (GC), gastro oesophageal junction (GEJ) or oesophageal adenocarcinoma (OAC) in combination with fluoropyrimidine and platinum-based combination chemotherapy.

The evidence in support of the claimed indication is based on results from the study CA209649 (CheckMate 649).

Design and conduct of clinical studies

The study CA209649 is a Phase 3, randomised, multicentre, open-label study of nivolumab plus ipilimumab or nivolumab in combination with chemotherapy (oxaliplatin plus fluoropyrimidine) versus chemotherapy (oxaliplatin plus fluoropyrimidine) in subjects with previously untreated advanced or metastatic GC, GEJ cancer or OAC. The nivolumab plus ipilimumab arm was closed to enrolment per DMC recommendation due to an increased early death rate and toxicity, although subjects randomized to this arm continued to receive treatment with study drugs per protocol. Data from the nivolumab+ipilimumab arm have not been provided with the current application.

The study was open-label, but considering one of the primary endpoints was overall survival (OS) and progression free survival (PFS) was assessed by a BIRC, this is considered acceptable.

Patient population

Overall, the inclusion and exclusion criteria for study CA209649 appear acceptable. Patients with advanced or metastatic GC, GEJ or distal oesophageal carcinoma with histologically confirmed predominant adenocarcinoma who were treatment naïve for advanced or metastatic disease, with an ECOG performance status or 0 or 1 were included in the study. Prior adjuvant/neoadjuvant chemotherapy, radiotherapy and/or chemoradiotherapy for GC or GEJ were allowed. This was also the case for OAC patients who were only eligible for enrollment in study CA209649 after the revised Protocol 04 (dated 05-Jan-2018). Patients with known HER2-positive status as well as those with untreated CNS metastases were excluded.

Patients were included in the study regardless 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

Treatment recommendations for advanced or metastatic GC, GEJ and OAC, are almost the same, therefore, the inclusion of these different types of tumours in the study is considered acceptable. Regimens including platinum compounds (oxaliplatin or cisplatin) plus fluoropyrimidine (capecitabine, fluorouracil) are considered the standard of care in the first-line setting in patients HER2-negative (ESMO 2016; NCCN 2020). Moreover, oxaliplatin may be preferred over cisplatin due to lower toxicity (NCCN 2020). Therefore, the comparator (i.e., XELOX or FOLFOX) is considered acceptable.

In study CA209649 patients were randomised in a 1:1:1 ratio to receive nivolumab + ipilimumab for 4 cycles followed by nivolumab monotherapy; nivolumab plus chemotherapy (XELOX or FOLFOX) or chemotherapy (XELOX or FOLXOX). According to the protocol, the investigator can choose either capecitabine or fluorouracil, based on local standards. Nivolumab was administered at a dose of 360 mg Q3W when administered in combination with XELOX (oxaliplatin + capecitabine) and at a dose of 240 mg Q2W when administered in combination with FOLFOX (oxaliplatin + leucovorin + fluorouracil). Treatment with nivolumab was continued until progressive disease, unacceptable toxicity, withdrawal consent or up to a maximum of 24 months.

The randomisation was changed twice during the trial. The trial initially had two arms, i.e. a nivolumab+ipilimumab arm and a chemotherapy arm. Later, on 07 Dec 2016, the nivolumab+chemotherapy arm was added. As outlined above enrolment in the nivolumab+ipilimumab arm was stopped on 5 Jun 2018 following a recommendation from the DMC due to the observed increased early death rate and the increased toxicity rate in that arm.

Stratification factors included the chemotherapy regimen (XELOX vs. FOLFOX), PD-L1 expression (≥1% vs. <1% or indeterminate), region (Asia vs. North America vs. rest of the world) and ECOG (0 vs. 1). Stratification factors are considered acceptable.

Sample size

Sample size was changed during the study several times (e.g., Protocol 02, 05, 08) from originally 1,349 to 2,005 in total based on different choice of primary analysis population (e.g. all comers, TC PD-L1 ≥1%, PD-L1 CPS≥5) and different timing of analysis (event or time driven).

The sample size at the final Protocol 09 was based on simulations assuming a piecewise exponential curve for PFS and OS in CPS≥5 in the chemotherapy arm, accounting for a delay in treatment effect. Assumptions of PFS were: a chemotherapy median of 5.5 months; HR=1 for 3 months (yielding 99% power) or 6 months (yielding 60% power) followed by HR=0.56 afterwards. For OS the power was 85% based on a chemotherapy arm median of 11 months; HR=1 for 6 months followed by HR=0.65.

Efficacy endpoints

The dual primary endpoints of the study were OS and PFS as assessed by BIRC per RECIST 1.1 criteria in patients with PD-L1 CPS≥5. Secondary endpoints included OS in patients with PD-L1 CPS≥1, CPS≥10 and all randomised subjects; PFS as assessed by BIRC in patients with PD-L1 CPS≥1, 10 and all randomised subjects and ORR (by BIRC) in subjects with PD-L1 CPS≥1, 5, 10 and all randomised subjects. Duration of response, time to symptom deterioration (TTSD), PFS and ORR according to investigator assessment and PFS2 were exploratory endpoints in study CA209649.

The choice of the primary and secondary endpoints is considered appropriate. However, several major changes in the endpoints as well as in the primary efficacy population were performed during the study (see protocol amendments below).

Statistical methods

The primary endpoints changed during the trial (see details below). Throughout the protocol changes, the different primary OS and possibly PFS type endpoints were analysed using a two-sided stratified log-rank test and a stratified Cox model with treatment as only covariate. Randomisation stratification factors included region, ECOG and PD-L1 ≥1 in all protocols. Since the addition of the nivolumab + chemotherapy arm (Protocol 02), the chemotherapy chosen before randomization (XELOX or FOLFOX) was added as stratification factor. Concurrent randomized patients were used for nivolumab + chemotherapy arm vs. the chemotherapy arm comparison (i.e. since the start of the 1:1:1 randomisation).

The OS in all comers in the nivolumab + chemotherapy arm vs. the chemotherapy arm (introduced since Protocol 02), was in most protocols not a primary endpoint, but in all protocols its analysis was stratified by region, ECOG, type of chemotherapy and PD-L1 status.

Multiple testing strategy changed during the study (see below) but were variants of the graphical approach (Bonferroni splits, hierarchical testing and alpha allocation). Therefore, each of the various strategies *per se* controlled the type I error.

The primary PFS definition censored for subsequent therapy. A secondary definition of PFS included the first PFS event regardless including when it occurred after start of new therapy from SAP version 2 onwards (Protocol 09).

Time to event endpoints (e.g. OS and PFS) were analysed using Kaplan-Meyer methodology and Cox proportional hazard models. Sensitivity analyses were planned regarding the impact of: non-proportional hazards (a max combo test to account for early or late separation of curves or analysing in two separate periods); disbalance in (possible) prognostic factors (multivariate Cox regression models); imbalance between the CPS strata (multivariate Cox regression); stratification (e.g. unstratified analyses).

Binary endpoints (e.g., ORR): the stratified difference was estimated using DerSimonian-Laird method; the stratified odds ratio using the Mantel-Haenszel method.

Efficacy data and additional analyses

A total of 2,687 patients were enrolled in the study, of whom 1,581 were randomised to receive either nivo+chemo (n=789) or chemo (n =792). According to the MAH, the frequency of subjects enrolled but not randomized, i.e. 1,106 not randomized out of the 2,687 enrolled subjects in the CA209649 Primary CSR (41.2%), is an overestimate that does not reflect the actual screen failure rate as subjects were randomized to 3 treatment arms. The screen failure rate for the entire study was 36.3% (1,155/3,186 enrolled subjects). Among the 1,155 subjects who were not randomized the most frequent reason was "subject no longer meets study criteria." This group consists of 900 subjects and the most common failed study criteria among them were: i) having known human epidermal growth

factor receptor 2 (HER2) positive status [130 (14.4%)], ii) not providing tumour tissue for biomarker analyses [130 (14.4%)] and iii) having (ECOG) Performance Status (PS) score ≥2 [108 (12.0%)]. There were 32 patients who were randomised but not treated, most of them in the control arm (25 [3.2%] vs. 7 [0.9%]) and in most cases due to withdrawal of consent.

At the time of the data cut-off, around 8% of patients remained on treatment (84 [10.7%] in the nivo+chemo arm and 39 [5.1%] in the chemo arm). The main reason for treatment discontinuation was disease progression in both treatment arms (66% nivo+chemo vs. 69% chemo). In the nivo+chemo arm there were 20 (2.6%) patients who discontinued treatment due to completion of the 2-year treatment period.

Conduct of the study

One of the main concerns of the study relates to the multiple and critical amendments of the protocol which call into question the integrity of the trial moreover considering that study CA209649 is open label and therefore more prone to bias. The original protocol was dated 4 May 2016 and thereafter 29 protocol amendments (including 9 global and 20 country specific) have been performed. The main critical changes are described below.

The original study design aimed to compare nivolumab + ipilimumab with chemotherapy, but early in the study (Protocol 02; dated 7 Dec 2016) a new nivolumab-plus-chemotherapy arm was added. This change was performed when only 3 patients had been enrolled. At the same time, the type of chemotherapy (i.e. XELOX vs. FOLFOX) was introduced as stratification factor (determined before patients were randomized). This strengthens the comparison. Before the randomization changed to 1:1:1, a total of 83 patients had already been randomized. However, the nivolumab + chemotherapy vs. chemotherapy comparison is only based on patients that were randomized since the introduction of this arm, which is methodologically sound. The primary endpoint (at that time) was OS in all PD-L1+ subjects.

With Amendment 17 (Protocol 04; dated 5 Jan 2018), the primary efficacy population was changed to all comers and PFS and ORR were added as primary endpoints in the nivo+chemo arm. Moreover, patients with distal oesophageal adenocarcinoma (OAC) were also allowed to enter the study.

As previously mentioned, the sample size has been modified several times.

Further, per Protocol 07 (Amendment 23; dated 14 Sep 2018) the primary population was changed to subjects with PD-L1 CPS≥5 when 1,449 patients had been randomised. CPS was defined as the number of PD-L1 positive cells (tumour cells, lymphocytes and macrophages) divided by the total number of viable tumour cells, multiplied by 100 (i.e. CPS is a composite score that incorporates both tumour and tumour-associated immune cell PD-L1 expression). As scoring could be done retrospectively and blindly, this is considered acceptable.

According to the Applicant, the change in the primary efficacy population was based on external data (i.e. studies KEYNOTE 059, KEYNOTE 061 and CA209032). While the rationale for using PD-L1 CPS instead of TC PD-L1 as a better predictor or response could be understood (Kelly. Am Soc Clin Oncol Educ Book. 2017), further justification was required regarding the chosen cut-off (i.e. CPS≥5). The MAH provided some additional details regarding that their choice, as outlined above, was only based on external data, i.e. results from study CA209032 and other CPS data available at that time from the literature (KEYNOTE-059 and KEYNOTE 061). The selected cut-off CPS≥5 can be considered reasonable even if others, e.g. CPS≥10 could also have been considered. Additional aspects such as expected prevalence could also have played a role in the final decision, favouring a lower cut-off.

The prevalence of subjects with PD-L1 CPS≥5 was initially not accurately known (estimated at 35%) and the possibility that an increase in sample size could be needed was prospectively contemplated. After a blinded review of the first 203 subjects' CPS score, an even lower than expected prevalence was reported (i.e. 27%) that lead to an increase in sample size by addition of 356 subjects (revised Protocol 08). In

March 2019, PD-L1 CPS results from one pathologist at one of the two central laboratories undergoing the scoring were identified by the MAH as having a lower proportion of CPS positive cases at the ≥1 threshold compared with other pathologists. The pathologist incorrectly interpreted/implemented one of the steps within the predefined CPS scoring algorithm/methodology and as a result, 914 of the 1,399 accessions were disqualified and re-scored. During the rescoring the pathologists were blinded to the previous CPS score and treatment information and no issues have been identified that can be considered to have an impact on the integrity/reliability of the (submitted) revised data.

Following resolution of the scoring issue of the samples detailed above the prevalence was reported as of 60%, almost double of the initially expected value. To justify that this discrepancy did not impact the reported results the MAH provided the results of pre-planned sensitivity analyses of OS and PFS for subjects with CPS ≥ 5 conducted to reflect the design per Revised Protocol 07 (based on sample size and events per the assumed 35% prevalence). The results were consistent to those of the primary analyses of both OS and PFS.

Indeed, the primary endpoints and/or sample size and/or the multiple testing strategy were changed multiple times. In all protocols OS in all comers was part of the multiple testing strategy. However, this strategy was changed between each of the following protocols: 02, 03, 04, 05, 07, 08 (SAP v1), and 09 (final protocol, SAP v2 and v3). Changes entailed: timing of analysis (event or time driven), order of testing of the endpoints before OS in all comers would be tested, statistical significance levels, presence of interim analyses and sample size (number of events/total number of patients). In this context a detailed justification/explanation of all the amendments performed in the protocol to further justify whether these changes were driven by external or internal data was submitted even if no new information was provided. A description of how access to data was controlled during the study was also provided and no major issues were identified that would have had an impact on the results and B/R assessment for the applied indication.

The original definition of PFS censored for subsequent therapy, thus aimed at estimating the effect as if no subsequent therapy would have been used (hypothetical strategy). However, censoring may be informative and thus the estimate could be biased. In the last protocol, a secondary definition of PFS included the first PFS event regardless including when it occurred after start of new therapy (treatment policy strategy). This is the analysis recommended in appendix 1 of the EMA anticancer guideline (CHMP/27994/2008 Rev. 1). BICR assessments were requested if investigator PD was determined and in case subsequent or local palliative therapy was started, if was requested to continue BIRC scans if clinically feasible. This limits informative censoring in the BICR assessment.

In addition to the above, previous EMA inspections revealed that BioClinica procedures allowed investigator sites to send and store images without proper de-identification. The process of transfer and storage of images used in study CA209649 has the potential to comply with the General Data Protection Regulation (GDPR) and ICH-GCP Guideline (E6(R2) and there are no indications that the privacy of trial participants in study CA209649 was violated. The fact that BioClinica allows submitting images with personal identifiers and investigators does not represent a robust process that ensures rights of the trial participants and this is still considered a weakness in the overall process and has the potential to violate the privacy of trial participants. The issue will not be further pursued within this type II variation, as it does not have a negative impact on the B/R. However, it remains the responsibility of the MAH that CROs involved in the clinical trials running within the EU will adhere to the GDPRand ICH-GCP Guideline.

With regards to protocol deviations, relevant protocol deviations were reported in 21 (1.3%) patients and it was comparable between treatment arms. In the nivo+chemo arm, use of prohibited anti-cancer therapy was the main reason (8 [1.0%] nivo+chemo vs. 4 [0.5%] chemo). Overall, no concern is raised over possible impact of protocol deviations on efficacy results.

Baseline data

Overall, baseline characteristics of patients included in the study were balanced between treatment arms and the patient population appears representative of the intended target population. Patients included in the study had a median age of 61 years (range: 18, 90), with 9.7% being 75 years or older. The majority of patients were male (70%), White (69%) and had an ECOG performance status of 0 (44%) or 1 (56%). Patients with ECOG ≥2 were not allowed to enter the study. Nearly half of patients (48%) were current/former smokers. In the majority of patients, the initial diagnosis was gastric cancer (70.2%), followed by GEJ cancer (16.4%) and EA (13.3%). The vast majority of patients had a metastatic disease. Liver and peritoneal metastases were present in 39% and 24%, respectively. It is important to note that per inclusion/exclusion criteria, patients with known HER2 positive status were not allowed to enter the study. However, there were 7 (0.4%) patients whose tumour was HER2 positive and in addition there were 643 (40.7 %) patients for whom HER2 status was undetermined, i.e. not reported (test was not performed; 634 patients) or unknown (test was performed but the result was unavailable; 9 patients). With regards to prior treatment, 13.7% of patients had received prior adjuvant (7.5%) or neo-adjuvant (6.9%) treatment. There was one patient in the nivo+chemo arm who received prior treatment in the metastatic setting, however this issue is not considered of clinical relevance.

Efficacy outcomes

All analyses were on patients concurrently randomized to the nivo+chemo or chemo arm (i.e. since start of 1:1:1 randomisation to nivo+ipi, nivo+chemo, chemo arms). Since Protocol 02, the OS analysis in all comers was stratified according to region, ECOG, type of chemotherapy and PD-L1 status.

The study met its primary endpoints. Nivo+chemo demonstrated a statistically significant and clinically meaningful improvement in OS (HR 0.71; 98.4% CI: 0.59, 0.86) and PFS (HR 0.68; 98% CI: 0.56, 0.81) over chemotherapy alone in patients with CPS≥5. Median OS was of 14.39 (95% CI: 13.11, 16.23) months in the nivo+chemo group and 11.10 (95% CI: 10.02, 12.09) months in the chemo group. Median PFS was of 7.69 (95% CI: 7.03, 9.17) and 6.05 (95% CI: 5.55, 6.90) months, in the nivo+chemo and chemo groups, respectively. At the time of the data cut-off the median follow-up in patients with PD-L1 CPS≥5 was 13.57 months in the nivo+chemo arm and 10.66 months in the chemo arm.

While patients with PD-L1 CPS≥5 represent the primary efficacy population, a broad indication was initially requested for nivo+chemo (i.e. regardless of PD-L1 CPS expression). OS in the all randomised patients (n=1581) was assessed as a secondary endpoint. However, since a hierarchical testing strategy was used, type I error control is warranted and therefore these results can be considered interpretable. OS in the overall population, with an event rate of 65% in the nivo+chemo arm and 75% in the chemo arm, showed a statistically significant benefit of nivo+chemo over chemo (HR 0.80; 99.3% CI: 0.68, 0.94). Median OS was of 13.83 (95% CI: 12.55, 14.55) months and 11.56 (95% CI: 10.87, 12.48) months in the experimental and control arm, respectively.

Results in terms of PFS in the overall population were consistent with the OS analysis and favoured also the nivo+chemo arm, although the benefit appears lower than in the PD-L1 CPS≥5 population (HR 0.77; 95% CI: 0.68, 0.87). Median PFS was 7.66 (95%CI: 7.10, 8.54) months in the nivo+chemo arm versus 6.93 (95% CI: 6.60, 7.13) months in the chemo arm. The ORR was higher in the nivo+chemo arm compared with the chemo arm (58% vs. 46.1%, respectively), in patients with measurable disease at baseline. Median duration of response was also higher in the nivo+chemo arm (8.51 months vs. 6.93 months). The median follow-up in the all-randomised patients was 13.1 months in the nivo+chemo arm and 11.1 months in the chemo arm.

Even though statistical significance was reached with nivo+chemo over chemo in terms of OS (and also PFS) in the all-randomised patient population, the effect appears to be driven by patients with PD-L1 CPS≥5. In patients with PD-L1 CPS <5 no clear benefit was observed with nivo+chemo over chemo (HR 0.94; 95% CI: 0.78, 1.13), with a median OS of 12.42 and 12.25 in the nivo+chemo and control arm, respectively. Although K-M curves tended to separate after 12 months, interpretation of the curve at

that timepoint was difficult due to high numbers of censoring. Also, a similar pattern was observed in patients with PD-L1 CPS <10 (HR 0.94; 95% CI: 0.80, 1.10]) and in subjects with PD-L1 CPS ≥5 and <10 (HR 0.92; 95% CI: 0.66, 1.28). Of note, PFS results were consistent with OS data in these subgroups of patients. While it was acknowledged that these results come from an exploratory analysis, considering that a broad indication was applied (i.e. regardless of PD-L1 CPS status), the MAH was requested to further justify the benefit of nivo+chemo in the intended target population. Updated efficacy data with a DBL of 16 Feb 2021, providing 7.3 months of additional follow-up (minimum follow-up 19.4 months) were submitted including updated efficacy data by PD-L1 CPS status using different cut-offs (i.e. 1, 5 and 10). Taking into account the new submitted data still no apparent benefit is observed in patients with PD-L1 CPS<5 in terms of OS (HR 0.94; 95% CI: 0.79, 1.13), with a median of 12.42 and 12.09 months, respectively, the same percentage of OS events, and KM curves overlapping. Bearing in mind the increased toxicity of the combination compared with chemo alone, a positive benefit-risk balance cannot be concluded for patients with PD-L1 CPS<5. Therefore, the indication was restricted to patients with PD-L1 CPS≥5, which in fact was the primary efficacy population in the study.

The results observed for OS in the all-randomised patient population were consistent for most of the subgroups analysed. However, the benefit of nivo+chemo over chemo appears less clear in patients with GEJ cancer (HR 0.9; 95% CI: 0.67, 1.21), OAC (HR 0.82; 95% CI: 0.60, 1.13), patients who had received prior radiotherapy (HR 0.92; 95% CI: 0.64, 1.33), patients with a diffuse type (HR 0.91; 95% CI: 0.74, 1.10), presence of Signet Ring Cell (HR 0.96; 95% CI: 0.73, 1.25) and in patients with peritoneal metastases (HR 1.03; 95% CI: 0.82, 1.29). GC/GEJC/OAC is known to be a heterogeneous disease and the details and discussion provided by the MAH allow to conclude that there is no well-established biological rationale / reason why the results in any of the above subgroups should be challenged, also considering that the trial was not powered to determine the effect in those subgroups. As discussed by the MAH the small(er) sample sizes and imbalances in various baseline disease characteristics and other factors, not a single one, are likely to have contributed to the lower treatment effect observed in those particular subgroups.

In contrast, the benefit of nivo+chemo seems higher in patients with microsatellite instability (MSI) high (HR 0.37; 95% CI: 0.16, 0.87) although data are limited due to the small number of patients (n=44). Determination of MSI status was performed retrospectively by central laboratories. Of the 1581 patients randomised, 44 (2.8%) were MSI-H while 1377 (87.1%) were microsatellite stable (MSS).

Finally, the MAH was requested to restrict the indication to HER2-negative patients given the inclusion/exclusion criteria and differences in prognosis and treatment of this patient population, unless a broad indication (i.e. HER2 agnostic) could be sufficiently justified. In this context the Applicant provided a discussion of the results from the subgroup analysis in patients with negative vs. undetermined HER2 status, with an observed HR for OS of 0.85 (95% CI: 0.73, 0.99) and 0.71 (95% CI: 0.59, 0.85), respectively. Since the actual rate of HER2 negative subjects among the HER2 not reported/unknown subjects in the study is not known, the MAH conducted some simulations aimed at demonstrating that the reported treatment benefit with nivo+chemo vs. chemo alone in the HER2 negative subgroup could in fact be an underestimation. Results from that analysis appear to support that as an increasing proportion of subjects who are not reported/unknown are included as HER2-negative, the HR decreases, indicating greater treatment effect from nivo+chemo vs. chemo, but caution is needed when interpreting these data. Further, the MAH discussed other factors that may have played a role in the reported efficacy differences between the two subgroups i.e. regional differences, status of the disease at baseline and subsequent therapy received. Based on those results/discussion the MAH proposed to revise the indication as follows (revisions underlined):
"*OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2 negative (or undetermined) advanced or metastatic gastric, gastro oesophageal junction or oesophageal adenocarcinoma (see sections 4.4*

and 5.1).". The revised proposal was not considered acceptable. The MAH argues that (descriptive) data showed clinical benefit in nivo+chemo over chemo in HER2 undetermined patients (40.3% of the study population), and that the safety profile was manageable and acceptable in these patients. While it can be acknowledged that patients with undetermined status appear to benefit from treatment (see above), the need to specify them in the indication is not considered appropriate. 'Undetermined' HER2 status does not constitute a recognized subgroup of patients within the target population and therefore the indication was amended to include treatment of HER2-negative patients only.

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical efficacy

Not applicable

2.4.1. Conclusions on the clinical efficacy

In study CA209649 treatment with nivolumab in combination with chemotherapy (XELOX or FOLFOX) showed a statistically significant OS and PFS benefit compared with chemotherapy (XELOX or FOLFOX) alone in patients with HER2-negative advanced or metastatic GC, GEJ or OAC whose tumours express PD-L1 with a CPS≥5.

2.5. Clinical safety

Introduction

Safety data from 782 subjects treated with first-line nivo+chemo (nivolumab 240 mg + FOLFOX Q2W or nivolumab 360 mg + XELOX Q3W) and from 767 control subjects (treated with FOLFOX or XELOX) from study CA209649 were used to characterize the safety profile of this combination regimen in subjects with advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

Patient exposure

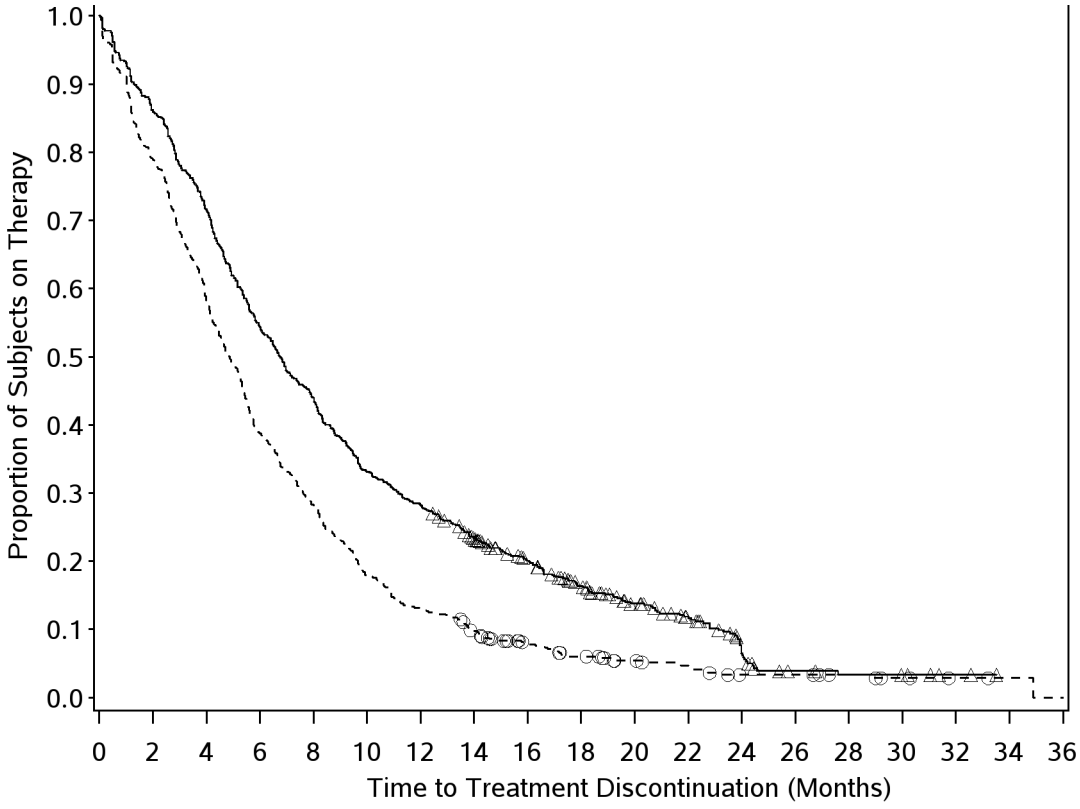
The last subject randomization occurred on 27-May-2019 and the clinical cutoff occurred on 27-May-2020. The DBL occurred on 10-Jul-2020. Minimum follow-up (date of the last subject randomized to LPLV) was 12.1 months. A total of 1581 subjects were concurrently randomized in the nivo+chemo and chemo arms: 789 to the nivo+chemo arm and 792 to the chemo arm. 1549 subjects were treated: 782 with nivo+chemo and 767 with chemo. Of the 1549 treated subjects, 123 (7.9%) subjects were continuing in the treatment at the time of database lock: 84 (10.7%) nivo+chemo-treated subjects and 39 (5.1%) chemo-treated subjects. The overall rates of discontinuation were 89.3% and 94.9% in the nivo+chemo and chemo arms, respectively. The primary reason for not continuing in the treatment period was disease progression in both treatment arms (1043 subjects, 67.3%): 515 (65.9%) nivo+chemo-treated subjects and 528 (68.8%) chemo-treated subjects. Overall, 61 (3.9%) subjects withdrew consent and did not complete the treatment period: 20 (2.6%) in the nivo+chemo arm and 41 (5.3%) in the chemo.

Overall, the median (min - max) duration of therapy was 6.75 (0.0 - 33.5) months in the nivo+chemo arm and 4.86 (0.0 - 34.9) months in the chemo arm (Figure 20). Among all treated subjects, 54.3% and 38.7% had a duration of therapy > 6 months in the nivo+chemo and chemo arms, respectively.

In the nivo+chemo arm, the median (min - max) duration of therapy was 6.49 (0.1 - 33.5) months with nivo+XELOX and 7.01 (0.0 - 30.0) months with nivo+FOLFOX.

In the chemo arm, the median (min - max) number of doses received by all treated subjects and the proportion of subjects who received ≥ 90% of the planned dose intensity are shown in Table 29. Of note, prior to revised Protocol 07 (Amendment 23), all components were delayed together if a dose delay was required.

Figure 20. Kaplan-Meier Plot of Time to Treatment Discontinuation - All Treated Subjects



Number of Subjects at Risk

Nivo + Chemo	782	674	560	425	344	259	221	175	134	99	69	51	22	8	6	5	2	0	0
Chemo	767	606	447	297	217	137	99	70	45	33	23	18	10	10	7	4	2	1	0

Nivo + Chemo (events : 698/782), median and 95% CI : 6.75 (6.11, 7.36)

Chemo (events : 728/767), median and 95% CI : 4.86 (4.47, 5.29)

Symbols represent censored observations

Source: Figure S.4.1.3

Table 29. Cumulative Dose and Relative Dose Intensity Summary - All Treated Subjects

	Nivo + Chemo N = 782			Chemo N = 767	
	Nivolumab+XELOX N1 = 360			XELOX N1 = 361	
	Nivolumab (mg) N = 360	Oxaliplatin (mg/m^2) N = 360	Capecitabine (mg/m^2) N = 360	Oxaliplatin (mg/m^2) N = 361	Capecitabine (mg/m^2) N = 361
NUMBER OF DOSES RECEIVED					
MEAN (SD)	11.36 (9.23)	6.48 (4.13)	10.88 (9.38)	6.70 (5.27)	9.27 (8.20)
MEDIAN	8.00	6.00	7.00	6.00	7.00
MIN - MAX	1.0 - 35.0	1.0 - 34.0	1.0 - 47.0	1.0 - 47.0	1.0 - 48.0
DURATION OF THERAPY (MONTHS)					
MEAN (SD)	7.90 (6.78)	4.32 (3.15)	8.01 (6.94)	4.39 (4.08)	6.64 (6.06)
MEDIAN	5.45	3.99	5.63	3.68	4.70
MIN - MAX	0.0 - 24.0	0.0 - 23.2	0.1 - 33.5	0.0 - 34.4	0.0 - 34.9
CUMULATIVE DOSE					
MEAN (SD)	4090.71 (3324.92)	759.27 (447.29)	252602.25 (211230.13)	787.22 (574.16)	241991.61 (378778.66)
MEDIAN	2880.00	726.60	176388.81	689.73	166729.48
MIN - MAX	240.0 - 12600.0	78.1 - 3676.0	1822.9 - 1059942.2	111.8 - 4356.6	961.5 - 5060929.3
RELATIVE DOSE INTENSITY					
>= 110%	0	2 (0.6)	13 (3.6)	3 (0.8)	11 (3.0)
90% TO < 110%	252 (70.0)	157 (43.6)	109 (30.3)	174 (48.2)	121 (33.5)
70% TO < 90%	102 (28.3)	132 (36.7)	109 (30.3)	137 (38.0)	118 (32.7)
50% TO < 70%	6 (1.7)	64 (17.8)	88 (24.4)	43 (11.9)	77 (21.3)
< 50%	0	5 (1.4)	41 (11.4)	4 (1.1)	34 (9.4)

	Nivo + Chemo N = 782				
	Nivolumab+FOLFOX N1 = 422				
	Nivolumab (mg) N = 422	Oxaliplatin (mg/m^2) N = 422	Leucovorin (mg/m^2) N = 422	5-Fluorouracil (mg/m^2) N = 420	5-Fluorouracil Continuous (mg/m^2) N = 422
NUMBER OF DOSES RECEIVED					
MEAN (SD)	17.17 (12.73)	9.37 (4.81)	14.67 (11.41)	13.92 (11.06)	15.25 (11.36)
MEDIAN	13.50	10.00	12.00	11.00	12.00
MIN - MAX	1.0 - 53.0	1.0 - 36.0	1.0 - 59.0	1.0 - 59.0	1.0 - 59.0
DURATION OF THERAPY (MONTHS)					
MEAN (SD)	8.47 (6.50)	4.58 (2.84)	7.16 (5.74)	6.84 (5.64)	7.56 (5.76)
MEDIAN	6.74	4.60	5.52	5.29	5.85
MIN - MAX	0.0 - 24.0	0.0 - 20.7	0.0 - 29.9	0.0 - 29.9	0.0 - 30.0
CUMULATIVE DOSE					
MEAN (SD)	4152.01 (3104.86)	764.90 (509.50)	5041.41 (4101.22)	5395.60 (4758.13)	36021.25 (28989.81)
MEDIAN	3240.00	749.20	3992.99	4004.53	27615.35
MIN - MAX	240.0 - 12720.0	83.2 - 6841.7	117.6 - 22096.0	393.4 - 44880.8	1195.9 - 233700.9
RELATIVE DOSE INTENSITY					
>= 110%	0	15 (3.6)	0	27 (6.4)	45 (10.7)
90% TO < 110%	238 (56.4)	145 (34.4)	155 (36.7)	155 (36.9)	136 (32.2)
70% TO < 90%	168 (39.8)	171 (40.5)	155 (36.7)	138 (32.9)	167 (39.6)
50% TO < 70%	12 (2.8)	78 (18.5)	81 (19.2)	81 (19.3)	60 (14.2)
< 50%	4 (0.9)	13 (3.1)	31 (7.3)	19 (4.5)	14 (3.3)
NOT REPORTED	0	0	0	0	0

	Chemo N = 767			
	FOLFOX N1 = 406			
	Oxaliplatin (mg/m^2) N = 406	Leucovorin (mg/m^2) N = 406	5-Fluorouracil (mg/m^2) N = 402	5-Fluorouracil Continuous (mg/m^2) N = 406
NUMBER OF DOSES RECEIVED				
MEAN (SD)	9.37 (6.14)	12.15 (9.73)	11.67 (9.34)	12.32 (9.73)
MEDIAN	9.00	10.00	9.00	10.00
MIN - MAX	1.0 - 51.0	1.0 - 64.0	1.0 - 64.0	1.0 - 64.0
DURATION OF THERAPY (MONTHS)				
MEAN (SD)	4.34 (3.14)	5.76 (4.97)	5.55 (4.74)	5.91 (4.96)
MEDIAN	4.24	4.63	4.40	4.80
MIN - MAX	0.0 - 26.6	0.0 - 33.1	0.0 - 33.1	0.1 - 33.2
CUMULATIVE DOSE				
MEAN (SD)	734.42 (454.68)	4228.36 (3270.75)	4409.69 (3365.00)	29032.41 (22852.52)
MEDIAN	697.07	3521.16	3577.95	22894.48
MIN - MAX	81.5 - 3094.7	39.6 - 24815.6	238.3 - 20412.0	568.3 - 152117.9
RELATIVE DOSE INTENSITY				
>= 110%	7 (1.7)	0	24 (6.0)	39 (9.6)
90% TO < 110%	176 (43.3)	182 (44.8)	174 (43.3)	168 (41.4)
70% TO < 90%	157 (38.7)	136 (33.5)	130 (32.3)	143 (35.2)
50% TO < 70%	62 (15.3)	70 (17.2)	65 (16.2)	48 (11.8)
< 50%	1 (0.2)	15 (3.7)	6 (1.5)	5 (1.2)
NOT REPORTED	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)

The Number of doses of Capecitabine is the number of cycles where at least one dose of Capecitabine was administered.
Source: Table S.4.2.3

Chemotherapy dose modifications were permitted per local standard starting with cycle 2. Dose reduction was not allowed for nivolumab. In all treated subjects, dose delays were the most common dose modification in both the nivo+chemo and chemo arms, while dose interruption and dose reductions were less common.

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

- Nivo+chemo arm:
  - Nivo+XELOX: 66.7% for nivolumab, 59.4% for oxaliplatin, and 66.4% for capecitabine.
  - Nivo+FOLFOX: 78.2% for nivolumab, 74.6% for oxaliplatin, 77.0% for leucovorin, 75.8% for 5-FU bolus, and 78.9% for 5-FU continuous.
- Chemo arm:
  - XELOX: 48.2% for oxaliplatin and 54.8% for capecitabine.
  - FOLFOX: 70.2% for oxaliplatin, 71.4% for leucovorin, 70.6% for 5-FU bolus, and 73.4% for 5-FU continuous.

Dose reductions of chemotherapy (proportion of subjects with at least 1 dose reduction) were reported as follows:

- Nivo+chemo arm:
  - Nivo+XELOX: 46.4% for oxaliplatin
  - Nivo+FOLFOX: 41.0% for oxaliplatin, 26.8% for leucovorin, 30.9% for 5-FU bolus, and 42.9% for 5-FU continuous.
- Chemo arm:
  - XELOX: 40.2% for oxaliplatin
  - FOLFOX: 44.6% for oxaliplatin, 34.5% for leucovorin, 36.3% for 5-FU bolus, and 37.2% for 5-FU continuous.

Infusion interruptions in all treated subjects occurred most frequently during oxaliplatin administration in both the nivo+chemo and chemo arms. The proportion of subjects with at least 1 infusion interrupted were reported as follows in all treated subjects:

- Nivo+chemo arm:
  - Nivo+XELOX: 3.1% for nivolumab, 6.7% for oxaliplatin
  - Nivo+FOLFOX: 4.0% for nivolumab, 15.6% for oxaliplatin, 8.8% for leucovorin, 1.0% for 5-FU, and 9.5% for 5-FU continuous.
- Chemo arm:
  - XELOX: 5.8% for oxaliplatin
  - FOLFOX: 7.6% for oxaliplatin, 4.2% for leucovorin, 2.0% for 5-FU bolus, and 5.9% for 5-FU continuous.

Infusion rate reductions in all treated subjects occurred most frequently during oxaliplatin administration in both the nivo+chemo and chemo arms. The proportion of subjects with at least 1 infusion rate reduction were reported as follows in all treated subjects:

- Nivo+chemo arm:

- Nivo+XELOX: 2.2% for nivolumab, 6.9% for oxaliplatin
- Nivo+FOLFOX: 3.6% for nivolumab, 16.6% for oxaliplatin, 10.0% for leucovorin, 10.9% for 5-FU bolus, and 10.2% for 5-FU continuous.

- Chemo arm:
  - XELOX: 5.3% for oxaliplatin
  - FOLFOX: 7.6% for oxaliplatin, 4.9% for leucovorin, 3.7% for 5-FU bolus, and 4.7% for 5-FU continuous.

The most commonly reported cause of dose delay for nivolumab and chemotherapy was AE. Please refer to the section discontinuations for a more detailed discussion of AEs leading to discontinuation, dose reductions, and dose delays.

Adverse events

Safety results are provided for all patients that were randomised and treated in the nivo+chemo and chemo arms in study CA209649 (N=1549). A summary of the safety profile is shown in the table below.

Table 30. Summary of Safety - All Treated Subjects

	No. of Subjects (%)			
Safety Parameters	**Nivo + Chemo (N = 782)**		**Chemo (N = 767)**	
Deaths	538 (68.8)		572 (74.6)	
Primary Reason for Death				
Disease	465 (59.5)		506 (66.0)	
Study Drug Toxicity	12 (1.5)		4 (0.5)	
Unknown	12 (1.5)		18 (2.3)	
Other	49 (6.3)		44 (5.7)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	423 (54.1)	281 (35.9)	335 (43.7)	229 (29.9)
Drug-related SAEs	172 (22.0)	131 (16.8)	93 (12.1)	77 (10.0)
All-causality AEs leading to DC	371 (47.4)	194 (24.8)	251 (32.7)	113 (14.7)
Drug-Related AEs leading to DC	284 (36.3)	132 (16.9)	181 (23.6)	67 (8.7)
All-causality AEs	776 (99.2)	540 (69.1)	752 (98.0)	456 (59.5)
Drug-related AEs	738 (94.4)	462 (59.1)	679 (88.5)	341 (44.5)
≥ 15% of Subjects in Any Treatment Group				
Nausea	323 (41.3)	20 (2.6)	292 (38.1)	19 (2.5)
Diarrhea	253 (32.4)	35 (4.5)	206 (26.9)	24 (3.1)
Neuropathy Peripheral	221 (28.3)	31 (4.0)	190 (24.8)	22 (2.9)
Anaemia	203 (26.0)	47 (6.0)	171 (22.3)	21 (2.7)
Fatigue	202 (25.8)	30 (3.8)	173 (22.6)	17 (2.2)
Vomiting	195 (24.9)	17 (2.2)	166 (21.6)	24 (3.1)
Neutropenia	191 (24.4)	118 (15.1)	181 (23.6)	93 (12.1)
Neutrophil Count Decreased	158 (20.2)	83 (10.6)	118 (15.4)	67 (8.7)
Thrombocytopenia	157 (20.1)	19 (2.4)	145 (18.9)	13 (1.7)
Decreased Appetite	157 (20.1)	14 (1.8)	139 (18.1)	13 (1.7)
Platelet Count Decreased	156 (19.9)	20 (2.6)	115 (15.0)	19 (2.5)
Peripheral Sensory Neuropathy	137 (17.5)	16 (2.0)	119 (15.5)	14 (1.8)

	No. of Subjects (%)			
Safety Parameters	**Nivo + Chemo (N = 782)**		**Chemo (N = 767)**	
Aspartate Aminotransferase Increased	122 (15.6)	12 (1.5)	69 (9.0)	5 (0.7)
All-causality Select AEs				
Endocrine	117 (15.0)	7 (0.9)	14 (1.8)	1 (0.1)
Gastrointestinal	315 (40.3)	48 (6.1)	260 (33.9)	29 (3.8)
Hepatic	267 (34.1)	45 (5.8)	186 (24.3)	29 (3.8)
Pulmonary	41 (5.2)	14 (1.8)	6 (0.8)	1 (0.1)
Renal	58 (7.4)	11 (1.4)	24 (3.1)	7 (0.9)
Skin	262 (33.5)	27 (3.5)	137 (17.9)	7 (0.9)
Hypersensitivity/Infusion Reactions	118 (15.1)	19 (2.4)	45 (5.9)	11 (1.4)
Drug-Related Select AEs				
Endocrine	107 (13.7)	5 (0.6)	3 (0.4)	0
Gastrointestinal	262 (33.5)	43 (5.5)	207 (27.0)	25 (3.3)
Hepatic	203 (26.0)	29 (3.7)	134 (17.5)	16 (2.1)
Pulmonary	40 (5.1)	14 (1.8)	4 (0.5)	1 (0.1)
Renal	26 (3.3)	6 (0.8)	8 (1.0)	1 (0.1)
Skin	214 (27.4)	26 (3.3)	105 (13.7)	6 (0.8)

Safety Parameters	No. of Subjects (%)			
	Nivo + Chemo (N = 782)		Chemo (N = 767)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypersensitivity/Infusion Reactions	111 (14.2)	17 (2.2)	42 (5.5)	11 (1.4)
All-causality IMAEs within 100 days of last dose				
Treated with Immune Modulating Medication				
Diarrhea/Colitis	26 (3.3)	17 (2.2)	0	0
Hepatitis	19 (2.4)	13 (1.7)	0	0
Pneumonitis	33 (4.2)	15 (1.9)	0	0
Nephritis/Renal Dysfunction	4 (0.5)	2 (0.3)	0	0
Rash	51 (6.5)	11 (1.4)	4 (0.5)	0
Hypersensitivity/Infusion Reactions	6 (0.8)	1 (0.1)	0	0
All-causality Endocrine IMAEs within 100 days of last dose				
With or Without Immune Modulating Medication				
Adrenal Insufficiency	5 (0.6)	1 (0.1)	2 (0.3)	2 (0.3)
Hypophysitis	6 (0.8)	3 (0.4)	0	0
Hypothyroidism/Thyroiditis	74 (9.5)	0	6 (0.8)	0
Diabetes Mellitus	2 (0.3)	1 (0.1)	0	0
Hyperthyroidism	23 (2.9)	0	2 (0.3)	0
All-causality OESIs within 100 days of last dose				
With or Without Immune Modulating Medication				
Pancreatitis	3 (0.4)	2 (0.3)	2 (0.3)	1 (0.1)
Encephalitis	1 (0.1)	1 (0.1)	0	0
Myositis/Rhabdomyolysis	0	0	2 (0.3)	2 (0.3)
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	1 (0.1)	1 (0.1)	0	0
Uveitis	1 (0.1)	1 (0.1)	0	0
Myocarditis	2 (0.3)	1 (0.1)	0	0
Graft Versus Host Disease	0	0	0	0

MedDRA version 23.0 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated (e.g. any time for deaths, 100 days for IMAEs and OESIs).
Abbreviations: AEs - adverse events, CTC - Common Toxicity Criteria, DC - discontinuation, IMAEs - immune-mediated adverse events, IMM - immune modulating medication, MedDRA - Medical Dictionary for Regulatory Activities, OESI - other events of special interest, SAEs - serious adverse events

Source: Table S.6.15.3 (deaths), Table S.6.3.1.2.5 (all-causality SAEs), Table S.6.3.1.2.6 (drug-related SAEs), Table S.6.4.2.5 (all-causality AEs leading to DC), Table S.6.4.2.6 (drug-related AEs leading to DC), Table S.6.1.31.3 (all-causality AEs); Table S.6.1.32.3 (drug-related AEs); Table S.6.5.2.9 (all-causality select AEs), Table S.6.5.2.11 (all-causality endocrine select AEs), Table S.6.5.2.10 (drug-related select AEs), Table S.6.5.2.12 (drug-related endocrine select AEs), Table S.6.202.16 (non-endocrine IMAEs), Table S.6.202.13 (endocrine IMAEs), Table S.6.5.3.3.5 (OESIs).

Adverse events (regardless of causality)

Any-grade AEs (regardless of causality) were reported in 776 (99.2%) subjects in the nivo+chemo arm, and 752 (98.0%) subjects in the chemo arm (Table 30 and Table 31).

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

- Nivo+chemo: nausea (47.6%), diarrhoea (39.4%), and anaemia (38.2%).

- Chemo: nausea (43.5%), diarrhoea (33.6%), and anaemia (33.1%).

Grade 3-4 AEs (regardless of causality) were reported in 540 (69.1%) subjects in the nivo+chemo arm, and 456 (59.5%) subjects in the chemo arm.

The most frequently reported Grade 3-4 AEs (regardless of causality) were:

- Nivo+chemo: neutropaenia (16.9%), decreased neutrophil count (11.5%), and anaemia (11.0%).
- Chemo: neutropaenia (13.0%), decreased neutrophil count (9.1%), and anaemia (7.3%).

Drug-related adverse events

Any grade drug-related AEs were reported in 738 (94.4%) subjects in the nivo+chemo arm, and 679 (88.5%) subjects in the chemo arms (Table 30 and Table 32).

The most frequently reported drug-related AEs were:

- Nivo+chemo: nausea (41.3%), diarrhoea (32.4%), and neuropathy peripheral (28.3%).
- Chemo: nausea (38.1%), diarrhoea (26.9%), and neuropathy peripheral (24.8%).

Grade 3-4 drug-related AEs were reported in 462 (59.1%) subjects in the nivo+chemo arm, and 341 (44.5%) subjects in the chemo arm.

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

- Nivo+chemo: neutropaenia (15.1%), decreased neutrophil count (10.6%), and anaemia (6.0%).
- Chemo: neutropaenia (12.1%), decreased neutrophil count (8.7%), and diarrhoea and vomiting (each 3.1%).

Table 81. Adverse Events by Worst CTC Grade in ≥ 5% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo+Chemo N = 782			Chemo N = 767		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	776 (99.2)	540 (69.1)	81 (10.4)	752 (98.0)	456 (59.5)	63 (8.2)
Gastrointestinal disorders	639 (81.7)	179 (22.9)	3 (0.4)	564 (73.5)	155 (20.2)	0
Nausea	372 (47.6)	25 (3.2)	0	334 (43.5)	28 (3.7)	0
Diarrhoea	308 (39.4)	40 (5.1)	0	258 (33.6)	28 (3.7)	0
Vomiting	245 (31.3)	33 (4.2)	0	221 (28.8)	32 (4.2)	0
Constipation	193 (24.7)	5 (0.6)	0	160 (20.9)	3 (0.4)	0
Abdominal pain	151 (19.3)	17 (2.2)	0	120 (15.6)	16 (2.1)	0
Abdominal pain upper	72 (9.2)	5 (0.6)	0	69 (9.0)	4 (0.5)	0
Dysphagia	66 (8.4)	15 (1.9)	0	57 (7.4)	18 (2.3)	0
Stomatitis	64 (8.2)	7 (0.9)	0	51 (6.6)	1 (0.1)	0
Abdominal distension	50 (6.4)	1 (0.1)	0	34 (4.4)	1 (0.1)	0
Nervous system disorders	517 (66.1)	94 (12.0)	1 (0.1)	472 (61.5)	65 (8.5)	0
Neuropathy peripheral	232 (29.7)	34 (4.3)	0	201 (26.2)	23 (3.0)	0
Peripheral sensory neuropathy	143 (18.3)	16 (2.0)	0	121 (15.8)	14 (1.8)	0
Headache	86 (11.0)	6 (0.8)	0	47 (6.1)	2 (0.3)	0
Paraesthesia	70 (9.0)	2 (0.3)	0	68 (8.9)	2 (0.3)	0
Dizziness	52 (6.6)	1 (0.1)	0	54 (7.0)	2 (0.3)	0
Dysgeusia	46 (5.9)	0	0	41 (5.3)	0	0
Hypoaesthesia	44 (5.6)	2 (0.3)	0	33 (4.3)	0	0
General disorders and administration site conditions	513 (65.6)	83 (10.6)	2 (0.3)	426 (55.5)	59 (7.7)	2 (0.3)
Fatigue	257 (32.9)	41 (5.2)	0	219 (28.6)	25 (3.3)	0
Pyrexia	147 (18.8)	8 (1.0)	0	83 (10.8)	3 (0.4)	0
Asthenia	115 (14.7)	17 (2.2)	0	111 (14.5)	15 (2.0)	0
Oedema peripheral	86 (11.0)	3 (0.4)	0	53 (6.9)	1 (0.1)	0
Mucosal inflammation	74 (9.5)	7 (0.9)	0	47 (6.1)	5 (0.7)	0
Malaise	52 (6.6)	2 (0.3)	0	50 (6.5)	2 (0.3)	0
Investigations	484 (61.9)	213 (27.2)	0	399 (52.0)	150 (19.6)	0
Neutrophil count decreased	170 (21.7)	90 (11.5)	0	124 (16.2)	70 (9.1)	0
Platelet count decreased	168 (21.5)	22 (2.8)	0	122 (15.9)	20 (2.6)	0
Aspartate aminotransferase increased	157 (20.1)	19 (2.4)	0	96 (12.5)	9 (1.2)	0
Weight decreased	135 (17.3)	10 (1.3)	0	117 (15.3)	5 (0.7)	0
White blood cell count decreased	117 (15.0)	25 (3.2)	0	80 (10.4)	13 (1.7)	0
Alanine aminotransferase increased	112 (14.3)	9 (1.2)	0	72 (9.4)	9 (1.2)	0
Lipase increased	106 (13.6)	55 (7.0)	0	65 (8.5)	28 (3.7)	0
Blood alkaline phosphatase increased	101 (12.9)	10 (1.3)	0	58 (7.6)	5 (0.7)	0
Amylase increased	90 (11.5)	24 (3.1)	0	41 (5.3)	3 (0.4)	0
Blood bilirubin increased	76 (9.7)	14 (1.8)	0	49 (6.4)	7 (0.9)	0

System Organ Class (%) Preferred Term (%)	Nivo+Chemo N = 782			Chemo N = 767		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Blood and lymphatic system disorders	477 (61.0)	230 (29.4)	2 (0.3)	397 (51.8)	167 (21.8)	0
Anaemia	299 (38.2)	86 (11.0)	0	254 (33.1)	56 (7.3)	0
Neutropenia	214 (27.4)	132 (16.9)	0	192 (25.0)	100 (13.0)	0
Thrombocytopenia	171 (21.9)	21 (2.7)	1 (0.1)	152 (19.8)	16 (2.1)	0
Leukopenia	67 (8.6)	5 (0.6)	0	62 (8.1)	12 (1.6)	0
Metabolism and nutrition disorders	426 (54.5)	94 (12.0)	0	363 (47.3)	68 (8.9)	1 (0.1)
Decreased appetite	224 (28.6)	28 (3.6)	0	203 (26.5)	19 (2.5)	0
Hypoalbuminaemia	105 (13.4)	2 (0.3)	0	62 (8.1)	2 (0.3)	0
Hypokalaemia	87 (11.1)	19 (2.4)	0	65 (8.5)	20 (2.6)	0
Hyperglycaemia	77 (9.8)	12 (1.5)	0	57 (7.4)	6 (0.8)	0
Hyponatraemia	66 (8.4)	19 (2.4)	0	46 (6.0)	13 (1.7)	0
Hypocalcaemia	47 (6.0)	4 (0.5)	0	26 (3.4)	0	0
Skin and subcutaneous tissue disorders	314 (40.2)	31 (4.0)	0	201 (26.2)	12 (1.6)	0
Palmar-plantar erythrodysaesthesia syndrome	103 (13.2)	12 (1.5)	0	90 (11.7)	6 (0.8)	0
Rash	86 (11.0)	7 (0.9)	0	20 (2.6)	0	0
Pruritus	73 (9.3)	1 (0.1)	0	15 (2.0)	0	0
Infections and infestations	283 (36.2)	68 (8.7)	4 (0.5)	184 (24.0)	39 (5.1)	0
Pneumonia	45 (5.8)	19 (2.4)	2 (0.3)	32 (4.2)	10 (1.3)	0
Respiratory, thoracic and mediastinal disorders	263 (33.6)	41 (5.2)	3 (0.4)	195 (25.4)	30 (3.9)	2 (0.3)
Cough	95 (12.1)	1 (0.1)	0	59 (7.7)	0	0
Dyspnoea	60 (7.7)	4 (0.5)	0	41 (5.3)	5 (0.7)	0
Musculoskeletal and connective tissue disorders	224 (28.6)	16 (2.0)	0	147 (19.2)	19 (2.5)	0
Back pain	77 (9.8)	5 (0.6)	0	59 (7.7)	10 (1.3)	0
Arthralgia	52 (6.6)	1 (0.1)	0	23 (3.0)	2 (0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	138 (17.6)	57 (7.3)	60 (7.7)	107 (14.0)	41 (5.3)	51 (6.6)
Malignant neoplasm progression	111 (14.2)	45 (5.8)	60 (7.7)	92 (12.0)	35 (4.6)	51 (6.6)
Injury, poisoning and procedural complications	127 (16.2)	23 (2.9)	0	81 (10.6)	12 (1.6)	0
Infusion related reaction	68 (8.7)	11 (1.4)	0	30 (3.9)	5 (0.7)	0
Vascular disorders	127 (16.2)	37 (4.7)	3 (0.4)	90 (11.7)	21 (2.7)	1 (0.1)
Hypertension	41 (5.2)	19 (2.4)	0	32 (4.2)	11 (1.4)	0

System Organ Class (%) Preferred Term (%)	Nivo+Chemo N = 782			Chemo N = 767		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Psychiatric disorders	108 (13.8)	2 (0.3)	0	91 (11.9)	7 (0.9)	0
Insomnia	53 (6.8)	0	0	59 (7.7)	2 (0.3)	0
Endocrine disorders	104 (13.3)	7 (0.9)	0	12 (1.6)	1 (0.1)	0
Hypothyroidism	77 (9.8)	0	0	10 (1.3)	0	0
Immune system disorders	85 (10.9)	10 (1.3)	0	33 (4.3)	6 (0.8)	0
Hypersensitivity	52 (6.6)	5 (0.6)	0	12 (1.6)	2 (0.3)	0

MedDRA Version: 23.0. CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Table S.6.1.31.3

Table 32. Drug-Related Adverse Events by Worst CTC Grade in ≥ 5% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo+Chemo N = 782			Chemo N = 767		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	738 (94.4)	462 (59.1)	4 (0.5)	679 (88.5)	341 (44.5)	0
Gastrointestinal disorders	520 (66.5)	88 (11.3)	1 (0.1)	456 (59.5)	73 (9.5)	0
Nausea	323 (41.3)	20 (2.6)	0	292 (38.1)	19 (2.5)	0
Diarrhoea	253 (32.4)	35 (4.5)	0	206 (26.9)	24 (3.1)	0
Vomiting	195 (24.9)	17 (2.2)	0	166 (21.6)	24 (3.1)	0
Constipation	73 (9.3)	2 (0.3)	0	61 (8.0)	0	0
Stomatitis	57 (7.3)	7 (0.9)	0	47 (6.1)	1 (0.1)	0
Abdominal pain	39 (5.0)	4 (0.5)	0	38 (5.0)	3 (0.4)	0
Nervous system disorders	466 (59.6)	69 (8.8)	1 (0.1)	427 (55.7)	45 (5.9)	0
Neuropathy peripheral	221 (28.3)	31 (4.0)	0	190 (24.8)	22 (2.9)	0
Peripheral sensory neuropathy	137 (17.5)	16 (2.0)	0	119 (15.5)	14 (1.8)	0
Paraesthesia	59 (7.5)	2 (0.3)	0	61 (8.0)	1 (0.1)	0
Dysgeusia	42 (5.4)	0	0	38 (5.0)	0	0
Headache	40 (5.1)	2 (0.3)	0	17 (2.2)	1 (0.1)	0
Investigations	413 (52.8)	178 (22.8)	0	299 (39.0)	116 (15.1)	0
Neutrophil count decreased	158 (20.2)	83 (10.6)	0	118 (15.4)	67 (8.7)	0
Platelet count decreased	156 (19.9)	20 (2.6)	0	115 (15.0)	19 (2.5)	0
Aspartate aminotransferase increased	122 (15.6)	12 (1.5)	0	69 (9.0)	5 (0.7)	0
White blood cell count decreased	112 (14.3)	23 (2.9)	0	77 (10.0)	13 (1.7)	0
Alanine aminotransferase increased	89 (11.4)	6 (0.8)	0	50 (6.5)	5 (0.7)	0
Lipase increased	89 (11.4)	45 (5.8)	0	34 (4.4)	16 (2.1)	0
Amylase increased	71 (9.1)	21 (2.7)	0	22 (2.9)	2 (0.3)	0
Blood alkaline phosphatase increased	52 (6.6)	5 (0.6)	0	34 (4.4)	2 (0.3)	0
Blood bilirubin increased	48 (6.1)	4 (0.5)	0	32 (4.2)	2 (0.3)	0
Weight decreased	45 (5.8)	2 (0.3)	0	33 (4.3)	1 (0.1)	0
Blood and lymphatic system disorders	390 (49.9)	185 (23.7)	1 (0.1)	331 (43.2)	127 (16.6)	0
Anaemia	203 (26.0)	47 (6.0)	0	171 (22.3)	21 (2.7)	0
Neutropenia	191 (24.4)	118 (15.1)	0	181 (23.6)	93 (12.1)	0
Thrombocytopenia	157 (20.1)	19 (2.4)	0	145 (18.9)	13 (1.7)	0
Leukopenia	63 (8.1)	5 (0.6)	0	55 (7.2)	11 (1.4)	0
General disorders and administration site conditions	376 (48.1)	49 (6.3)	0	311 (40.5)	35 (4.6)	0
Fatigue	202 (25.8)	30 (3.8)	0	173 (22.6)	17 (2.2)	0
Asthenia	73 (9.3)	7 (0.9)	0	81 (10.6)	10 (1.3)	0
Pyrexia	64 (8.2)	4 (0.5)	0	22 (2.9)	1 (0.1)	0
Mucosal inflammation	62 (7.9)	6 (0.8)	0	45 (5.9)	5 (0.7)	0
Malaise	42 (5.4)	2 (0.3)	0	36 (4.7)	0	0

System Organ Class (%) Preferred Term (%)	Nivo+Chemo N = 782			Chemo N = 767		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Skin and subcutaneous tissue disorders	251 (32.1)	28 (3.6)	0	153 (19.9)	9 (1.2)	0
Palmar-plantar erythrodysaesthesia syndrome	94 (12.0)	11 (1.4)	0	81 (10.6)	6 (0.8)	0
Rash	74 (9.5)	7 (0.9)	0	12 (1.6)	0	0
Pruritus	54 (6.9)	1 (0.1)	0	8 (1.0)	0	0
Metabolism and nutrition disorders	227 (29.0)	36 (4.6)	0	193 (25.2)	28 (3.7)	0
Decreased appetite	157 (20.1)	14 (1.8)	0	139 (18.1)	13 (1.7)	0
Endocrine disorders	95 (12.1)	5 (0.6)	0	2 (0.3)	0	0
Hypothyroidism	70 (9.0)	0	0	2 (0.3)	0	0
Injury, poisoning and procedural complications	75 (9.6)	12 (1.5)	0	38 (5.0)	5 (0.7)	0
Infusion related reaction	66 (8.4)	11 (1.4)	0	30 (3.9)	5 (0.7)	0
Immune system disorders	73 (9.3)	9 (1.2)	0	27 (3.5)	6 (0.8)	0
Hypersensitivity	48 (6.1)	4 (0.5)	0	10 (1.3)	2 (0.3)	0

MedDRA Version: 23.0. CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.1.32.3

Potential overlapping AEs

The potential overlapping AEs of nivolumab and chemotherapy, such as gastrointestinal, respiratory, skin and liver toxicities, that were numerically higher in the nivo+chemo arm compared with the chemo arm, as well as nivolumab monotherapy, suggest potentially additive toxicity of the two drugs when used in combination. The most frequently reported potential overlapping AEs (regardless of causality) were the following:

- Nivo+chemo: nausea (47.6%), diarrhoea (39.4%), fatigue (32.9%), vomiting (31.3%), increased aspartate aminotransferase (20.1%), increased alanine aminotransferase (14.3%), palmar-plantar erythrodysaesthesia syndrome (13.2%), increased blood alkaline phosphatase (12.9%), rash (11.0%), increased blood bilirubin (9.7%), pruritis (9.3%), stomatitis (8.2%), and pneumonia (5.8%).
- Chemo: nausea (43.5%), diarrhoea (33.6%), vomiting (28.8%), fatigue (28.6%), increased aspartate aminotransferase (12.5%), palmar-plantar erythrodysaesthesia syndrome (11.7%), increased alanine aminotransferase (9.4%), blood alkaline phosphatase (7.6%), stomatitis (6.6%), increased blood bilirubin (6.4%), pneumonia (4.2%), rash (2.6%), and pruritis (2.0%).

The most frequently reported potential overlapping drug-related AEs were the following:

- Nivo+chemo: nausea (41.3%), diarrhoea (32.4%), fatigue (25.8%), vomiting (24.9%), increased aspartate aminotransferase (15.6%), palmar-plantar erythrodysaesthesia syndrome (12.0%), increased alanine aminotransferase (11.4%), rash (9.5%), stomatitis (7.3%), pruritis (6.9%), blood alkaline phosphatase (6.6%), increased blood bilirubin (6.1%), and pneumonitis (4.5%).
- Chemo: nausea (38.1%), diarrhoea (26.9%), fatigue (22.6%), vomiting (21.6%), palmar-plantar erythrodysaesthesia syndrome (10.6%), increased aspartate aminotransferase (9.0%), increased alanine aminotransferase (6.5%), stomatitis (6.1%), blood alkaline phosphatase (4.4%), increased blood bilirubin (4.2%), rash (1.6%), pruritis (1.0%), and pneumonitis (0.3%).

Exposure-adjusted adverse events rates

When the AE occurrences were exposure-adjusted, AE incidence rates (per 100 person-year [P-Y]) were 2273.3 with nivo+chemo treatment and 2139.1 with chemo treatment. The most frequently reported exposure adjusted AEs (all causality) for both the nivo+chemo and chemo arms were within the SOC of gastrointestinal disorders (475.5/100 P-Y for nivo+chemo vs. 533.3/100 P-Y for chemo). Nausea was the most frequently reported PT (116.0/100 P-Y for nivo+chemo vs. 128.4/100 P-Y for chemo).

When the drug-related AE occurrences were exposure-adjusted, drug-related AE incidence rates (per 100 P-Y) were 1368.0 with nivo+chemo treatment and 1305.2 for chemo treatment. In the nivo+chemo arm, the most frequently reported exposure adjusted drug-related AEs were within the SOC of investigations with decreased neutrophil count as the most frequently reported PT (64.5/100 P-Y). In the chemotherapy arm, the most frequently reported exposure adjusted drug-related AEs were within the SOC of gastrointestinal disorders with nausea as the most frequently reported PT (110.6/100 P-Y).

Select adverse events

In order to characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, 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 (e.g., 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, endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each of these were grouped into endocrine, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select AE categories, respectively. Hypersensitivity/infusion reactions were analysed along with the select AE categories, because multiple event terms may be used to describe such events and pooling of terms was, therefore, necessary for full characterisation. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered select AEs.

The majority of select AEs were Grade 1-2 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 (Table 30):

- Nivo+chemo: gastrointestinal (33.5%), skin (27.4%) and hepatic (26.0%).
- Chemo: gastrointestinal (27.0%), hepatic (17.5%), and skin (13.7%).

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

- Nivo+chemo: diarrhoea (32.4%), increased AST (15.6%), and palmar-plantar erythrodysaesthesia syndrome (12.0%).
- Chemo: diarrhoea (26.9%), palmar-plantar erythrodysaesthesia syndrome (10.6%), and increased AST (9.0%).

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

- Nivo+chemo: diarrhoea (2.2%), pneumonitis (2.2%), and infusion related reaction (0.8%).
- Chemo: diarrhoea (1.3%).

Across the select AE categories, the majority of events in the nivo+chemo arm were manageable using the established algorithms, with resolution occurring when immune-modulating medications (mainly systemic corticosteroids) were administered (Table 33). Most drug-related select AEs with nivo+chemo had resolved (ranging from 43.0% to 98.2% across categories) at the time of database lock. The median time to resolution ranged from 0.14 to 23.43 weeks for select AEs. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Table 33. Onset, Management, and Resolution of Drug-Related Select AEs - Nivolumab + Chemotherapy Treated Subjects (N = 782)

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), wks	% Treated Subj. with Drug-related Select AE Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median Time[b] to Resolution of Drug-related Select AE (range), wks[c,d,e]	% Subj. with Drug-related Select AE that Resolved[d,e]
Endocrine	13.7 / 0.6	15.00 (2.0 - 124.3)	0.4	12.1 / 5.6	72.14 (0.4 - 139.1+)	43.0
Gastrointestinal	33.5 / 5.5	4.29 (0.1 - 93.6)	2.8	10.7 / 8.0	1.57 (0.1 - 117.6+)	87.4
Hepatic	26.0 / 3.7	7.86 (0.1 - 61.3)	1.2	11.3 / 8.9	10.14 (0.4 - 150.6+)	78.0
Pulmonary	5.1 / 1.8	23.93 (1.6 - 96.9)	1.9	77.5 / 65.0	10.14 (0.3+ - 121.3+)	70.0
Renal	3.3 / 0.8	12.36 (1.7 - 59.4)	1.2	23.1 / 15.4	3.14 (0.1 - 42.4+)	73.1
Skin	27.4 / 3.3	9.64 (0.1 - 97.4)	1.4	39.3 / 6.5	23.43 (0.1 - 153.6+)	57.9
Hypersensitivity/ Infusion Reaction	14.2 / 2.2	10.43 (0.1 - 84.0)	3.3	37.8 / 23.4	0.14 (0.1 - 47.9+)	98.2

[a] Denominator is based on the number of subjects who experienced the event

[b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value.

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

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

Abbreviations: AE - adverse event, DC - discontinuation, IMM - immune-modulating medication, N.A. - not available/not applicable, subj. - subjects, wks - weeks

Source: Table S.6.5.2.10 (select AEs), Table S.6.5.2.12 (select endocrine AEs), Table S.6.117.1 (time to onset of select AEs), Table S.6.5.1.3.6 (drug-related select AEs leading to DC), Table S.6.5.1.3.8 (drug-related select endocrine AEs leading to DC), Table S.6.12.9.3 (duration of IMM for select AEs), Table S.6.121.1 (time to resolution of select AEs). These outputs also include Grade 3-5 and chemotherapy results.

Immune-mediated adverse events

IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (i.e., with extended follow-up). These analyses included IMAE categories (diarrhoea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, hypersensitivity/infusion reactions, and endocrine) with PTs describing specific events regardless of causality. These analyses were limited to subjects who received immune-modulating medication 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 and an immune mediated component.

Overall, the majority of IMAEs were Grade 1-2. The most frequently reported IMAEs (any grade) by category were as follows in each treatment arm (Table 30):

- Nivo+chemo: hypothyroidism/thyroiditis (9.5%), rash (6.5%), and pneumonitis (4.2%).
  - Of the treated subjects who experienced non-endocrine IMAEs, a higher frequency of Grade 3-4 IMAEs was observed in the following categories: hepatitis (13/19 subjects), diarrhoea/colitis (17/26 subjects), nephritis and renal dysfunction (2/4 subjects) and pneumonitis (15/33 subjects).
  - Of the treated subjects who experienced endocrine IMAEs; a higher frequency of Grade 3-4 IMAEs was observed in hypophysitis (3/6 subjects) and diabetes mellitus (1/2 subjects).
- Chemo: hypothyroidism/thyroiditis (0.8%) and rash (0.5%).

Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered (Table 34). Except for some endocrine events, most IMAEs with nivo+chemo treatment had resolved at the time of DBL. Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy (Table 34).

Re-challenge information was also summarized for subjects who continued to receive nivolumab treatment after the onset of an IMAE (Table 34). A re-challenge was considered as an unsuccessful or positive re-challenge if, after resolution of the IMAE, a new IMAE of the same type occurred with re-treatment of study drug. A re-challenge was considered as a successful or negative re-challenge if, after resolution of the IMAE, no new IMAEs of the same type occurred with re-treatment.

Table 34. Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - Nivolumab + Chemotherapy Treated Subjects (N = 782)

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[d,e]	Median[b] Time to Resolution (range), wks[c,d,e]	% Subj. with Recurrence after Reinitiation
Pneumonitis	4.2 / 1.9	25.43 (4.4 - 98.6)	1.8 / 2.0	100 / 84.8	9.29 (0.1 - 94.1)	63.6	14.86 (0.3+ - 66.6+)	28.6 (2 / 7)
Diarrhea/Colitis	3.3 / 2.2	11.29 (1.6 - 59.1)	2.0 / 1.5	100 / 69.2	6.71 (0.3 - 63.9)	84.6	4.57 (0.6 - 52.0+)	33.3 (1 / 3)
Hepatitis	2.4 / 1.7	8.43 (2.1 - 48.0)	0.8 / 1.2	100 / 78.9	6.14 (0.1 - 100.6)	89.5	8.00 (1.0 - 36.1+)	42.9 (3 / 7)
Nephritis/Renal Dysfunction	0.5 / 0.3	14.71 (4.4 - 26.1)	0.4 / 0.4	100 / 50	11.43 (6.1 - 14.4)	75.0	12.07 (1.1 - 26.4+)	50.0 (1 / 2)
Rash	6.5 / 1.4	8.14 (0.1 - 91.3)	0.1 / 1.3	100 / 23.5	7.14 (0.4 - 97.0)	78.4	7.00 (0.7 - 135.9+)	42.9 (3 / 7)
Hypersensitivity	0.8 / 0.1	3.64 (0.1 - 23.3)	0.1 / 0	100 / 83.3	0.21 (0.1 - 6.0)	100	0.14 (0.1 - 8.0)	N.A.
Adrenal Insufficiency	0.6 / 0.1	40.86 (15.0 - 57.4)	0 / 0.1	60 / 0	35.86 (15.1 - 41.0)	20.0	N.A. (1.4 - 52.9+)	0 (0 / 0)
Hypophysitis	0.8 / 0.4	32.86 (16.9 - 49.3)	0 / 0.5	83.3 / 33.3	24.57 (4.7 - 63.1)	66.7	6.93. (0.4 - 61.9+)	0 (0 / 3)
Hypothyroidism/ Thyroiditis	9.5 / 0	17.57 (2.0 - 57.9)	0.3 / 0.9	5.4 / 5.4	4.64 (0.4 - 5.1)	36.5	N.A. (1.4 - 139.1+)	0 (0 / 2)
Hyperthyroidism	2.9 / 0	11.86 (3.3 - 46.3)	0 / 0.3	4.3 / 0	16.00 (16.0 - 16.0)	78.3	10.00 (1.0 - 68.1+)	N.A.
Diabetes Mellitus	0.3 / 0.1	29.64 (15.9 - 43.4)	0 / 0	50 / 0	0.43 (0.4 - 0.4)	0	N.A. (62.7+ - 88.0+)	N.A.

[a] Denominator is based on the number of subjects who experienced the event.

[b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value.

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

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

Abbreviations: DC - discontinuation, IMAE - immune-mediated adverse events, IMM - immune-modulating medication, N.A. - not available/not applicable, subj. - subjects, wks - weeks

Source: Table S.6.202.13 (endocrine IMAEs), Table S.6.202.14 (endocrine IMAEs leading to DC), Table S.6.202.15 (endocrine IMAEs leading to dose delay/reduction), Table S.6.202.16 (non-endocrine IMAEs), Table S.6.202.17 (non-endocrine IMAEs leading to DC), Table S.6.202.18 (non-endocrine IMAEs leading to dose delay/reduction), Table S.6.12.91.3 (duration of IMM for IMAE management), Table S.6.217.5 (time to onset of endocrine IMAEs), Table S.6.217.6 (time to onset of non-endocrine IMAEs), Table S.6.219.5 (time to resolution of endocrine IMAEs), Table S.6.219.6 (time to resolution of non-endocrine IMAEs), Table S.6.223.3 (re-challenge with nivolumab). These outputs also include Grade 3-5 and chemotherapy results.

Other events of special interest (OESIs)

OESIs are events that do not fulfill all criteria to qualify as IMAEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow-up (100-day window); and OESIs included the following categories: demyelination, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, uveitis, encephalitis, myocarditis, graft versus host disease, and myositis/rhabdomyolysis. OESIs (regardless of causality or IMM treatment) with extended follow-up are summarized by category in Table 30 .

OESIs (regardless of causality or IMM treatment, with extended follow-up) were infrequent in both treatment arms (Table 30 and Table 35). Overall, OESIs were reported in 8/782 (1.0%) subjects (10 events) in the nivo+chemo arm and 4/767 (0.5%) subjects (5 events) in the chemo arm. 9/10 OESIs in the nivo+chemo arm and 4/5 OESIs in the chemo arm were resolved at the time of database lock (Table 35). 7/10 and 1/5 OESIs were resolved with IMM treatment in the nivo+chemo and chemo arms, respectively.

Table 35. Treatment, Onset, and Resolution Information for Other Events of Special Interest by Subject -All Treated Subjects

Event Description	Immune-modulating Medication	Onset Date (Study Day)	Duration of Event (Days)	Resolution (Yes/No)
Nivo+Chemo				
Guillain-Barre syndrome				
Grade 3 drug-related SAE of Guillain-Barre syndrome	meprednisone, gamma globulin, prednisone, hydrocortisone	13-Sep-2018 (35)	35	Yes
Pancreatitis				
Grade 4 drug-related SAE of pancreatitis	hydrocortisone, dexamethasone	12-Jul-2019 (463)	9	Yes
Grade 3 drug-related SAE of acute pancreatitis	None	29-Mar-2018 (78)	9	Yes
Grade 2 drug-related AE of autoimmune pancreatitis	prednisolone	15-Feb-2018 (53)	34	Yes
Grade 1 drug-related AE of autoimmune pancreatitis	prednisolone	20-Mar-2018 (86)	59	Yes
Uveitis				
Grade 3 drug-related SAE of chorioretinitis	methylprednisolone	18-Apr-2018 (59)	4	Yes
Encephalitis				
Grade 3 SAE of encephalitis	prednisolone, methylprednisolone, dexamethasone	15-Jun-2018 (179)	ongoing	No
Myocarditis				
Grade 1 drug-related AE of myocarditis	methylprednisolone, prednisolone	13-Dec-2018 (56)	110	Yes
Grade 1 AE of myocarditis	none	02-Apr-2019 (166)	22	Yes
Grade 3 drug-related SAE of autoimmune myocarditis	methylprednisolone, prednisolone	04-Oct-2019 (376)	12	Yes
Chemo				
Pancreatitis				
Grade 2 drug-related SAE of acute pancreatitis	none	19-Aug-2018 (4)	5	Yes
Grade 3 AE of pancreatitis	none	01-Aug-2019 (85)	11	Yes
Myositis/Rhabdomyolysis				
Grade 3 SAE of myositis	none	14-Mar-2019 (24)	ongoing	No
Grade 1 AE of myositis	none	May-2019 (N.A.)	107	Yes
Grade 3 SAE of myositis	prednisolone	16-Aug-2019 (354)	4	Yes

Abbreviations: N.A. - not available

Source: Appendix 6.83.1 (by-subject listing, OESIs, immune-modulating medication), Appendix 6.1.1.1 (seriousness, duration of event), Appendix 6.1.1 (duration of event)

Serious adverse event and deaths

Serious adverse events

The overall frequencies of SAEs (all-causality and drug-related) were numerically higher with nivo+chemo than with chemo (Table 30, Table 36, Table 37).

Any Grade SAEs (regardless of causality) were reported in 423 (54.1%) subjects in the nivo+chemo arm vs. 335 (43.7%) subjects in the chemo arm. Grade 3-4 SAEs were reported in 281 (35.9%) subjects in the nivo+chemo arm and 229 (29.9%) subjects in the chemo arm.

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

- Nivo+chemo: malignant neoplasm progression (13.9%), vomiting (3.2%), and anaemia (3.1%).
- Chemo: malignant neoplasm progression (11.7%), vomiting (3.1%), and dysphagia (2.1%).

Any-grade drug-related SAEs were reported in 172 (22.0%) subjects in the nivo+chemo arm, and 93 (12.1%) subjects in the chemo arm. Grade 3-4 drug-related SAEs were reported in 131 (16.8%) subjects in the nivo+chemo arm, and 77 (10.0%) subjects in the chemo arm.

The most frequently reported drug-related SAEs were:

- Nivo+chemo: diarrhoea (2.2%), pneumonitis (2.2%), and febrile neutropaenia (2.0%).
- Chemo: vomiting (2.3%), diarrhoea (1.3%), and decreased appetite (1.0%).

Table 36. Serious Adverse Events Reported in ≥ 2% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo+Chemo N = 782			Chemo N = 767		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	423 (54.1)	281 (35.9)	81 (10.4)	335 (43.7)	229 (29.9)	63 (8.2)
Gastrointestinal disorders	133 (17.0)	103 (13.2)	3 (0.4)	123 (16.0)	100 (13.0)	0
Vomiting	25 (3.2)	17 (2.2)	0	24 (3.1)	19 (2.5)	0
Diarrhoea	19 (2.4)	14 (1.8)	0	12 (1.6)	9 (1.2)	0
Dysphagia	10 (1.3)	9 (1.2)	0	16 (2.1)	15 (2.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	123 (15.7)	55 (7.0)	60 (7.7)	100 (13.0)	39 (5.1)	51 (6.6)
Malignant neoplasm progression	109 (13.9)	45 (5.8)	60 (7.7)	90 (11.7)	33 (4.3)	51 (6.6)
Infections and infestations	72 (9.2)	53 (6.8)	4 (0.5)	33 (4.3)	28 (3.7)	0
Pneumonia	22 (2.8)	16 (2.0)	2 (0.3)	10 (1.3)	9 (1.2)	0
Blood and lymphatic system disorders	52 (6.6)	42 (5.4)	2 (0.3)	24 (3.1)	22 (2.9)	0
Anaemia	24 (3.1)	18 (2.3)	0	9 (1.2)	8 (1.0)	0
Febrile neutropenia	18 (2.3)	16 (2.0)	1 (0.1)	7 (0.9)	7 (0.9)	0
Respiratory, thoracic and mediastinal disorders	45 (5.8)	27 (3.5)	3 (0.4)	29 (3.8)	19 (2.5)	2 (0.3)
Pneumonitis	17 (2.2)	11 (1.4)	0	1 (0.1)	0	0
General disorders and administration site conditions	40 (5.1)	19 (2.4)	2 (0.3)	30 (3.9)	15 (2.0)	2 (0.3)
Pyrexia	20 (2.6)	5 (0.6)	0	10 (1.3)	3 (0.4)	0

MedDRA Version: 23.0. CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.3.1.2.5

Table 37. Drug-Related Serious Adverse Events Reported in ≥ 1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo+Chemo N = 782			Chemo N = 767		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	172 (22.0)	131 (16.8)	4 (0.5)	93 (12.1)	77 (10.0)	0
Gastrointestinal disorders	56 (7.2)	39 (5.0)	1 (0.1)	44 (5.7)	36 (4.7)	0
Diarrhoea	17 (2.2)	13 (1.7)	0	10 (1.3)	8 (1.0)	0
Vomiting	12 (1.5)	7 (0.9)	0	18 (2.3)	14 (1.8)	0
Blood and lymphatic system disorders	36 (4.6)	32 (4.1)	1 (0.1)	16 (2.1)	14 (1.8)	0
Febrile neutropenia	16 (2.0)	14 (1.8)	1 (0.1)	6 (0.8)	6 (0.8)	0
Anaemia	11 (1.4)	10 (1.3)	0	4 (0.5)	3 (0.4)	0
Respiratory, thoracic and mediastinal disorders	20 (2.6)	13 (1.7)	0	6 (0.8)	2 (0.3)	0
Pneumonitis	17 (2.2)	11 (1.4)	0	0	0	0
General disorders and administration site conditions	12 (1.5)	7 (0.9)	0	14 (1.8)	8 (1.0)	0
Pyrexia	8 (1.0)	3 (0.4)	0	3 (0.4)	1 (0.1)	0
Metabolism and nutrition disorders	5 (1.4)	5 (1.4)	0	5 (1.4)	5 (1.4)	0
Decreased appetite	3 (0.4)	3 (0.4)	0	8 (1.0)	8 (1.0)	0

MedDRA Version: 23.0. CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Table S.6.3.1.2.6

Deaths

As of the 10-Jul-2020 database lock, the number of treated subjects who died in the nivo+chemo arm was numerically lower vs. the chemo arm (Table 38). Disease progression was the most common cause of death in both arms.

Note that only events that led to death within 24 hours were documented as Grade 5. Events leading to death > 24 hours after onset are reported with the grade at presentation.

Table 38. Death Summary - All Treated Subjects

	Nivo+Chemo N = 782	Chemo N = 767
NUMBER OF SUBJECTS WHO DIED (%)	538 (68.8)	572 (74.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	465 (59.5)	506 (66.0)
STUDY DRUG TOXICITY	12 (1.5)	4 (0.5)
UNKNOWN	12 (1.5)	18 (2.3)
OTHER	49 (6.3)	44 (5.7)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	103 (13.2)	89 (11.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	67 (8.6)	62 (8.1)
STUDY DRUG TOXICITY	10 (1.3)	4 (0.5)
UNKNOWN	3 (0.4)	1 (0.1)
OTHER	23 (2.9)	22 (2.9)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	291 (37.2)	266 (34.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	236 (30.2)	222 (28.9)
STUDY DRUG TOXICITY	12 (1.5)	4 (0.5)
UNKNOWN	4 (0.5)	2 (0.3)
OTHER	39 (5.0)	38 (5.0)

Source: Table S.6.15.3

Deaths attributed to study drug toxicity

Death attributed to study drug toxicity was reported in 12 (1.5%) and 4 (0.5%) treated subjects in the nivo+chemo and chemo arms, respectively (Table 38). Per Investigator assessment in the nivo+chemo arm, 3 deaths were due to nivolumab, 2 deaths were due to nivolumab and chemotherapy, and 7 deaths were due to chemotherapy:

- The causes of death due to nivolumab were pulmonitis, intertistial lung disease and pneumonitis.
- The causes of death due to nivolumab and chemotherapy were infection and gastrointestinal toxicity.
- The causes of death due to chemotherapy were neutropaenic fever, intestinal mucositis, stroke, gastrointestinal bleeding, septic shock, pneumonia, and febrile neutropaenia.

Details of deaths due to study drug toxicity are presented below (Table 39).

Table 39. Study Drug Toxicity Deaths - All Treated Subjects

Randomization Date	First Dose Date	Last Dose Date	Death Date	Days Since Last Dose	Cause of Death (AE/SAE)	Agent with Suspected Causal Relationship
Nivo+chemo Arm						
04FEB2019	04FEB2019	16FEB2019	22FEB2019	7	NEUTRPENIC FEVER	OXALIPLATIN, CAPECITABINE
02OCT2017	03OCT2017	15OCT2017	23OCT2017	9	INTESTINAL MUCOSITIS	CAPECITABINE
16OCT2017	17OCT2017	31OCT2017	03NOV2017	4	STROKE	CAPECITABINE
07JUN2018	07JUN2018	13SEP2018	13DEC2018	92	INFECTION	NIVOLUMAB, OXALIPLATIN, CAPECITABINE
08AUG2017	08AUG2017	11SEP2017	25SEP2017	15	GASTROINTESTINAL BLEEDING	OXALIPLATIN, CAPECITABINE
30NOV2018	30NOV2018	21DEC2018	05JAN2019	16	SEPTIC SHOCK	CAPECITABINE
14AUG2018	15AUG2018	07DEC2018	22DEC2018	16	PNEUMONIA	OXALIPLATIN, FLUOROURACIL, LEUCOVORIN
04JUL2017	06JUL2017	21OCT2017	20NOV2017	31	PULMONITIS	NIVOLUMAB
21AUG2018	22AUG2018	16NOV2018	14DEC2018	29	INTERTISTIAL LUNG DISEASE	NIVOLUMAB
13FEB2018	14FEB2018	06JUL2018	22SEP2018	79	PNEUMONITIS	NIVOLUMAB
30OCT2017	30OCT2017	30OCT2017	09NOV2017	11	FEBRILE NEUTROPENIA	OXALIPLATIN, FLUOROURACIL
12DEC2018	17DEC2018	19APR2019	07MAY2019	19	GASTROINTESTINAL TOXICITY	NIVOLUMAB, OXALIPLATIN, FLUOROURACIL, LEUCOVORIN
Chemo Arm						
06JUL2017	06JUL2017	13JUL2017	02AUG2017	21	PULMONARY TROMBOEMBOLISM	OXALIPLATIN
03APR2019	04APR2019	27JUN2019	12JUL2019	16	ASTHENIA and HIPOREXY SEVERE	OXALIPLATIN, CAPECITABINE
26APR2018	27APR2018	28APR2018	10MAY2018	13	STUDY DRUG TOXICITY WITH DIARRHEA	OXALIPLATIN, CAPECITABINE
11DEC2018	12DEC2018	02APR2019	24APR2019	23	ADVERSE EVENT INTERSTICIAL PNEUMONIA	OXALIPLATIN, FLUOROURACIL, LEUCOVORIN

Deaths may be captured on death, AE, ECOG performance status, status, and follow-up CRF pages. The primary source of death date is the death CRF. If the date is missing, the death date reported on the adverse event case report form is reported. Abbreviations: AE = adverse event; SAE = serious adverse event. Source: Table S.6.15.3, Appendix 6.16.1.

Deaths attributed to other reasons

Deaths attributed to other reasons were reported in 49 (6.3%) and 44 (5.7%) of treated subjects in the nivo+chemo and chemo arms, respectively (Table 38). There were 4 events reported as "related" per investigator: thrombosis mesenteric vessel, disseminated intravascular coagulation, cerebral infarction and pneumonitis. All 4 subjects were in the nivo+chemo arm. Per investigator, the pneumonitis was reported as related to nivolumab and the other 3 events were reported as related to both nivolumab and chemotherapy (Table 40 below)

Table 40. Deaths Attributed to Other Reasons

Randomization Date	First Dose Date	Last Dose Date	Death Date	Days Since Last Dose	Cause of Death	Specify
Nivo+chemo Arm						
04DEC2018	05DEC2018	26FEB2019	27FEB2019	2	OTHER	THE CAUSE OF DEATH OF THE PATIENT WAS CONSIDERED TO BE MESENTERIC THROMBOSIS
04APR2019	04APR2019	17SEP2019	19OCT2019	33	OTHER DISSEMINATED INTRAVASCULAR COAGULATION	IT HAS RELATED TO STUDY DRUG TOXICITY, IT HAS RELATED TO DISEASES
13APR2018	13APR2018	11SEP2019	26SEP2019	16	OTHER	ACUTE CEREBRAL INFARCTION
16APR2019	17APR2019	24OCT2019	01DEC2019	39	OTHER	PNEUMONITIS

Deaths may be captured on death, AE, ECOG performance status, status, and follow-up CRF pages. The primary source of death date is the death CRF. If the date is missing, the death date reported on the adverse event case report form is reported.
Source: Appendix 6.16.1

Laboratory findings

A summary of clinical laboratory parameters that worsened relative to baseline is presented in Table 41.

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2. Grade 3 or 4 haematologic abnormalities reported in ≥ 5% of subjects were as follows (Table 41):

- Nivo+chemo: decreased absolute neutrophil count (29.3%), decreased haemoglobin (13.9%), decreased absolute lymphocytes (12.2%), decreased leukocytes (11.8%), and decreased platelet count (6.8%)
- Chemo: decreased absolute neutrophil count (22.8%), decreased haemoglobin (9.5%), decreased absolute lymphocytes (9.2%), and decreased leukocytes (9.0%)

Serum chemistry

Liver tests

During the treatment period, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases were reported more frequently with nivo+chemo (37.0% and 51.7%, respectively) compared with chemo (29.5% and 47.5%, respectively) (Table 41).

Based on laboratory results reported after the first dose and within 30 days of last dose of study therapy, 13/764 (1.7%) subjects in the nivo+chemo arm had concurrent ALT or AST > 3 × upper limit of normal (ULN) with total bilirubin > 2 × ULN within 1 or 30 days, while 6/737 (0.8%) and 7/737 (0.9%) subjects in the chemo arm had concurrent ALT or AST > 3 × ULN with total bilirubin > 2 × ULN within 1 day and within 30 days, respectively (Table 42).

There were 13 subjects in the nivo+chemo arm and 7 subjects in the chemo arm with concurrent ALT or AST >3×ULN with total bilirubin >2×ULN).

In the nivo+chemo arm:

- In 3 subjects, the abnormal hepatic laboratory findings were reported as related to nivolumab alone or to both nivolumab and chemotherapy.
  - All 3 subjects were treated with high dose immune-modulating medication (IMM) and improved after treatment. This improvement supported the etiology as immune-mediated.
  - In 1 of the 3 subjects, the abnormal hepatic laboratory findings led to study treatment discontinuation.
- In 10 subjects, the abnormal hepatic laboratory findings were reported as not-related to study treatment, and other etiologies were implicated.
  - In 6 subjects, abnormal hepatic laboratory findings were due to disease progression with liver or pancreatic metastasis (new lesions or increased existing lesions).
  - In 4 subjects, abnormal hepatic laboratory findings were due to biliary duct stone or biliary duct infections.

In the chemo arm:

- In 2 subjects, abnormal hepatic laboratory findings were reported as related to chemotherapy.

- In both subjects, the abnormal hepatic laboratory findings led to study treatment discontinuation.

- In 5 subjects, abnormal hepatic laboratory findings were due to disease progression with liver metastasis (new lesions or existing lesion increased).

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 (increased) were primarily reported as Grade 1 or 2. Grade 3-4 increased creatinine level was reported in 8 (1.0%) subjects in the nivo+chemo arm and 4 (0.5%) subjects in the chemo arm (Table 41).

Thyroid function tests

Thyroid-stimulating hormone (TSH) increases (> ULN) from baseline (≤ ULN) were reported in 158/709 (22.3%) subjects in the nivo+chemo arm, and 8/146 (5.5%) subjects in the chemo arm. Decreases (< lower limit of normal [LLN]) from baseline (>= LLN) were reported in 104/709 (14.7%) subjects in the nivo+chemo arm, and 2/146 (1.4%) subjects in the chemo arm (Table 43).

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 or 4 abnormalities in electrolytes were observed in ≥ 5% of treated subjects with on-treatment laboratory results (Table 41):

- Nivo+chemo: hypokalaemia (6.5%), hyponatraemia (6.3%)
- Chemo: hyponatraemia (5.5%)

Table 49. Summary of On-Treatment Worst CTC Grade (Grade 1-4 and Grade 3-4) Laboratory Parameters that Worsened Relative to Baseline with 30 Days Follow Up - (SI Conventional Units) - All Treated Subjects

	Number of Subjects (%)					
	Nivo + Chemo			Chemo		
Lab Test Description	N(A)	Grade 1-4	Grade 3-4	N(A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	765	450 (58.8)	106 (13.9)	735	439 (59.7)	70 (9.5)
PLATELET COUNT	762	515 (67.6)	52 (6.8)	732	458 (62.6)	32 (4.4)
LEUKOCYTES	764	524 (68.6)	90 (11.8)	733	433 (59.1)	66 (9.0)
LYMPHOCYTES (ABSOLUTE)	763	446 (58.5)	93 (12.2)	732	361 (49.3)	67 (9.2)
ABSOLUTE NEUTROPHIL COUNT	764	556 (72.8)	224 (29.3)	732	456 (62.3)	167 (22.8)
ASPARTATE AMINOTRANSFERASE	764	395 (51.7)	35 (4.6)	731	347 (47.5)	14 (1.9)
ALANINE AMINOTRANSFERASE	764	283 (37.0)	26 (3.4)	731	216 (29.5)	14 (1.9)
BILIRUBIN, TOTAL	761	182 (23.9)	23 (3.0)	732	163 (22.3)	15 (2.0)
CREATININE	765	115 (15.0)	8 (1.0)	735	67 (9.1)	4 (0.5)
HYPERNATREMIA	767	84 (11.0)	4 (0.5)	733	52 (7.1)	0
HYPONATREMIA	767	258 (33.6)	48 (6.3)	733	177 (24.1)	40 (5.5)
HYPERKALEMIA	766	110 (14.4)	11 (1.4)	733	77 (10.5)	5 (0.7)
HYPOKALEMIA	766	203 (26.5)	50 (6.5)	733	177 (24.1)	35 (4.8)
HYPERCALCEMIA	748	46 (6.1)	2 (0.3)	725	41 (5.7)	1 (0.1)
HYPOCALCEMIA	748	326 (43.6)	12 (1.6)	725	271 (37.4)	7 (1.0)
HYPERGLYCEMIA	408	166 (40.7)	17 (4.2)	407	155 (38.1)	11 (2.7)
HYPOGLYCEMIA	407	48 (11.8)	3 (0.7)	405	37 (9.1)	1 (0.2)

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 GA.USPI.6.6

Table 102. On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects

Abnormality (%)	Nivo + Chemo N = 782	Chemo N = 767	Total N = 1549
	N = 766	N = 737	N = 1503
ALT OR AST > 3XULN	107 (14.0)	55 (7.5)	162 (10.8)
ALT OR AST > 5XULN	42 (5.5)	18 (2.4)	60 (4.0)
ALT OR AST > 10XULN	13 (1.7)	2 (0.3)	15 (1.0)
ALT OR AST > 20XULN	3 (0.4)	1 (0.1)	4 (0.3)
	N = 764	N = 737	N = 1501
TOTAL BILIRUBIN > 2XULN	39 (5.1)	41 (5.6)	80 (5.3)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	13 (1.7)	6 (0.8)	19 (1.3)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	13 (1.7)	7 (0.9)	20 (1.3)

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.7.6.4 [SI units]

Table 43. On-Treatment Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All Treated Subjects With At Least One On-Treatment TSH Measurement

Abnormality (%)	Nivo + Chemo N = 709	Chemo N = 146	Total N = 855
TSH > ULN	222 (31.3)	25 (17.1)	247 (28.9)
TSH > ULN WITH TSH <= ULN AT BASELINE	158 (22.3)	8 (5.5)	166 (19.4)
TSH > ULN WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	111 (15.7)	12 (8.2)	123 (14.4)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	84 (11.8)	8 (5.5)	92 (10.8)
WITH FT3/FT4 TEST MISSING (A)(B)	27 (3.8)	5 (3.4)	32 (3.7)
TSH < LLN	119 (16.8)	6 (4.1)	125 (14.6)
TSH < LLN WITH TSH >= LLN AT BASELINE	104 (14.7)	2 (1.4)	106 (12.4)
TSH < LLN WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	45 (6.3)	3 (2.1)	48 (5.6)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	57 (8.0)	2 (1.4)	59 (6.9)
WITH FT3/FT4 TEST MISSING (A)(B)	17 (2.4)	1 (0.7)	18 (2.1)

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

Source: Table S.7.6.3 [SI units]

Pregnancy tests

All pregnancy tests were negative during the study.

Vital signs and physical findings

Vital signs and oxygen saturation by pulse oximetry were monitored and recorded at the site per institutional standard of care during screening and treatment visits. These assessments were intended to be used as safety monitoring by the treating physician. Any clinically meaningful safety events related to these vital signs were captured and reported as adverse events (AEs) or serious adverse events (SAEs) (Table 30). There was a higher frequency of vital sign related AEs and SAEs in nivo+chemo vs. chemo treated subjects, consistent with the entire safety profile; however, overall these events were infrequent. The majority of events in both treatment arms were Grade 1-2, and Grade 3-4 events were rare. There was 1 drug-related Grade 5 febrile neutropenia event reported in the nivo+chemo arm, as well as 2 Grade 5 arrhythmia events (1 in each treatment arm) that were unrelated to study treatment.

Table 44. Summary of Adverse Events Related to Vital Signs - All Treated Subjects from CA209649 (10-Jul-2020 Database Lock)

Safety Parameters	No. of Subjects (%)			
	Nivo+Chemo (N =782)		Chemo (N =767)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs				
Pyrexia	20 (2.6)	5 (0.6)	10 (1.3)	3 (0.4)
Febrile neutropenia	18 (2.3)	16 (2.0)	7 (0.9)	7 (0.9)
Hypotension	1 (0.1)	1 (0.1)	0	0
Arrhythmia	1 (0.1)	0	1 (0.1)	0
Tachycardia	1 (0.1)	0	1 (0.1)	0
Drug-related SAEs				
Febrile neutropenia	16 (2.0)	14 (1.8)	6 (0.8)	6 (0.8)
Pyrexia	8 (1.0)	3 (0.4)	3 (0.4)	1 (0.1)
All-causality AEs				
Pyrexia	147 (18.8)	8 (1.0)	83 (10.8)	3 (0.4)
Hypertension	41 (5.2)	19 (2.4)	32 (4.2)	11 (1.4)
Hypotension	24 (3.1)	4 (0.5)	15 (2.0)	1 (0.1)
Febrile neutropenia	22 (2.8)	19 (2.4)	11 (1.4)	11 (1.4)
Chills	16 (2.0)	0	12 (1.6)	0
Tachycardia	12 (1.5)	0	6 (0.8)	0
Bradycardia	1 (0.1)	0	3 (0.4)	0
Arrhythmia	1 (0.1)	0	1 (0.1)	0
Drug-related AEs				
Pyrexia	64 (8.2)	4 (0.5)	22 (2.9)	1 (0.1)
Febrile neutropenia	20 (2.6)	17 (2.2)	9 (1.2)	9 (1.2)
Hypertension	9 (1.2)	5 (0.6)	5 (0.7)	2 (0.3)
Chills	5 (0.6)	0	4 (0.5)	0
Hypotension	4 (0.5)	0	2 (0.3)	0
Tachycardia	3 (0.4)	0	1 (0.1)	0
Bradycardia	1 (0.1)	0	0	0

MedDRA Version: 23.0; CTC Version 4.0. Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Refer to Table S.6.1.1.1 (All-causality AEs), Table S.6.1.32.3 (Drug-related AEs), Table S.6.3.1.2.5 (All-causality SAEs), and Table S.6.3.1.2.6 (Drug-related SAEs) of the CA209649 Primary CSR

Safety in special populations

Intrinsic and extrinsic factors

The frequencies of drug-related AEs in the nivo+chemo arm for subgroups of age, gender, race, geographic region are shown in Table 45. The following differences were observed:

- Among all nivo+chemo treated subjects, the frequencies of drug-related Grade 3-4 AEs in the US (includes US and Canada) (72.1%) appeared to be higher than those in other regions (Asia [54.2%] and ROW [57.4%) and also higher compared with the all-treated population (59.1%).
  - Of note, drug-related Grade 3-4 AEs in the nivo+chemo arm were higher with nivo+FOLFOX (67.8%) compared with nivo+XELOX (48.9%) and drug-related Grade 3-4 AEs in the chemo arm were higher with FOLFOX (49.5%) compared with XELOX (38.8%). Most treated subjects from the US and Canada received FOLFOX: 92.2% (119/129) of subjects in the nivo+chemo arm and 91.1% (113/124) of subjects in the chemo arm.
- In both treatment arms, the frequencies of Grade 3-4 drug-related AEs appeared to be higher in female subjects compared with male subjects (67.5% vs. 55.2% in the nivo+chemo arm, 54.9% vs. 40.1% in the chemo arm).
- The frequencies of Grade 3-4 drug-related AEs in the nivo+chemo arm were numerically higher (with at least a 10% difference) compared with the chemo arm for the most of the subgroups of age, gender, race and geographic region; this is consistent with all treated subjects, where drug-related Grade 3-4 AEs were 14.6% higher with nivo+chemo vs. chemo.

Table 45. Drug-Related Adverse Events by Worst CTC Grade and by Age, Gender, Race, Region, and Chemotherapy Backbone - All Treated Subjects (CA209649)

	Drug-related Adverse Events (n/N [%])					
	Nivo+Chemo			Chemo		
	Any Grade	Grade 3-4	Grade 5[a]	Any Grade	Grade 3-4	Grade 5[a]
Total	738/782 (94.4)	462/782 (59.1)	4/782 (0.5)	679/767 (88.5)	341/767 (44.5)	0
By Age (years)						
< 65	445/470 (94.7)	270/470 (57.4)	1/470 (0.2)	419/475 (88.2)	208/475 (43.8)	0
≥ 65	293/312 (93.9)	192/312 (61.5)	3/312 (1.0)	260/292 (89.0)	133/292 (45.5)	0
≥ 65 and < 75	219/235 (93.2)	145/235 (61.7)	2/235 (0.9)	202/221 (91.4)	98/221 (44.3)	0
≥ 75	74/77 (96.1)	47/77 (61.0)	1/77 (1.3)	58/71 (81.7)	35/71 (49.3)	0
≥ 75 and < 85	72/75 (96.0)	46/75 (61.3)	1/75 (1.3)	53/65 (81.5)	33/65 (50.8)	0
≥ 85	2/2 (100.0)	1/2 (50.0)	0	5/6 (83.3)	2/6 (33.3)	0
By Sex						
Male	499/533 (93.6)	294/533 (55.2)	3/533 (0.6)	476/543 (87.7)	218/543 (40.1)	0
Female	239/249 (96.0)	168/249 (67.5)	1/249 (0.4)	203/224 (90.6)	123/224 (54.9)	0
By Race						
White	517/551 (93.8)	332/551 (60.3)	4/551 (0.7)	449/523 (85.9)	228/523 (43.6)	0
Asian (including China)	182/185 (98.4)	104/185 (56.2)	0	174/183 (95.1)	87/183 (47.5)	0
By Region						
North America	125/129 (96.9)	93/129 (72.1)	0	118/124 (95.2)	63/124 (50.8)	0
Rest of the World	439/476 (92.2)	273/476 (57.4)	4/476 (0.8)	396/469 (84.4)	198/469 (42.2)	0
Asia (including China)	174/177 (98.3)	96/177 (54.2)	0	165/174 (94.8)	80/174 (46.0)	0
By Chemo						
XELOX	342/360 (95.0)	176/360 (48.9)	2/360 (0.6)	314/361 (87.0)	140/361 (38.8)	0
FOLFOX	396/422 (93.8)	286/422 (67.8)	2/422 (0.5)	365/406 (89.9)	201/406 (49.5)	0

[a] 12 subjects in the nivo+chemo arm and 4 subjects in the chemo arm died due to study drug toxicity per investigator assessment. Note that only events that led to death within 24 hours were documented as Grade 5. Events leading to death > 24 hours after onset were reported with the grade at presentation.

MedDRA Version: 23.0; CTC Version 4.0; Includes events reported between first dose and 30 days after last dose of study therapy.

Database lock: 10-Jul-2020; Minimum follow-up was 12.1 months

Source: refer to Table S.6.1.32.3 (all treated), Table S.6.1.5.7 (age), Table S.6.1.5.5 (sex), Table S.6.1.5.6 (race), Table S.6.1.5.8 (region), and Table S.6.1.7.2 (chemo) in the CA209649 Primary CSR)

The special population "age groups" is discussed in more detail. The frequencies of all causality total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group are presented for nivo+chemo and chemo treated subjects in Table 46.

The frequencies of all causality AEs for subgroups of age < 65, 65 to 74, and 75 to 84 years were generally similar to the frequencies reported for the overall study population by treatment, with a few exceptions:

- Nivo+chemo:
  - Numerically lower frequencies (≥ 10% difference) were reported in the 75 to 84 years of age subgroup vs. the overall population for total SAEs (41.3% vs. 54.1), SAEs with

hospitalization/prolongation (34.7% vs. 46.9%), and anticholinergic syndrome (22.7% vs. 35.8%).

- Chemo:
  - Numerically higher frequencies (≥ 10% difference) were reported in the 75 to 84 years of age subgroup vs. the overall population for SAEs with fatal (death) outcome (27.7% vs. 13.8%), and sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures (21.5% vs. 10.4%).

Interpretation is limited by the small number of subjects in the > 85 years of age subgroup.

Safety in subgroups by chemotherapy backbone

Safety data for all treated subjects by chemotherapy backbone (XELOX and FOLFOX) are presented in Table 47. The frequencies of any grade AEs (all causality) and drug-related AEs were generally similar between the nivo+chemo arm compared with the chemo arm regardless of the backbone chemotherapy (FOLFOX or XELOX); however numerically higher frequencies of Grade 3-4 AEs (all causality) and Grade 3-4 drug-related AEs were observed in the nivo+chemo arm compared with the chemo arm, regardless of the backbone chemotherapy (FOLFOX or XELOX). Also numerically higher frequencies of Grade 3-4 all causality AEs and Grade 3-4 drug-related AEs were observed in subjects who received FOLFOX as backbone chemotherapy compared with XELOX; this was observed in both the nivo+chemo and chemo arms. The frequencies of all causality and drug-related select AEs and IMAEs were generally similar between nivo+FOLFOX and nivo+XELOX.

Safety in subjects with PD-L1 CPS ≥ 5 and CPS ≥ 1

Safety data for all treated subjects with PD-L1 CPS ≥ 5 in the nivo+chemo and the chemo arms were consistent with the safety data for all treated subjects.

With nivo+chemo treatment, the overall frequency of death was numerically higher for subjects with PD-L1 CPS < 5 (73.9%) compared with subjects with PD-L1 CPS ≥ 5 (65.2%). This difference was attributed mainly to disease progression, where the frequency was 65.0% in subjects with PD-L1 CPS < 5 vs. 55.6% in subjects with PD-L1 CPS ≥ 5. The frequency of death due to study drug toxicity for treated subjects in the nivo+chemo arm was comparable for subjects with PD-L1 CPS < 5 (1.0%) and subjects with PD-L1 CPS ≥ 5 (1.7%). The frequencies of AEs (all causality and drug-related), SAEs (all causality and drug-related), AEs leading to discontinuation (all causality and drug-related), select AEs, and OESI were comparable in subjects with PD-L1 CPS ≥ 5 and PD-L1 CPS < 5. The numerically higher frequencies of all causality and drug related SAEs and AEs leading to discontinuation that were observed with nivo+chemo vs. chemo in all treated subjects, were also observed in the PD-L1 CPS ≥ 5 and < 5 subgroups (with similar differences for nivo+chemo vs. chemo in the 2 subgroups).

Also for the subgroup with PD-L1 CPS ≥ 1, safety data were consistent with the safety data for all treated subjects.

Table 46. Summary of Safety Results by Age Group - All Treated Subjects

Treatment group: Nivolumab + Chemotherapy N = 782

MedDRA Terms (%)	Age Group (Years) < 65 N = 470	65-74 N = 235	75-84 N = 75	>= 85 N = 2	Total N = 782
TOTAL SUBJECTS WITH AN EVENT	468 (99.6)	232 (98.7)	74 (98.7)	2 (100.0)	776 (99.2)
SERIOUS AE - TOTAL	260 (55.3)	131 (55.7)	31 (41.3)	1 (50.0)	423 (54.1)
FATAL (DEATH)	73 (15.5)	44 (18.7)	11 (14.7)	0	128 (16.4)
HOSPITALIZATION/PROLONGATION	229 (48.7)	111 (47.2)	26 (34.7)	1 (50.0)	367 (46.9)
LIFE-THREATENING	15 (3.2)	7 (3.0)	2 (2.7)	0	24 (3.1)
CANCER	3 (0.6)	1 (0.4)	0	0	4 (0.5)
DISABILITY/INCAPACITY	3 (0.6)	0	0	0	3 (0.4)
AE LEADING TO DISCONTINUATION	210 (44.7)	121 (51.5)	39 (52.0)	1 (50.0)	371 (47.4)
PSYCHIATRIC DISORDERS	65 (13.8)	32 (13.6)	11 (14.7)	0	108 (13.8)
NERVOUS SYSTEM DISORDERS	313 (66.6)	151 (64.3)	53 (70.7)	0	517 (66.1)
ACCIDENT AND INJURIES	29 (6.2)	15 (6.4)	8 (10.7)	1 (50.0)	53 (6.8)
CARDIAC DISORDERS	30 (6.4)	20 (8.5)	6 (8.0)	0	56 (7.2)
VASCULAR DISORDERS	69 (14.7)	40 (17.0)	17 (22.7)	1 (50.0)	127 (16.2)
CEREBROVASCULAR DISORDERS	7 (1.5)	8 (3.4)	3 (4.0)	0	18 (2.3)
INFECTIONS AND INFESTATIONS	161 (34.3)	99 (42.1)	23 (30.7)	0	283 (36.2)
ANTICHOLINERGIC SYNDROME	168 (35.7)	95 (40.4)	17 (22.7)	0	280 (35.8)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	45 (9.6)	31 (13.2)	6 (8.0)	1 (50.0)	83 (10.6)

Treatment group: Chemotherapy N = 767

MedDRA Terms (%)	Age Group (Years) < 65 N = 475	65-74 N = 221	75-84 N = 65	>= 85 N = 6	Total N = 767
TOTAL SUBJECTS WITH AN EVENT	466 (98.1)	219 (99.1)	61 (93.8)	6 (100.0)	752 (98.0)
SERIOUS AE - TOTAL	202 (42.5)	96 (43.4)	33 (50.8)	4 (66.7)	335 (43.7)
FATAL (DEATH)	55 (11.6)	32 (14.5)	18 (27.7)	1 (16.7)	106 (13.8)
HOSPITALIZATION/PROLONGATION	175 (36.8)	78 (35.3)	25 (38.5)	3 (50.0)	281 (36.6)
LIFE-THREATENING	11 (2.3)	5 (2.3)	0	0	16 (2.1)
CANCER	3 (0.6)	1 (0.5)	0	0	4 (0.5)
DISABILITY/INCAPACITY	0	0	0	0	0
AE LEADING TO DISCONTINUATION	142 (29.9)	77 (34.8)	29 (44.6)	3 (50.0)	251 (32.7)
PSYCHIATRIC DISORDERS	64 (13.5)	20 (9.0)	6 (9.2)	1 (16.7)	91 (11.9)
NERVOUS SYSTEM DISORDERS	295 (62.1)	132 (59.7)	40 (61.5)	5 (83.3)	472 (61.5)
ACCIDENT AND INJURIES	22 (4.6)	20 (9.0)	8 (12.3)	0	50 (6.5)
CARDIAC DISORDERS	26 (5.5)	14 (6.3)	2 (3.1)	0	42 (5.5)
VASCULAR DISORDERS	48 (10.1)	37 (16.7)	4 (6.2)	1 (16.7)	90 (11.7)
CEREBROVASCULAR DISORDERS	5 (1.1)	5 (2.3)	2 (3.1)	0	12 (1.6)
INFECTIONS AND INFESTATIONS	110 (23.2)	54 (24.4)	19 (29.2)	1 (16.7)	184 (24.0)
ANTICHOLINERGIC SYNDROME	129 (27.2)	55 (24.9)	17 (26.2)	1 (16.7)	202 (26.3)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	43 (9.1)	23 (10.4)	14 (21.5)	0	80 (10.4)

MedDRA Version: 23.0; CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy
Source: Appendix GC.424-EUSCS

Table 47. Summary of Safety in Subgroups by Chemotherapy Backbone - All Treated Subjects

Safety Parameters	No. of Subjects (%)							
	XELOX				FOLFOX			
	Nivo + XELOX (N=360)		XELOX (N=361)		Nivo + FOLFOX (N=422)		FOLFOX (N=406)	
	Adverse Event Grades							
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality AEs	357 (99.2)	209 (58.1)	353 (97.8)	192 (53.2)	419 (99.3)	331 (78.4)	399 (98.3)	264 (65.0)
Drug-Related AEs	342 (95.0)	176 (48.9)	314 (87.0)	140 (38.8)	396 (93.8)	286 (67.8)	365 (89.9)	201 (49.5)
All-causality Select AEs								
Endocrine	59 (16.4)	5 (1.4)	5 (1.4)	1 (0.3)	58 (13.7)	2 (0.5)	9 (2.2)	0
Gastrointestinal	139 (38.6)	19 (5.3)	118 (32.7)	19 (5.3)	176 (41.7)	29 (6.9)	142 (35.0)	10 (2.5)
Hepatic	142 (39.4)	23 (6.4)	109 (30.2)	13 (3.6)	125 (29.6)	22 (5.2)	77 (19.0)	16 (3.9)
Pulmonary	14 (3.9)	3 (0.8)	4 (1.1)	0	27 (6.4)	11 (2.6)	2 (0.5)	1 (0.2)
Renal	28 (7.8)	1 (0.3)	10 (2.8)	4 (1.1)	30 (7.1)	10 (2.4)	14 (3.4)	3 (0.7)
Skin	137 (38.1)	15 (4.2)	82 (22.7)	3 (0.8)	125 (29.6)	12 (2.8)	55 (13.5)	4 (1.0)
Hypersensitivity/ Infusion Reaction	40 (11.1)	6 (1.7)	20 (5.5)	5 (1.4)	78 (18.5)	13 (3.1)	25 (6.2)	6 (1.5)
Drug-Related Select AEs								
Endocrine	55 (15.3)	3 (0.8)	0	0	52 (12.3)	2 (0.5)	3 (0.7)	0
Gastrointestinal	115 (31.9)	17 (4.7)	98 (27.1)	17 (4.7)	147 (34.8)	26 (6.2)	109 (26.8)	8 (2.0)
Hepatic	113 (31.4)	17 (4.7)	80 (22.2)	7 (1.9)	90 (21.3)	12 (2.8)	54 (13.3)	9 (2.2)
Pulmonary	14 (3.9)	3 (0.8)	3 (0.8)	0	26 (6.2)	11 (2.6)	1 (0.2)	1 (0.2)
Renal	10 (2.8)	0	3 (0.8)	0	16 (3.8)	6 (1.4)	5 (1.2)	1 (0.2)
Skin	116 (32.2)	14 (3.9)	74 (20.5)	3 (0.8)	98 (23.2)	12 (2.8)	31 (7.6)	3 (0.7)
Hypersensitivity/ Infusion Reaction	37 (10.3)	4 (1.1)	19 (5.3)	5 (1.4)	74 (17.5)	13 (3.1)	23 (5.7)	6 (1.5)

Safety Parameters	No. of Subjects (%)							
	XELOX				FOLFOX			
	Nivo + XELOX (N=360)		XELOX (N=361)		Nivo + FOLFOX (N=422)		FOLFOX (N=406)	
	Adverse Event Grades							
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality IMAEs within 100 days of last dose treated with Immune Modulating Medication								
Diarrhea/Colitis	13 (3.6)	7 (1.9)	0	0	13 (3.1)	10 (2.4)	0	0
Hepatitis	12 (3.3)	8 (2.2)	0	0	7 (1.7)	5 (1.2)	0	0
Pneumonitis	11 (3.1)	4 (1.1)	0	0	22 (5.2)	11 (2.6)	0	0
Nephritis/Renal Dysfunction	1 (0.3)	0	0	0	3 (0.7)	2 (0.5)	0	0
Rash	25 (6.9)	5 (1.4)	1 (0.3)	0	26 (6.2)	6 (1.4)	3 (0.7)	0
Hypersensitivity/ Infusion Reaction	NR	NR	NR	NR	6 (1.4)	1 (0.2)	0	0
All-causality Endocrine IMAEs within 100 days of last dose with or without Immune Modulating Medication								
Adrenal Insufficiency	2 (0.6)	0	1 (0.3)	1 (0.3)	3 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Hypophysitis	5 (1.4)	2 (0.6)	0	0	1 (0.2)	1 (0.2)	0	0
Hypothyroidism/ thyroiditis	29 (8.1)	0	1 (0.3)	0	45 (10.7)	0	5 (1.2)	0
Diabetes Mellitus	2 (0.6)	1 (0.3)	0	0	NR	NR	NR	NR
Hyperthyroidism	14 (3.9)	0	2 (0.6)	0	9 (2.1)	0	0	0

MedDRA v23.0; CTC v4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated (e.g. any time for deaths, 100 days for IMAEs).
Abbreviations: AEs - adverse events, CTC - Common Toxicity Criteria, DC - discontinuation, IMAEs - immune-mediated adverse events, IMM - immune modulating medication, MedDRA - Medical Dictionary for Regulatory Activities, NR - none reported; OESI - other events of special interest, SAEs - serious adverse events
Source: Refer to Table S.6.1.7.1 (all causality AEs), Table S.6.1.7.2 (drug-related AEs), of the CA209649 Primary CSR[1] and Table S.6.5.2.1.A.1 (all causality Select AEs), Table S.6.5.2.1.A.2 (Select endocrine AEs), Table S.6.5.2.1.A.3 (drug-related Select AEs), Table S.6.5.2.1.A.4 (drug-related endocrine AEs), Table S.6.202.1.A.2 (IMAEs), Table S.6.202.1.A.1 (endocrine IMAEs) in Appendix 1

Safety related to drug-drug interactions and other interactions

No data provided.

Discontinuation due to adverse events

AEs leading to discontinuation were defined as events when 1 or more study drugs of a multidrug regimen were discontinued, even if the subject remained on treatment or in follow-up. The overall frequencies of all-causality and drug-related AEs leading to discontinuation were numerically higher in the nivo+chemo arm compared with the chemo arm (Table 30).

Any-grade AEs leading to discontinuation (regardless of causality) were reported in 371 (47.4%) subjects in the nivo+chemo arm, and 251 (32.7%) subjects in the chemo arm (Table 30). Grade 3-4 AEs leading to discontinuation were reported in 194 (24.8%) subjects in the nivo+chemo arm, and 113 (14.7%) subjects in the chemo arm.

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

- Nivo+chemo: neuropathy peripheral (7.8%), malignant neoplasm progression (4.7%), and peripheral sensory neuropathy (4.5%).
- Chemo: neuropathy peripheral (5.3%), peripheral sensory neuropathy (4.7%) and malignant neoplasm progression (3.7%).

Any-grade drug-related AEs leading to discontinuation were reported in 284 (36.3%) subjects in the nivo+chemo arm, and 181 (23.6%) subjects in the chemo arm. Grade 3-4 AEs leading to discontinuation were reported in 132 (16.9%) subjects in the nivo+chemo arm, and 67 (8.7%) subjects in the chemo arm.

The most common drug-related AEs leading to discontinuation were:

- Nivo+chemo: neuropathy peripheral (7.5%) and peripheral sensory neuropathy (4.5%).
- Chemo: neuropathy peripheral (5.2%) and peripheral sensory neuropathy (4.7%).

The most common reason for AEs leading to dose delays or reductions in both the nivo+chemo and chemo arms was haematologic toxicity. Dose reductions were not permitted with nivolumab treatment, but they were permitted with chemotherapy as per local standard. The most frequently reported AEs of any grade leading to dose delay or reduction were as follows:

- Nivo+chemo arm: neutropaenia (20.1%), decreased neutrophil count (13.7%), decreased platelet count (10.7%), thrombocytopaenia (10.1%), and diarrhoea (7.8%).
- Chemo arm: neutropaenia (16.6%), decreased neutrophil count (10.2%), decreased platelet count (8.3%), thrombocytopaenia (7.0%), and diarrhoea (6.8%).

The most frequently reported drug-related AEs of any grade leading to dose delay or reduction were as follows:

- Nivo+chemo arm: neutropaenia (18.2%), decreased neutrophil count (13.2%), decreased platelet count (10.5%), thrombocytopaenia (9.5%), and diarrhoea (7.3%).
- Chemo arm: neutropaenia (15.9%), decreased neutrophil count (9.9%), decreased platelet count decreased (8.0%), thrombocytopaenia (6.8%), and diarrhoea (6.4%).

Immunological events

Of the 681 nivolumab ADA evaluable subjects in the nivo+chemo arm, 33 (4.8%) subjects were nivolumab ADA positive at baseline and 60 (8.8%) subjects were nivolumab ADA positive after the start of treatment (Table 4.1.2-1). The number of nivolumab ADA positive subjects was similar in subjects who received nivo+XELOX vs. nivo+FOLFOX (33 [10.3%] vs. 27 [7.5%]).

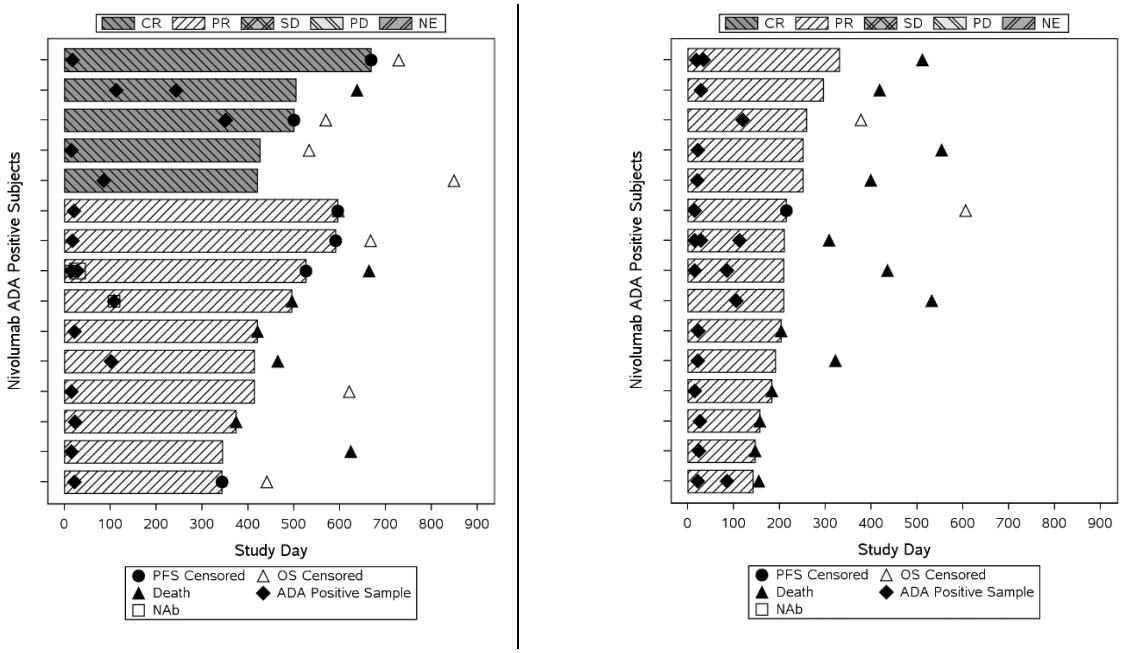
- One (0.1%) subject was considered persistent positive and 2 (0.3%) subjects were neutralizing ADA positive.
- The highest titer value observed in nivolumab ADA positive subjects was 256. All other titers were low, ranging from 0 to 32.

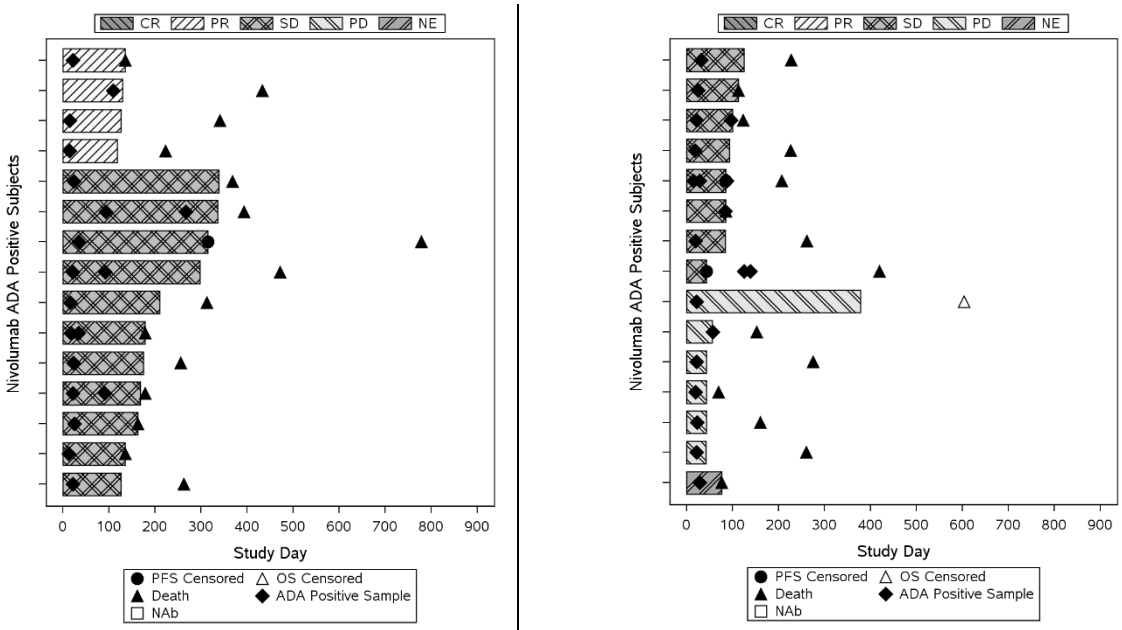
Effect of immunogenicity on efficacy

Of the 60 subjects that were nivolumab ADA positive after nivo+chemo treatment, 5 subjects (8.3%) had a CR, 29 (48.3%) had a PR, and 19 (31.7%) had SD. The ORR among the ADA positive subjects (56.7%) was similar to the ORR (58.0%) in all randomized subjects in the nivo+chemo arm. An ADA positive result at the first testing timepoint did not appear to correlate with early disease progression or death. For the 2 subjects with neutralizing ADA positive, both had PR with a PFS of more than 1 year. Overall, the incidence of ADA or neutralizing ADA did not appear to have negative effects on the efficacy of nivo+chemo in this population.

A swimmers plot of ADA and NAb occurrence in relation to PFS, BOR per BICR and OS in all randomized subjects is presented in Figure 21.

Figure 91. Anti-Drug Antibody and NAb Occurence in Relation to PFS, BOR per BICR and OS - All Treated Subjects with ADA Positive





Bar indicates progression free survival. Source: Figure S.7.2

Effect of immunogenicity on safety

The effect of immunogenicity on safety was assessed in the nivo+chemo arm. The frequency of hypersensitivity/infusion reactions in the ADA-evaluable subjects was 18.3% (11/60) in nivolumab ADA positive subjects and 15.8% (98/621) in nivolumab ADA negative subjects (Table 48).

Table 48. Select Adverse Events of Hypersensitivity/Infusion Reaction by ADA status (Positive, Negative) - All Treated Subjects with ADA Positive or ADA Negative

	Nivo + Chemo	
Preferred Term (%)	Nivolumab ADA Positive N = 60	Nivolumab ADA Negative N = 621
TOTAL SUBJECTS WITH AN EVENT	11 (18.3)	98 (15.8)
Anaphylactic reaction	2 (3.3)	3 (0.5)
Bronchospasm	0	1 (0.2)
Hypersensitivity	3 (5.0)	45 (7.2)
Infusion related hypersensitivity reaction	0	3 (0.5)
Infusion related reaction	6 (10.0)	57 (9.2)

MedDRA Version: 23.0
CTC Version 4.0
Includes events between first dose and within the last dose of therapy + 100 days.
Source: Table S.7.11

Post marketing experience

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and in the EU, and for other indications as monotherapy (e.g., metastatic NSCLC, advanced renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, and esophageal squamous cell carcinoma). In US, nivolumab monotherapy was also approved for hepatocellular carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, and small cell lung cancer.

The MAH states that based on pharmacovigilance activities conducted by BMS Worldwide Patient Safety, review of post marketing safety data is consistent with, and confirms the clinical trial safety data for

nivolumab. The safety profile of nivolumab in the post marketing setting remains favourable. Post marketing data for nivolumab are subject to continued active pharmacovigilance monitoring and reporting as per applicable safety reporting requirements. Continuous safety monitoring ensures that updated safety information is available in a timely manner and that any future changes to the benefit-risk profile of nivolumab are appropriately managed and reported. For the most current company assessment of post marketing data and risk management actions for nivolumab, the MAH refers to nivolumab Periodic Benefit-Risk Evaluation Report (PBRER) Number 10 (submitted in a separate procedure).

Safety to support the SmPC

In Section 4.8 of the proposed OPDIVO SmPC for the current application, a new column for the CA209649 data is added to the adverse reaction table (Table 8), which contains approved data for Study CA2099LA (Adverse reactions with nivolumab in combination with other therapeutic agents). The newly added column is for the 782 subjects with advanced or metastatic GC/GEJC/EAC from Study CA209649 treated with first-line nivo+chemo (nivolumab 240 mg + FOLFOX Q2W or nivolumab 360 mg + XELOX Q3W). This regimen has a different composition than other approved regimens; therefore, these data are not pooled.

Also in Section 4.8 of the proposed OPDIVO SmPC for the current application, a new column in Table 11 has been added (Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen, nivolumab in combination with other therapeutic agents). The newly added column presents data for nivo+chemo (nivolumab 240 mg + FOLFOX Q2W or nivolumab 360 mg + XELOX Q3W) for the first-line treatment of advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma (CA209649).

Remapping of preferred terms

Some Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) were remapped for the purposes of generating summary tables to support Section 4.8 of the nivolumab SmPC (nivolumab 240 mg + FOLFOX Q2W or nivolumab 360 mg + XELOX Q3W in first-line advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma). Remapping allows for pooling of PTs representing the same or similar clinical conditions.

Identification of clinically relevant adverse reactions

Selection of specific adverse reactions to be presented in Section 4.4 and Section 4.8 of the nivolumab SmPC was based on clinical relevance as determined by the BMS medical reviewer. PTs that met 1 or more of the following criteria were excluded from the SmPC:

- Overly general/non-specific
- No suspected causal relationship to nivolumab per BMS medical review
- Single case events with limited data
- Medical concept captured under a different term

Presentation of clinically relevant adverse reactions

The list of clinically relevant adverse reactions with nivolumab in combination with chemotherapy in gastric, GEJ, or oesophageal adenocarcinoma is presented in Table 49 alongside the approved data from CA2099LA (and also in Section 4.8 of the OPDIVO SmPC). In this table, the frequencies are presented by system organ class and by frequency grouping as follows: very common (≥ 1/10); common ≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 49. Adverse Reactions with Nivolumab in Combination with Chemotherapy or Ipilimumab and Chemotherapy

	Nivolumab in combination with chemotherapy	Nivolumab in combination with ipilimumab and chemotherapy
Infections and infestations		
Very common	upper respiratory tract infection	
Common	pneumonia	conjunctivitis, pneumonia, respiratory tract infection
Blood and lymphatic system disorders		
Common	febrile neutropaenia, eosinophilia	febrile neutropaenia
Uncommon		eosinophilia
Immune system disorders		
Common	hypersensitivity, infusion related reaction	infusion-related reaction, hypersensitivity
Endocrine disorders		
Very common		hypothyroidism
Common	hypothyroidism, hyperthyroidism	hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis
Uncommon	hypopituitarism, adrenal insufficiency, hypophysitis, diabetes mellitus	hypopituitarism, hypoparathyroidism
Metabolism and nutrition disorders		
Very common	decreased appetite	decreased appetite
Common		dehydration, hypoalbunaemia, hypophosphataemia
Nervous system disorders		
Very common	peripheral neuropathy, headache	
Common	paraesthesia , dizziness	peripheral neuropathy, dizziness
Uncommon	Guillain-Barré syndrome	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis
Eye disorders		
Common	dry eye, blurred vision	dry eye
Uncommon	uveitis	blurred vision, episcleritis
Cardiac disorders		
Common	tachycardia	
Uncommon	myocarditis	tachycardia, atrial fibrillation, bradycardia
Vascular disorders		
Common	thrombosis, hypertension	
Uncommon		hypertension
Respiratory, thoracic and mediastinal disorders		
Very common	cough	
Common	pneumonitis, dyspnoea	pneumonitis, dyspnoea, cough
Uncommon		pleural effusion
Gastrointestinal disorders		
Very common	diarrhoea, stomatitis, vomiting, nausea, abdominal pain, constipation	nausea, diarrhoea, vomiting
Common	colitis, dry mouth	constipation, stomatitis, abdominal pain, colitis, dry mouth, pancreatitis
Uncommon	pancreatitis	
Hepatobiliary disorders		
Common		hepatitis
Uncommon	hepatitis	
Skin and subcutaneous tissue disorders		

Very common	palmar-plantar erythrodysaesthaesia syndrome, rash[a]	rash[a], pruritus
Common	pruritus, skin hyperpigmentation, alopecia, dry skin, erythema	alopecia, dry skin, erythema, urticaria
Uncommon		psoriasis, Stevens-Johnson syndrome, vitiligo
Not known		lichen sclerosus, other lichen disorders
Musculoskeletal and connective tissue disorders		
Very common	musculoskeletal pain[b]	
Common	arthralgia, muscular weakness	musculoskeletal pain[b], arthralgia, arthritis
Uncommon		muscular weakness, muscle spasms, polymyalgia rheumatica
Renal and urinary disorders		
Common	renal failure,	renal failure (including acute kidney injury)
Uncommon	nephritis, cystitis noninfective[e]	nephritis, cystitis noninfective[e]
General disorders and administration site conditions		
Very common	fatigue, pyrexia, oedema (including peripheral oedema)	fatigue
Common		pyrexia, oedema (including peripheral oedema)
Uncommon		chills, chest pain
Investigations		
Very common	anaemia[c,d], thrombocytopaenia[c], leucopoenia[c], lymphopaenia[c], neutropaenia[c], increased transaminases[c], increased total bilirubin[c], increased creatinine[c], hypernatraemia[c], hyponatraemia[c], hyperkalaemia[c], hypokalaemia[c], hypocalcaemia[c], hypoglycaemia[c], hyperglycaemia[c], increased lipase, increased alkaline phosphatase, increased amylase	anaemia[c,d], thrombocytopaenia[c], leucopoenia[c], lymphopaenia[c], neutropaenia[c], increased alkaline phophatase[c], increased transaminases[c], increased creatinine[c], increased amylase[c], increased lipase[c], hypokalaemia[c], hypomagnesaemia[c], hyponatraemia[c]
Common	hypercalcaemia [c]	increased total bilirubin[c], increased thyroid stimulating hormone
Uncommon		increased gamma-glutamyltransferase

[a] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash macular, rash morbilliform, rash papular, rash generalised, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, drug eruption, exfoliative rash, nodular rash, and rash vesicular.

[b] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, spinal pain, and musculoskeletal discomfort.

[c] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements.

[d] Anaemia is a composite term which includes iron deficiency anaemia and haemoglobin decreased.

[e] Reported in clinical studies and in the post-marketing setting.

To calculate the frequencies of laboratory adverse reactions, the MAH used the laboratory abnormality change from baseline tables, except for hyperglycemia in advanced or metastatic GC/GEJC/EAC; hyperglycemia was based on the reported adverse reaction. This presentation is a conservative approach intended to capture the frequency of all laboratory abnormalities regardless of causality. In doing so, the denominator used to compute frequency is the number of patients for whom laboratory abnormalities data were reported, as opposed to all treated patients. Hence, there is variability in the denominator for each individual laboratory abnormality and their respective reported frequencies.

Posology and method of administration (section 4.2), and special warnings and precautions for use (section 4.4) - Update of information related to adverse reactions of special interest

Text on the proposed dosage and administration of OPDIVO in combination with XELOX or FOLFOX is provided in Section 4.2 of the OPDIVO SmPC.

Guidelines for permanent discontinuation or withholding of OPDIVO in combination with chemotherapy are provided in Section 4.2 of the OPDIVO SmPC.

Guidelines for the management of immune-related adverse reactions are provided in Section 4.4 of the OPDIVO SmPC. In this application, no amendments or changes in the management of immune-related adverse reactions is proposed based on the data from CA209649.

The following disease-specific precaution is added to Section 4.4 of the proposed OPDIVO SmPC: Patients who had baseline ECOG performance score ≥ 2, untreated CNS metastases, active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial in gastric, GEJ or oesophageal adenocarcinoma (see sections 4.5 and 5.1 of the OPDIVO SmPC). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis. Study CA209649 excluded patients with known HER2-positive status. Patients with undetermined status were allowed in the study and represented 40.3% of patients (see section 5.1 of the OPDIVO SmPC).

The MAH proposed to pool the following studies: nivolumab monotherapy, nivolumab in combination with chemotherapy, nivolumab in combination with ipilimumab (with or without chemotherapy), and maintain the nivolumab combination with cabozantinib separate due to the distinct safety profile.

The general approach will be that pooled data will be assessed side by side, to identify any potential differential safety profile of clinical relevance. Then, each pool will be displayed side by side with data from studies of the same tumour type within that pool. Based on these assessments text will be developed for the SmPC to describe any major potential differences of clinical relevance between and within pools warranting different management for an indication or specific treatment combination, or awareness.

The plan for pooling and assessment of the pooled data are acceptable, as in line with the SmPC Guidance and the approach as described in Appendix 3 to the Guideline on the clinical evaluation of anticancer medicinal products, i.e. the Summary of Product Characteristics for an Anticancer medicinal product – mock-up of 4.8. This will be pursued in a future worksharing procedure for nivolumab and ipilimumab.

2.5.1. Discussion on clinical safety

The database to characterise the safety profile of nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma is based on 782 patients treated with nivo+chemo in the investigational arm (360 in combination with XELOX, 422 in combination with FOLFOX) and 767 patients treated with chemo in the control arm (361 XELOX, 406 FOLFOX) in study CA209649. In the nivo+chemo arm patients were treated with nivolumab 360 mg plus XELOX Q3W or nivolumab 240 mg plus FOLFOX Q2W. The chemo arm included XELOX Q3W and FOLFOX Q2W. Subjects were treated until disease progression, unacceptable toxicity, or a maximum of 2 years (for nivolumab treatment). The last patient was randomised in May 2019 and DBL occurred in July 2020.

Patient exposure- Minimum follow-up of the 1549 patients treated in study CA209649 was 12.1 months. Median (min-max) duration of therapy was 6.75 (0.0-33.5) months in the nivo+chemo arm and 4.86 (0.0-34.9) months in the chemo arm. It is noted that in the nivo+chemo group median duration of therapy of the nivolumab component was longer than for the chemotherapy component. Especially

exposure of oxaliplatin was shorter, which was also observed in the chemo control arm. Median duration of chemotherapy was longer in the nivo+chemo arm compared to the chemo arm, suggesting that tolerability to chemotherapy did not decrease by the addition of nivolumab. In the nivo+chemo arm 89.3% discontinued and 94.9% in the chemo arm. The primary reason for discontinuation of treatment was disease progression in both treatment arms: 65.9% in the nivo+chemo group and 68.8% in the chemo group. In the nivo+XELOX arm the proportion of patients receiving ≥ 90% of the planned dose intensity was 70.0% for nivolumab, 44.2% for oxaliplatin, and 33.9% for capecitabine. In the nivo+FOLFOX arm this was 56.4% for nivolumab, 38.0% for oxaliplatin, 36.7% for leucovorin, 43.3% for 5-FU bolus, and 42.9% for 5-FU continuous. In the chemo arm 49.0% for oxaliplatin and 36.5% for capecitabine received ≥ 90% of the planned dose intensity in the XELOX arm and for the FOLFOX arm this was 45.0% for oxaliplatin, 44.8% for leucovorin, 49.3% for 5-FU bolus, and 51.0% for 5-FU continuous. Prior to revised protocol 07, all components of the combination treatment were delayed together if a dose delay was required which can explain the relatively low dose intensity of all components including nivolumab. The majority of patients received ≥ 70% of the planned dose intensities of each component and exposure to chemotherapy was generally comparable in the nivo+chemo vs. chemo arm. This implies that adding nivolumab to a XELOX or FOLFOX regimen does not lead to a decreased dose intensity of the chemotherapy component.

Adverse events- Almost all patients reported an AE during study treatment (99.2% in the nivo+chemo group vs. 98.0% in the chemo group). The most reported AEs were nausea (47.6%), diarrhoea (39.4%), and anaemia (38.2%) for the nivo+chemo arm. In the chemo arm nausea (43.5%), diarrhoea (33.6%), and anaemia (33.1%) were most commonly reported. When looking specifically to drug-related AEs, most often nausea (41.3%), diarrhoea (32.4%), and neuropathy peripheral (28.3%) were seen in the nivo+chemo arm. For the chemo arm, most frequently drug-related AEs reported were also nausea (38.1%), diarrhoea (26.9%), and neuropathy peripheral (24.8%). Grade 3-4 AEs were observed in 69.1% vs. 59.5% in the nivo+chemo vs. chemo arm, respectively. Neutropaenia (16.9%), decreased neutrophil count (11.5%), and anaemia (11.0%) were the most commonly seen Grade 3-4 AEs in the nivo+chemo arm; neutropaenia (13.0%), decreased neutrophil count (9.1%), and anaemia (7.3%) in the chemo arm. As shown by the frequencies of the most common AEs, the type of AEs are overlapping (gastrointestinal toxicity, bone marrow depression, and peripheral neuropathy) but the incidences are numerically higher in the nivo+chemo vs. the chemo arm suggesting additive toxicity when combining nivolumab with chemotherapy. The observed AEs are also more severe in grade, with a 10% difference in reported Grade 3-4 AEs between the treatment groups.

Serious adverse events- The overall frequencies of SAEs (all-causality and drug-related) were numerically higher with nivo+chemo than with chemo. Any Grade SAEs (regardless of causality) were reported in 54.1% in the nivo+chemo arm vs. 43.7% in the chemo arm. The most frequently reported SAEs in the nivo+chemo group were malignant neoplasm progression (13.9%), vomiting (3.2%), and anaemia (3.1%). For the chemo arm these were malignant neoplasm progression (11.7%), vomiting (3.1%), and dysphagia (2.1%). Any-grade drug-related SAEs were reported in 22.0% in the nivo+chemo arm and in 12.1% in the chemo arm. The most frequently reported drug-related SAEs were diarrhoea (2.2%), pneumonitis (2.2%), and febrile neutropaenia (2.0%) in the nivo+chemo arm. These numbers again show that the toxicity observed in the nivo+chemo group is more severe than in the chemo group.

Deaths- The number of treated patients who died in the nivo+chemo arm was numerically lower compared to the chemo arm. Disease progression was the most common cause of death in both arms. Death attributed to study drug toxicity was reported in 12 (1.5%) and 4 (0.5%) treated patients in the nivo+chemo and chemo arms, respectively. Per investigator assessment, 3 deaths were due to nivolumab, 2 deaths were due to nivolumab and chemotherapy, and 7 deaths were due to chemotherapy in the nivo+chemo arm. The causes of death due to nivolumab were pulmonitis, interstitial lung disease and pneumonitis. The causes of death due to nivolumab and chemotherapy were infection and

gastrointestinal toxicity. The causes of death due to chemotherapy were neutropaenic fever, intestinal mucositis, stroke, gastrointestinal bleeding, septic shock, pneumonia, and febrile neutropaenia. Deaths attributed to other reasons were reported in 6.3% and 5.7% of treated patients in the nivo+chemo and chemo arms, respectively. There were 4 events reported as "related" per investigator (all in nivo+chemo arm): thrombosis mesenteric vessel, disseminated intravascular coagulation, cerebral infarction and pneumonitis. Per investigator, the pneumonitis was reported as related to nivolumab and the other 3 events were reported as related to both nivolumab and chemotherapy. The MAH explained that in the 4 cases of death "attributed to other reasons" that were reported as "related" per investigator, the investigators captured the deaths as "other" because the cause of death was attributed to multiple factors or in case study drug toxicity could not be fully ruled out.

Discontinuations- The overall frequencies of all-causality and drug-related AEs leading to discontinuation were numerically higher in the nivo+chemo (47.4% and 36.3%) arm compared with the chemo arm (32.7% and 23.6%). The most common AEs leading to discontinuation (regardless of causality) were neuropathy peripheral (7.8%), malignant neoplasm progression (4.7%), and peripheral sensory neuropathy (4.5%) in the nivo+chemo arm. For the chemo arm these were neuropathy peripheral (5.3%), peripheral sensory neuropathy (4.7%) and malignant neoplasm progression (3.7%). The most frequently observed drug-related AEs leading to discontinuation in the nivo+chemo arm were neuropathy peripheral (7.5%) and peripheral sensory neuropathy (4.5%). The most common reason for AEs leading to dose delays or reductions in both the nivo+chemo and chemo arms was haematologic toxicity. Although the reasons for discontinuation are not unexpected, the number of discontinuations are high in both arms with a 15% higher incidence in the nivo+chemo arm compared to the chemo arm. The high number of discontinuations due to AEs in the control arm reflect that toxicity of first-line chemotherapy treatment with XELOX or FOLFOX in this patient population is considerable and the addition of nivolumab worsens the toxicity profile.

Adverse events of special interest- Based on previous experience with (nivolumab) immunotherapy, the MAH defined AEs of special interest and reported on select adverse events, immune-mediated adverse events (IMAEs) and other events of special interest (OESIs). Endocrine, gastrointestinal, hepatic, pulmonary, renal, skin and hypersensitivity/infusion reactions were analysed as select AE categories. The most frequently reported drug-related select AE categories were gastrointestinal (33.5%), skin (27.4%) and hepatic (26.0%) in the nivo+chemo arm and gastrointestinal (27.0%), hepatic (17.5%), and skin (13.7%) in the chemo arm. On PT level, diarrhoea (32.4%), increased AST (15.6%), and palmar-plantar erythrodysaesthesia syndrome (12.0%) were most commonly reported in the nivo+chemo arm. In the chemo arm, these were diarrhoea (26.9%), palmar-plantar erythrodysaesthesia syndrome (10.6%), and increased AST (9.0%). Most select AEs were Grade 1-2 and had resolved at the time of database lock with a median time to resolution ranging from 0.14 to 72.14 weeks. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

IMAEs included diarrhoea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, hypersensitivity/infusion reactions, and endocrine events occurring within 100 days of the last dose irrespective of causality but identified by the investigator with no clear etiology and an immune-mediated component. With the exception of endocrine events, IMAEs were limited to events needing immune-modulating medication. The majority of IMAEs were Grade 1-2 and the most frequently reported IMAEs in the investigational arm were hypothyroidism/thyroiditis (9.5%), rash (6.5%), and pneumonitis (4.2%). In the chemo arm hypothyroidism/thyroiditis and rash were most frequently observed with an incidence of <1%. The majority of events were manageable using the established management algorithms, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered. Except for some endocrine events, most IMAEs with nivo+chemo treatment had resolved at the time of DBL.

OESIs are events that do not fulfill all criteria to qualify as IMAEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Overall, OESIs were reported in 8/782 (1.0%) patients (10 events) in the nivo+chemo arm and 4/767 (0.5%) patients (5 events) in the chemo arm. The events observed in the nivo+chemo arm were Grade 3 Guillain-Barre syndrome, Grade 2 chorioretinitis, Grade 3 encephalitis, 4 events of pancreatitis (Grade 1-4), and 3 events of myocarditis (Grade 1 and 3). 9/10 OESIs in the nivo+chemo arm and 4/5 OESIs in the chemo arm were resolved at the time of database lock. 7/10 and 1/5 OESIs were resolved with immune-modulating medication in the nivo+chemo and chemo arms, respectively.

The provided data on adverse events of special interest show that the toxicity profile of nivo+chemo is not only overlapping (see section on AEs above), but also differs from the chemo arm with the occurrence of immune-related adverse events. There are no suggestions that the addition of XELOX or FOLOX to nivolumab induces unexpected immune-related adverse events based on experience with previously approved indications.

Laboratory findings- On-treatment laboratory abnormalities were more frequently observed in the nivo+chemo arm vs. the chemo arm, for haematology (main difference was found in decreased absolute neutrophil count), liver tests, kidney functions tests, and thyroid tests. Most laboratory abnormalities were Grade 1-2. Based on laboratory results reported after the first dose and within 30 days of last dose of study therapy, 13/764 (1.7%) patients in the nivo+chemo arm had concurrent ALT or AST >3×ULN with total bilirubin >2×ULN within 1 or 30 days, while 6/737 (0.8%) and 7/737 (0.9%) patients in the chemo arm had concurrent ALT or AST >3×ULN with total bilirubin >2×ULN within 1 day and within 30 days, respectively. In 3 of the 13 cases in the nivo+chemo arm, the abnormal hepatic laboratory findings were reported as related to nivolumab alone or to both nivolumab and chemotherapy. All 3 patients were treated with high dose immune-modulating medication and improved after treatment, supporting that the aetiologie was immune-mediated. In 1 case the patients had to discontinue study treatment due to the abnormal hepatic laboratory findings led to study treatment discontinuation.

Safety in subgroups- Differences between frequencies of drug-related AEs were observed for subgroups. In the group of patients treated with nivo+chemo the frequency of Grade 3-4 AEs was higher in the US/Canada population (72.1%) vs. other regions (~55% and overall 59%). Of note, most patients in the US/Canada regions received FOLFOX and the number of Grade 3-4 AEs was higher in the FOLFOX versus XELOX group (67.8% in the nivo+FOLFOX group and 49.5% in the nivo+XELOX group), possibly explaining the differences found based on geographic region. In both treatment arms, female patients experienced more Grade 3-4 drug-related AEs compared to males.

The frequencies of all causality AEs for subgroups of age <65, 65 to 74, and 75 to 84 years were generally similar to the frequencies reported for the overall study population by treatment. It is noted that for the age group 75-84 years treated with nivo+chemo, the number of SAEs, vascular disorders and anticholinergic syndrome were lower. Conclusions are however difficult to draw with the small number of patients in this group (n=75). Only 2 patients older than 85 years were treated with nivo+chemo.

Safety data for all treated patients with PD-L1 CPS ≥5 or ≥1 in the nivo+chemo and the chemo arms were consistent with the safety data for all treated patients.

Immunogenicity- Of the 681 nivolumab ADA evaluable patients in the nivo+chemo arm, 33 (4.8%) patients were nivolumab ADA positive at baseline and 60 (8.8%) patients were nivolumab ADA positive after the start of treatment. One (0.1%) patient was considered persistent positive and 2 (0.3%) patients were neutralizing ADA positive. The ORR among the ADA positive subjects (56.7%) was similar to the ORR (58.0%) in all randomised patients in the nivo+chemo arm. For the 2 patients with neutralising ADA positive, both had PR with a PFS of more than 1 year. The frequency of hypersensitivity/infusion reactions in the ADA-evaluable patients was 18.3% (11/60) in nivolumab ADA positive patients and 15.8% (98/621) in nivolumab ADA negative patients. The incidence of ADA's is similar to what is

previously reported for nivolumab in other tumour types. The presence of ADA's did not appear to have an effect on the occurrence of hypersensitivity/infusion reactions.

This is the first application combining nivolumab mono-immunotherapy with chemotherapy and it is therefore difficult to put the toxicity profile into perspective with what is known for nivolumab. When comparing reported frequencies with the approved indication of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy for first-line metastatic NSCLC, all causality AEs and drug-related deaths appear to occur in similar frequencies. Grade 3-4 AEs (mainly drug-related), Grade 3-4 SAEs and discontinuations are reported more often in the study investigating gastric cancer (study CA209649) compared with the NSCLC study (study CA2099LA; see also EPAR procedure EMEA/H/C/xxxx/WS/1783). It is however also noted that for the treatment of NSCLC, patients were treated with only 2 cycles of chemotherapy and also the toxicity of the chemo arm in the study with gastric patients is higher than in the chemo arm of study with NSCLC patients. Furthermore, the patients groups studied (NSCLC or gastric cancer) are different populations. Definitive conclusions about how the safety profile found in CA209649 compares to other nivolumab studies are therefore difficult to make.

Data for the nivo+ipi arm were not provided in this procedure. Enrollment was stopped in this arm due to observed increased early death rate in nivolumab plus ipilimumab arm as well as the increased toxicity rate. The final analysis of the nivo+ipi arm is planned for July 2021 and data submission for Q4 2021. The nivo+ipi arm of study CA209649 is added to the Letter of Recommendation. Of note, at the most recent safety review of the study in March 2021, the DMC recommended that the study should continue as planned.

2.5.2. Conclusions on clinical safety

Treatment of nivo+chemo is characterised by substantial toxicity with a high number of discontinuations. Nivo+chemo treatment is less tolerated than treatment with chemo only as shown by the higher number of (drug-related) AEs, Grade 3-4 AEs, SAEs, drug-related deaths due to AEs, and AEs leading to discontinuations. It is noted that the toxicity profile of the chemo control arm in this first-line population is already considerable. Next to nivolumab and chemotherapy overlapping toxicities such as gastro-intestinal AEs, bone marrow depression, and peripheral neuropathy, also nivolumab-specific toxicity with immune-related AEs are observed with the addition of nivolumab to the chemotherapy regimen. Although the type of AEs are reflective of the known safety profile of nivolumab immunotherapy and chemotherapy and no new safety issues were identified, the severity of the toxicity is considerable and should be valued against the observed benefit in patients with advanced or metastatic gastric, gastro-oesophageal or oesophageal adenocarcinoma.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 21.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 21.2 with the following content:

Safety concerns

Table : Summary of Safety Concerns

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

Pharmacovigilance plan

Table: Ongoing and Planned Additional Pharmacovigilance Activities

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

Table: **Ongoing and Planned Additional Pharmacovigilance Activities**

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
		solid organ transplant rejection, and VKH), and infusion reactions		
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCTOngoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission	With PSUR starting at DLP 03-Jul-2017 06-2019 4Q2022

Risk minimisation measures

Table : **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

Table : Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

2.7. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1.

2.7.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

The MAH is seeking an extension of indication for *OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastrooesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS)≥5.*

3.1.1. Disease or condition

Gastric cancer (GC) is the 5th leading cancer and the 3rd leading cause of cancer-related deaths worldwide. Oesophageal cancer is the 7th leading cancer and the 6th leading cause of cancer-related deaths worldwide. GC/gastric oesophageal junction carcinoma (GEJC)/oesophageal adenocarcinoma (OAC) remain a leading cause of cancer-related mortality worldwide, with an estimated 1 million deaths worldwide in 2018.

Adenocarcinoma is the most common (> 90%) histological subtype for GCs worldwide and OAC has increased in North America and Europe (EU).

3.1.2. Available therapies and unmet medical need

Treatment recommendations for advanced or metastatic GC, GEJ and OAC, are almost the same. Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur/gimeracil/oteracil potassium) are considered first-line standard-of-care treatments for metastatic GC/GEJC/OAC across geographic regions (ESMO 2016; NCCN 2020).

In patients with HER2 positive tumour, the addition of trastuzumab to platinum and fluoropyrimidine-based chemotherapy is recommended.

3.1.3. Main clinical studies

The evidence in support of the claimed indication is based on results from the **study CA209649** (CheckMate 649). The study CA209649 is a Phase 3, randomised, multicentre, open-label study of nivolumab plus ipilimumab or nivolumab in combination with chemotherapy (oxaliplatin plus fluoropyrimidine) versus chemotherapy (oxaliplatin plus fluoropyrimidine) in subjects with previously untreated advanced or metastatic gastric, gastro oesophageal junction (GEJ) cancer or oesophageal adenocarcinoma (OAC).

The primary endpoints were overall survival (OS) and progression free survival (PFS), as assessed by BIRC per RECIST 1.1 criteria, in patients with PD-L1 CPS≥5. OS in patients with PD-L1 CPS≥1 and all randomised patients were included as secondary endpoints. Other secondary endpoint were PFS and ORR. A hierarchical testing strategy was used for the primary endpoints and OS in PD-L1 CPS≥1 and all-randomised patients.

All the analyses presented below are on patients concurrently randomized to the nivo+chemo or chemo arm. A total of 1,581 were randomised to receive either nivo+chemo (n=789) or chemo (n =792).

3.2. Favourable effects

Primary endpoints (PD-L1 **CPS≥5**)

OS results (even rate 65.3% nivo+chemo vs. 75.1% chemo) showed a statistically significant improvement in favour of the nivo+chemo arm over chemo arm (HR 0.71; 98.4% CI: 0.59, 0.86). Median OS was of 14.39 (95% CI: 13.11, 16.23) months in the nivo+chemo group and 11.10 (95% CI: 10.02, 12.09) months in the chemo group.

PFS results were also statistically significant in favour of the nivo+chemo arm (HR 0.68; 98% CI: 0.56, 0.81). Median PFS was 7.69 (95% CI: 7.03, 9.17) months and 6.05 (95% CI: 5.55, 6.90) months, in the nivo+chemo and chemo groups, respectively.

Secondary endpoints

In patients with PD-L1 CPS≥1 a statistically significant improvement in OS was observed with nivo+chemo over chemo (HR 0.77; 99.3 CI: 0.64, 0.92). Median PFS was 13.96 (95% CI: 12.55, 14.98) months in the nivo+chemo arm vs. 11.33 (95% CI: 10.64, 12.25) months in the chemo arm.

OS in the **all-randomised patients** (event rate of 69% in the nivo+chemo arm and 75% in the chemo arm), show a statistically significant benefit of nivo+chemo over control (**HR** of **0.80 [99.3% CI: 0.68, 0.94]**). Median OS was of 13.83 (95% CI: 12.55, 14.55) months and 11.56 (95% CI: 10.87, 12.48) months in the experimental and control arm, respectively.

Results in terms of **PFS** in the **all-randomised patients** were consistent with the OS analysis and favoured also the nivo+chemo arm (HR 0.77; 95% CI: 0.68, 0.87). Median PFS was 7.66 (95%CI: 7.10, 8.54) months in the nivo+chemo arm versus 6.93 (95% CI: 6.60, 7.13) months in the chemo arm.

The **ORR** was higher in the nivo+chemo arm compared with the chemo arm (58% vs. 46.1%, respectively), in the **all-randomised patients** with measurable disease at baseline.

Updated efficacy data

During the procedure updated efficacy data, including OS as well as PFS, ORR and DoR per BICR, providing 7.3 months of additional follow-up (DBL of 16-Feb-2021) were submitted. Results are consistent with those previously reported.

3.3. Uncertainties and limitations about favourable effects

While statistically significant benefit of nivo+chemo over chemo in terms of OS (and also PFS) was observed in the all-randomised patient population the effect appears to be driven by patients with PD-L1 CPS≥5, which comprises the primary efficacy population in this study. In patients with PD-L1 CPS <5 no clinically meaningful benefit was observed. Therefore, the indication has been restricted to patients with PD-L1 CPS≥5.

Patients with known HER2-positive status were not allowed to enter the study. However, there were 643 (40.7%) patients for whom HER2 status was undetermined. Although it is expected that most of these patients were HER2-negative (based on the expected prevalence of HER2 positivity in the intended target population) this has not been confirmed. In the absence of such confirmation, no conclusion can be drawn on whether HER2-positive patients could also benefit from the addition of nivolumab to chemotherapy treatment. This has been reflected in the wording of the indication. In fact, to demonstrate the effect of nivolumab+chemotherapy in HER2-positive patients a different study design, with a comparator including trastuzumab, would normally have been required.

3.4. Unfavourable effects

The database used for the safety profile of nivo+chemo in patients with advanced or metastatic gastric, gastro-oesophageal or oesophageal adenocarcinoma consists of 782 patients treated with nivo+chemo and is compared with 767 patients treated with chemo control with a minimum follow-up of 12.1 months.

Median duration of therapy was 6.75 months in the nivo+chemo arm and 4.86 months in the chemo arm.

Nivo+chemo treatment is less well tolerated than treatment with chemo only as shown by the higher number of (drug-related) AEs (all causality 99.2% vs. 98.0%, drug-related 94.4% vs. 88.5%), Grade 3-4 AEs (69.1% vs. 59.5%), SAEs (54.1% vs. 43.7%), drug-related deaths due to AEs (1.5% vs. 0.5%), and AEs leading to discontinuations (47.4% vs. 32.7%).

Next to nivolumab and chemotherapy overlapping toxicities such as gastro-intestinal AEs, bone marrow depression, and peripheral neuropathy, also nivolumab-specific toxicity with immune-related AEs are observed. The most commonly reported AEs in the nivo+chemo group were nausea (47.6%), diarrhoea (39.4%), and anaemia (38.2%). When looking specifically to drug-related AEs, most often nausea (41.3%), diarrhoea (32.4%), and neuropathy peripheral (28.3%) were seen in the nivo+chemo arm. As expected, select AEs, immune-mediated adverse events (IMAEs), and other events of special interest (OESIs) occurred more frequently with nivo+chemo relative to chemotherapy.

The most common AEs leading to discontinuation in the nivo+chemo arm (regardless of causality) were neuropathy peripheral (7.8%), malignant neoplasm progression (4.7%), and peripheral sensory neuropathy (4.5%).

The causes of death due to nivolumab were pulmonitis, interstitial lung disease and pneumonitis. The causes of death due to nivolumab and chemotherapy were infection and gastrointestinal toxicity.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile is based on an open-label design study which might introduce bias in the reporting of AEs. The type of AEs reported is however not unexpected with what is known about nivolumab and XELOX/FOLFOX treatments.

3.6. Effects Table

Effects Table for nivolumab in combination with oxaliplatin plus fluoropyrimidine for the treatment of adult patients with previously untreated advanced or metastatic gastric, gastroesophageal junction cancer or esophageal adenocarcinoma (GC/GEJC/EAC) (data cut-off: July 2020) - Study CA209649 (CheckMate 649)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoints (PD-L1 CPS≥5; n=955)						
OS	Overall survival Time from randomisation until death from any cause	Median, months (95%CI)	14.39 (13.11, 16.23)	11.10 (10.02, 12.09)	HR 0.71 (98.4% CI: 0.59, 0.86) p<0.0001	CSR
PFS	Progression free survival	Median, months (95%CI)	7.69 (7.03, 9.17)	6.05 (5.55, 6.90)	HR 0.68 (98% CI: 0.56, 0.81) P<0.0001	CSR
Secondary endpoints (All randomised patients; n=1581)						
OS	Overall survival	Median, months	13.83 (12.55,	11.56 (10.87,	HR 0.80	CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
		(95%CI)	14.55)	12.48)	(99.3% CI: 0.68, 0.94) p=0.0002	
PFS	Progression free survival	Median, months (95%CI)	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)	HR 0.77 (95% CI: 0.68, 0.87)	CSR
ORR	Overall response rate per BIRC (complete response + partial response) in subjects with measurable disease	% (95% CI)	58.0	46.1	Difference 12.8 (95% CI: 7.3, 18.2)	CSR
Unfavourable Effects						
Grade 3-4 AEs	All causality (drug-related)	%	69.1 (59.1)	59.5 (44.5)	Open label study, compared to control chemotherapy	CSR
SAEs	All causality (drug-related)	%	54.1 (22.0)	43.7 (12.1)		CSR
AEs leading to DC	All causality (drug-related)	%	47.4 (36.3)	32.7 (23.6)		CSR
Deaths	Deaths due to study drug toxicity	%	1.5	0.5		CSR
Select AEs	All causality select AE Endocrine Gastrointestinal Hepatic Pulmonary Renal Skin Hypersensitivity/IR	%	 15.0 40.3 34.1 5.2 7.4 33.5 15.1	 1.8 33.9 24.3 0.8 3.1 17.9 5.9		CSR

Abbreviations: OS=overall survival, PFS=progression free survival, ORR=overall response rate, AE= adverse event, CI= confidence interval, CSR= clinical study report, DC= discontinuation, HR= hazard ratio, IR= infusion reaction, SAE= serious adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In study CA209649 treatment with nivolumab in combination with chemotherapy (XELOX or FOLFOX) showed a statistically significant OS benefit compared with chemotherapy (XELOX or FOLFOX) alone in the all-randomised patient population. However, results appear to be driven by patients with PD-L1 CPS≥5 with lack of efficacy benefit observed in patients with PD-L1 CPS <5. Therefore, the indication has been restricted to patients with PD-L1 CPS≥5, which in fact was the primary efficacy population in this study.

From a safety point of view, treatment of nivo+chemo is characterised by substantial toxicity with a high number of discontinuations. Nivo+chemo treatment is less tolerated than treatment with chemo only as shown by the higher number of (drug-related) AEs, Grade 3-4 AEs, SAEs, drug-related deaths due to AEs, and AEs leading to discontinuations. It is noted that the toxicity profile of the chemo control arm in this first-line population is already considerable. Next to nivolumab and chemotherapy overlapping toxicities such as gastro-intestinal AEs, bone marrow depression, and peripheral neuropathy, also nivolumab-specific toxicity with immune-related AEs are observed with the addition of nivolumab to the chemotherapy regimen. Although the type of AEs are reflective of the known safety profile of nivolumab immunotherapy and chemotherapy and no new safety issues were identified, the severity of the toxicity is considerable and should be valued against the observed benefit in patients with advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

Finally, the wording of the indication has been revised to include treatment of HER2-negative patients only.

3.7.2. Balance of benefits and risks

In study CA209649 nivolumab in combination with chemotherapy demonstrated superiority over chemotherapy alone in OS, PFS and ORR in the overall population (i.e. regardless of PD-L1 CPS status). However, considering the lack of efficacy benefit observed with nivolumab+chemotherapy in patients with PD-L1 CPS<5 and that the proposed combination is more toxic and less well tolerated than chemotherapy alone, the benefit/risk ratio in patients with PD-L1 CPS<5 is currently considered negative. Therefore, the indication has been restricted to patients with PD-L1 CPS≥5.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The benefit/risk ratio of OPDIVO in combination with fluoropyrimidine- and platinum-based chemotherapy for the first-line treatment of adult patients with HER2-negative advanced or metastatic GC, GEJ or OAC is considered positive for patients whose tumours express PD-L1 with a CPS≥5.

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 use OPDIVO (nivolumab) in combination with fluoropyrimidine- and platinum-based combination chemotherapy, in first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5 (Study CA209649); as a

consequence, sections 4.1, 4.2, 4,4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21.2 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0096'

[1] Rizvi NA, Hellmann MD, Brahmer JR, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small cell lung cancer. Journal of Clinical Oncology 2016; 34:2969-2979.

[2] Fuchs CS, Ohtsu A, Tabernero J, et al. Preliminary safety data from KEYNOTE-059: pembrolizumab plus 5-fluorouracil (5-FU) and cisplatin for first-line treatment of advanced gastric cancer. Journal of Clinical Oncology 2016; 34:4037-4037.

[3] Kang Y-K, Kato K, Chung HC, et al. Interim safety and clinical activity of nivolumab (Nivo) in combination with S-1/capecitabine plus oxaliplatin in patients (pts) with previously untreated unresectable advanced or recurrent gastric/ gastroesophageal junction (G/GEJ) cancer: part 1 study of ATTRACTION-04 (ONO-4538-37). Annals of Oncology 2017; 28:Abstract 671P.

[4] Smyth E and Petty R. Pembrolizumab versus paclitaxel in gastro-oesophageal adenocarcinoma. Lancet 2018; 392:97-98.

[5] Kulangara K, Guerrero L, Posch A, et al. Investigation of PD-L1 expression and response to pembrolizumab (pembro) in gastric cancer (GC) and cervical cancer (CC) using combined positive score (CPS) and tumour proportion score (TPS). Journal of Clinical Oncology 2018; 36:4065.