EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2021
EMA/CHMP/395647/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0095

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
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CRF	case report form
CRT	chemoradiotherapy
CSR	clinical study report
CTC	Common Terminology Criteria
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DBL	database lock
DFS	disease free survival
DMFS	distant metastasis free survival
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group
ECS	Esophageal Cancer Subscale
EQ-5D-3L	EuroQol 5 dimensional 3-level index
FACT-E	Functional Assessment of Cancer Therapy-Esophageal
FACT-G7	Functional Assessment of Cancer Therapy-General 7-item version
GC	gastric cancer
GCP	good clinical practice
GEJC	gastric oesophageal junction carcinoma
GI	gastrointestinal
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
ISR	incurred sample reanalysis
IV	intravenous
K-M	Kaplan-Meier
LLN	lower limit of normal
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NA	not available
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Nivo	nivolumab
OAC	oesophageal adenocarcinoma
OC	oesophageal cancer
OESI	other events of special interest
OS	overall survival

OSSC	oesophageal squamous cell carcinoma
PBMC	peripheral blood mononuclear cell
PBRER	Periodic Benefit-Risk Evaluation Report
pCR	pathological complete response
PD-L1	programmed cell death ligand 1
PD-L2	programmed death-ligand 2
PFS	progression free survival
PFS2	progression-free survival after subsequent systemic therapy
PK	pharmacokinetics
PP	persistent positive
PS	performance status
PT	preferred term
PWB	physical well-being
Q2W	every 2 weeks
Q4W	every 4 weeks
QOL	quality of life
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SI	International System of Units
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
SOC	system organ class
SWB	social well-being
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VAS	visual analog scale

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 24 November 2020 an application for a variation.

The following variation was requested:

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

Extension of indication to include adjuvant treatment of adult patients with resected oesophageal, or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy for OPDIVO (study CA209577) as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 22.0 of the RMP has also been submitted.

The variation requested 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 seek Scientific Advice at the CHMP on the design of study CA209577, the pivotal trial for this application (EMEA/H/SA/2253/9/2018/II). Questions referred to the choice of primary endpoints and protocol amendments.

1.2. Steps taken for the assessment of the product

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

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

Timetable	Actual dates
Submission date	24 November 2020
Start of procedure:	26 December 2020
CHMP Rapporteur's preliminary assessment report circulated on:	2 March 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 Rapporteur's updated assessment report circulated on:	21 March 2021
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 March 2021
MAH's responses submitted to the CHMP on:	22 April 2021
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	4 June 2021
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 May 2021
PRAC RMP advice and assessment overview adopted by PRAC on:	10 June 2021
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	17 June 2021
CHMP opinion:	24 June 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Oesophageal cancer (OC) is the seventh most common cancer globally in terms of incidence with over 572,000 new cases annually. It is the sixth most common cause of deaths worldwide, accounting for over 500,000 deaths annually. In the US, OC is a leading cause of death in males; an incidence analysis of 232,639 patients conducted between 2001 and 2015 indicated a higher number of male patients (181,995 [78%]) than female patients (50,644 [22%]) with OC.[1,2,3,4]

[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.

The 2 distinct histologic types of OC are squamous cell carcinoma (SCC) and adenocarcinoma (AC). Globally, OSCC remains the predominant histological subtype; however, the incidence of OSCC has been decreasing, while the incidence of OAC has been increasing rapidly, particularly in Western Europe, North America, and Australia. SCC continues to be the more common EC in Asia. Gastro-oesophageal junction (GEJ) cancer incidence has dramatically increased in the Western population, and the rates of GEJ cancers have increased between 4%-10% every year in the US since 1976. GEJ cancers are considered either gastric or oesophageal cancers because they lie in between the 2 anatomically; this is a short transition zone from the distal third of the oesophagus to the proximal part of the stomach. The definition of GEJ cancers has been an area of controversy and disagreement in the past, which has led to discrepancies in the literature regarding the classification, pathophysiology, surgical approach, and prognosis. Other names used to describe GEJ cancers include distal oesophageal cancers, proximal gastric cancers (GC), and cancers of cardia. The most widely accepted definition for GEJ cancer was proposed by Sievert et al. and resulted in tumours being classified as a distinct entity from gastric or oesophageal cancers. In recent guidelines from the American Joint Committee on Cancer (AJCC; 8th edition), GEJ tumours with epicenter in the distal oesophagus or less than 2 cm into the proximal stomach (Siewert types I and II) based on surgical resection specimens are included under the OC staging classification.

State the claimed therapeutic indication

Proposed Indication

OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with resected oesophageal (OC) or gastro-oesophageal junction cancer (GEJC) who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (CRT).

Proposed Dosage and Administration

The recommended dose is nivolumab 240 mg (30-minute intravenous [IV]) infusion) every 2 weeks (Q2W) or 480 mg (30-minute IV infusion) every 4 weeks (Q4W) for 16 weeks, followed by 480 mg (30-minute IV infusion) Q4W for a total treatment duration of 1 year.

Epidemiology and risk factors, screening tools/prevention

Exact causes of OC or GEJC are unclear. The major risk factors for OSCC are tobacco, smoking and alcohol drinking. Several major risk factors have been linked to both OAC and GEJ AC, such as gastroesophageal reflux, obesity, and smoking. Reflux is also an etiological factor for gastric cardia AC. Combinations of smoking, elevated BMI, and reflux may account for almost 70% of total cases. [5]

Clinical presentation, diagnosis and stage/prognosis

SCCs are mainly located in the upper or middle oesophagus, while ACs mainly arise in the distal third of the oesophagus and GEJ. ACs in the GEJ include the first ~2.5 cm of the stomach. Histologically, the large majority of GEJCs are ACs and are considered biologically similar to OACs.

Approximately 50% of ECs will be locally or locoregionally advanced at diagnosis, and thus amenable to potentially curative loco-regional therapy. Five-year survival rates for all patients with OC have shown modest improvements over the past 35 years, from 5% in 1975 to approximately 20% for

[5] Olsen CM, Pandeya N, Green AC, et al. Population Attributable Fractions of Adenocarcinoma of the Esophagus and Gastroesophageal Junction. Am J Epidemiol. 2011;174(5):582-90.

patients diagnosed in 2004. Five-year survival rates for loco-regionally advanced disease treated with surgery alone have been consistently poor, ranging from 6% to 26%.[6],[7],[8]

Management

The management of OC and GEJC often requires a multi-disciplinary approach, with treatment decisions involving surgical, radiation, and medical oncology expertise. Recommendations by treatment guidelines for OC are based on histology (i.e., SCC vs. AC). In patients with locally advanced disease with SCC histology, treatment options include neoadjuvant CRT followed by curative resection or definitive CRT with or without resection. Treatment options for those with AC histology include neoadjuvant CRT or perioperative chemotherapy followed by resection. GEJC is historically treated like either OC or GC.

Neoadjuvant CRT followed by surgery (trimodality therapy) is a mainstay in the curative treatment of resectable locally advanced EC or GEJC and is a widely accepted standard of care in these patients (per National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], and European Society of Medical Oncology [ESMO] guidelines).

In a study of CRT for EC and GEJC followed by surgery (CROSS study), the CROSS regimen showed significant improvement in overall survival (OS); median OS was 48.6 months (95% confidence interval [CI]: 32.1, 65.1) in the CROSS regimen group and 24.0 months (14.2–33.7) in the surgery alone group (HR 0.68 [95% CI: 0.53, 0.88]). The CROSS regimen also showed an improvement in 5-year OS (47% vs. 33%; HR 0.67 [0.51–0.87]) compared with surgery alone; however, only 29% of patients who were treated with the CROSS regimen achieved pCR.

Perioperative chemotherapy is also considered standard in locally advanced AC of EC and GEJ cancers. In Europe, a perioperative approach has widely been adopted for patients with locally advanced GEJ and GC on the basis of 2 large Phase 3, randomized controlled trials. In the United Kingdom (UK) Medical Research Council (MRC) MAGIC trial, the chemotherapy arm (ECF:Epirubicin/cisplatin/5-FU) showed significant improvement in 5-year OS (36% vs. 23%; p = 0.009) compared with surgery alone. A similar improvement in OS was reported in the French FNCLCC/FFCD trial. The German AIO's FLOT4 study evaluating perioperative taxane + oxaliplatin/fluropyrimidine combination (FLOT) resulted in a median OS of 35 months (95% CI: 27.35, 46.26) in the ECF/ECX group and 50 months (95% CI: 38.33, not reached) in the FLOT group (HR = 0.77; 95% CI: 0.63, 0.94; p = 0.012); however, a significant proportion of patients did not appear to tolerate post-operative therapy with this regimen. In Asia, adjuvant chemotherapy is a standard of care for GEJ/GC based on 2 Phase 3 trials (ACTS GC and Classics) demonstrating OS improvement over curative surgery alone. [9], [10]Despite these advances, improvements in the outcomes for patients with gastric or GEJ AC treated with chemotherapy need to be made.

Despite previously published clinical improvements (2012) compared with surgery alone when patients with local and locoregional EC and GEJC tumours were treated with trimodality therapy, there still

[6] GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and prevalence Worldwide in 2012 http://globocan.iarc.fr.

[7] Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335:462-7.

[8] Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer N Engl J Med. 1998;339(27):1979-84.

[9] Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine [published correction appears in N Engl J Med. 2008 May 1;358(18):1977]. N Engl J Med. 2007;357(18):1810-20.

[10] Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379(9813):315-321.

exists a substantial unmet medical need in the US and Europe. The risk of disease recurrence following trimodality therapy remains high, with 70%-75% of patients failing to achieve pCR after trimodality therapy, and a prognosis worse than that for patients with pCR. The 5-year OS rate was 52% (95% CI: 44, 62) for pCR patients and was only 41% (95% CI: 37, 45) for non-pCR patients. Based on the pivotal CROSS trial, only 29% of the patients who received trimodality therapy achieved pCR. Reynolds et al [11] reported even lower pCR rates (19%); in the non-pCR population, the median OS was 33 months in node-negative patients and only 9 months in node-positive patients. Five-year OS was 37% in node-negative patients and 17% in node-positive patients. Similar findings were reported by Depypere et al [12] . Thus, long term survival is relatively short, considering this is in the curative setting. Moreover, there is no established standard of care in the adjuvant setting for patients who had received neoadjuvant CRT followed by surgery.

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 and recently for the treatment of unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma following prior treatment (OPDIVO SmPC).

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

The MAH overall followed the recommendations of the CHMP scientific advice (EMEA/H/SA/2253/9/2018/II).

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 was considered acceptable by the CHMP.

[11] Reynolds JV, Muldoon C, Hollywood D, et al. Long-term outcomes following neoadjuvant chemoradiotherapy for esophageal cancer. Ann Surg. 2007;245(5):707-16.

[12] Depypere LP, Vervloet G, Lerut T, et al. ypT0N+: the unusual patient with pathological complete tumor response but with residual lymph node disease after neoadjuvant chemoradiation for esophageal cancer, what's up? J Thorac Dis. 2018;10(5):2771-8.

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.

2.3. 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

Table 1: Phase 3 study supporting the proposed indication of nivolumab for the adjuvant treatment of adult patients with resected oesophageal or gastro-oesophageal junction cancer

Study/ Phase/ Status	Study Design	Study Population	Primary Efficacy Endpoint	Treatment	Number of Subjects
Esophageal / GEJC Cancer studies					
CA209577/ Phase 3/ Ongoing	Randomized, double-blind, placebo-controlled (adjuvant setting)	Subjects with esophageal or GEJC cancer (SCC or AC) who underwent CRT followed by complete resection and who have residual pathologic disease.	DFS	Nivo 240 mg IV Q2W for 16 weeks (Cycles 1-8), followed by Nivo 480 mg IV Q4W until recurrence or discontinuation from study up to 1 year or Placebo with the same dosing schedule and treatment duration as Nivo.	1085 enrolled 794 randomized 792 treated

2.3.2. Pharmacokinetics

PK analytical methods

Pre-study validation

In support of study CA209577, 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 CA209577

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 RGBB 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 August 25th, 2017 to May 05th, 2020.

A total of 3672 samples were received and 2490 samples were analysed (1198 samples were not analysed per protocol SOP) in 122 bioanalytical runs (110 runs met the acceptance criteria). Out of 2490 samples, 2442 samples were reported and 48 samples were not reported in data transfer files since subjects were not dosed with nivolumab (placebo group), samples collected outside of protocol or samples outstanding reconciliation with Watson database].

The between-run precision (%CV) and accuracy (%Bias) of the calibration curve standards ranged from 0.873% to 5.32% and from 0.108% to 3.43%, respectively. A total of five calibration standards were rejected. In all valid runs, no more than one was rejected at the same run. In one run the ULOQ was rejected (samples were re-analysed using the next acceptable lower calibration standard).

The between-run precision (%CV) and accuracy (%Bias) of the QCs ranged from 5.22% to 5.98% and from 0.479% to 6.41%, respectively (including all QCs). A total of four QCs were outside the acceptance range. In all valid runs, no more than one QC was outside the acceptance range at the same run.

A total of 98 samples were re-analysed due to the following reasons: sample results above ULOQ, diluted sample quantitated below limit of quantitation, confirmatory re-analysis performed to support Run 17RGBB potential anomaly (for these samples de initial values were reported), inadvertently re-assayed at same dilution factor, re-assayed inadvertently.

A total of 294 samples were subjected for ISR. Out these, 292 samples met the ISR acceptance criteria (± 30%), which has resulted in 99.3% ISR pass rate for study samples.

The maximum storage for samples was 1009 days at nominally -80 ºC. The long-term stability of nivolumab in human plasma covers 2373 days at nominally -80 ºC.

WuXi AppTec Study No.: 400040-191700-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 December 16th, 2019 to May 06th, 2020.

A total of 88 samples were received and 62 samples were analysed (26 placebo samples were not analysed per protocol SOP) in 4 bioanalytical runs (all of them met the acceptance criteria). Out of 62 analysed samples, 58 samples were reported and 4 samples were not reported in data transfer files (placebo samples were analysed in error).

The between-run precision (%CV) and accuracy (%Bias) of the calibration curve standards ranged from 0.4% to 3.3% and from -0.5% to 4.3%, respectively. No calibration curve standard was rejected.

The between-run precision (%CV) and accuracy (%Bias) of the QCs ranged 5.8% to 10.2% and from 0.0% to 3.8%, respectively). No QC was outside the acceptance range.

No samples were re-analysed.

Incurred sample reproducibility will be performed and reported in a subsequent report or final report.

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

The nivolumab PPK analysis was conducted using data from 7 clinical studies conducted in 1493 subjects with EC, GEJC, NSCLC, renal cell carcinoma (RCC), or other malignancies. The data included are from two Phase 1 studies (CA209001 [multiple tumours types] and CA209003 [multiple tumour types; only melanoma, NSCLC, and RCC were included]), one Phase 2 study (ONO 4538-07 [EC]), and four Phase 3 studies (CA209017 [squamous (SQ)-NSCLC], CA209057 [nonsquamous (NSQ) NSCLC], CA209473 [EC], and CA209577 [EC and GEJC]). NSCLC studies were included since this tumour type was the reference used in a prior nivolumab PPK analysis and enabled the comparison across PPK analyses.

Table 2: Summary of clinical studies included in pharmacometric population pharmacokinetic analyses

Protocol #: Title Study Population	Treatment	Planned Sample Size[a]	Nominal PK/PD Sampling Schedule	Analysis
CA209001 Phase 1, open-label, multicenter, dose-escalation study to evaluate the safety and PK 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*	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
CA209003 Phase 1, open-label, multicenter, multidose, dose-escalation study to evaluate the safety and tolerability of BMS-936588 in subjects with selected advanced or recurrent malignancies *Adult subjects with pathologically verified and advanced or recurrent and progressing colorectal adenocarcinoma, melanoma, NSCLC, castration- resistant prostate adenocarcinoma, and RCC*	0.1, 0.3, 1, 3, or 10 mg/kg IV infusion depending upon tumor type, administered over 60 minutes Q2W for up to twelve 8-week cycles	306	Pre-Amendment: Cycle 1: End of Infusion and pre-infusion levels on infusion days: Days 1, 15, 29, and 43 and Cycle 2: Single samples were collected Post-Amendment: Serial PK samples were collected from all subjects enrolled in 0.1, 0.3, and 1 mg/kg melanoma cohorts and first 16 subjects each from 3 and 10 mg/kg NSCLC cohorts. Cycle 1: Day 1 (after 60-minute infusion, 4, 8hr), 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, 15	PPK Only include subjects with melanoma, NSCLC, and RCC

			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, 15 Each treatment cycle is comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 of the cycle	
CA209017 An open-label, randomized Phase 3 trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic SQ NSCLC *Subjects with SQ NSCLC*	Dose: 3 mg/kg, 1-hr IV infusion Regimen: Q2W	132	Day 1 (Cycle 1) and Day 99 (Cycle 8), pre-infusion, after 60- minute infusion and pre-infusion at Cycles 2 and 3 and every 8th cycle after Cycle 8 Day 1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle	PPK
CA209057 An open-label, randomized Phase 3 trial of BMS-936558 (nivolumab) versus docetaxel in previously treated advanced or metastatic NSQ NSCLC *Subjects with NSQ NSCLC*	Dose: 3 mg/kg, 1-hr IV infusion Regimen: Q2W	287	Day 1 (Cycle 1) and Day 99 (Cycle 8), pre-infusion, after 60- minute infusion and pre-infusion at Cycles 2 and 3 and every 8th cycle after Cycle 8 Day 1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle	PPK
ONO-4538-07 ONO-4538 Phase 2 study, a multicenter, open-Label, uncontrolled study in patients with esophageal cancer *Subjects with esophageal cancer*	Dose: 3 mg/kg, 1-hr IV infusion Regimen: Q2W	60	Cycle 1: Pre-dose and immediately post dose on Day 1, pre-dose on Day 15, 29 Cycle 2, 4, 5, 7, 9: Pre-dose on Day 1 and immediately post dose on Day 1 (Cycle 4) Follow-up visits Each cycle consists of 6 weeks.	PPK
ONO-4538-24/CA209473 ONO-4538 Phase 3 study, a multicenter, randomized, open-label study in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs *Subjects with esophageal cancer*	Dose: 240 mg, 30-min IV infusion Regimen: Q2W	195	Cycle 1: Pre-dose on Day 1 and Day 29 Cycle 4, 9: Pre-dose on Day 1 Follow-up visits Each cycle consists of 6 weeks.	PPK
CA209577 A randomized, multicenter, double blind, Phase 3 study of adjuvant nivolumab or placebo in subjects with resected esophageal or GEJC	Dose: 240 mg, 30-min IV infusion, Q2W for 16 weeks followed by 480 mg Q4W	506	Cycle 1, 3, 10, 13, 17: Pre-dose on Day1 Cycle 9: Pre-dose on Day 1 and EOI	PPK

Abbreviations: BMS = Bristol-Myers Squibb; EOI = end of infusion; GEJC = gastroesophageal junction cancer; IV = intravenous; min = minutes; NSCLC = non-small cell lung cancer; NSQ NSCLC = non-squamous cell non-small cell lung cancer; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PPK = population pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; RCC = renal cell carcinoma; SQ NSCLC = squamous cell non-small cell lung cancer.

a As per protocol for nivolumab treated.

Table 3: Subjects Included in the Population Pharmacokinetic Analysis Dataset by Study

Study	No. of Subjects			
	Nivolumab Treated	PK Database[a]	Flagged	Included (% of Subjects in PK Database)
MDX1106-01 (CA209001)	39	39	0	39 (100)
MDX1106-03 (CA209003)	304	310	6	304 (98.1)
CA209017	125	127	2	125 (98.4)
CA209057	280	282	2	280 (99.3)
ONO-4538-07	65	65	0	65 (100)
CA209473	186	186	0	186 (100)
CA209577	494	526	32	494 (93.9)
Total	1493	1535	42	1493 (97.3)

Analysis-Directory: /global/pkms/data/CA/209/adj-ec-gej/prd/nivo-ppk/final

Program Source: Analysis-Directory/sas/

Source: Analysis-Directory/reports/Table3.3.1.1-1.rtf

Abbreviations: PK = pharmacokinetic(s).

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

Table 4: Samples Included in the Population Pharmacokinetic Analysis Dataset

Study	PK Database[a]	Day 1 Pre-Dose[b]	Missing dose or sample information	Duplicate samples at same time (set up for NCA)	LLOQ[c]	Conc >2000 µg/mL	Samples included in analysis (%)[d]
MDX1106-01 (CA209001)	915	40	33	0	42	0	800 (91.4)
MDX1106-03 (CA209003)	3733	331	32	76	74	2	3218 (94.6)
CA209017	585	122	0	0	9	0	454 (98.1)
CA209057	1355	267	13	0	15	0	1060 (97.4)
ONO-4538-07	431	65	0	1	3	0	362 (98.9)
CA209473	618	184	0	0	0	0	434 (100.0)
CA209577	2503	507	8	1	2	1	1984 (99.4)
Total	10140	1516	86	78	145	3	8312 (96.4)

Analysis-Directory: /global/pkms/data/CA/209/adj-ec-gej/prd/nivo-ppk/final

Program Source: Analysis-Directory/sas/

Source: Analysis-Directory/reports/Table3.3.1.2-1.rtf

Abbreviations: Conc = concentration; LLOQ = lower limit of quantification; NCA = noncompartmental analysis; PK = pharmacokinetic(s).

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

[b] Day 1 Pre-dose samples are excluded from the calculation of the percentage of samples included in analysis.

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

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

Table 5: Summary of Covariates Included in PPK Analysis by Study and Overall

Subject Characteristic		CA209001 (n = 39)	CA209003 (n = 304)	CA209017 (n = 125)	ONO-4538-07 (n =65)	CA209057 (n = 280)	CA209473 (n = 186)	CA209577 (n =494)	Overall (n = 1493)
Baseline Body Weight (kg)	Mean (SD)	84.5 (18.5)	81.8 (19.1)	76.3 (17.1)	54.3 (10.3)	71.2 (15.3)	55.6 (9.9)	71.5 (16.2)	71.6 (18.1)
	Median	81.3	79.9	75	53.2	69.8	55.4	70.8	70
	Min, Max	54.8, 136	41.6, 153	46.3, 136	35.5, 83.1	43.5, 158	34.1, 83	34.5, 119	34.1, 158
	Missing n (%)	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.067)
Baseline GFR (mL/min/1.73m2)	Mean (SD)	77.5 (20.2)	80.4 (20.3)	83.3 (19.4)	85.7 (17.4)	83.1 (19.4)	87.2 (17.1)	94.7 (14.4)	86.8 (18.7)
	Median	85.4	82.7	83.6	89.4	84.7	92.2	95.7	90.5
	Min, Max	34.5, 104	31.2, 135	40.6, 128	38.7, 123	31.9, 128	31.2, 123	39.3, 136	31.2, 136
	Missing n (%)	0 (0)	5 (1.64)	0 (0)	0 (0)	0 (0)	0 (0)	23 (4.66)	28 (1.88)
Baseline Serum Albumin (g/dL)	Mean (SD)	3.79 (0.375)	4.08 (0.48)	3.92 (0.538)	3.84 (0.473)	3.89 (0.492)	3.97 (0.408)	3.96 (0.388)	3.96 (0.453)
	Median	3.8	4.1	4	3.9	3.9	4	4	4
	Min, Max	2.3, 4.7	2.5, 5.1	2.2, 5.2	2.7, 5.1	1.9, 5.1	2.7, 5.2	2.7, 5.1	1.9, 5.2
	Missing n (%)	0 (0)	5 (1.64)	4 (3.2)	0 (0)	7 (2.5)	0 (0)	28 (5.67)	44 (2.95)
Age (yrs)	Mean (SD)	63.1 (9.72)	62.2 (11.5)	62.5 (7.97)	62.4 (7.24)	60.9 (9.33)	62.7 (8.56)	60.5 (9.25)	61.5 (9.56)
	Median	63	63	63	62	61	64	62	62
	Min, Max	43, 85	29, 85	39, 85	49, 80	37, 84	37, 82	26, 82	26, 85
	Missing n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20 (4.05)	20 (1.34)
Sex, n (%)	Male	22 (56.4)	202 (66.4)	102 (81.6)	54 (83.1)	144 (51.4)	158 (84.9)	417 (84.4)	1099 (73.6)
	Female	17 (43.6)	102 (33.6)	23 (18.4)	11 (16.9)	136 (48.6)	28 (15.1)	77 (15.6)	394 (26.4)
	0	13 (33.3)	128 (42.1)	27 (21.6)	29 (44.6)	81 (28.9)	93 (50.0)	292 (59.1)	663 (44.4)
	1	26 (66.7)	170 (55.9)	98 (78.4)	36 (55.4)	197 (70.4)	93 (50.0)	202 (40.9)	822 (55.1)

Subject Characteristic		CA209001 (n = 39)	CA209003 (n = 304)	CA209017 (n = 125)	ONO-4538-07 (n =65)	CA209057 (n = 280)	CA209473 (n = 186)	CA209577 (n =494)	Overall (n = 1493)
Baseline Performance Status, n (%)	2	0 (0)	6 (2.0)	0 (0)	0 (0)	2 (0.7)	0 (0)	0 (0)	8 (0.5)
Race, n (%)	White	29 (74.4)	282 (92.8)	112 (89.6)	0 (0)	256 (91.4)	5 (2.7)	403 (81.6)	1087 (72.8)
	Black/African American	10 (25.6)	15 (4.9)	6 (4.8)	0 (0)	6 (2.1)	0 (0)	4 (0.8)	41 (2.7)
	Asian	0 (0)	4 (1.3)	4 (3.2)	65 (100.0)	9 (3.2)	181 (97.3)	77 (15.6)	340 (22.8)
	Others	0 (0)	2 (0.7)	1 (0.8)	0 (0)	7 (2.5)	0 (0)	10 (2.0)	20 (1.3)
	Unknown[a]	0 (0)	1 (0.3)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	2 (0.1)
	Missing n (%)[b]	0 (0)	0 (0)	2 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)
Patient Population, n (%)	EC/GEJC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	494 (100.0)	494 (33.1)
	2L NSCLC	0 (0)	25 (8.2)	125 (100.0)	0 (0)	243 (86.8)	0 (0)	0 (0)	393 (26.3)
	2L+ EC	0 (0)	0 (0)	0 (0)	65 (100.0)	0 (0)	186 (100.0)	0 (0)	251 (16.8)
	OTHER[c]	39 (100.0)	279 (91.8)	0 (0)	0 (0)	37 (13.2)	0 (0)	0 (0)	355 (23.8)
Japanese Ethnicity, n (%)	Japanese	0 (0)	0 (0)	0 (0)	65 (100.0)	0 (0)	125 (67.2)	49 (9.9)	239 (16.0)
	Non-Japanese Asian	0 (0)	4 (1.3)	4 (3.2)	0 (0)	9 (3.2)	56 (30.1)	28 (5.7)	101 (6.8)
	Non-Asian	39 (100.0)	300 (98.7)	119 (95.2)	0 (0)	271 (96.8)	5 (2.7)	417 (84.4)	1151 (77.1)
	Missing	0 (0)	0 (0)	2 (1.6)	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)	12 (2.4)	12 (0.8)
	Non-Chinese Asian	0 (0)	4 (1.3)	4 (3.2)	65 (100.0)	9 (3.2)	181 (97.3)	65 (13.2)	328 (22.0)

Subject Characteristic		CA209001 (n = 39)	CA209003 (n = 304)	CA209017 (n = 125)	ONO-4538-07 (n =65)	CA209057 (n = 280)	CA209473 (n = 186)	CA209577 (n =494)	Overall (n = 1493)
	Non-Asian	39 (100.0)	300 (98.7)	119 (95.2)	0 (0)	271 (96.8)	5 (2.7)	417 (84.4)	1151 (77.1)
	Missing	0 (0)	0 (0)	2 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)

Analysis-Directory: /global/pkms/data/CA/209/ adj-ec-gej/prd/nivo-ppk/final

Program Source: Analysis-Directory/sas/

Source: Analysis-Directory/reports/Table3.3.1.5-1.rtf

Abbreviations: EC = esophageal cancer; GEJC = gastroesophageal junction cancer; GFR = glomerular filtration rate; HCC = hepatocellular carcinoma; Max = maximum; Min =minimum; n =number of subjects; NCSLC = non-small cell lung cancer; SD = standard deviation.

a Unknown race was defined as race that could not be determined.

b Missing race was defined as race criterion was not selected.

c The Other population included subjects with melanoma, prostate, renal cell, or colorectal cancer in Studies CA209001 and CA209003, 3L+ NSCLC in Studies CA209001, CA209017, 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.

The nivolumab PPK model was developed in two steps: base model and full model. Base model development consisted of a re-estimation of the parameters of the final PPK model developed to support the nivolumab monotherapy 2L EC submission (including a population-type effect on baseline nivolumab CL).

Base model

The base model was a 2-compartment, zero-order IV infusion PK model with time-varying CL (sigmoidal-Emax function). The base model used the same structure model as that was used in the previous final PPK model in 2L EC. The base model contained baseline body weight (BBWT), estimated baseline GFR (BGFR), baseline albumin (BALB), baseline LDH (BLDH), performance status (PS), sex, race (Asian versus non-Asian), and patient population (POP; combining tumour type and line of therapy) on baseline CL, BBWT and sex on VC, BBWT on inter-compartmental clearance (Q), and BBWT on VP.

Table 6: Parameter Estimates of the Base Population Pharmacokinetic Model

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval[d]
		Fixed Effects		
CL_{REF} [mL/h][e]	θ_1	11.5	0.461 (4.00)	10.6 - 12.4
VC_{REF} [L][e]	θ_2	4.38	0.0558 (1.27)	4.28 - 4.49
Q_{REF} [mL/h][e]	θ_3	32.4	3.89 (12.0)	24.8 - 40.0
VP_{REF} [L][e]	θ_4	2.97	0.164 (5.52)	2.65 - 3.29
CL_{BBWT}[f]	θ_7	0.563	0.0529 (9.40)	0.460 - 0.667
CL_{GFR}[f]	θ_8	0.126	0.0403 (32.0)	0.0467 - 0.205
CL_{SEX}[g]	θ_9	-0.174	0.0262 (15.0)	-0.225 - -0.123
CL_{PS}[g]	θ_{10}	0.0599	0.0186 (31.0)	0.0235 - 0.0964
CL_{RAAS}[g]	θ_{11}	-0.0380	0.0319 (83.7)	-0.100 - 0.0244
CL_{BALB}[f]	θ_{12}	-0.827	0.0830 (10.0)	-0.990 - -0.665
CL_{BLDH}[f]	θ_{13}	0.341	0.120 (35.3)	0.105 - 0.577
CL_{POPOTH}[g]	θ_{14}	0.0642	0.0319 (49.7)	0.00168 - 0.127

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval[d]
$CL_{POPEC2L}$[g]	θ_{15}	-0.0594	0.0373 (62.7)	-0.133 - 0.0136
$CL_{POPADJEC}$[g]	θ_{16}	-0.195	0.0290 (14.8)	-0.252 - -0.138
VC_{BBWT}[f]	θ_{17}	0.654	0.0337 (5.15)	0.588 - 0.720
VC_{SEX}[g]	θ_{18}	-0.185	0.0271 (14.6)	-0.239 - -0.132
EMAX	θ_{19}	-0.326	0.0543 (16.7)	-0.432 - -0.219
T50 [h]	θ_{20}	1360	152 (11.2)	1070 - 1660
HILL [-]	θ_{21}	2.87	0.854 (29.8)	1.19 - 4.54
Random Effects[h]				
ω^2 -CL [-]	$\omega_{1,1}$	0.0773 (0.278)	0.00749 (9.69)	0.0626 - 0.0919
ω^2 -VC [-]	$\omega_{2,2}$	0.0955 (0.309)	0.0162 (17.0)	0.0638 - 0.127
ω^2 -VP [-]	$\omega_{3,3}$	0.230 (0.480)	0.0336 (14.6)	0.164 - 0.296
ω^2 -EMAX [-]	$\omega_{4,4}$	0.0401 (0.200)	0.0142 (35.3)	0.0124 - 0.0679
ω^2 CL: ω^2 VC [-]	$\omega_{1,2}$	0.0375 (0.437)	0.00581 (15.5)	0.0261 - 0.0489
Residual Error				
Proportional [-]	θ_6	0.225	0.00889 (3.96)	0.207 - 0.242

Analysis-Directory: /global/pkms/data/CA/209/adj-ec-gej/prd/nivo-ppk/final

Source: Analysis-Directory/psn/base.dir1/reports/base_origin_RTF.rtf

Abbreviations: BALB = baseline serum albumin; BBWT = baseline body weight; BGFR = baseline glomerular filtration rate; BLDH = baseline lactate dehydrogenase; CL = clearance; EMAX = maximum effect; HILL = sigmoidicity of the relationship with time; POPADJEC = adjuvant esophageal cancer patient population; POPEC2L = second-line esophageal carcinoma patient population; POPOTH = other patient population; PS = performance status; Q = inter-compartmental clearance; RAAS = race Asian; RSE = relative standard error; VC = volume of the central compartment; VP = volume of the peripheral compartment.

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

b Random effects 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 CL_{REF}, VC_{REF}, Q_{REF}, and VP_{REF} are typical values of CL, VC, Q, and VP at the reference covariate values. Covariate effects were estimated relative to a reference subject who is a male, weighing 80 kg, estimated GFR of 90 mL/min/1.73 m^2, serum albumin of 4 g/dL, BLDH of 200 U/mL, PS of 0, race = white or other, defined as not Asian, and population type of 2L NSCLC. The same reference values that were selected in the previous 2L+ EC PPK model were chosen.

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

Full model

The full model was developed from the base model by incorporating additional covariates representing the effect of population type (adjuvant EC/GEJC, 2L+ EC, 2L NSCLC, and others) and PS effect on the time-varying CL (EMAX). Time-varying and stationary CL on adjuvant EC/GEJC were evaluated during full model development.

Nivolumab serum concentration-time data were well-described by a linear, 2-compartment model with zero-order IV infusion, first-order elimination, and time-varying CL. The full model with time-varying CL in all population types provided a better description of observed data relative to the model with adjuvant EC/GEJC as stationary CL. The covariate effects from the full model are shown in Figure 3. The PK parameter estimates were similar with those in a previous PPK analysis in 2L+ EC.

Table 7: Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model (Full Model)

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval[d]
Fixed Effects[e,f,g]				
CL_{REF} [mL/h]	θ_1	11.2	0.498 (4.47)	9.84 - 12.3
VC_{REF} [L]	θ_2	4.37	0.0547 (1.25)	4.26 - 4.47
Q_{REF} [mL/h]	θ_3	32.3	3.78 (11.7)	25.9 - 45.0
VP_{REF} [L]	θ_4	2.92	0.152 (5.21)	2.60 - 3.61
CL_{BBWT}	θ_7	0.561	0.0526 (9.37)	0.457 - 0.665
CL_{BGFR}	θ_8	0.127	0.0405 (31.9)	0.0519 - 0.207
CL_{SEX}	θ_9	-0.173	0.0262 (15.1)	-0.225 - -0.121
CL_{PS}	θ_{10}	0.0900	0.0272 (30.2)	0.0277 - 0.149
CL_{RAAS}	θ_{11}	-0.0422	0.0317 (75.2)	-0.109 - 0.0190
CL_{BALB}	θ_{12}	-0.825	0.0825 (10.0)	-1.00 - -0.677
CL_{BLDH}	θ_{13}	0.358	0.119 (33.2)	0.148 - 0.586
CL_{POPOTH}	θ_{14}	0.0779	0.0414 (53.2)	-0.0111 - 0.158
$CL_{POPEC2L}$	θ_{15}	-0.00989	0.0469 (474)	-0.107 - 0.0879
$CL_{POPADJEC}$	θ_{16}	-0.0863	0.0427 (49.5)	-0.174 - 0.0228
VC_{BBWT}	θ_{17}	0.670	0.0347 (5.18)	0.596 - 0.735
VC_{SEX}	θ_{18}	-0.178	0.0271 (15.2)	-0.232 - -0.128
$EMAX_{REF}$	θ_{19}	-0.239	0.0569 (23.8)	-0.370 - -0.0812
T50 [h]	θ_{20}	1260	178 (14.2)	682 - 1600
HILL	θ_{21}	2.47	0.544 (22.1)	1.69 - 64.4
$EMAX_{PS}$	θ_{22}	-0.0558	0.0372 (66.7)	-0.138 - 0.0270
$EMAX_{POPOTH}$	θ_{23}	-0.0317	0.0570 (180)	-0.144 - 0.0882
$EMAX_{POPEC2L}$	θ_{24}	-0.0978	0.0545 (55.7)	-0.216 - 0.0102
$EMAX_{POPADJEC}$	θ_{25}	-0.189	0.0544 (28.8)	-0.334 - -0.0890
Random Effects[h]				
ω^2 -CL [-]	$\omega_{1,1}$	0.0766 (0.277)	0.00746 (9.73)	0.0613 - 0.0916
ω^2 -VC [-]	$\omega_{2,2}$	0.0946 (0.308)	0.0161 (17.0)	0.0647 - 0.128
ω^2 -VP [-]	$\omega_{3,3}$	0.234 (0.484)	0.0352 (15.0)	0.168 - 0.325
ω^2 -EMAX [-]	$\omega_{4,4}$	0.0404 (0.201)	0.0153 (38.0)	0.0122 - 0.0688
ω^2 CL: ω^2 VC [-]	$\omega_{1,2}$	0.0380 (0.447)	0.00565 (14.9)	0.0265 - 0.0504

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (%RSE)[c]	95% Confidence Interval[d]
Residual Error				
Proportional [-]	θ_6	0.225	0.00886 (3.95)	0.207 - 0.242

Analysis-Directory: /global/pkms/data/CA/209/adj-ec-gej/prd/nivo-ppk/final

Source: Analysis-Directory/psn/full-1.dir1/reports/full-1_origin_RTF.rtf

Source: Analysis-Directory/psn/reports/bs-full-1_RTF.rtf

Abbreviations: BALB = baseline serum albumin; BBWT = baseline body weight; BGFR = baseline glomerular filtration rate; BLDH = baseline lactate dehydrogenase; CL = clearance; EMAX = maximum effect; HILL = sigmoidicity of the relationship with time; POPADJEC = adjuvant esophageal cancer patient population ; POPEC2L = second-line esophageal carcinoma patient population; POPOTH = other patient population; PS = performance status; Q = Inter-compartmental clearance; RAAS = race Asian; RSE = relative standard error; VC = volume of the central compartment; VP = volume of the peripheral compartment.

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

[b] Random effects and residual error parameter estimates are shown as variance (standard deviation) for diagonal elements 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 (839 successful out of a total of 1000).

[e] CL_{REF},VC_{REF}, Q_{REF}, VP_{REF}, and $EMAX_{REF}$ are typical values of CL, VC, Q, VP, and EMAX at the reference covariate values. Covariate effects were estimated relative to a reference subject who is a male, weighing 80 kg, estimated GFR of 90 mL/min/1.73 m^2, serum albumin of 4 g/dL, BLDH of 200 U/mL, PS of 0, race = white or other, defined as not Asian, and population type of 2L NSCLC. The reference values for continuous valued covariates were selected to be approximately the median of the covariate values in the analysis dataset.

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

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

$$CL_{t,i} = CL_i \times \exp\left(\frac{EMAX_i \times time^{HILL}}{T50_i^{HILL} + time^{HILL}}\right)$$

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

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

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

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

$$CL_{TV,i} = CL_{REF} \times (e^{CL_{PS}})^{PS_i} \times (e^{CL_{SEX}})^{SEX_i} \times (e^{CL_{RAAS}})^{RAAS_i} \times (e^{CL_{POPOTH}})^{POPOTHi} \times (e^{CL_{POPEC2L}})^{POPEC2Li} \times (e^{CL_{POPADJEC}})^{POPADJECi}$$

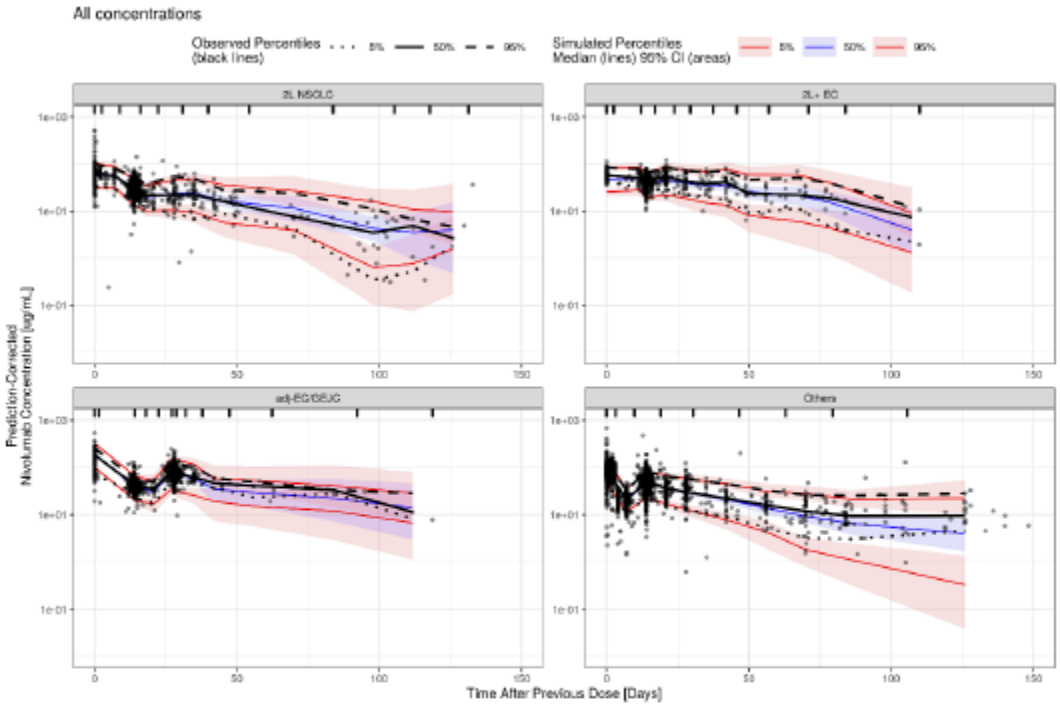
$$VC_{TV,i} = VC_{REF} \times (e^{VC_{SEX}})^{SEX_i}$$

$$EMAX_{TV,i} = EMAX_{REF} + (EMAX_{PS})^{PS_i} + (EMAX_{POPEC2L})^{POPEC2L_i} + (EMAX_{POPADJEC})^{POPADJEC_i} + (EMAX_{POPOTH})^{POPOTH_i}$$

[h] Eta shrinkage: ETA_CL: 18.7%, ETA_VC: 26.9%, ETA_VP: 46.5%, ETA_EMAX: 53.9%; Epsilon shrinkage: 13.9%

Note: The condition number was 441, indicating there was no evidence for ill-conditioning.

Figure 1: Prediction-corrected Visual Predictive Check of All Concentrations (Log Scale) Versus Actual Time After Previous Dose for Data by Patient Populations



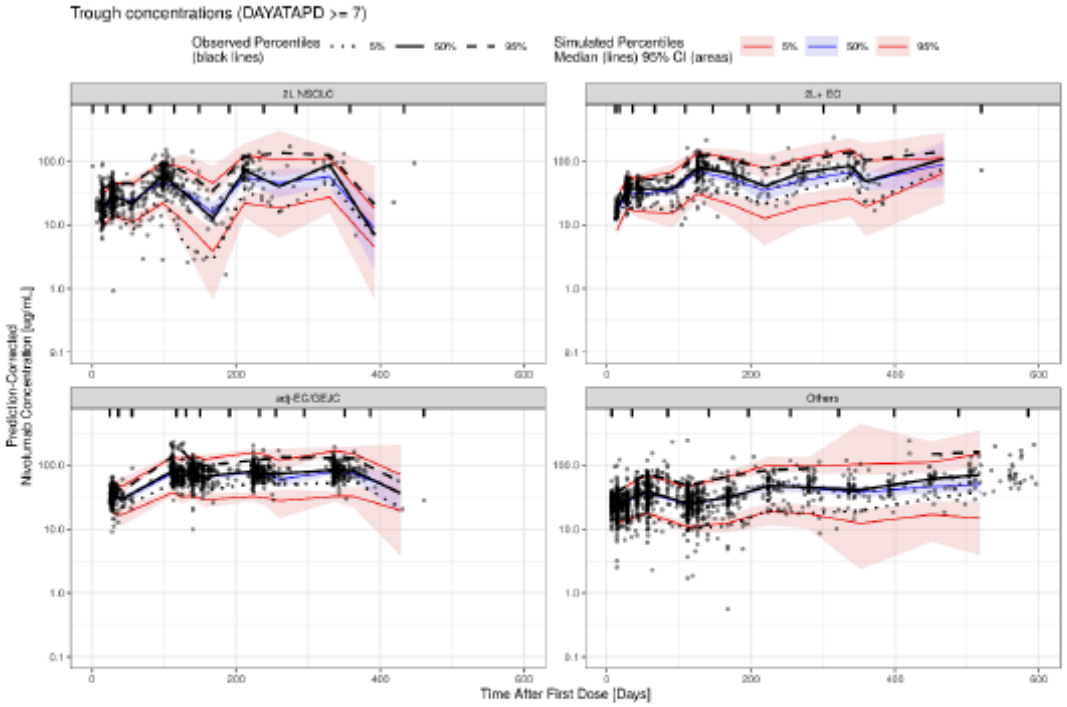
Analysis-Directory: /global/pkms/data/CA/209/adj-ec-gej/prd/nivo-ppk/final

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

Source: Analysis-Directory/R/plots/full-1-vpc-all-atapd-bin-jenks.png

Abbreviations: 2L = second-line; adj = adjuvant; CI = confidence interval; EC = esophageal cancer; GEJC = gastroesophageal junction cancer; NSCLC = non-small cell lung cancer.

Figure 2: Prediction-corrected Visual Predictive Check of Trough Concentrations (Log Scale) Versus Actual Time After First Dose for Data by Patient Populations



Analysis-Directory: /global/pkms/data/CA/209/adj-ec-gej/prd/nivo-ppk/final

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

Source: Analysis-Directory/R/plots/full-1-vpc-trough-atafd-bin-jenks.png

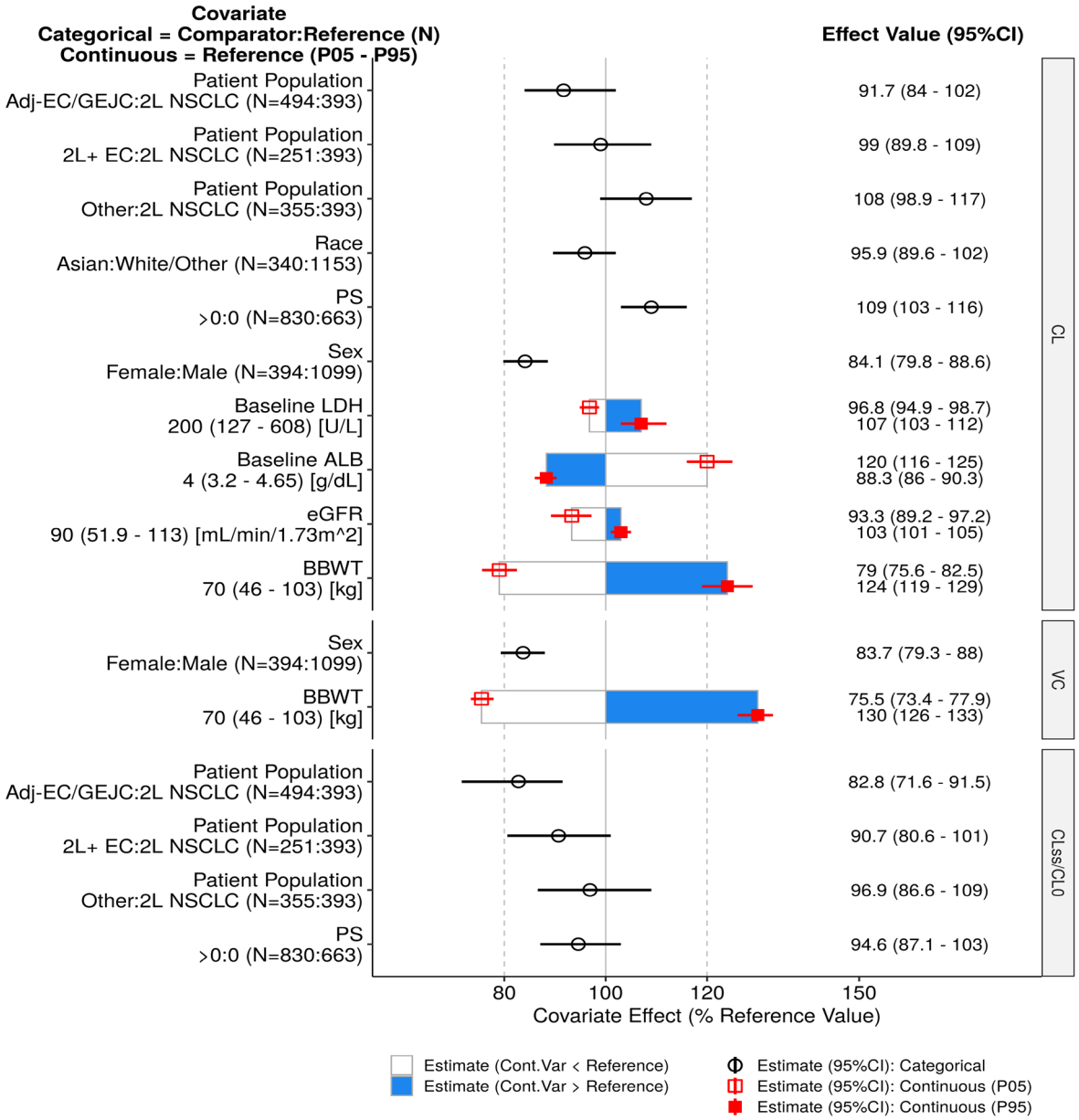
Abbreviations: 2L = second-line; adj = adjuvant; CI = confidence interval; DAYATAPD = actual time after previous dose (unit = day); EC = esophageal cancer; GEJC = gastroesophageal junction cancer; NSCLC = non-small cell lung cancer.

Note: The trough concentration was defined as the nivolumab concentration with an actual time after previous dose (DAYATAPD) greater than 7 days.

The effects of population type on baseline CL and time-vary CL were less than 20%, indicating that nivolumab PK does not substantially differ between adjuvant EC/GEJC and other population types (2L + EC, 2L NSCLC, and others). The magnitudes of the covariate effects on CL, VC, and time-varying CL (Emax) were within the ± 20% boundaries for the covariates, except BBWT.

CL and VC were higher in subjects with higher body weight. The magnitude of the body weight effect was consistent with previous PPK results in 2L EC, and body weight was associated with a 21% decrease and a 24% increase in CL in the 5th and 95th percentiles of body weight, relative to the reference value of 70 kg, respectively. Body weight was associated with a 25% decrease and 30% increase in VC in the 5th and 95th percentiles of body weight, relative to the reference value of 70 kg, respectively. In addition, the exposures at steady state were higher (≤ 28%) in adjuvant EC/GEJC subjects with lower body weight (at 5th percentile) and were lower (≤ 19%) in subjects with higher body weight (at 95th percentile) relative to the exposure in typical subjects with a median body weight of 70 kg.

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



Source: Refer to Figure 5.1.1.2-1 in the CA209577 PPK Report.

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, BBWT = 70 kg, baseline ALB = 4 g/dL, baseline LDH of 200 U/mL, 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.

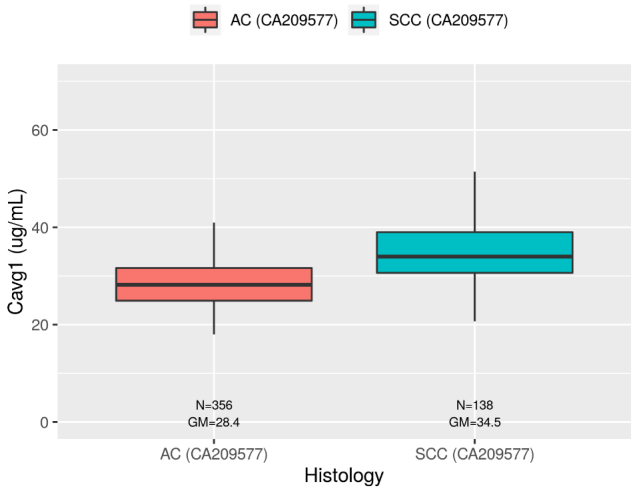
Note 4: Confidence Interval values are taken from bootstrap calculations (839 successful out of a total of 1,000).

Note 5: The effect of BBWT was also added on inter-compartment clearance (Q) and volume of distribution of peripheral compartment (VP), and their estimates were fixed to be similar to CL and VC, respectively.

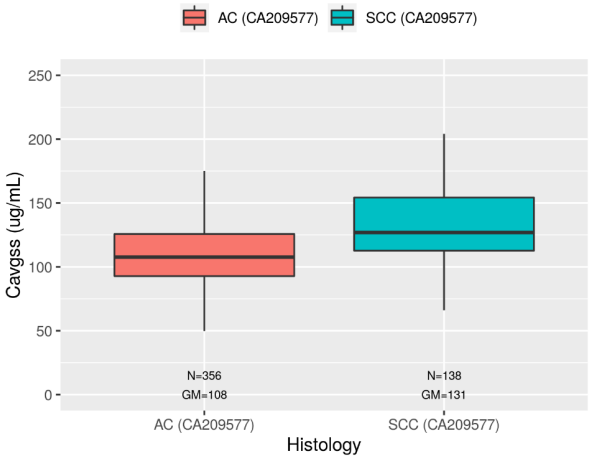
Abbreviations: 2L = second-line; Adj = adjuvant; ALB = albumin; BBWT = baseline body weight; CI = confidence interval; CLss/CL0 = exp(EMAX); EC = esophageal cancer; eGFR = estimated glomerular filtration rate; GEJC = gastroesophageal junction cancer; LDH = lactate dehydrogenase; NSCLC = non-small cell lung cancer; PS = performance status.

Figure 4: Distribution of Nivolumab Exposure for A) Cavg1 and B) Cavgss by Histology Status in Study CA209577

A) Nivolumab Cavg1



B) Nivolumab Cavgss



Source: Refer to Figure 5.1.3.4-2 in the CA209577 PPK Report.

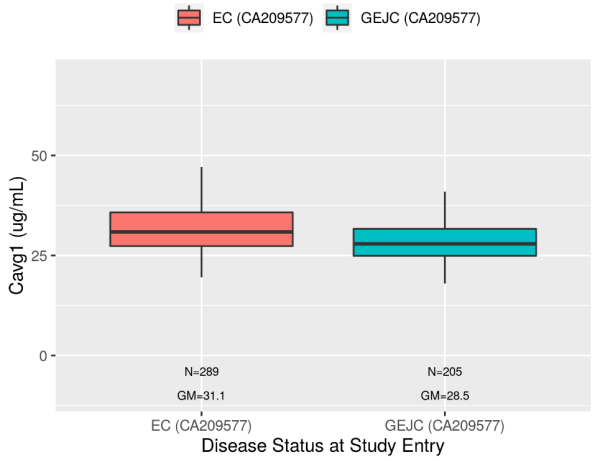
Note 1: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Note 2: Exposures are for the nominal nivolumab treatment regimen per the protocol (adjuvant EC/GEJC: 240 mg Q2W for 16 weeks followed by 480 mg Q4W).

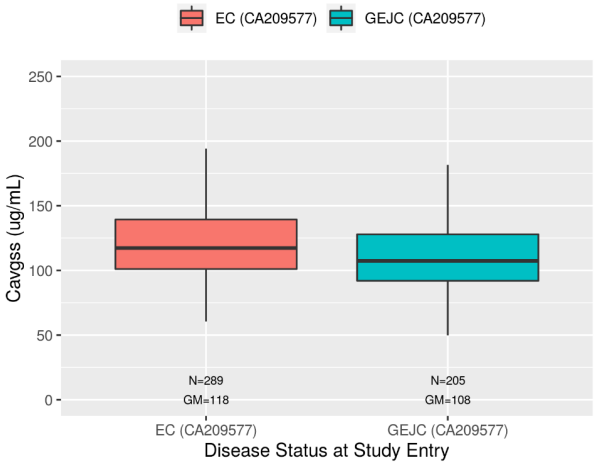
Abbreviations: AC = adenocarcinoma; Cavg1 = time-averaged serum concentration over the first dosing interval, Cavgss = time-averaged serum concentration at steady state; GM = geometric mean; SCC = squamous cell carcinoma.

Figure 5: Distribution of Nivolumab Exposure for A) Cavg1 and B) Cavgss by Disease at Initial Diagnosis in Study CA209577

A) Nivolumab Cavg1



B) Nivolumab Cavgss



Source: Refer to Figure 5.1.3.5-2 in the CA209577 PPK Report.

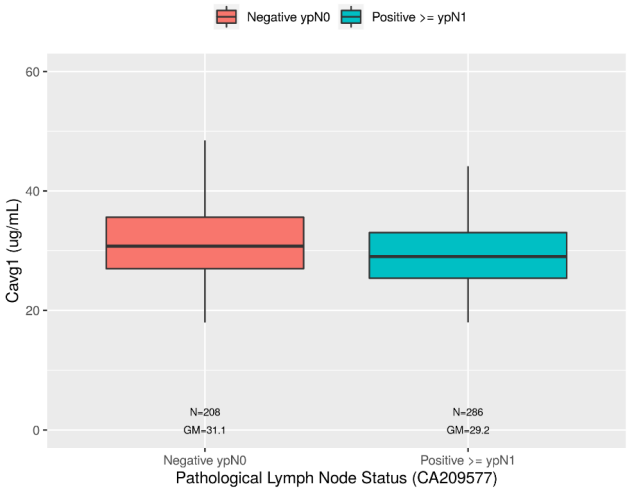
Note 1: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Note 2: Exposures are for the nominal nivolumab treatment regimen per the protocol (adjuvant EC/GEJC: 240 mg Q2W for 16 weeks followed by 480 mg Q4W).

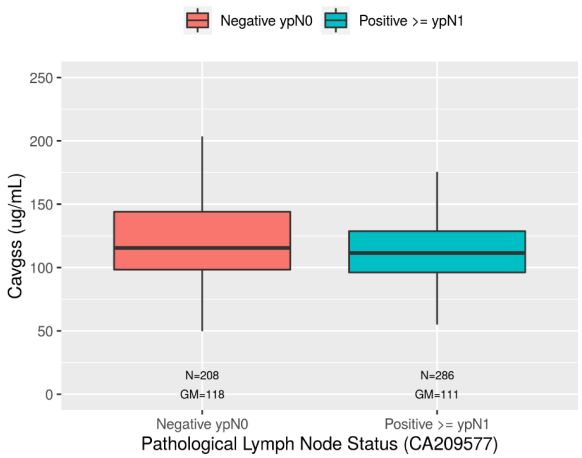
Abbreviations: Cavg1 = time-averaged serum concentration over the first dosing interval, Cavgss = time-averaged serum concentration at steady state; EC = esophageal cancer; GEJC = gastroesophageal junction cancer; GM = geometric mean.

Figure 6: Distribution of Nivolumab Exposure for A) Cavg1 and B) Cavgss by Pathologic Lymph Node Status in Study CA209577

A) Nivolumab Cavg1



B) Nivolumab Cavgss



Source: Refer to Figure 5.1.3.6-2 in the CA209577 PPK Report.

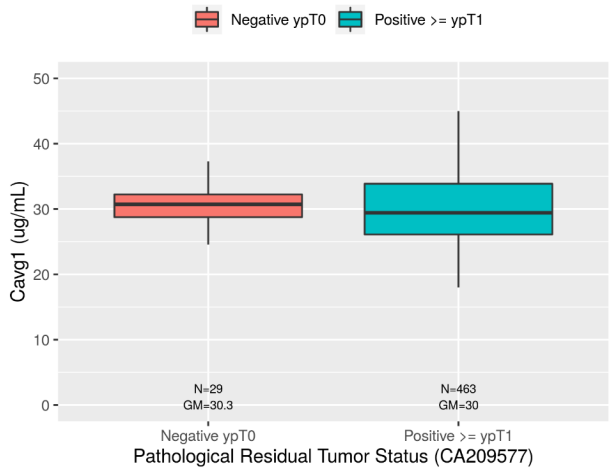
Note 1: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Note 2: Exposures are for the nominal nivolumab treatment regimen per the protocol (adjuvant EC/GEJC: 240 mg Q2W for 16 weeks followed by 480 mg Q4W).

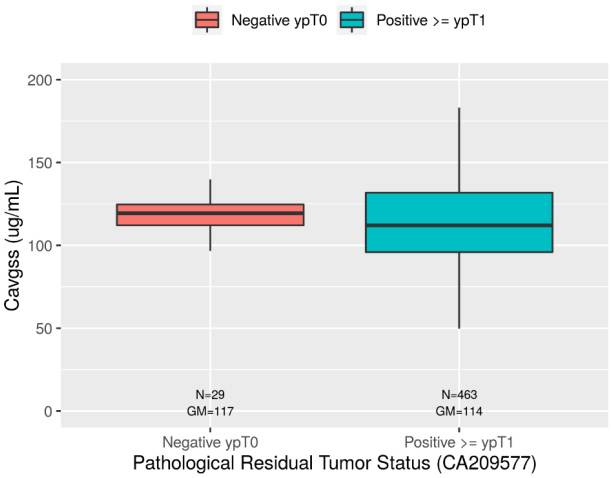
Abbreviations: Cavg1 = time-averaged serum concentration over the first dosing interval, Cavgss = time-averaged serum concentration at steady state; GM = geometric mean.

Figure 7: Distribution of Nivolumab Exposure for A) Cavg1 and B) Cavgss by Pathologic Residual Tumour Status in Study CA209577

A) Nivolumab Cavg1



B) Nivolumab Cavgss



Source: Refer to Figure 5.1.3.7-2 in the CA209577 PPK Report.

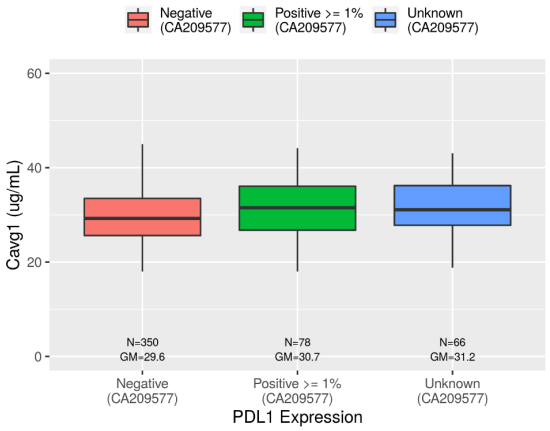
Note 1: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Note 2: Exposures are for the nominal nivolumab treatment regimen per the protocol (adjuvant EC/GEJC: 240 mg Q2W for 16 weeks followed by 480 mg Q4W).

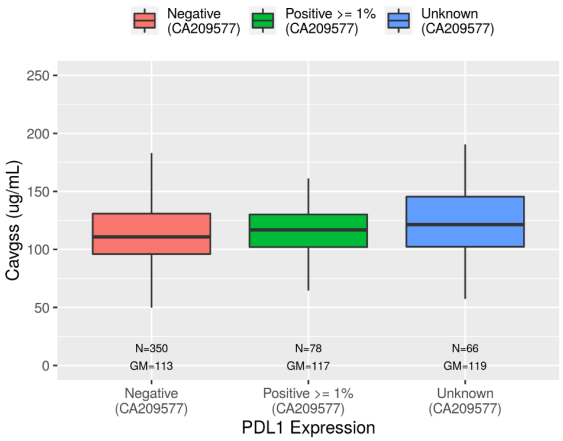
Abbreviations: Cavg1 = time-averaged serum concentration over the first dosing interval, Cavgss = time-averaged serum concentration at steady state; GM = geometric mean.

Figure 8: Distribution of Nivolumab Exposure for A) Cavg1 and B) Cavgss by Baseline PD-L1 Status in Study CA209577

A) Nivolumab Cavg1



B) Nivolumab Cavgss



Source: Refer to Figure 5.1.3.8-2 in the CA209577 PPK Report.

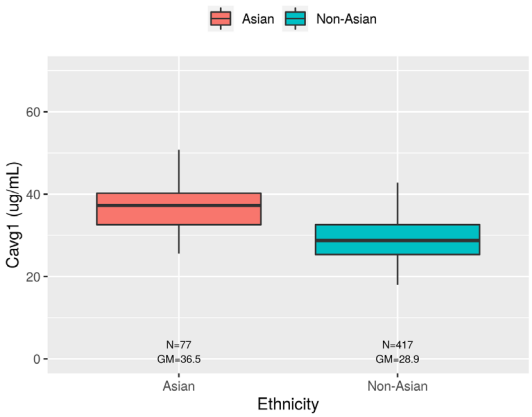
Note 1: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Note 2: Exposures are for the nominal nivolumab treatment regimen per the protocol (adjuvant EC/GEJC: 240 mg Q2W for 16 weeks followed by 480 mg Q4W).

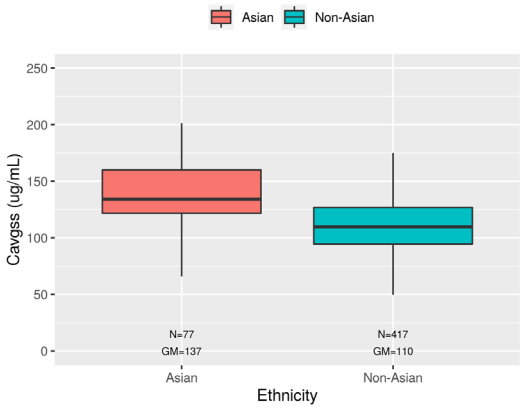
Abbreviations: Cavg1 = time-averaged serum concentration over the first dosing interval, Cavgss = time-averaged serum concentration at steady state; GM = geometric mean.

Figure 9: Distributions of Exposure (Cavg1 and Cavgss) of Nivolumab in the Adjuvant EC/GEJC in Study CA209577 in Relation to Asians Versus Non-Asians

A) Nivolumab Cavg1



B) Nivolumab Cavgss



Program Source: /global/pkms/data/CA/209/adj-ec-gej/prd/nivo-ppk/final/R/scripts/7-additional-analysis-SCP.Rmd

Source: /global/pkms/data/CA/209/adj-ec-gej/prd/nivo-ppk/final/R/plots/Figure_CAVG1-by-asian.png and Figure_CAVGSS-by-asian.png

Note 1: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Note 2: Exposures are for the nominal nivolumab treatment regimen per the protocol (eg, adjuvant EC/GEJC: 240 mg Q2W for 16 weeks followed by 480 mg Q4W).

Abbreviations: Cavg1 = time-averaged serum concentration over the first dosing interval, Cavgss = time-averaged serum concentration at steady state; EC = esophageal cancer; GEJC = gastroesophageal junction cancer; GM = geometric mean.

Dosing regimen evaluation

The summary of simulated nivolumab exposures and PK profiles in subjects undergoing adjuvant treatment of EC/GEJC for the proposed dosing regimens (nivolumab 480 mg Q4W for 16 weeks followed by 480 mg IV Q4W versus 240 mg/kg Q2W for 16 weeks followed by 480 mg Q4W up to 1 year) are presented in Table 8 and Figure 8 respectively.

As expected, the steady-state exposures for the two dosing regimens were equivalent, as 480 mg Q4W was given after 16 weeks in both of the proposed dosing regimens. The largest exposure difference between 240 mg Q2W and 480 mg Q4W was Cmax1 (99.7% higher), which results from the doubling of the dose level (480 mg) at the first dose (relative to 240 mg) [Table 8]. Neither 480 mg Q4W nor 240 mg Q2W provided exposures exceeding those at 10 mg/kg Q2W (Figure 8), indicating that exposures with these regimens are all expected to be within the well-tolerated range previously confirmed in cancer patients.

Table 8: Geometric Mean Exposure for Nivolumab 240 mg Q2W for 16 Weeks followed by 480 mg Q4W up to 1 Year and 480 mg Q4W for 16 Weeks Followed by 480 mg Q4W up to 1 Year in Adjuvant EC and GEJC (N = 494)

Summary Exposure	Nivolumab 240 mg Q2W GM [µg/mL] (%CV)	Nivolumab 480 mg Q4W GM [µg/mL] (%CV)	% Difference GM (480 mg) G2-G1[a]
Cmax1	60.6 (24.8)	121 (24.8)	99.7
Cavg1	30.0 (20.6)	46.3 (21.1)	54.3
Cmin1	20.2 (22.1)	25.8 (24.2)	27.7
Cavgd28	38.3 (20.8)	46.3 (21.1)	20.9
Cmind28	33.6 (22.7)	25.8 (24.2)	-23.2
Cmaxw17	197 (23.2)	184 (23.4)	-6.6
Cavgw17	109.0 (24.0)	99.6 (24.3)	-8.6
Cminw16	75.5 (25.8)	61.9 (27.7)	-18.0
Cmaxss	202 (24.2)	202 (24.1)	0
Cavgss	114 (26.8)	114 (26.8)	0
Cminss	79.2 (31.8)	79.2 (31.7)	0

Source: Refer to Table 5.1.3.11-1 in the CA209577 PPK Report.

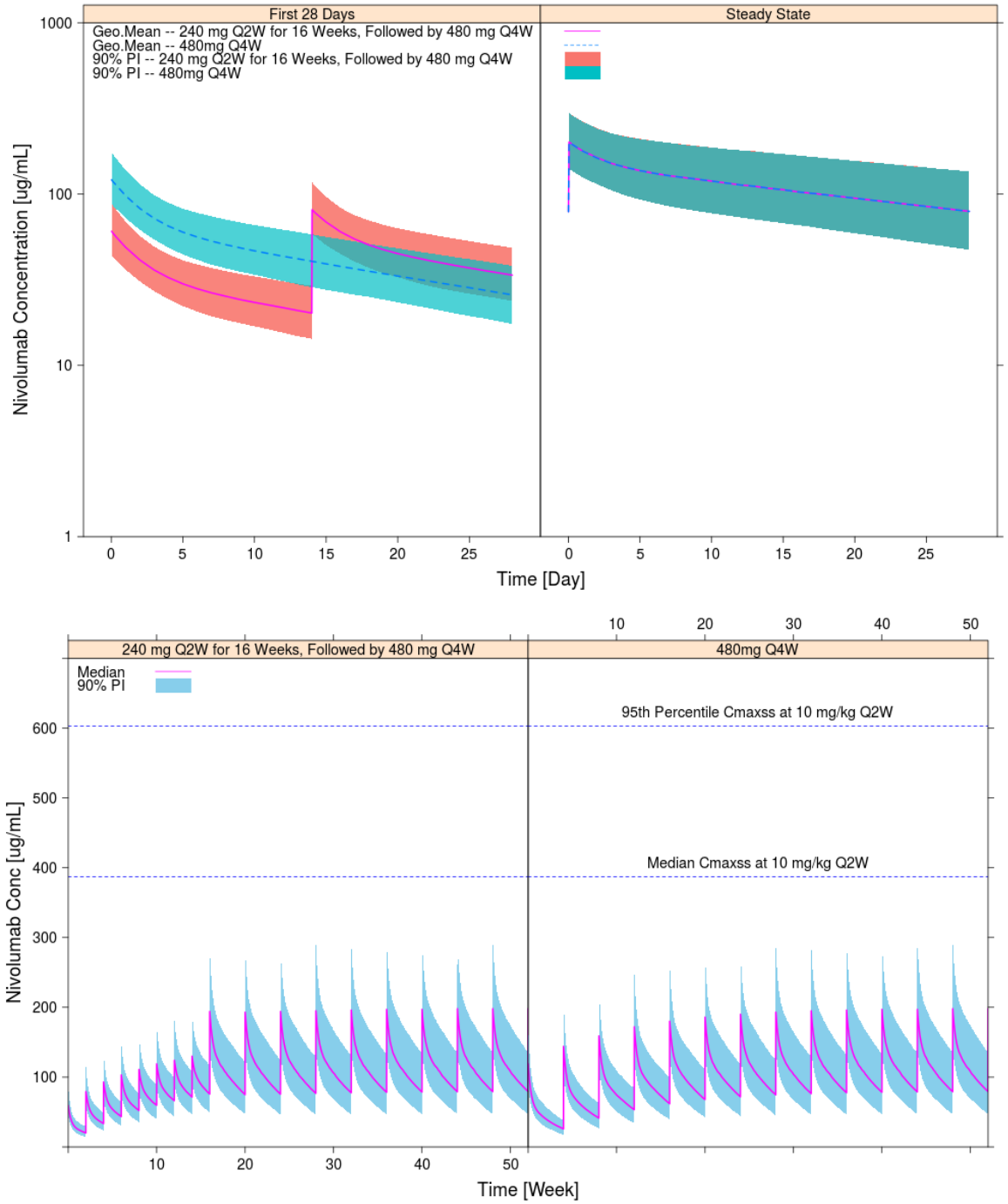
Note 1: Steady-state concentrations for Cavg, Cmax, and Cmin represent the geometric means of the predicted values for individual subjects at 1 years after nivolumab treatment initiation.

Note 2: Cminw16, Cmaxw17 and Cavgw17 represent trough (pre-dose), maximal concentration and average concentration of the first 480 mg Q4W when switching from 240 mg after Week 16.

Abbreviations: %CV = coefficient of variation expressed as a percentage; Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgd28 = time-averaged concentration over the first 28 days of treatment; Cavgss = time-averaged serum concentration at steady state; Cavgw17 = time-averaged serum concentration at Week 17; Cmax 1 = post dose 1 peak serum concentration; Cmaxss = peak serum concentration at steady state; Cmaxw17 = peak serum concentration at Week 17; Cmin1 = trough serum concentration after the first nivolumab dose (14 days for Q2W and 28 days for Q4W); Cmind28 = trough concentration at Day 28; Cminss = trough serum concentration at steady state; Cminw16 = trough serum concentration at Week 16; EC = esophageal cancer; GEJC = gastroesophageal junction cancer; GM = geometric mean; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] Geometric mean (GM) difference in percentage of 480 mg Q4W (G2) relative to 240 mg Q2W (G1).

Figure 10: Predicted Geometric Mean (with 90% PI) Nivolumab Concentration-Time Profiles (First 28 Days and Steady State) [Log Scale], by Dosing Regimen (240 mg Q2W and 480 mg Q4W), in Subjects with Adjuvant EC and GEJC



Source: Refer to Figure 5.1.3.11-1 in the CA209577 PPK Report.

Note: Median and 95th percentile Cmaxss at 10 mg/kg Q2W was calculated from 157 subjects receiving 10 mg/kg Q2W nivolumab from Studies MDX1106-01, MDX1106-03, and CA209005.

Abbreviations: EC = esophageal cancer; GEJC = gastroesophageal junction cancer; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Immunogenicity

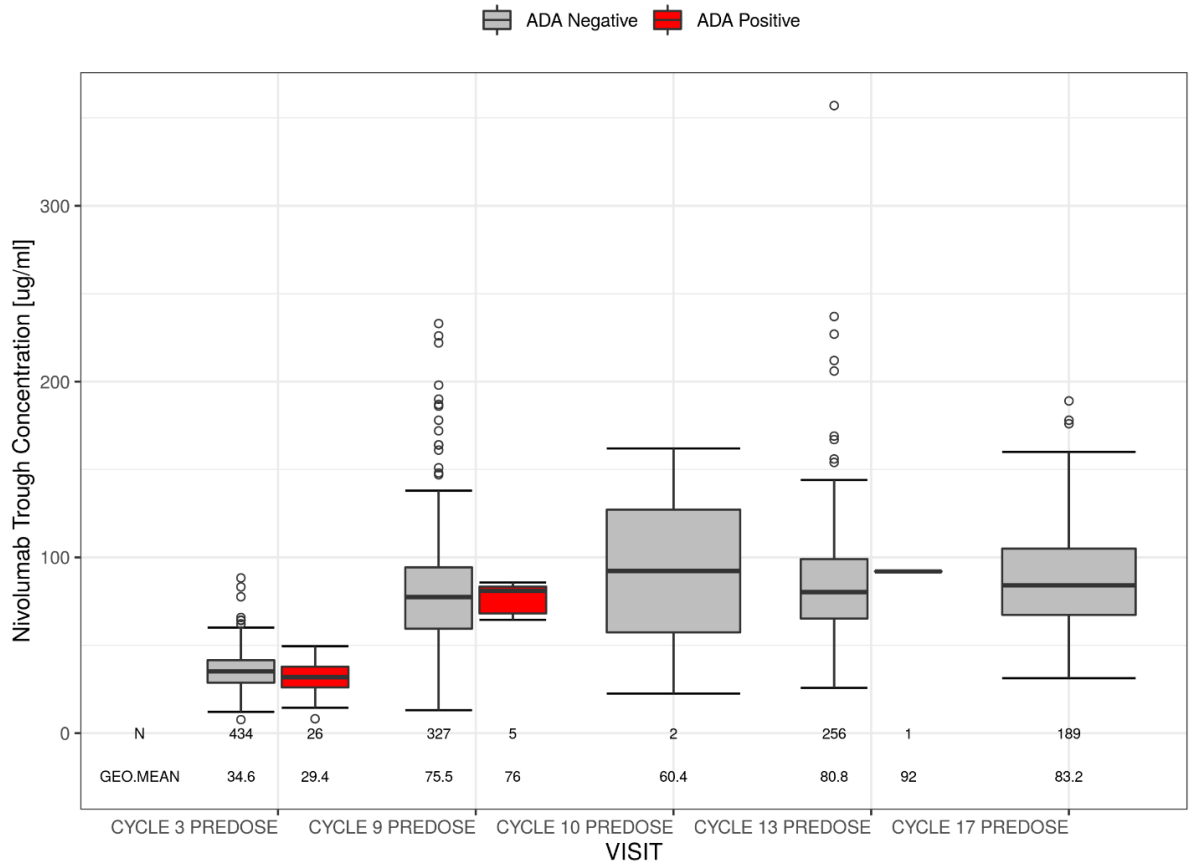
In Study CA209577, the incidence of nivolumab anti-drug antibodies (ADA) was 4.5% (21/464).[i] No subjects were considered persistent positive (ADA-positive sample at 2 or more consecutive time points, at least 16 weeks apart), and the incidence of neutralizing antibodies (NAb) was 0.2% (1/464).

There was no apparent trend showing an effect of ADA or NAb on the efficacy (DFS) of nivolumab.[i] The incidence of nivolumab ADA did not appear to have an effect on the safety of the tested regimen, as the incidence of hypersensitivity/infusion reaction was 3.2% (14/442) in nivolumab ADA-negative subjects and zero (0/21) in nivolumab ADA-positive subjects. In addition, the overall nivolumab exposure distributions were similar between ADA-positive subjects versus ADA-negative subjects in Study CA209577.

The observed incidence of nivolumab ADA in Study CA209577 was generally consistent with those observed in other tumour types following nivolumab monotherapy.

The effect of immunogenicity on nivolumab PK in adjuvant EC/GEJC was also evaluated using PPK model predicted exposure. The Cavg1 and Cavgss were similar between subjects with negative and positive ADA status (< 10% difference) in Study CA209577 (Figure 10).

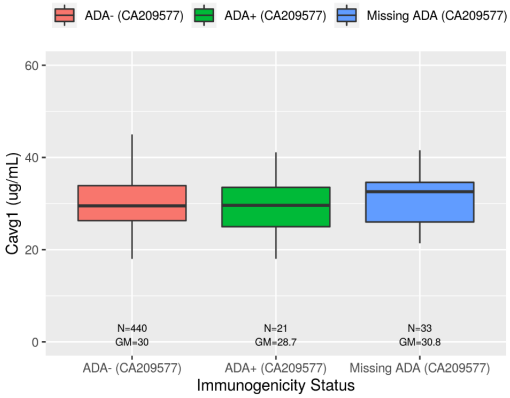
Figure 11: Distributions of Nivolumab Trough Concentrations by Study Visit for ADA Status Positive (Red) Versus ADA Status Negative (Gray) in Study CA209577



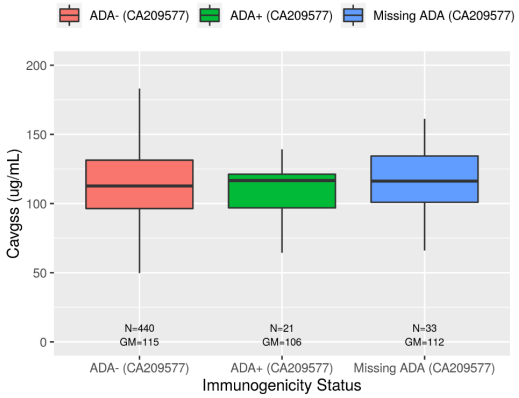
Source: Refer to Figure 3.3.1.6-1 in the CA209577 PPK Report.
Cycle 3 = Week 5, Cycle 9 = Week 17, Cycle 10 = Week 21, Cycle 13 = Week 33 and Cycle 17 = Week 49.
Note: The number below each boxplot is the number of pre-treatment PK samples at each visit by ADA status.
Abbreviations: ADA = anti-drug antibody; Geo. Mean = geometric mean.

Figure 1: Distribution of Nivolumab Exposure for A) Cavg1 and B) Cavgss in ADA+ and ADA- Subjects in Study CA209577

A) Nivolumab Cavg1



B) Nivolumab Cavgss



Source: Refer to Figure 5.1.3.2-2 in the CA209577 PPK Report.

Note 1: The box plots represent median (bold line), 25th, and 75th percentiles of the parameter distribution. The whiskers represent 5th and 95th percentiles of the distribution.

Note 2: Exposures are for the nominal nivolumab treatment regimen per the protocol (adjuvant EC/GEJC: 240 mg Q2W for 16 weeks followed by 480 mg Q4W).

Abbreviations: ADA = anti-drug antibody, Cavg1 = time-averaged serum concentration over the first dosing interval, Cavgss = time-averaged serum concentration at steady state; GM = geometric mean.

2.3.1. Pharmacodynamics

Mechanism of action

No mechanism of action studies were submitted in this application.

Primary and secondary pharmacology

The relationship between nivolumab exposure and disease free survival (DFS)/ grade 2+(Gr2+) immune mediated adverse events (IMAEs) was characterized in subjects with EC or GEJC in Study CA209577.

DFS was chosen as the measure of efficacy, as it was the primary endpoint in Study CA209577 supporting the benefit-risk assessment of nivolumab monotherapy. The E-R analysis was based on DFS from the locked data of the interim analysis on 03-Jul-2020[i]. As defined in the CA209577 study protocol, DFS is the time between the randomization date and the first date of recurrence or death, whichever occurs first. For subjects who remain alive and without recurrence, DFS was censored on the date of last evaluable disease assessment. Cavg1 obtained from the PPK analysis was used as the summary measure of exposure for nivolumab. This early measure of exposure was selected to avoid the potential confounding effect of time-varying CL with nivolumab in the characterization of E–R relationships, as the extent of the temporal change in CL has been shown to be associated with the extent of clinical benefit.[ii] Cmind28 was also explored as another exposure measure to further support a less frequent dosing of 480 mg Q4W. It was selected as the most conservative summary measure, as the PPK simulated Cmind28 was lower (~23%) in 480 mg Q4W than that in 240 mg Q2W (Table).

The E-R relationship for safety was characterized with respect to time to the first occurrence of Gr2+ IMAEs. This endpoint was selected to reflect the adverse events (AEs) that are specific to cancer immunotherapy, due to the increased activity of the immune system from the treatment. IMAEs are

specific events that include diarrhea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, hypersensitivity/infusion reactions, and endocrine AEs (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus). The time-varying daily Cavg of nivolumab, derived from the PPK analysis, was used as the measure of exposure since this exposure measure can account for high and low changes in concentration that occur throughout the dosing interval, which are then linked directly to the safety event.

2.3.2. PK/PD modelling

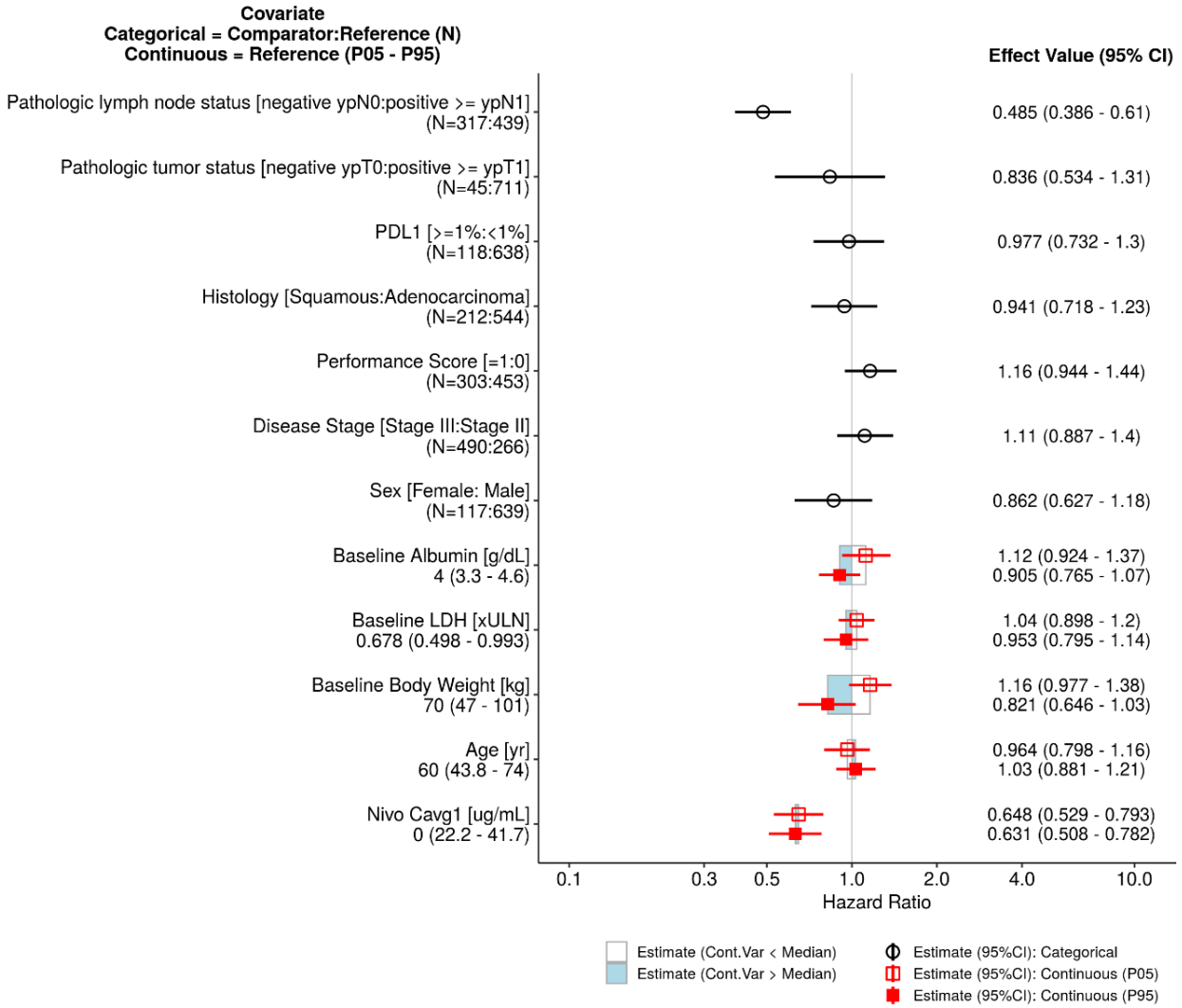
Exposure-efficacy relationship

The relationship between nivolumab exposure (Cavg1) and DFS was described by a semi-parametric Cox Proportional-Hazards (CPH) model, and the E-R analysis also included the assessments of the modulatory effect of covariates on the E-R relationship in adjuvant EC/GEJC. Among the evaluated functional forms of exposure effect (ie, linear and log-linear), the log-linear function of nivolumab Cavg1 had a lower BIC value and therefore was selected for the full model development. Values of nivolumab exposure were imputed to be zero (or 0.001 µg/mL to enable log-linear assessments) for subjects in the placebo arm of Study CA209577.

Figure13 is a graphical presentation of all the estimated effects in the full model, showing the HRs of DFS across the predictor ranges and the associated 95% CIs. The estimated effect of nivolumab Cavg1 indicated that DFS was improved in subjects who received nivolumab treatment compared with placebo (95% CI of 5th and 95th percentile of exposure effect relative to placebo did not include 1). More importantly, the DFS was similar across the entire range of nivolumab Cavg1 produced by the dosing regimen in Study CA209577, as suggested by the comparable HRs of DFS relative to placebo at the 5th and 95th percentile of Cavg1 (0.648 versus 0.631). This indicated the E-R relationship of DFS was flat across the Cavg1 exposure range achieved with the dosing regimen investigated in Study CA209577.

The covariate that had a significant effect on DFS was pathologic lymph node status (negative [ypN0] versus positive [>= ypN1]) [95% CI of effect did not include 1]. All other evaluated covariates did not have statistically significant effects on DFS (95% CI of effect included 1).

Figure13: Estimated Covariate Effects on the Hazard Ratio of Disease-Free Survival (Full Model)

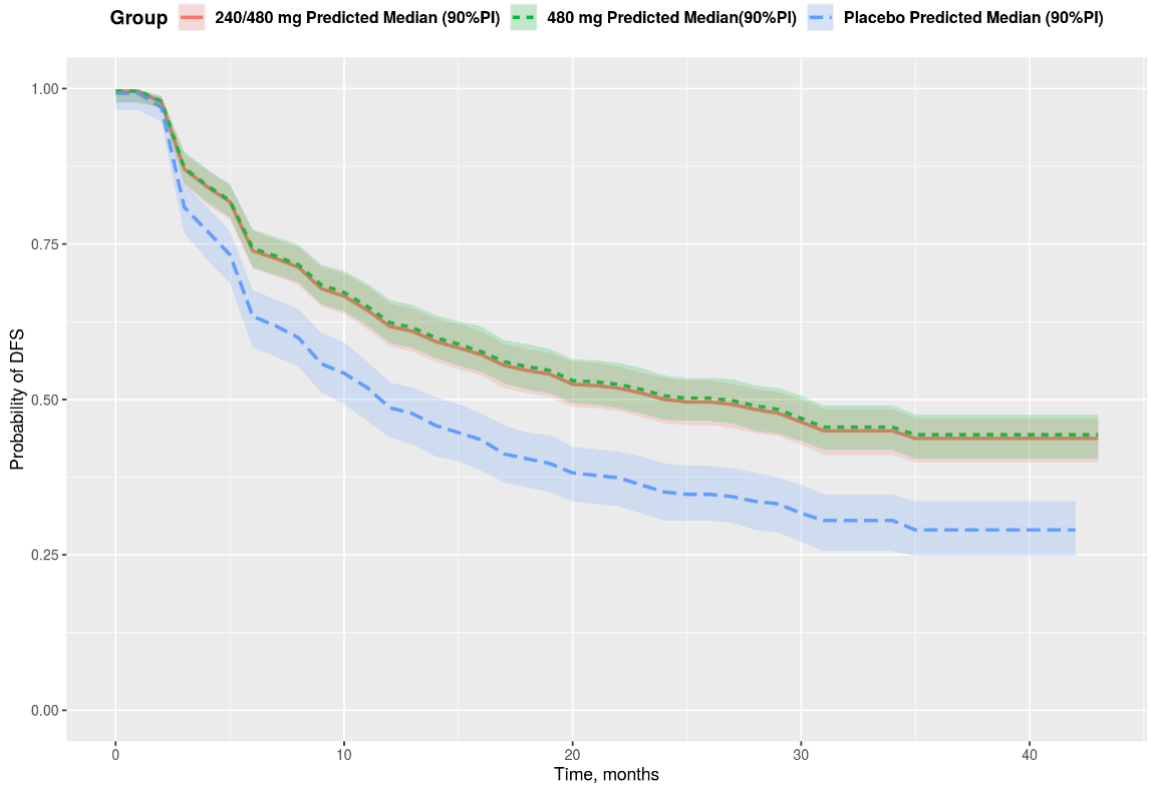


Source: Refer to Figure 5.1.1.1-1 in the CA209577 E-R Report.

The full E-R DFS model was used to predict the HR of DFS for the proposed dosing regimens: nivolumab 240 mg Q2W or 480 mg Q4W for 16 weeks followed by 480 mg Q4W for adjuvant EC/GEJC. The model predicted that DFS with 480 mg Q4W was similar to the model-predicted probability of DFS in the studied regimen of 240 mg Q2W for 16 weeks followed by 480 mg Q4W up to 1 year (Figure 14). Both recommended nivolumab dosing regimens showed improved DFS compared with the placebo group.

Similar results were observed for the sensitivity analysis in which the model predicted DFSs, based on Cmind28, were also similar between the 2 proposed nivolumab dosing regimens (Figure 14).

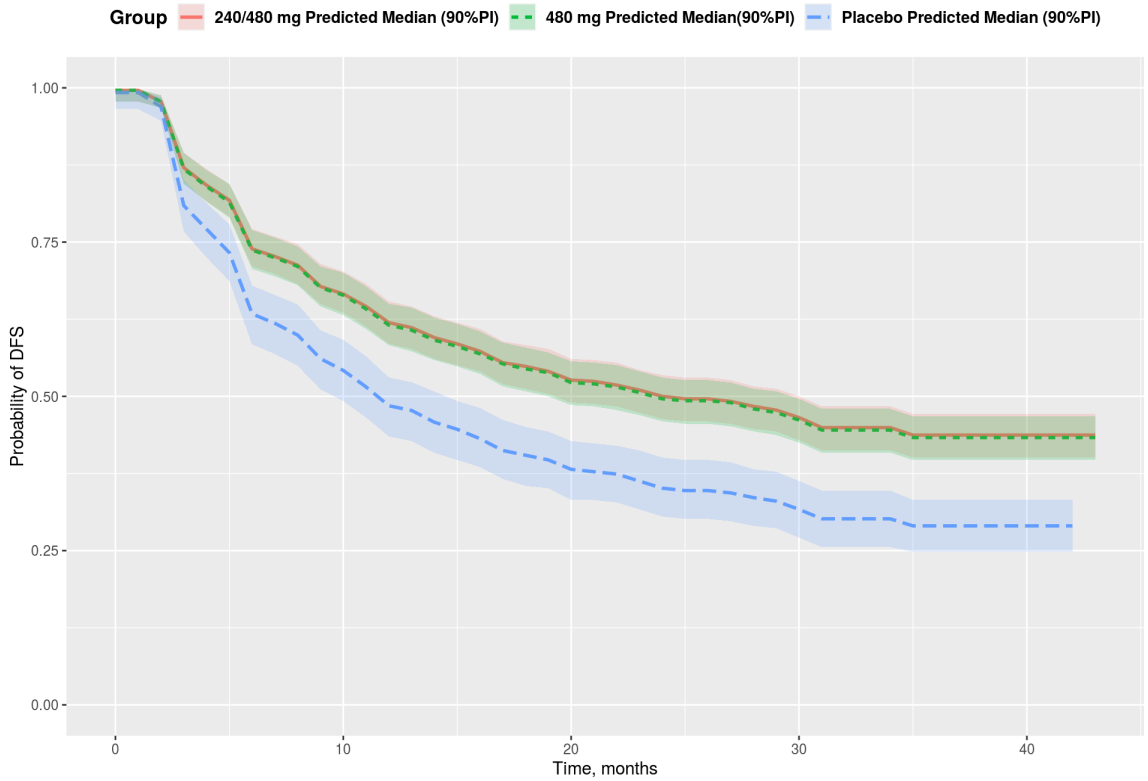
Figure 14: Predicted Median Probability of DFS Using Predicted Cavg1 from 2 Proposed Dosing Regimens (240 mg Q2W or 480 mg Q4W for 16 Weeks Followed by 480 mg Q4W up to 1 Year) in Adjuvant EC/GEJC



Source: Refer to Figure 5.1.3-1 in the CA209577 E-R Report.

Abbreviations: 240/480 mg = nivolumab 240 mg Q2W followed by 480 mg Q4W; 480 = nivolumab 480 mg Q4W; Cavg1 = average concentration after the first dose; DFS = disease-free survival; EC = esophageal cancer; GEJC = gastroesophageal junction cancer; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure 15: Predicted Median Probability of DFS Using Predicted Cmind28 from 2 Proposed Dosing Regimens (240 mg Q2W or 480 mg Q4W for 16 Weeks Followed by 480 mg Q4W up to 1 Year) in Adjuvant EC/GEJC



Source: Refer to Figure 5.1.3-2 in the CA209577 E-R Report.

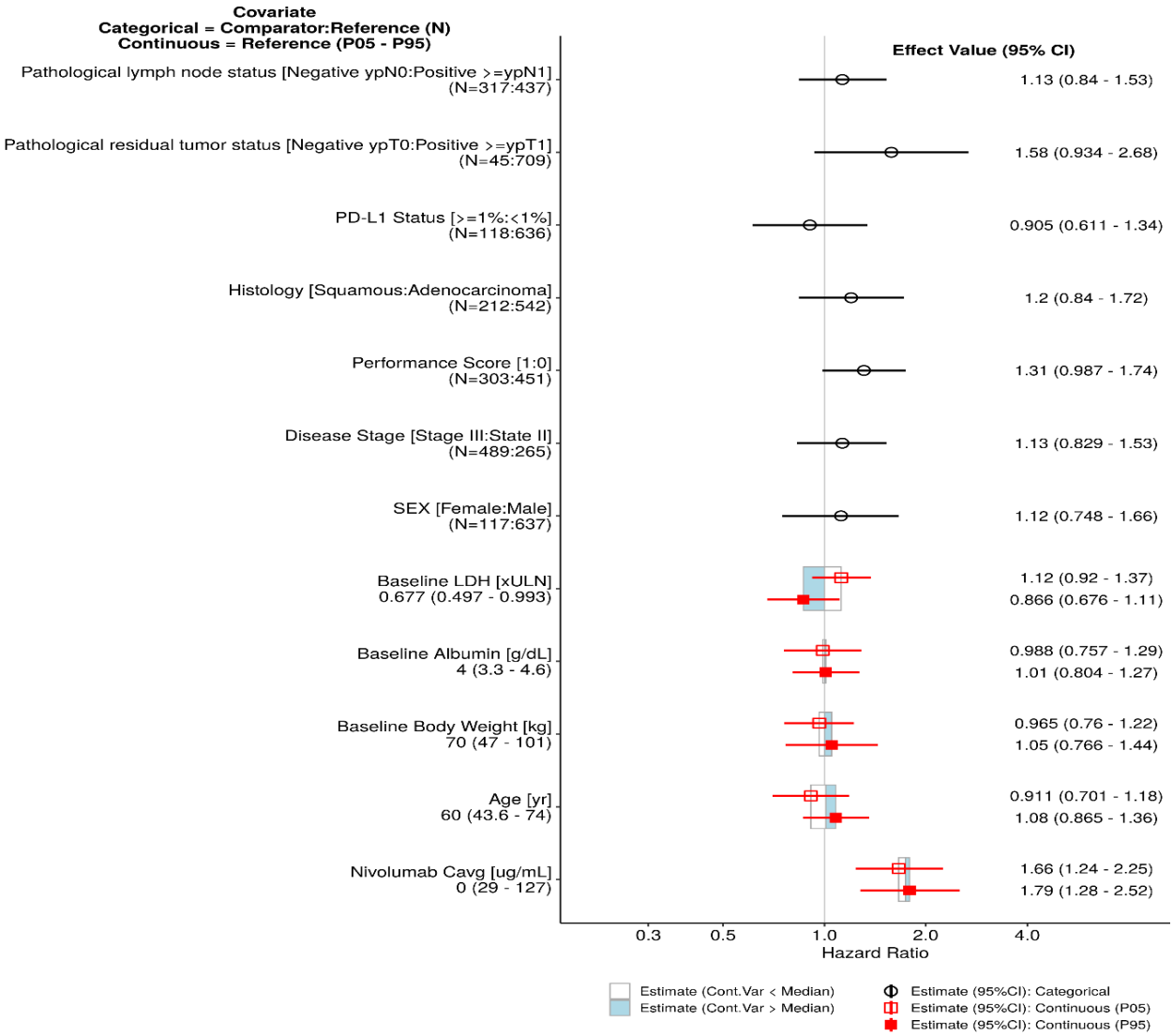
Abbreviations: 240/480 mg = nivolumab 240 mg Q2W followed by 480 mg Q4W; 480 = nivolumab 480 mg Q4W; Cmind28 = minimal concentration at Day 28; DFS = disease-free survival; EC = esophageal cancer; GEJC = gastroesophageal junction cancer; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Exposure-safety relationship

The relationship between nivolumab exposure (time-varying daily Cavg) and time to the first occurrence of Gr2+ IMAEs was described by a semi-parametric CPH model. Among the evaluated functional forms of exposure effect (ie, linear and log-linear), the log-linear function of nivolumab daily Cavg had the lowest BIC value and therefore was selected for the full model development. Values of nivolumab exposure were imputed to be zero (or 0.001 µg/mL to enable log-linear assessments) for subjects in the placebo arm of Study CA209577.

Nivolumab daily Cavg was identified as a significant covariate of the risk of Gr2+ IMAEs (95% CI excluded 1, Table 5.2.1.1-2 in the E-R Report). The risk of Gr2+ IMAEs was higher in subjects who received nivolumab compared with placebo. Within the nivolumab exposure range achieved with the monotherapy, the HRs for the 5th and 95th percentiles of exposure range were similar (Figure 16), and the 95% CIs were overlapping, suggesting a flat E-R relationship. None of the tested covariates had a significant impact on risk of Gr2+ IMAEs (95% CI included 1).

Figure 16: Estimated Covariate Effects of the Exposure-Response of Gr2+ IMAEs (Full Model)



Source: Refer to Figure 5.2.1.1-1 in the CA209577 E-R Report.

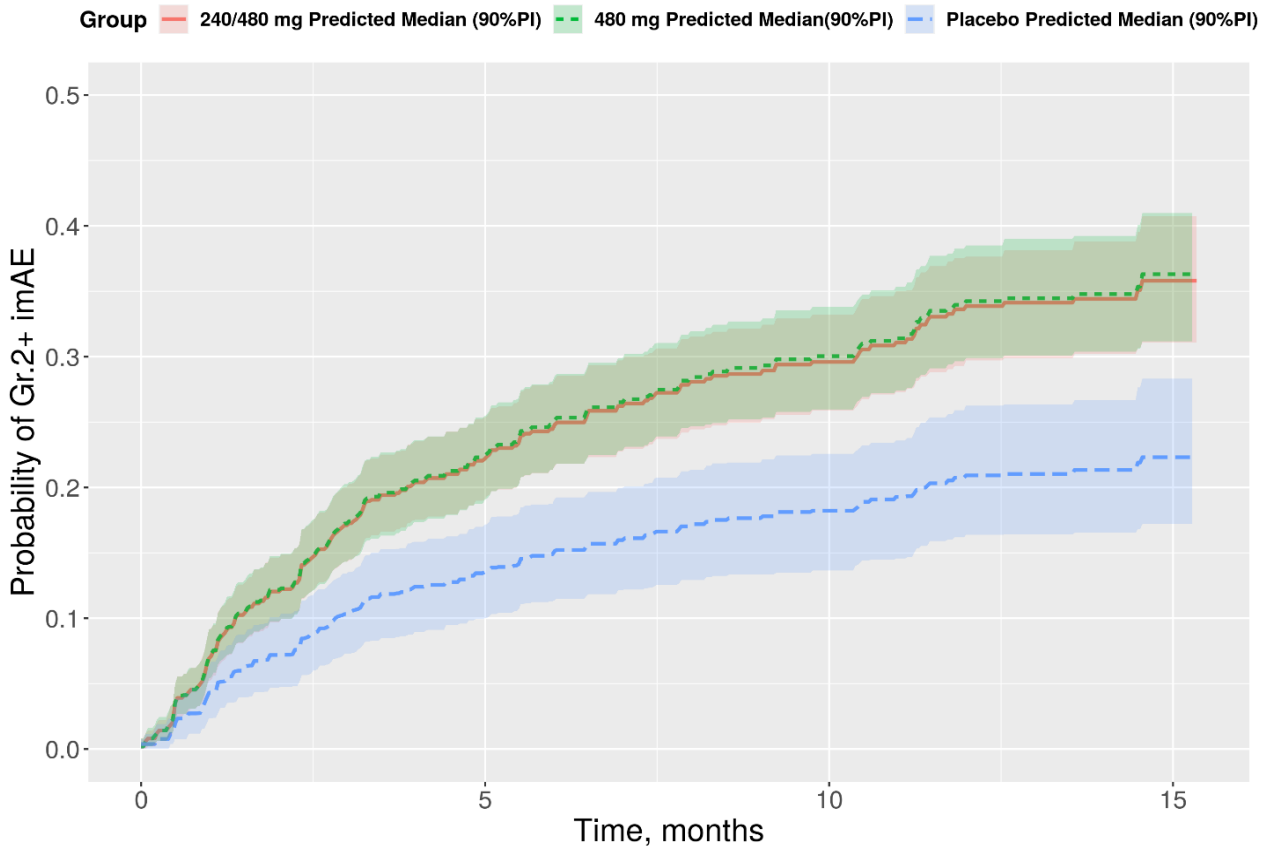
Note 1: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 2: Reference subject: who had nivolumab Cavg = 0 (placebo arm), median value of LDH = 0.677, albumin = 4 g/dL, body weight = 70 kg, age = 60 yr, adenocarcinoma, pathological tumour status positive (>= ypT1) and lymph node status positive (>= ypN1), performance score = 0, with Disease Stage II, tumour cell PD-L1 < 1%, and male.

Abbreviations: Cavg = the averaged concentration of the daily Cavg values from Day 1 to the day of event/censor; CI = confidence interval; Gr2+ IMAEs = Grade ≥ 2 immune mediated adverse events; LDH = lactate dehydrogenase; PD-L1 = programmed death ligand 1; ULN = upper limit of normal.

The full E-R safety model was used to predict the HR of Gr2+ IMAEs for the proposed dosing regimens: nivolumab 240 mg Q2W or 480 mg Q4W for 16 weeks followed by 480 mg Q4W for adjuvant EC/GEJC. The model-predicted probability of Gr2+ IMAEs in 480 mg Q4W was similar to the model-predicted probability of Gr2+ IMAEs in the studied regimen of 240 mg Q2W for 16 weeks followed by 480 mg Q4W up to 1 year (Figure 17), suggesting a comparable safety profile between the 2 proposed dosing regimens.

Figure 17: Predicted Median Cumulative Probability of Gr2+ IMAEs Using Predicted Time Varying Daily Cavg from the 2 Proposed Dosing Regimens (240 mg Q2W for 480 mg Q4W or 16 Weeks Followed by 480 mg Q4W) in Adjuvant EC/GEJC



Source: Refer to Figure 5.2.3-1 in the CA209577 E-R Report.

Abbreviations: 240/480 mg = nivolumab 240 mg Q2W followed by 480 mg Q4W; 480 = nivolumab 480 mg Q4W; Cavg = time-averaged concentration; EC = esophageal cancer; GEJC = gastroesophageal junction cancer; Gr2+ IMAEs = Grade ≥ 2 immune-mediated adverse events; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

2.3.3. Discussion on clinical pharmacology

Both analytical methods used for the quantification of BMS-936558 in human serum samples in support of study CA209577 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 data obtained were reliable and they can be compared and used.

Both in-study validations show acceptable calibration standards and QCs. No sample was re-analysed at WuXi AppTec and the reasons for the samples re-assayed at PPD Inc. are considered acceptable. Incurred Sample Reproducibility was performed only for samples analysed at PPD, Inc. and the reanalysis confirms the validity and performance of the Analytical Method Procedure for all analytes. No ISR was submitted for samples analysed at WuXi AppTec. This is a minor issue since it is not a bioequivalence study and the ISR has been performed before in other clinical studies with acceptable results.

The MAH has conducted a Phase 3 study (CA209577) to characterize the pharmacokinetics, immunogenicity, and exposure-response relationship of nivolumab in patients with resected EC or GEJC who have received chemoradiotherapy (CRT) followed by surgery to support the administration

of nivolumab 240 mg every 2 weeks (Q2W) or nivolumab 480 mg every 4 weeks (Q4W) intravenous (IV) for 16 weeks, followed by 480 mg Q4W up to 1 year, for the adjuvant treatment of patients with resected esophageal (EC) or gastroesophageal junction (GEJC) cancer.

The modelling strategy consisted in a pooled analysis of PK data in adjuvant EC/GEJC from Study CA209577 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 resected EC or GEJC based on the GOF, pc-VPC and parameter estimates. Some covariate effects (CL_RAAS, CL_POPOTH, CL_POPEC2L, CL_POPADJEC, EMAX_PS, EMAX_POPTH, EMAX_POPEC2L) demonstrated low precision (based on the RSE and 95% CI) although they were retained in the model to reduce the bias in the estimation of the contribution of each covariate. The development of a full covariate PK model did not impact on population parameters nor PK exposure endpoints. The magnitudes of the BBWT effects on PK parameters and exposures were consistent with previous analyses and are not considered to be clinically relevant due to the flat E-R relationships of efficacy and safety in Study CA209577. Overall, no covariates were found to have a clinically relevant impact on nivolumab PK.

A forest plot 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. The clinical relevance has been also assessed on PK exposure endpoints (Cavg_C1, Cavg_ss), showing no major differences in exposure, except between Asian (26% and 25% higher, respectively) and non-Asian patients, possibly due to differences in body weight. The MAH provided a stratified analysis between Chinese, Non-Asian and Non-Chinese Asian in study CA209577 and all patients, showing similar differences compared to all patients.

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.

An exposure-efficacy relationship has been established to characterize the probability of disease-free survival (DFS) and predict the hazard-ratio of DFS for the proposed dosing regimens (nivolumab 240 mg Q2W or 480 mg Q4W for 16 weeks followed by 480 mg Q4W for adjuvant EC/GEJC). An improvement in the probability of DFS over time compared to placebo is observed and no differences were predicted among the dosing regimens, suggesting similar efficacy profile over time. The forest plot analysis of the Hazard Ratio among the different covariates suggests no clinically relevant changes in efficacy among the different covariates.

The exposure-safety analysis characterized the probability of Gr2+ imAE for the proposed dosing regimens (nivolumab 240 mg Q2W or 480 mg Q4W for 16 weeks followed by 480 mg Q4W for adjuvant EC/GEJC). The results show higher probability (50-100%) of Gr2+ imAE compared to placebo group and no differences between the proposed dosing regimens.

2.3.4. Conclusions on clinical pharmacology

The clinical pharmacology properties of nivolumab for the adjuvant treatment of patients with resected oesophageal or gastroesophageal junction cancer have been adequately characterized through a pooled analysis using previous clinical data together with experimental evidence from study CA209577. The population PK model, which shares the same structural elements as previous submissions, adequately describes the experimental data. The assessment of the clinical pharmacology properties is adequately addressed.

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(ies)

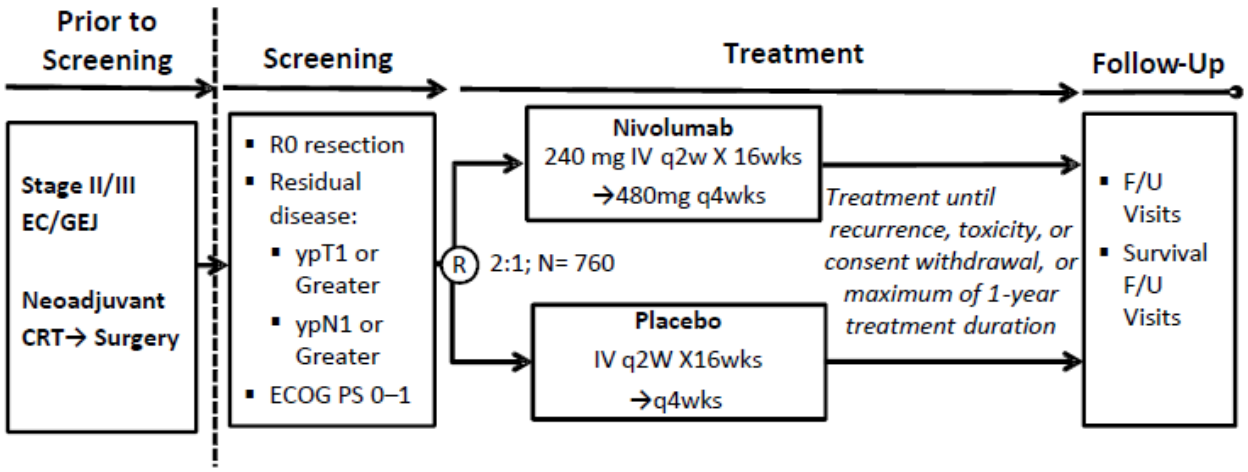
Study CA209577: A randomized, multicentre, double blind, phase III study of adjuvant nivolumab or placebo in subjects with resected oesophageal or gastroesophageal junction cancer

Methods

CA209577 is a Phase 3, randomized, double-blind, placebo-controlled study of adjuvant nivolumab in subjects with resected oesophageal cancer (OC) or gastroesophageal cancer (GEJC) who have received CRT followed by surgery.

Subjects who completed neoadjuvant chemoradiotherapy (CRT), had complete resection (R0), and did not achieve pathological complete response (non-pCR) as confirmed by the investigator, were randomized in a blinded fashion, in a 2:1 ratio to treatment with nivolumab or placebo.

Study design schematic



Note: After enrollment was completed in the CA209577 study, 794 subjects were randomized.

Abbreviations: CRT = chemoradiotherapy, EC = esophageal cancer, ECOG = Eastern Cooperative Oncology Group, F/U = follow-up, GEJ = gastroesophageal junction cancer, IV = intravenous, PS = performance status, q2w = every 2 weeks, q4w = every 4 weeks, R = randomization, R0 = resection, wks = weeks, ypT1/ypN1 = types of cancer staging

Source: Figure 3.1-1 in the CA209577 protocol (Appendix 1.1)

Subjects were to be assessed for recurrence (until distant recurrence) by computed tomography (CT) or magnetic resonance imaging (MRI) at baseline, on-treatment and in the follow-up period. Baseline assessments of the chest and abdomen were performed within 28 days prior to randomization utilizing CT or MRI. Subsequent assessments included chest and abdomen and any clinically indicated sites. Subjects were evaluated for disease recurrence every 12 weeks (Q12W) from the date of first treatment (± 7 days) for the first 12 months, then Q12W (± 14 days) between months 12 and 24, and then according to local standards with a minimum of 1 scan every 6 to 12 months between years 3

and 5. Subjects who discontinued study drug were continued to be followed for collection of recurrence (until distant recurrence) and/or survival follow-up data as required until death or the conclusion of the study.

Study participants

Main inclusion criteria

a) Males and Females, ≥ 18 years of age

b) All subjects must have Stage II or Stage III (per American Joint Committee on Cancer [AJCC] 7th edition) carcinoma of the oesophagus or gastro-oesophageal junction and have histologically confirmed predominant adenocarcinoma or squamous cell carcinoma oesophageal or gastro-oesophageal junction cancer at the time of initial diagnosis.

c) Subjects must complete pre-operative (neoadjuvant) chemoradiotherapy followed by surgery prior to randomization. Platinum based chemotherapy should be used. Chemotherapy and radiation regimens can be followed as local standards of care per NCCN or ESMO guidelines.

d) Subject must have complete resection (R0), have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumour present within 1 mm of the proximal, distal, or circumferential resection margins. Subject must have residual pathologic disease, i.e. non-pathologic complete response (non-pCR) of their OC or GEJ, with at least ypN1 or ypT1 listed in the pathology report of resected specimens. For any cases of uncertainty (e.g. ypNx), it is recommended that the Medical Monitor or designee be consulted prior to randomization. The pathology reports of detectable lesion(s) confirming malignancy must be reviewed, dated, and signed by the investigator prior to randomization.

e) Complete resection must be performed in a window of 4-16 weeks prior to randomization. [The original time window was 4 to 14 weeks but later increased to up to 16 weeks (Revised Protocol 02, 04-May-2017)].

f) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

g) All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT/MRI scan of chest and abdomen.

h) Tumour tissue from the resected site of disease (after completion of CRT treatment) must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 status classification (≥1%, < 1% or indeterminate or non-evaluable) as determined by the central laboratory during the screening period (tumour cell PD-L1 immunohistochemistry –IHC- testing). If insufficient tumour tissue content is provided for analysis, acquisition of additional archived tumour tissue (block and /or slides) for the biomarker analysis is required.

Main exclusion criteria

a) Subjects with cervical oesophageal carcinoma. Location of tumour as it relates to eligibility can be discussed with BMS medical monitor.

b) Subjects who do not receive concurrent CRT prior to surgery. Subjects who only receive chemotherapy or only radiation prior to surgery are not eligible.

c) Subjects with Stage IV resectable disease.

d) Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

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

Treatments

Subjects randomized to the nivolumab treatment arm received nivolumab 240 mg intravenous (IV) infusion over 30 minutes every 2 weeks (Q2W) for 16 weeks (Cycles 1-8) followed by nivolumab 480 mg IV infusion over 30 minutes every 4 weeks (Q4W) beginning at Week 17 (2 weeks after the 8th dose) [Cycles 9-17] for a total duration of 1 year.

Subjects randomized to the placebo arm received placebo IV infusion over 30 minutes with the same dosing schedule as nivolumab.

No dose reductions were permitted for the management of toxicities of individual subjects.

Doses of nivolumab were allowed to be interrupted, delayed, or discontinued depending on how well the subject tolerated the treatment.

Dosing visits were not skipped, only delayed.

Subjects were treated until disease recurrence, unacceptable toxicity, or subject withdrawal of consent, with a maximum of 1-year total duration of study treatment.

Prior and concomitant treatment

Subjects must have completed pre-operative CRT (with platinum-based chemotherapy) followed by surgery prior to randomization. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration were not permitted for inclusion in this study. Inhaled or topical steroids, and adrenal replacement steroids > 10 mg daily prednisone equivalent, were permitted in the absence of active autoimmune disease.

Objectives

Primary objective

- To compare disease-free survival (DFS) of nivolumab versus placebo in subjects with resected OC or GEJ cancer.

Secondary objectives

- To compare overall survival (OS) of nivolumab versus placebo in subjects with resected EC or GEJ cancer.
- To evaluate 1, 2, and 3 year survival rates of nivolumab versus placebo in subjects with resected EC or GEJ cancer.

Exploratory objectives

- To assess the overall safety and tolerability of nivolumab versus placebo in subjects with resected EC or GEJ cancer.
- To evaluate the distant metastasis free survival (DMFS) in subject with resected EC or GEJ cancer.
- To evaluate whether tumour cell PD-L1 status is a predictive biomarker for DFS and OS in subjects with resected EC or GEJ cancer.
- To evaluate tumour cell PD-L1 status prior to CRT and at the time of surgery in subjects with resected EC or GEJ cancer.
- To explore potential biomarkers associated with clinical efficacy (DFS, and OS) and/or incidence of adverse events of nivolumab by analysing biomarker measures within the tumour microenvironment and periphery (e.g., blood, serum, plasma, and PBMCs) in comparison to clinical outcomes.
- To assess the effect of natural genetic variation (single nucleotide polymorphisms [SNPs]) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA4 on clinical endpoints and/or the incidence of adverse events.
- To characterize the pharmacokinetics (PK) and explore exposure-response relationships with respect to safety and efficacy.
- To characterize the immunogenicity of nivolumab.
- To assess the subject's overall health status using the 3-level version of the EQ-5D (EQ-5D-3L) index and visual analog scale.
- To assess the subject's cancer-related quality of life using the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire and selected components, including the Esophageal Cancer Subscale (ECS) and 7-item version of the FACT-General (FACT-G7).
- To assess progression-free survival after the next line of the subsequent therapy (PFS2) as assessed by investigators.

Outcomes/endpoints

Objective	Endpoint(s)	Endpoint Description
Primary		
Compare DFS of nivolumab versus placebo	DFS	DFS was defined as the time between randomization date and first date of recurrence or death from all causes, whichever occurred first. Recurrence is defined as the appearance of one or more new lesions, which can be local, regional, or distant in location from the primary resected site (by imaging or pathology). For subjects who remained alive and without recurrence, DFS was censored on the date of last evaluable disease assessment. As the primary definition, subjects who started subsequent therapy (radiotherapy, surgery, or systemic therapy) or developed a second primary cancer without recurrence, were censored on the last disease assessment date prior to the start of subsequent therapy or development of second primary cancer. The *sensitivity* definition of DFS was defined similarly to the primary definition except that events (recurrence or death) and disease assessments that occurred on or after subsequent anti-cancer therapy and development of a

Objective	Endpoint(s)	Endpoint Description
		second primary cancer were considered (no time point truncation).
Secondary		
Compare OS of nivolumab versus placebo in subjects with resected EC or GEJC	OS	OS is defined as the time from randomization to the date of death from any cause. For subjects that are alive, their survival time will be censored at the date of last contact date (or last known alive date). Overall survival will be censored at the date of randomization for subjects who were randomized but had no follow-up.
Evaluate 1, 2, and 3-year survival rates of nivolumab versus placebo in subjects with resected EC or GEJC	OS rates	OS rate at 1, 2, and 3 years is defined as the probability that a subject is alive at 1, 2, and 3 years using KM method, respectively, following randomization.
Exploratory		
Assess the overall safety and tolerability of nivolumab versus placebo in subjects with resected EC or GEJC	Overall Safety/Tolerability	The assessment of safety was based on frequency of AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose modification (delay/reduction), OESIs, and specific clinical laboratory abnormalities. IMAEs and select AE analyses included incidence, time-to-onset, and time-to-resolution. Analyses were conducted using the 30-day safety window for general AEs and select AEs and/or the 100-day safety window for IMAEs from the date of last dose received. AEs were coded using MedDRA version 23.0 AEs and laboratory values were graded for severity using NCI CTCAE version 4.0.
Evaluate the DMFS	DMFS	DMFS was defined as the time between the date of randomization and the date of first distant recurrence or date of death from all causes, whichever occurred first. The distant recurrence was based on CRF page disease recurrence (Y/N) determined by investigator. Local or regional recurrence were not considered as an event for DMFS. For subjects who remained alive and distant recurrence-free, DMFS was censored on the date of last disease assessment regardless of subsequent radiotherapy, surgery, or systemic therapy.
Evaluate whether tumor cell PD-L1 status is a predictive biomarker for DFS	PD-L1 status	PD-L1 expression was defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay. Analyses for tumor cell PD-L1 were based on baseline PD-L1 positive status using 1%, 5%, and 10% cutoffs. The PD-L1 status for this objective considered the tumor tissues after completion of CRT treatment unless only the tumor tissues prior to CRT was available in the locked database or there was no quantifiable PD-L1 from the tumor tissues post-CRT. The baseline PD-L1 was the last quantifiable test result before first dose date (or randomization date if never treated). If there was no quantifiable test result available, the baseline PD-L1 was the last indeterminate or non-evaluable result.
Evaluate tumor cell PD-L1 status prior to CRT and at the time of surgery	PD-L1 status	See above. The PD-L1 status for this objective was based on the PD-L1 prior to CRT.

Objective	Endpoint(s)	Endpoint Description
Characterize the immunogenicity of nivolumab	Immunogenicity	Samples collected from subjects were evaluated for development of ADA and characterization of neutralizing antibodies for nivolumab by validated methods. The subject's immunogenicity status was assessed using the follow criteria: **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 positive with ADA-positive sample in the last sampling timepoint. ***Other Positive*:** Not persistent positive 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 the initiation of treatment.

Objective	Endpoint(s)	Endpoint Description
Assess the subjects' overall health status using the 3-level version of the EQ-5D (EQ-5D-3L) index and visual analog scale	EQ-5D-3L responses	Overall health status was assessed using the EuroQoL Group's EQ-5D-3L. EQ-5D-3L has 2 components: the descriptive system and the VAS. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. A VAS allows respondents to rate their own current health on a 100-point scale ranging from 0 = "worst imaginable" health to 100 = "best imaginable" health state.
Assess the subjects' cancer-related quality of life using the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire and selected components, including the Esophageal Cancer Subscale (ECS) and 7-item version of the FACT-General (FACT-G7)	FACT-E, ECS, and FACT-G7 responses and cancer-related QOL	The FACT-E includes the 27-item FACT-General (FACT-G) to assess symptoms and treatment-related effects impacting physical well-being (PWB; 7 items), social/family well-being (SWB; 7 items), emotional well-being (EWB; 6 items), and functional well-being (FWB; 7 items). 7 of these items comprise the FACT-G7, an abbreviated version of the FACT-G that provides a rapid assessment of general HRQoL in cancer patients. In addition, the FACT-E includes a 17-item disease-specific ECS that assesses concerns related to swallowing, vocalization, breathing, dry mouth, eating, disrupted sleep due to coughing, stomach pain, and weight loss. Each FACT-E item is rated on a 5-point scale ranging from 0 (not at all) to 4 (very much). Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic HRQoL, while the FACT-G and ECS scores can be combined to produce a total score for the FACT-E, which provides a composite measure of general and targeted HRQoL.
Assess PFS after subsequent systemic therapy (PFS2) as assessed by investigators	PFS2	PFS2 in this adjuvant setting considers events occurred when subjects progressed on subsequent systemic therapy, subjects started second subsequent systemic therapy, or subjects died. • For subjects who received subsequent systemic therapy, PFS2 was the time between randomization date and the date of disease progression on subsequent systemic therapy or the date of the start of second subsequent systemic therapy or the date of death, whichever occurred first. • For subjects who did not receive subsequent systemic therapy, PFS2 was the time between randomization date and death date. Subjects without PFS2 events were censored at the last known alive date.

Abbreviations: ADA = anti-drug antibody, AE = adverse event, CRF = case report form, CRT = chemoradiotherapy, CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, DFS = disease-free survival, DMFS = distant metastasis-free survival, OC = oesophageal cancer, ECS = Esophageal Cancer Subscale, EQ-5D-3L = EuroQol 5 dimensional 3-level index, FACT-E = Functional Assessment of Cancer Therapy-Esophageal, FACT-G7 = Functional Assessment of Cancer Therapy-General 7-item version, GEJC = gastroesophageal junction cancer, IHC = immunohistochemistry, HRQoL = health-related quality of life, IMAE = immune-mediated adverse event, K-M = Kaplan-Meier, MedDRA = Medical Dictionary for Regulatory Activities, NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, OESI = other events of special interest, PBMC = peripheral blood mononuclear cell, PD-L1 = programmed death-ligand 1, PD-L2 = programmed death-ligand 2, PFS2 = progression-free survival after subsequent systemic therapy, PP = persistent positive, PWB = physical well-being, QOL = quality of life, SAE =

serious adverse event, SAP = statistical analysis plan, SNP = single nucleotide polymorphism, SWB = social well-being, VAS = visual analog scale

Source: Appendix 1.1 (CA209577 protocol) and Appendix 1.11 (CA209577 SAP)

Sample size

The sample size determination took into consideration the comparison of the primary endpoint of DFS between the two treatment arms. DFS was assumed to follow a piecewise exponential distribution, and the hazard ratio (HR) was modelled as piecewise hazard ratios (HR) with a HR of 1 for the first 3 months followed by a HR of 0.667 after 3 months and 0.8 after 5 years, with the overall average HR of 0.72. According to the assumptions for DFS, the study required approximately 760 subjects to be randomized in a 2:1 ratio to treatment with nivolumab or placebo. The observation was that, at least, 440 DFS events were needed to achieve approximately 91% power to detect an average hazard ratio (HR) of 0.72 with a 2-sided alpha of 0.05. This sample-size determination accounted for one planned DFS interim analysis (IA) when at least 85% of the events would be observed.

OS was assumed to follow a piecewise exponential distribution, and the HR was modelled as piecewise HRs with a HR of 1 versus placebo arm for the first 4 months followed by a HR of 0.685 after 4 months and 0.8 after 6 years, with the overall average HR of 0.73. With the sample size of 760 subjects, at least 460 OS events at the final OS analysis would provide approximately 90% power to detect an average HR of 0.73 at a 2-sided alpha of 0.05. The power of the OS final analysis accounted for 2 OS IAs that would occur at the same time as the DFS interim and DFS final analyses, respectively.

As stated above, 1 interim and 1 final analyses for DFS (primary endpoint), and 2 interim and 1 final analyses for OS (secondary endpoint) were planned for Study CA209577.

OS would be tested following the overall hierarchical testing procedure upon demonstration of superiority in DFS at either the interim or the final analyses of DFS for all randomized subjects.

- The DFS IA was planned when at least 85% of all 440 DFS events (374 DFS events) were to be observed. OS IA 1 was planned to occur the same time and it was projected that approximately 65% of OS events (299 OS events) would be observed under protocol assumptions.
- The final analysis of DFS (DFS FA) was planned to occur when at least 440 DFS events would be observed. OS IA 2 was planned to occur the same time and it was projected that approximately 80% of OS events would be observed under protocol assumptions.
- The final analysis of OS (OS FA) was planned to occur when 460 OS events would be observed.

Randomisation

After initial eligibility was established and the informed consent was obtained, subjects were enrolled in the study via Interactive Response Technology (IRT) [i.e., Interactive Web Response System (IWRS)].

Patients were randomized in a blinded fashion, in a 2:1 ratio to treatment with nivolumab or placebo. Randomization stratification factors included: 1) Tumour cell programmed death-ligand 1 (PD-L1) status (≥ 1% vs. < 1% or indeterminate/non-evaluable) 2) Pathologic lymph node status (positive [≥ ypN1] vs. negative [ypN0]) 3) Histology (squamous vs. adenocarcinoma).

Blinding (masking)

BMS, subjects, investigators and site staff were blinded to the study therapy administered through the database lock (DBL) for this CSR. BMS remained blinded to OS variables after the DBL. The study continues for evaluation of the secondary endpoint of OS and the collection of clinical data (stable) is set back to be blinded without subject-level treatment information.

Statistical methods

Efficacy Analyses

DFS was compared between treatment arms using a 2-sided log rank test, stratified by the 3 randomization stratification factors (tumour cell PD-L1 status: [≥ 1% vs. < 1% or indeterminate/non-evaluable], pathologic lymph node status [positive (≥ ypN1) vs. negative (ypN0)], and histology [squamous vs. adenocarcinoma]) as recorded in the IRT. The HR for DFS with its corresponding alpha-adjusted 2-sided 96.4% confidence interval (CI) was estimated via a stratified Cox model with treatment arm as the only covariate in the model. Adjustment on the CI was based on the actual alpha level. DFS for each treatment arm was estimated and plotted using the Kaplan-Meier (K-M) product-limit method. Median DFS was computed using the K-M estimate and a 95% CI for the median was computed based on a log-log transformation of the survivor function. DFS rates at 6 months for each treatment arm were derived from the K-M estimate and their corresponding CIs were derived based on the Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. The sensitivity definition of DFS including DFS events and assessment on/after subsequent therapy and development of a second primary cancer was analysed similarly to the primary definition of DFS above.

The HR for DMFS with its corresponding 2-sided 95% CI was estimated via a stratified Cox model with treatment arm as the only covariate in the model. The analysis was stratified by the 3 randomization stratification factors as recorded in IRT. DMFS for each treatment arm was estimated and plotted using the K-M product-limit method.

Median survival time was computed using the K-M estimate and a 95% CI for the median was computed based on a log-log transformation of the survivor function.

The HR for PFS2 with its corresponding 2-sided 95% CI was estimated via a stratified Cox model with treatment arm as the only covariate in the model. The analysis was stratified by the 3 randomization stratification factors as recorded in IRT. PFS2 for each treatment arm was estimated and plotted using the K-M product-limit method. Median survival time was computed using the K-M estimate and a 95% CI for the median was computed based on a log-log transformation of the survivor function.

OS would be tested following the overall hierarchical testing procedure upon demonstration of superiority in DFS at the time of the DFS IA. OS would be compared between treatment arms using a stratified 2-sided log-rank test.

Biomarker Analyses

Analyses were based on all randomized subjects if not otherwise specified. Evaluation whether tumour cell PD-L1 status is a predictive biomarker for DFS was an exploratory objective. For this objective, tumour cell PD-L1 expression was defined as the percent of tumour cells membrane staining in a minimum of 100 evaluable tumour cells per validated Dako PD-L1 IHC assay. Analyses for tumour cell PD-L1 were based on baseline PD-L1 positive status using 1%, 5%, and 10% cut-offs. The tumour cell PD-L1 status considered the tumour tissues after completion of CRT treatment unless only the tumour tissues prior to CRT was available in the locked database or there was no quantifiable test result before

the first dose date (or randomization date if never treated). If there was no quantifiable test result available, the baseline tumour cell PD-L1 was the last indeterminate or non-evaluable result. For the association between tumour cell PD-L1 status and DFS, a curve was estimated using the KM product limit method for each treatment arm. Within each PD-L1 status subgroup, a HR (with corresponding 2-sided 95% CI) was estimated via an unstratified Cox model with treatment arm as the only covariate in the model. A Forest plot of HRs with 95% CIs was generated.

Results

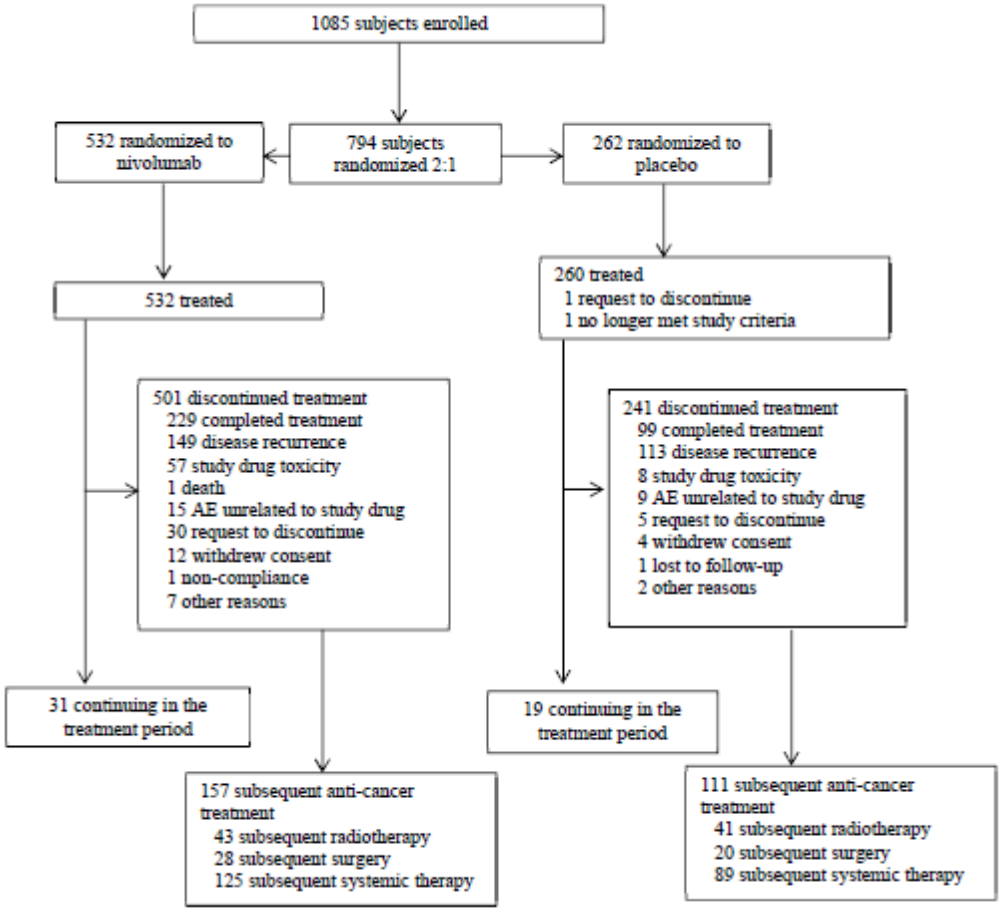
Participant flow

Subject Disposition - All Enrolled, Randomized, and Treated Subjects

	Nivolumab	Placebo	Total
SUBJECTS ENROLLED			1085
SUBJECTS RANDOMIZED	532	262	794
SUBJECTS TREATED (%) (A)	532 (100.0)	260 (99.2)	792 (99.7)
SUBJECTS NOT TREATED (%) (A)	0	2 (0.8)	2 (0.3)
REASON FOR NOT BEING TREATED (%) (A)			
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	1 (0.4)	1 (0.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.4)	1 (0.1)
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%) (B)	31 (5.8)	19 (7.3)	50 (6.3)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%) (B)	501 (94.2)	241 (92.7)	742 (93.7)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%) (B)			
COMPLETED TREATMENT	229 (43.0)	99 (38.1)	328 (41.4)
DISEASE RECURRENCE	149 (28.0)	113 (43.5)	262 (33.1)
STUDY DRUG TOXICITY	57 (10.7)	8 (3.1)	65 (8.2)
DEATH	1 (0.2)	0	1 (0.1)
ADVERSE EVENT UNRELATED TO STUDY DRUG	15 (2.8)	9 (3.5)	24 (3.0)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	30 (5.6)	5 (1.9)	35 (4.4)
SUBJECT WITHDREW CONSENT	12 (2.3)	4 (1.5)	16 (2.0)
LOST TO FOLLOW-UP	0	1 (0.4)	1 (0.1)
POOR/NON-COMPLIANCE	1 (0.2)	0	1 (0.1)
OTHER	7 (1.3)	2 (0.8)	9 (1.1)
CONTINUING IN THE STUDY (C) (D)	507 (95.3)	248 (95.4)	755 (95.3)
NOT CONTINUING IN THE STUDY (C)	25 (4.7)	12 (4.6)	37 (4.7)
REASON FOR NOT CONTINUING IN THE STUDY			
DEATH	8 (1.5)	4 (1.5)	12 (1.5)
SUBJECT WITHDREW CONSENT	13 (2.4)	5 (1.9)	18 (2.3)
LOST TO FOLLOW-UP	3 (0.6)	2 (0.8)	5 (0.6)
OTHER	1 (0.2)	1 (0.4)	2 (0.3)

(A) Percentages based on subjects randomized
(B) Percentages based on subjects that were treated
(C) Subject status at end of treatment
(D) Includes subjects still on treatment and subjects off treatment continuing in the follow-up period

Figure 28: Participant Flow Chart - CA209577 (03-Jul-2020 DBL)



Recruitment

This study was conducted at 170 sites in 29 countries.

The enrolment period was approximately 37 months from Jul-2016 to Aug-2019. The last subject was randomized on 07-Nov-2019, the clinical cut-off occurred on 12-May-2020, and the DBL occurred on 03-Jul-2020.

For this IA, the minimum follow-up time was 6.2 months and the median follow-up time was 24.4 months (range: 6.2 to 44.9 months)

Conduct of the study

The original protocol for this study was dated 06-Jan-2016. As of 12-May-2020, there were 2 global amendments leading to revised protocols that were issued for this study. There were also 5 country-specific amendments. A total of 3 administrative letters were issued for this study.

In the Revised Protocol 03 (date of issue: 06-Jun-2019, 700 subjects randomized at the time of this revision), the following major changes were made:

1) DFS became the single primary endpoint in the study, and OS changed from a dual primary endpoint to the first secondary endpoint, to be tested hierarchically.

2) PFS2 was added as an exploratory endpoint to the study per EMA guidance. PFS2 has been proposed as an early endpoint to reflect survival status for OS, particularly for trials evaluating maintenance therapy.

The actual enrolment in this study was much slower than initial projections. The enrolment period was re-estimated to be 26 months (versus 15 months in the original protocol) in Revised Protocol 02 (04-May-2017). In Revised Protocol 03, it was re-projected to approximately 36 months.

In addition to the impact of slow enrolment, the impact of external data emerging during conduct of this study was also considered. The data from the CRT followed by surgery (CRT + S) arm in the CROSS trial with long-term follow up (CROSS LT) were considered the most relevant data to the study population. In consultation with external clinical experts and using data from the CROSS LT trial, it was concluded that the median DFS and OS in the placebo arm should be much longer than the original assumption. The new assumption of longer median DFS and OS resulted in the original hazard ratios for DFS and OS as being too aggressive. Therefore, changes in the study design were needed in order to ensure that the study was adequately powered. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) Scientific Advice Working Party consultations were held prior to this protocol revision, and the meeting outcomes are presented below:

- The FDA noted a substantial and clinically meaningful improvement in DFS that is statistically persuasive and accompanied by an acceptable risk-benefit profile, as well as supportive OS that may be considered for a regulatory decision.
- The FDA noted that the analysis plan for DFS, including sample size, target treatment effect, and interim analyses was acceptable.
- The Committee for Medicinal Products for Human Use (CHMP) noted that DFS has previously been accepted as a primary endpoint for adjuvant clinical trials supported by non-detrimental OS for a long-term benefit assessment.
- The CHMP noted that the new evidence presented, including new assumptions of median DFS, was acceptable support for adaptations to the ongoing trial.
- The CHMP noted that the change in the primary endpoint could be acceptable, but advised against the first IA due to immature OS at that time.

None of the protocol amendments seemed to affect the integrity or quality of the study.

Protocol amendments:

Document (Amendment) / Date	Summary of Changes	Subjects Randomized at Time of Protocol Amendment
Revised Protocol 01 (Amendment 05) / 24-Aug-2016	Modified the criteria for nivolumab dose delay (Section 4.5.2 of the protocol), resuming treatment (Section 4.5.4 of the protocol), and discontinuation of subjects from treatment (Section 4.5.5 of the protocol) to align with the US Package Insert and EU Summary of Product Characteristics. Changes impacted guidance for AST, ALT, total bilirubin, and creatinine abnormalities as well as endocrinopathies including adrenal insufficiency and neurologic toxicity.	2
Revised Protocol 02 (Amendment 06) / 04-May-2017	Modified the inclusion criteria to increase the time between complete resection and randomization from 4-14 weeks to 4-16 weeks to provide sites with greater operational flexibility to include subjects in this trial while still ensuring that subjects were receiving treatment shortly after their surgery. Other changes in this amendment included: • Revised the term 'PD-L1 expression', 'PD-L1 expression level', and 'PD-L1 evaluable status' to 'PD-L1 status' to account for the inclusion of patients where the PD-L1 results were indeterminate or non-evaluable. Updated the stratifications to account for the inclusion of patients with a PD-L1 result of indeterminate or non-evaluable. • Revised the estimated enrollment and study duration, time to achieve 455 DFS events, and time to achieve 330 deaths and 440 deaths based on the current subject accrual rate. • Revised the maximum dose delay window to 42 days during Cycles 1-8 and 70 days during Cycles 9-17. • Revised the study design/schematic to remove the reference to 'distant' recurrence. • Revised the screening window from 28 days to 49 days. • Revised the study drug dosing window. For Cycles 1-8, subjects may have study drug administered up to 2 days before or 3 days after the scheduled dosing date. For Cycles 9-17, subjects may be dosed within a +/- 3 day window. • Clarified that the biomarker assessments during the Follow-Up Phase only need to be collected upon the first recurrence of disease. • Clarified that the biomarkers collected upon disease recurrence only need to be collected upon the first recurrence of disease during the Treatment or Follow-Up Phase. • Clarified that if the biomarker samples are collected at the scheduled time, but subsequently the dose of study drug is delayed, additional biomarker samples are not required to be collected.	98
Revised Protocol 03 / 06-Jun-2019	• Added exclusion criteria, on-study, and post-study requirements regarding live/attenuated vaccines. • Updated language regarding hepatitis B or C virus exclusion criteria, and for WOCBP in Section 3.3.3 and Appendix.	700

Document (Amendment) / Date	Summary of Changes	Subjects Randomized at Time of Protocol Amendment
	• Moved OS from co-primary endpoint to secondary endpoint, and added PFS2 as an exploratory endpoint with follow-up procedures. • Added language regarding monitoring for infusion-related reactions, and regarding dose interruptions, delays, and discontinuation, and clarified language regarding diagnosis of recurrence. • Added myocarditis to Grade 3 non-skin drug-related adverse events (AEs) in the Discontinuation of Subjects from Treatment section, to bring in line with current program standards. • Removed AE assessment from survival follow-up visits. • Added option for review of reports by a blinded independent central review at a later date. • Replaced original sample-size determinations based on co-primary endpoints. • Added new sections to provide data for the assumptions regarding DFS and OS in the control arm, to provide data for the assumed treatment effect, and to update sample size and power estimates based on new assumptions. • Added updates to provide new triggers and timing for the interim and final analyses. The rationale was to have an interim DFS analysis when there is 85% of all DFS in order to have a timely read-out given the potential plateau of the DFS curve after 3 years and to ensure the maturity of the OS data. • Added explanation of how timing of DFS/OS analyses will be adjusted to maintain a strong control of type I error. • Moved discussion of addressing family-wise error rate across DFS and OS analyses at interim and final analyses to a new section. • Moved error-rate discussion to new section and removed mention of OS as a primary endpoint. • Added two separate sections to address each the DFS and OS analyses.	

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, ANMAT = Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica (National Administration of Drugs, Foods, and Medical Devices), ANSM = Agence Nationale de Sécurité du Médicament et des Produits de Santé (The French Agency for the Safety of Health Products), AST = aspartate aminotransferase, DFS = disease-free survival, EU = Europe, HIV = human immunodeficiency virus, OS = overall survival, PEI = Paul Erlich Institute, PFS2 = progression-free survival on subsequent systemic therapy, US = United States, WOCBP = women of child bearing potential

Source: CA209577 protocol and revised protocols and administrative letters in Appendix 1.1.

Changes to Planned Analyses

Following the DBL on 03-Jul-2020, the additional following analyses were performed:

The median, minimum and maximum of the time between randomization and clinical data cut-off date was summarized to provide the follow-up duration time.

Median DFS (95% CI) was calculated in ADA positive subjects to assess the potential impact of ADA on efficacy.

The timing of the tumour tissues for the baseline PD-L1 status relative to the time of CRT was summarized.

The relative dose intensity (%) of nivolumab calculation was revised using the corrected intensity formula.

$$100 \times \frac{cumulative\ dose\ (mg)}{(Last\ dose\ date\ of\ nivo - first\ dose\ date\ of\ nivo + X) \times \frac{120\ (mg)}{7\ (days)}}$$

X is 14 days if the last dose of nivolumab the subject plans to receive is 240 mg,

X is 28 days if the last dose of nivolumab the subject plans to receive is 480 mg.

Significant Protocol Deviations

Significant protocol deviations were defined as study conduct that differed significantly from the protocol, and are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

CA209577 Summary of Significant Protocol Deviations – All Enrolled Subjects

Protocol Deviation Classification	Total
Other	**113**
Required labs not performed prior to dosing, or performed out of time window range	85
Per protocol, tumor recurrence must be diagnosed by CT/MRI and biopsy, if applicable. This process of diagnosis of tumor recurrence was not followed	8
Subject did not complete the EQ-5D ECS, FACT-E, FACT-G7 questionnaires at appropriate dosing cycles or follow-up visits	6
Pregnancy tests not performed as per protocol specified schedule	4
Required additional tumor assessments not completed	3
Subject received concurrent anti-cancer therapy during the study	2
Subject not treated within 3 days of randomization	3
Infusion not interrupted for Grade 3 adverse event	1
Per protocol, if recurrence is equivocal, a follow-up imaging evaluation should occur in 4 weeks. Site completed prior to this time window	1
Failure to report all SAEs in accordance with the time period required by GCP, the protocol, BMS, and applicable regulations	**72**
Incorrect dosing or study treatment assignment	**37**
Inclusion or exclusion criteria	**51**
Baseline assessments not performed	8
Complete resection performed out of time window or did not have negative margins	10
Baseline or screening labs/tests not collected/or out of window	15
Subject had a primary malignancy active within previous 3 years, was not disease free at study entry, or had a cancer type that did not meet inclusion criteria	6
Incorrect tumor tissue collected for PD-L1 testing at screening	5
Baseline lab value out of required range	2
Subject did not complete preoperative CRT followed by surgery, or did not have concurrent CRT before surgery	2
Site incorrectly entered pathological lymph node status in the IWRS	3
Failure to obtain written informed consent prior to each subject's participation in the study	**9**
Prohibited Concomitant Medication	**5**
Grand Total*	**287**

* Grand total is the sum of all events, but that does not mean the total of subjects, as one subjects may have more than one deviation.

Abbreviations: CRT = chemoradiotherapy, CT = computed tomography, EQ-5D ECS = EuroQol 5-dimensional Esophageal Cancer Subscale, FACT-E = Functional Assessment of Cancer Therapy - Esophageal, FACT-G7 = Functional Assessment of Cancer Therapy - General 7 item version, GCP = Good Clinical Practice, IWRS = Interactive Web Response System, MRI = magnetic resonance imaging, PD-L1 = programmed death-ligand 1, SAE = serious adverse event

Source: Appendix 2.1

Relevant protocol deviations

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

Relevant Protocol Deviations - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab N = 532	Placebo N = 262	Total N = 794
SUBJECTS WITH AT LEAST ONE DEVIATION	16 (3.0)	4 (1.5)	20 (2.5)
AT ENTRANCE			
SUBJECTS WITHOUT ESOPHAGEAL OR GASTROESOPHAGEAL JUNCTION CANCER OR THE STAGE AT INITIAL DIAGNOSIS IS NOT STAGE II OR III	2 (0.4)	0	2 (0.3)
SUBJECTS WHO DID NOT RECEIVE CONCURRENT CRT PRIOR TO COMPLETE RESECTION	5 (0.9)	2 (0.8)	7 (0.9)
SUBJECTS WHO RECEIVED DIRECTED TREATMENT AFTER COMPLETE RESECTION	1 (0.2)	0	1 (0.1)
SUBJECTS WITHOUT RESIDUAL DISEASE	2 (0.4)	0	2 (0.3)
SUBJECTS WHO HAD COMPLETE RESECTION > 18 WEEKS BEFORE RANDOMIZATION	0	0	0
SUBJECTS WITH BASELINE ECOG PERFORMANCE STATUS > 1	0	0	0
SUBJECTS WHO ARE NOT DISEASE-FREE BY IMAGING	0	0	0
ON-TREATMENT DEVIATIONS			
SUBJECTS WHO RECEIVED CONCURRENT ANTI-CANCER THERAPY	6 (1.1)	2 (0.8)	8 (1.0)
SUBJECTS TREATED DIFFERENTLY AS RANDOMIZED	0	0	0

Source: Table S.2.4

Baseline data

The median age was 62.0 years (range: 26 - 86 years). Subjects either had a baseline ECOG PS of 0 (58.4%) or 1 (41.6%). The majority of subjects were white (81.6%) and male (84.5%). 38.2% of subjects were from Europe, 32.1% of subjects were from US/Canada, 13.4% of subjects were from Asia, and 16.4% were from the rest of the world (ROW).

59.8% of subjects had EC and 40.2% subjects had GEJC at diagnosis; 64.7% of subjects had Stage III disease and 35.0% of subjects had Stage II disease at initial diagnosis. 70.9% of subjects had histological confirmation of adenocarcinoma and 29.0% of subjects had squamous cell carcinoma. 57.6% of subjects had a positive pathologic lymph node status of ≥ ypN1. 42.3% of subjects had a negative pathologic lymph node status of ypN0. Baseline tumour cell PD-L1 expression was as follows: 71.8% with < 1%, 16.2% with ≥ 1%, and 12.0% with 'indeterminate/non-evaluable' (11.7% of the 'indeterminate/non-evaluable' subjects had 'non-evaluable' tumour cell PD-L1).

Table 9: Key Demographic and Baseline Characteristics - All Randomized Subjects

Parameter	Nivolumab (N = 532)	Placebo (N = 262)	Total (N = 794)
Age (years)			
Median (range)	62.0 (26 - 82)	61.0 (26 - 86)	62.0 (26 - 86)
<65	333 (62.6)	174 (66.4)	507 (63.9)
≥65	199 (37.4)	88 (33.6)	287 (36.1)
≥65 - < 75	175 (32.9)	70 (26.7)	245 (30.9)
≥75	24 (4.5)	18 (6.9)	42 (5.3)
Sex, n (%)			
Male	449 (84.4)	222 (84.7)	671 (84.5)
Female	83 (15.6)	40 (15.3)	123 (15.5)
Race, n (%)			
White	432 (81.2)	216 (82.4)	648 (81.6)
Asian	83 (15.6)	34 (13.0)	117 (14.7)
Country by geographic location, n (%)			
US/Canada	167 (31.4)	88 (33.6)	255 (32.1)
Europe	202 (38.0)	101 (38.5)	303 (38.2)
Asia	77 (14.5)	29 (11.1)	106 (13.4)
Rest of the World (RoW)	86 (16.2)	44 (16.8)	130 (16.4)
ECOG Performance Status, n (%)			
0	308 (57.9)	156 (59.5)	464 (58.4)
1	224 (42.1)	106 (40.5)	330 (41.6)
Disease at initial diagnosis, n (%)			
EC	320 (60.2)	155 (59.2)	475 (59.8)
GEJC	212 (39.8)	107 (40.8)	319 (40.2)
Disease stage at initial diagnosis, n (%)			
Stage II	179 (33.6)	99 (37.8)	278 (35.0)
Stage III	351 (66.0)	163 (62.2)	514 (64.7)
Histology (CRF), n (%)			
Adenocarcinoma	376 (70.7)	187 (71.4)	563 (70.9)
Squamous cell carcinoma	155 (29.1)	75 (28.6)	230 (29.0)

Table 9: Key Demographic and Baseline Characteristics - All Randomized Subjects

Parameter	Nivolumab (N = 532)	Placebo (N = 262)	Total (N = 794)
Pathologic TN classification at study entry (CRF): tumour, n (%)			
YPT0	31 (5.8)	16 (6.1)	47 (5.9)
YPT1	83 (15.6)	33 (12.6)	116 (14.6)
YPT2	119 (22.4)	73 (27.9)	192 (24.2)
YPT3	286 (53.8)	138 (52.7)	424 (53.4)
YPT4	10 (1.9)	2 (0.8)	12 (1.5)
Unknown	3 (0.6)	0	3 (0.4)
Pathologic TN classification at study entry (CRF): nodes, n (%)			
YPN0	227 (42.7)	109 (41.6)	336 (42.3)
YPN1	186 (35.0)	87 (33.2)	273 (34.4)
YPN2	94 (17.7)	49 (18.7)	143 (18.0)
YPN3	25 (4.7)	16 (6.1)	41 (5.2)
Unknown	0	1 (0.4)	1 (0.1)
Baseline tumour cell PD-L1 expression, n (%)			
< 1%	374 (70.3)	196 (74.8)	570 (71.8)
≥ 1%	89 (16.7)	40 (15.3)	129 (16.2)
< 5%	403 (75.8)	208 (79.4)	611 (77.0)
≥ 5%	60 (11.3)	28 (10.7)	88 (11.1)
< 10%	416 (78.2)	212 (80.9)	628 (79.1)
≥ 10%	47 (8.8)	24 (9.2)	71 (8.9)
Indeterminate / non-evaluable	69 (13.0)	26 (9.9)	95 (12.0)
Indeterminate	2 (0.4)	0	2 (0.3)
Non-evaluable	67 (12.6)	26 (9.9)	93 (11.7)

Abbreviations: CRF = case report form, EC = esophageal cancer, ECOG = Eastern Cooperative Oncology Group, GEJ = gastroesophageal junction, PD-L1 = programmed death-ligand

Subsequent anti-cancer therapy

Of the 532 subjects randomized to the nivolumab arm, 157 (29.5%) received subsequent therapy, including 123 (23.1%) who received subsequent chemotherapy. Of the 262 subjects randomized to the placebo arm, 111 (42.4%) received subsequent therapy, including 85 (32.4%) who received subsequent chemotherapy. The most common form of subsequent anti-cancer therapy was systemic therapy: 125 (23.5%) subjects in the nivolumab arm and 89 (34.0%) subjects in the placebo arm.

Four (0.8%) subjects in the nivolumab arm and 17 (6.5%) subjects in the placebo arm received subsequent anti-PD1 therapy (Table 10)

Table -10: Subsequent Cancer Therapy - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab N = 532	Placebo N = 262	Total N = 794
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	157 (29.5)	111 (42.4)	268 (33.8)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY	43 (8.1)	41 (15.6)	84 (10.6)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY	28 (5.3)	20 (7.6)	48 (6.0)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY	125 (23.5)	89 (34.0)	214 (27.0)
IMMUNOTHERAPY	4 (0.8)	19 (7.3)	23 (2.9)
ANTI-PD1	4 (0.8)	17 (6.5)	21 (2.6)
INVESTIGATIONAL ANTINEOPLASTIC (2)	0	3 (1.1)	3 (0.4)
NIVOLUMAB	3 (0.6)	8 (3.1)	11 (1.4)
PEMBROLIZUMAB	1 (0.2)	7 (2.7)	8 (1.0)
ANTI-PDL1	0	2 (0.8)	2 (0.3)
AVELUMAB	0	2 (0.8)	2 (0.3)
ANTI-CTLA4	0	1 (0.4)	1 (0.1)
IPILIMUMAB	0	1 (0.4)	1 (0.1)
OTHER IMMUNOTHERAPY	0	0	0
TARGETED THERAPY	13 (2.4)	11 (4.2)	24 (3.0)
BEVACIZUMAB	0	1 (0.4)	1 (0.1)
INVESTIGATIONAL ANTINEOPLASTIC (3)	0	2 (0.8)	2 (0.3)
RAMUCIRUMAB	13 (2.4)	9 (3.4)	22 (2.8)
OTHER SYSTEMIC CANCER THERAPY-EXPERIMENTAL DRUGS	0	0	0
OTHER SYSTEMIC CANCER THERAPY-CHEMOTHERAPY	123 (23.1)	85 (32.4)	208 (26.2)
ANTINEOPLASTIC	1 (0.2)	0	1 (0.1)
BICALUTAMIDE	0	1 (0.4)	1 (0.1)
CAPECITABINE	20 (3.8)	20 (7.6)	40 (5.0)
CARBOPLATIN	7 (1.3)	9 (3.4)	16 (2.0)
CETUXIMAB	1 (0.2)	0	1 (0.1)
CISPLATIN	27 (5.1)	13 (5.0)	40 (5.0)
CYCLOPHOSPHAMIDE	1 (0.2)	1 (0.4)	2 (0.3)
DOCETAXEL	13 (2.4)	7 (2.7)	20 (2.5)
EPIRUBICIN	1 (0.2)	0	1 (0.1)
ETOPOSIDE	1 (0.2)	0	1 (0.1)
FLUOROURACIL	80 (15.0)	50 (19.1)	130 (16.4)
FLUR/IRINOT/LEUCO	1 (0.2)	0	1 (0.1)
FLUR/LEUCO	2 (0.4)	0	2 (0.3)
FLUR/LEUCO/OXAL	7 (1.3)	8 (3.1)	15 (1.9)
GEMCITABINE	1 (0.2)	1 (0.4)	2 (0.3)
GIMER/OTERA/TEGFUR	7 (1.3)	3 (1.1)	10 (1.3)
IRINOTECAN	20 (3.8)	11 (4.2)	31 (3.9)
METHOTREXATE	0	1 (0.4)	1 (0.1)
NEDAPLATIN	3 (0.6)	0	3 (0.4)
OXALIPLATIN	71 (13.3)	50 (19.1)	121 (15.2)
PACLITAXEL	32 (6.0)	23 (8.8)	55 (6.9)
TEGAFUR	0	1 (0.4)	1 (0.1)
TEGFUR/URACIL	0	1 (0.4)	1 (0.1)
TRASTUZUMAB	10 (1.9)	12 (4.6)	22 (2.8)
UNASSIGNED	52 (9.8)	38 (14.5)	90 (11.3)
ACID FOLINIC	1 (0.2)	0	1 (0.1)
CALCIUM FOLINATE	1 (0.2)	1 (0.4)	2 (0.3)
DENOSUMAB	2 (0.4)	1 (0.4)	3 (0.4)
FOLIC ACID	0	2 (0.8)	2 (0.3)
FOLIN ACID Q2W	0	1 (0.4)	1 (0.1)

Table 10: Subsequent Cancer Therapy - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab N = 532	Placebo N = 262	Total N = 794
FOLINACID	0	1 (0.4)	1 (0.1)
FOLINIC ACID	6 (1.1)	1 (0.4)	7 (0.9)
FOLINSAURE	2 (0.4)	0	2 (0.3)
LEUCOOVORIN	1 (0.2)	0	1 (0.1)
LEUCOVARIN	0	1 (0.4)	1 (0.1)
LEUCOVORIN	30 (5.6)	24 (9.2)	54 (6.8)
LEUCOVORIN CALCIUM	1 (0.2)	0	1 (0.1)
LEUCOVORINA	1 (0.2)	0	1 (0.1)
LEUCOVORINE	2 (0.4)	1 (0.4)	3 (0.4)
LEVOFOLIC	0	1 (0.4)	1 (0.1)
LEVOFOLIN ACID	1 (0.2)	0	1 (0.1)
LEVOFOLINATE	2 (0.4)	0	2 (0.3)
LEVOFOLINATE CALCIUM	0	1 (0.4)	1 (0.1)
LEVOFOLINIC ACID	1 (0.2)	2 (0.8)	3 (0.4)
LEVOLEUCOVORIN	1 (0.2)	1 (0.4)	2 (0.3)
RIBOFOLIN	1 (0.2)	0	1 (0.1)
UNK	1 (0.2)	0	1 (0.1)
ZOLEDRONIC ACID	1 (0.2)	0	1 (0.1)
ZOMERA	1 (0.2)	0	1 (0.1)
THE NUMBER OF LINES OF SUBSEQUENT SYSTEMIC THERAPY			
1	82 (15.4)	60 (22.9)	142 (17.9)
2	30 (5.6)	18 (6.9)	48 (6.0)
3	10 (1.9)	9 (3.4)	19 (2.4)
>=4	3 (0.6)	2 (0.8)	5 (0.6)

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started
(2) Includes PEMBROLIZUMAB VS PLACEBO, PEMBROLIZUSUMAB VS PLACEBO, SINTILIMAB.
(3) Includes ANLOTINIB HYDROCHLORIDE CAPSULES, CABIRALIZUMAB.
Abbreviations: PD1 = programmed death 1 receptor, PD-L1 = program death-ligand 1, CTLA4 = cytotoxic T-lymphocyte associated protein 4
Source: Table S.6.23

Numbers analysed

Study Initiation Date: 14-Jul-2016 - The study is ongoing.

The last patient last visit (LPLV) for the Clinical Database Lock (DBL): 12-May-2020.

Clinical DBL: 03-Jul-2020

Analysis Populations in this CSR

Population	Total Number of Subjects
Enrolled: Enrolled subjects who signed an ICF and were registered in IRT (used for pre-treatment disposition).	1085
Randomized: Subjects randomized to any treatment arm (used for demography, protocol deviations, baseline characteristics, and efficacy).	794
Treated: Treated subjects, who received at least 1 dose of study drug (used for drug exposure and safety).	792
Immunogenicity subjects: Nivolumab treated subjects with baseline and at least 1 post-baseline assessment for ADA (used for immunogenicity).	464

Abbreviations: ADA = anti-drug antibody, ICF = informed consent form, IRT = Interactive Response Technology
Source: Table S.2.5 (all enrolled subjects), Table S.2.6A (all randomized subjects), Table S.2.7 (all treated subjects), Table S.7.10 (ADA summary)

Outcomes and estimation

Summary of Efficacy - All Randomized Subjects

	Nivolumab N= 532 (%)		Placebo N= 262 (%)
DFS (per Investigator)			
Events, n (%)	241 (45.3)		155 (59.2)
Median DFS (95% CI), mo.[a]	22.41 (16.62, 34.00)		11.04 (8.34, 14.32)
HR[b]		0.69	
(96.4% CI)		(0.56, 0.86)	
(95% CI)		(0.56, 0.85)	
p-value[c]		0.0003	
6-month DFS Rates (95% CI), %[a]	72.3 (68.2, 76.0)		63.4 (57.2, 69.0)
DMFS			
Events, n (%)	218 (41.0)		134 (51.1)
Median DMFS (95% CI), mo.[a]	28.32 (21.26, N.A.)		17.61 (12.45, 25.40)
HR[b]		0.74	
(95% CI)		(0.60, 0.92)	
6-month DMFS Rates (95% CI), %[a]	78.1 (74.3, 81.5)		71.1 (65.1, 76.2)
PFS2			
Events, n (%)	163 (30.6)		100 (38.2)
Median PFS (95% CI), mo.[a]	N.A. (34.00, N.A.)		32.07 (24.15, N.A.)
HR[b]		0.77	
(95% CI)		(0.60, 0.99)	

Database lock: 03-Jul-2020

Minimum follow-up was 6.2 months. Median follow-up time was 24.4 months (range: 6.2 to 44.9 months)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. Hazard Ratio is Nivolumab over Placebo. This model was stratified by PD-L1 status (≥1% vs <1% or indeterminate/non-evaluable), pathologic lymph node status (positive ≥ypN1 vs negative ypN0) and histology (squamous vs adenocarcinoma) as entered into the IRT.

[c] Log-rank test stratified by PD-L1 status (≥1% vs <1% or indeterminate/non-evaluable), pathologic lymph node status (positive ≥ypN1 vs negative ypN0) and histology (squamous vs adenocarcinoma) as entered into the IRT. 2-sided p-values from stratified log-rank test. Boundary for statistical significance p-value <0.036. Additional accuracy for p-value: 0.000339.

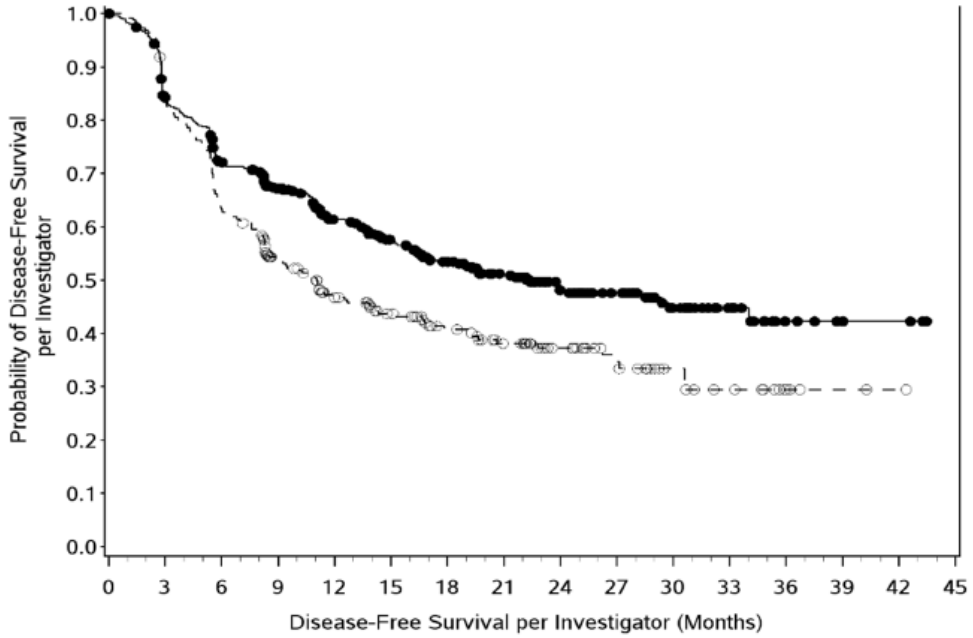
Abbreviations: CI = confidence interval; DFS = disease-free survival, n = number, DMFS = distant metastasis-free survival, mo = months, HR = hazard ratio; NA = not available, PFS2 = progression free survival on subsequent systemic therapy.

Primary endpoint

Disease-Free Survival

Nivolumab monotherapy in this study demonstrated a statistically significant improvement in DFS compared with placebo: HR = 0.69 (96.4% CI: 0.56, 0.86), stratified log-rank p-value = 0.0003; significance level = 0.036. Median DFS (95% CI) was 22.41 [16.62, 34.00] months for nivolumab compared with 11.04 [8.34, 14.32] months for placebo.

Kaplan Meier Plot of Disease Free Survival - All Randomized Subjects



Number of Subjects at Risk

Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

Nivolumab (events: 241/532), median and 95% CI: 22.41 (16.62, 34.00)

Placebo (events: 155/262), median and 95% CI: 11.04 (8.34, 14.32)

Nivolumab vs. Placebo - hazard ratio and 96.4% CI: 0.69 (0.56, 0.86), p-value: 0.0003

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

Source: Figure S.5.1.2

Table 11: Reasons for Censoring, Disease Free Survival - All Randomized Subjects

	Nivolumab N = 532	Placebo N = 262	Total N = 794
NUMBER OF EVENTS (%)	241 (45.3)	155 (59.2)	396 (49.9)
TYPE OF EVENTS (%)			
RECURRENCE (1)	219 (41.2)	147 (56.1)	366 (46.1)
LOCAL RECURRENCE	33 (6.2)	20 (7.6)	53 (6.7)
REGIONAL RECURRENCE	32 (6.0)	24 (9.2)	56 (7.1)
DISTANT RECURRENCE	154 (28.9)	103 (39.3)	257 (32.4)
DEATH WITHOUT RECURRENCE	22 (4.1)	8 (3.1)	30 (3.8)
NUMBER OF SUBJECTS CENSORED (%)	291 (54.7)	107 (40.8)	398 (50.1)
CENSORED ON DATE OF RANDOMIZATION	15 (2.8)	4 (1.5)	19 (2.4)
NO BASELINE DISEASE ASSESSMENT	0	0	0
NEVER TREATED	0	0	0
OTHER	0	0	0
NO ON-STUDY DISEASE ASSESSMENT AND NO DEATH (2)	14 (2.6)	3 (1.1)	17 (2.1)
NEVER TREATED	0	1 (0.4)	1 (0.1)
OTHER	14 (2.6)	2 (0.8)	16 (2.0)
NO ON-STUDY DISEASE ASSESSMENT BUT DEATH WITH PRIOR SUBSEQUENT THERAPY OR SECOND PRIMARY CANCER (2)	1 (0.2)	1 (0.4)	2 (0.3)
NEVER TREATED	0	0	0
OTHER	1 (0.2)	1 (0.4)	2 (0.3)
CENSORED ON DATE OF LAST EVALUABLE DISEASE ASSESSMENT ON-STUDY	276 (51.9)	103 (39.3)	379 (47.7)
RECEIVED SUBSEQUENT ANTI-CANCER THERAPY (3)	0	0	0
SECOND NON-ESOPHAGEAL AND NON-GEJ PRIMARY CANCER (3)	8 (1.5)	2 (0.8)	10 (1.3)
STILL ON TREATMENT	31 (5.8)	19 (7.3)	50 (6.3)
IN FOLLOW-UP	229 (43.0)	81 (30.9)	310 (39.0)
OFF STUDY	8 (1.5)	1 (0.4)	9 (1.1)
LOST TO FOLLOW-UP	1 (0.2)	1 (0.4)	2 (0.3)
SUBJECT WITHDREW CONSENT	6 (1.1)	0	6 (0.8)
OTHER	1 (0.2)	0	1 (0.1)

(1) Investigator Determined
(2) Disease assessments after the start of subsequent therapy or second primary cancer diagnosis were not considered.
(3) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy or were diagnosed with second primary cancer without a prior reported DFS event. Those subjects were censored at the last evaluable tumor assessment prior to/on start date of subsequent anti-cancer therapy or second primary cancer diagnosis.
Source: Table S.5.24.1

Secondary endpoints

- **Overall Survival (OS)**

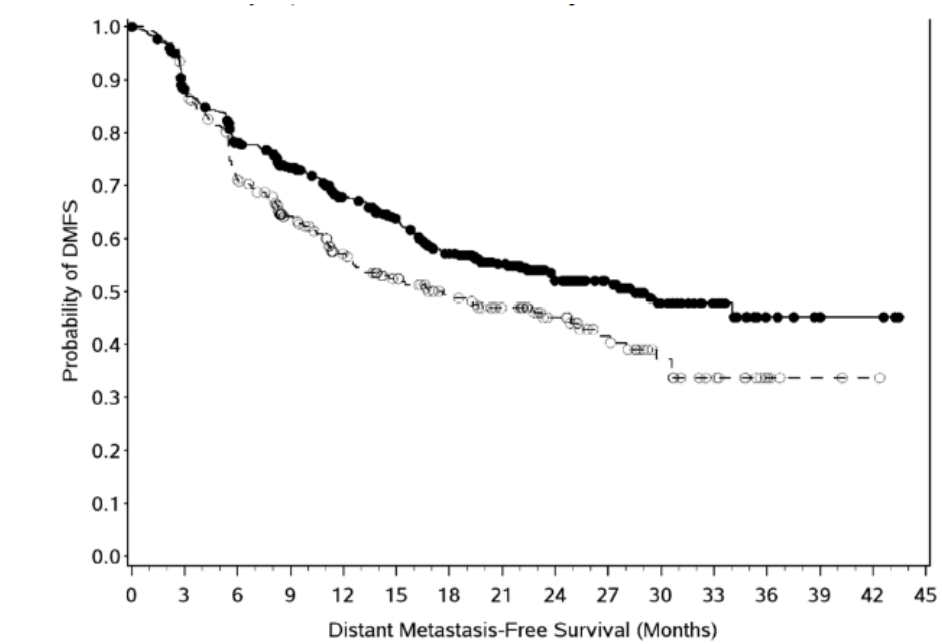
The significance level of 0.003 for OS at OS IA1 was based on actual pooled OS events (228, 49.6% out of total 460 OS events) observed at the time of the DFA IA/OS IA1 The OS data were not mature at that time (49.6% of total OS events were observed vs. 65.0% planned OS events), and the pre-specified boundary for declaring the statistical significance of p = 0.003 was not met.

Exploratory endpoints

- **Distant Metastasis-Free Survival**

Median DMFS (95% CI) was longer in the nivolumab arm compared with the placebo arm: 28.32 (21.26, N.A.) vs 17.61 (12.45, 25.40) months, with a HR of 0.74 (95% CI: 0.60, 0.92). A total of 352 DMFS events were reported for 218 (41.0%) subjects in the nivolumab arm and 134 (51.1%) subjects in the placebo arm.

Figure 39: Kaplan Meier Plot of Distant Metastasis-Free Survival (Exploratory Analysis) - All Randomized Subjects



Number of Subjects at Risk

Nivolumab	532	449	392	332	276	235	195	160	102	75	44	23	8	4	3	0
Placebo	262	226	180	142	113	93	77	64	46	33	21	14	5	2	1	0

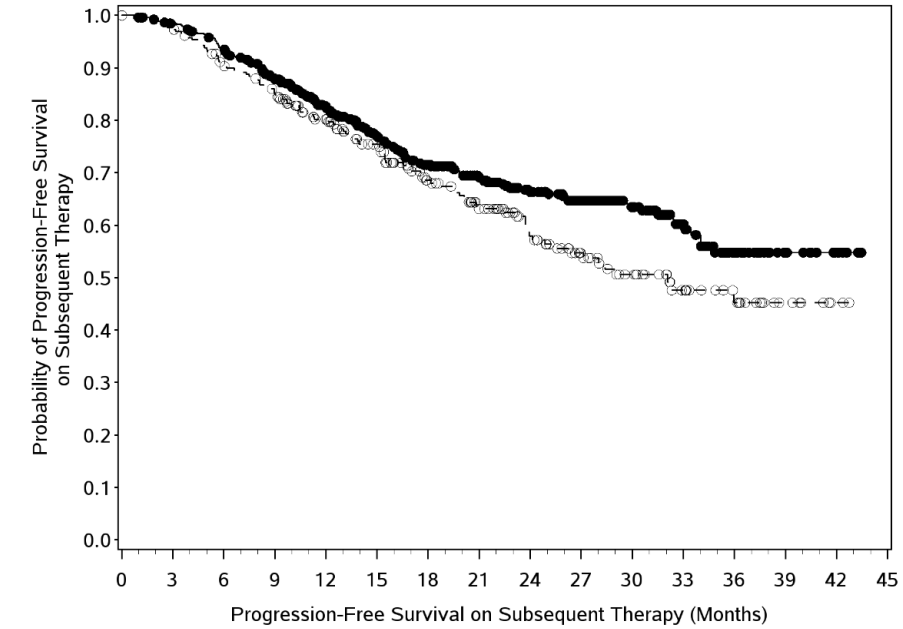
Nivolumab (events: 218/532), median and 95% CI: 28.32 (21.26, N.A.)
Placebo (events: 134/262), median and 95% CI: 17.61 (12.45, 25.40)
Nivolumab vs. Placebo - hazard ratio and 95% CI: 0.74 (0.60, 0.92)

Note: Statistical model for hazard ratio: stratified Cox proportional hazard model. Symbols represent censored observations.
Source: Figure S.5.30

- **Progression-Free Survival on Subsequent Systemic Therapy (PFS2) per Investigator**

Median PFS2 per investigator was not reached in the nivolumab arm. The median PFS2 was 32.07 months (95% CI: 24.15, N.A.) in the placebo arm. HR favoured the nivolumab arm over the placebo arm: 0.77 (95% CI: 0.60, 0.99) with an upper 95% CI below 1.

Figure 20: Kaplan Meier Plot of PFS2 per Investigator - All Randomized Subjects



Number of Subjects at Risk

Nivolumab	532	517	487	441	368	301	262	213	174	135	102	61	35	14	6	0
Placebo	262	255	231	215	179	152	118	98	77	58	44	29	19	8	2	0

—●— Nivolumab (events: 163/532), median and 95% CI: N.A. (34.00, N.A.)
– ⊖ – Placebo (events: 100/262), median and 95% CI: 32.07 (24.15, N.A.)
Nivolumab vs. Placebo - hazard ratio and 95% CI: 0.77 (0.60, 0.99)

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

Table 12: Reason for Event or Censoring, Progression-Free Survival on Subsequent Systemic Therapy per Investigator - All Randomized Subjects

	Nivolumab N = 532	Placebo N = 262	Total N = 794
NUMBER OF EVENTS (%)	163 (30.6)	100 (38.2)	263 (33.1)
PROGRESSION ON SUBSEQUENT SYSTEMIC THERAPY	50 (9.4)	34 (13.0)	84 (10.6)
START OF SECOND SUBSEQUENT SYSTEMIC THERAPY	15 (2.8)	9 (3.4)	24 (3.0)
DEATH	98 (18.4)	57 (21.8)	155 (19.5)
NUMBER OF SUBJECTS CENSORED (%)	369 (69.4)	162 (61.8)	531 (66.9)
NO SUBSEQUENT SYSTEMIC THERAPY	335 (63.0)	133 (50.8)	468 (58.9)
SUBSEQUENT SYSTEMIC THERAPY BUT NO PROGRESSION AND NO DEATH	34 (6.4)	29 (11.1)	63 (7.9)

Source: Table S.5.39

- **Patient Reported Outcomes (PROs)**

Functional Assessment of Cancer Therapy - Esophageal (FACT-E)

96.8% of subjects completed the FACT-E at baseline in the nivolumab arm while 96.9% of placebo subjects had a baseline assessment. Completion rates were >80% in both treatment arms at all subsequent on treatment assessments with sufficient data (≥10 subjects) through Week 53. Similar

compliance rates were seen for the Esophagus Cancer Subscale (ECS) and the subset of items included in the FACT-G and the FACT-G7.

At baseline, mean FACT-E total scores in all randomized subjects were similar for the nivolumab (133.40, SD: 20.97) and placebo (134.03, SD: 20.40) arms. Mean changes from baseline increased for both treatment arms at all times (where there were ≥ 10 subjects) during the "on treatment" phase and at follow-up visits 1 & 2. Similar results were observed for the ECS subscale, and the subset of items, which constitute the FACT-G and FACT-G7, with the exception of the placebo arm, which had a decrease from baseline at follow-up visit 2 for the FACT-G7 and both follow-up visits 1 & 2 for the placebo arm. During Survival follow-up subjects in both arms had mean increases from baseline for the ECS subscale and a decrease at most time points for the FACT-G7.

EQ-5D Visual Analogue (VAS) Scale

95.7% of subjects completed the EQ-5D-3L VAS at baseline in the nivolumab arm while 95.8% of placebo subjects had a baseline assessment. Completion rates were >80% in both treatment arms at all subsequent on treatment assessments with sufficient data (≥10 subjects) through Week 53.

At baseline, mean EQ-5D-3L Visual Analog Scale (VAS) scores in all randomized subjects were similar for the nivolumab (70.4, SD: 22.3) and placebo (69.1, SD: 24.1) arms. Mean changes from baseline increased for both treatment arms at all times (where there were ≥10 subjects) during the "on treatment" phase and at follow-up visits 1 & 2. During Survival follow-up subjects in both arms had mean increases from baseline for all time points where there were at least 10 subjects.

EQ-5D Utility Index

95.1% of subjects completed the EQ-5D-3L Descriptive System at baseline in the nivolumab arm while 94.7% of placebo subjects had a baseline assessment. Completion rates were >80% in both treatment arms at all subsequent on treatment assessments with sufficient data (≥10 subjects) through Week 53.

At baseline, mean EQ-5D-3L Utility Index scores (based on the UK value set) in all randomized subjects were similar for the nivolumab (0.8203, SD: 0.1790) and placebo (0.8310, SD: 0.1629) arms. Mean changes from baseline increased at all time points during the "on treatment" phase (with ≥ 10 subjects) starting at Week 9 for nivolumab subjects and Week 13 for placebo subjects. Subjects in the placebo arm had a mean decrease from baseline at all follow-up time points where there were at least 10 subjects, while subjects in the nivolumab arm had mean decreases from baseline only at follow-up visit 1 and survival follow-up visits 4 and 8.

Ancillary analyses

Sensitivity analyses

DFS accounting for assessments on/after subsequent therapy- all randomized subjects

Results for a DFS sensitivity analysis (244 [45.9%] events in the nivolumab and 157 [59.9%] in the placebo arms) accounting assessments on/after subsequent therapy and development of a second primary cancer showed a HR of 0.69 (96.4% CI: 0.56, 0.86), which was consistent with the primary DFS analysis.

	Nivolumab N = 532	Placebo N = 262
# EVENTS / # SUBJECTS (%)	244/532 (45.9)	157/262 (59.9)
MEDIAN DFS (MONTHS) (1) (95% CI)	22.21 (16.66, 29.73)	11.04 (8.31, 14.32)
HR	0.69 (A)	
(95% CI)	(0.56, 0.85)	
(96.4% CI)	(0.56, 0.86)	
P-Value (2)	0.0003	

(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab over Placebo.
(2) Log-rank test stratified by PD-L1 Status (>=1% vs <1% / indeterminate / non-evaluable), Pathologic Lymph Node Status
(positive >=ypN1 vs negative ypN0) and Histology (squamous vs adenocarcinoma) as entered into the IRT.
2 sided p values from stratified log-rank test.
Boundary for statistical significance p-value < 0.036 Additional accuracy for p-value: 0.000305

DFS accounting for two or more consecutively missing disease assessments prior to event

	Nivolumab N = 532	Placebo N = 262
# EVENTS / # SUBJECTS (%)	237/532 (44.5)	155/262 (59.2)
MEDIAN DFS (MONTHS) (1) (95% CI)	23.95 (16.66, N.A.)	11.04 (8.34, 14.32)
HR	0.68 (A)	
(95% CI)	(0.56, 0.84)	
(96.4% CI)	(0.55, 0.85)	
P-Value (2)	0.0002	

(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab over Placebo.
(2) Log-rank test stratified by PD-L1 Status (>=1% vs <1% / indeterminate / non-evaluable), Pathologic Lymph Node Status
(positive >=ypN1 vs negative ypN0) and Histology (squamous vs adenocarcinoma) as entered into the IRT.
2 sided p values from stratified log-rank test.
Boundary for statistical significance p-value < 0.036 Additional accuracy for p-value: 0.000243

DFS accounting for recurrence-free subjects lost to follow-up

	Nivolumab N = 532	Placebo N = 262
# EVENTS / # SUBJECTS (%)	242/532 (45.5)	156/262 (59.5)
MEDIAN DFS (MONTHS) (1) (95% CI)	22.21 (16.62, 34.00)	11.04 (8.31, 14.32)
HR	0.69 (A)	
(95% CI)	(0.56, 0.84)	
(96.4% CI)	(0.56, 0.86)	
P-Value (2)	0.0003	

(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab over Placebo.
(2) Log-rank test stratified by PD-L1 Status (>=1% vs. <1% / indeterminate / non-evaluable), Pathologic Lymph Node Status (positive >=ypN1 vs. negative ypN0) and Histology (squamous vs. adenocarcinoma) as entered into the IRT.
2 sided p values from stratified log-rank test.
Boundary for statistical significance p-value < 0.036 Additional accuracy for p-value: 0.000305

Maturity of DFS – Post-hoc analyses

To evaluate the maturity of DFS in relation to the extent of follow-up, post-hoc analyses were conducted for a subset of randomized subjects with 1-year and 2-year minimum follow up.

DFS by the extent of follow-up

The post-hoc analyses of DFS in a subset of randomized subjects with 1-year and 2-year minimum follow up support the stability of the DFS curves and robustness of the treatment effect observed in all randomized subjects.

- At the time of DFS IA (396 DFS [90% actual] events observed), 683/794 (86.0%) randomized subjects had the 1-year minimum follow-up and 406/794 (51.1%) subjects had the 2-year minimum follow-up. Demographic and baseline characteristics were generally comparable in these subsets of randomized subjects. Demographic and baseline characteristics of randomized subjects with the minimum follow up of 1 year and 2-year were also consistent with the demographics and baseline characteristics of all randomized subjects.
- Overlaid KM curves show comparable KM DFS curves among all randomized subjects and the subsets of subjects with 1-year (86.0%) and 2-year (51.1%) minimum follow up. In addition, separation of the DFS curves for nivolumab and placebo arms continued beyond 36 months, favouring nivolumab in subjects with 1-year or 2-year minimum follow-up, consistent with all randomized subjects.
- Treatment effect in terms of DFS HRs using un-stratified Cox model were consistent between the subset of subjects with either the 1-year or 2-year minimum follow up and all randomized subjects.
    - Subjects with 1-year minimum follow-up: HR = 0.71 (95% CI: 0.57, 0.87)
    - Subjects with All randomized subjects (N = 794): HR = 0.70 (95% CI: 0.58, 0.86)

Subgroup analyses

DFS by Subgroups

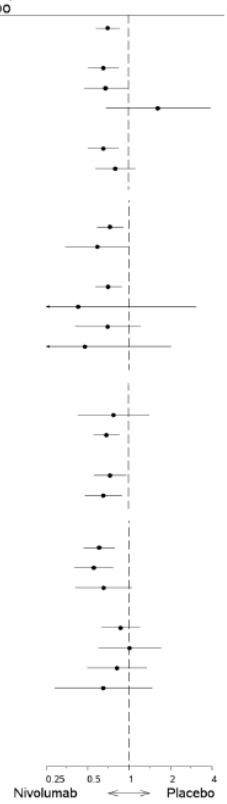
Histology: squamous cell carcinoma (HR = 0.61, 95% CI: 0.42, 0.88) and adenocarcinoma (HR = 0.75, 95% CI: 0.59, 0.96)

Pathologic lymph node status: positive (≥ ypN1) [HR = 0.67, 95% CI: 0.53, 0.86] and negative (ypN0) [HR = 0.74, 95% CI: 0.51, 1.06]

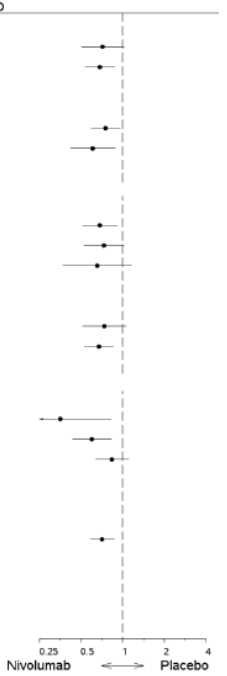
Tumour cell PD-L1 status: PD-L1 ≥ 1% (HR = 0.75, 95% CI: 0.45, 1.24), PD-L1 < 1% (HR = 0.73, 95% CI: 0.57, 0.92) and indeterminate/non-evaluable tumour cell PD-L1 (HR = 0.54, 95% CI: 0.27, 1.05)

Forest Plot of Treatment Effect on Disease-Free Survival in Predefined Subsets - All Randomized Subjects

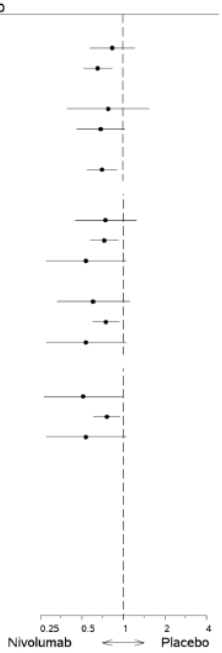
	N	Nivolumab N of Events (N of Subjects)	Nivolumab mDFS (95% CI)	Placebo N of Events (N of Subjects)	Placebo mDFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
Overall	794	241 (532)	22.41 (16.62, 34.00)	155 (262)	11.04 (8.34, 14.32)	0.70 (0.58, 0.86)
Age Categorization 1						
< 65	507	145 (333)	24.41 (17.48, N.A.)	101 (174)	10.81 (7.59, 13.83)	0.65 (0.51, 0.84)
>= 65 and < 75	245	81 (175)	19.65 (11.70, N.A.)	46 (70)	11.14 (5.55, 17.84)	0.68 (0.47, 0.98)
>= 75	42	15 (24)	11.33 (3.45, 29.73)	8 (18)	22.80 (9.23, 27.04)	1.64 (0.68, 3.91)
Age Categorization 2						
< 65	507	145 (333)	24.41 (17.48, N.A.)	101 (174)	10.81 (7.59, 13.83)	0.65 (0.51, 0.84)
>= 65	287	96 (199)	16.95 (11.56, N.A.)	54 (88)	13.93 (8.15, 19.65)	0.80 (0.57, 1.12)
Sex						
Male	671	207 (449)	21.42 (16.30, 29.37)	132 (222)	11.10 (8.31, 15.21)	0.73 (0.59, 0.91)
Female	123	34 (83)	N.A. (13.31, N.A.)	23 (40)	11.04 (5.49, 30.59)	0.59 (0.35, 1.00)
Race						
White	648	198 (432)	21.26 (16.30, 34.00)	128 (216)	10.91 (8.15, 16.66)	0.71 (0.57, 0.88)
Black or African American	9	3 (7)	14.39 (3.81, N.A.)	2 (2)	8.26 (5.49, 11.04)	0.43 (0.06, 3.06)
Asian	117	37 (83)	23.98 (11.14, N.A.)	20 (34)	10.15 (5.55, N.A.)	0.70 (0.41, 1.22)
Other	20	3 (10)	N.A. (4.50, N.A.)	5 (10)	14.13 (1.74, N.A.)	0.48 (0.11, 2.02)
Region						
Asia	106	35 (77)	23.98 (11.14, N.A.)	16 (29)	14.32 (5.45, N.A.)	0.78 (0.43, 1.41)
ROW [Including US/Canada, Europe]	688	206 (455)	21.42 (16.49, N.A.)	139 (233)	11.04 (8.31, 14.13)	0.69 (0.56, 0.86)
Baseline ECOG Performance Status						
0	464	134 (308)	29.37 (18.89, N.A.)	88 (156)	11.14 (8.21, 19.65)	0.73 (0.56, 0.96)
1	330	107 (224)	16.95 (14.13, 28.32)	67 (106)	10.91 (7.59, 13.93)	0.66 (0.48, 0.89)
Disease At Study Entry						
Esophageal Cancer	462	141 (311)	23.98 (16.49, N.A.)	98 (151)	8.34 (6.01, 11.47)	0.61 (0.47, 0.78)
Lower Third	298	86 (202)	34.00 (16.49, N.A.)	62 (96)	8.34 (5.78, 13.83)	0.55 (0.40, 0.77)
Middle Third	128	40 (82)	23.98 (10.84, N.A.)	30 (46)	9.23 (5.78, 17.84)	0.65 (0.41, 1.05)
Upper Third	36	15 (27)	8.74 (4.63, N.A.)	6 (9)	5.39 (2.79, N.A.)	N.A.
Gastroesophageal Junction Cancer	332	100 (221)	22.41 (15.15, N.A.)	57 (111)	20.63 (9.49, 30.59)	0.87 (0.63, 1.21)
Siewert-Stein Type I	140	40 (91)	21.42 (13.83, N.A.)	22 (49)	30.59 (9.26, N.A.)	1.01 (0.60, 1.70)
Siewert-Stein Type II	145	45 (99)	23.95 (12.62, N.A.)	24 (46)	16.66 (8.21, N.A.)	0.82 (0.50, 1.34)
Siewert-Stein Type III	40	14 (26)	16.30 (6.14, N.A.)	10 (14)	9.17 (2.83, 27.14)	0.65 (0.29, 1.47)
Not Reported	7	1 (5)	N.A. (4.60, N.A.)	1 (2)	N.A. (10.81, N.A.)	N.A.



	N	Nivolumab N of Events (N of Subjects)	Nivolumab mDFS (95% CI)	Placebo N of Events (N of Subjects)	Placebo mDFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
Disease Stage at Initial Diagnosis						
Stage II	278	72 (179)	34.00 (16.95, N.A.)	55 (99)	13.93 (9.26, 30.59)	0.72 (0.51, 1.02)
Stage III	514	169 (351)	19.35 (14.13, 28.32)	100 (163)	8.51 (6.57, 12.55)	0.68 (0.53, 0.88)
Not Reported	2	0 (2)	N.A.	0 (0)		N.A.
Histology (CRF)						
Adenocarcinoma	563	176 (376)	19.35 (15.93, 29.37)	107 (187)	11.10 (8.25, 16.79)	0.75 (0.59, 0.96)
Squamous Cell Carcinoma	230	65 (155)	29.73 (14.39, N.A.)	48 (75)	11.04 (7.59, 17.84)	0.61 (0.42, 0.88)
Other	1	0 (1)	N.A.	0 (0)		N.A.
Histological Grade (CRF)						
G1/G2	438	125 (302)	29.37 (21.42, N.A.)	77 (136)	13.93 (8.31, 26.25)	0.68 (0.51, 0.91)
G3/G4	253	89 (165)	14.13 (9.76, 19.61)	57 (88)	9.17 (5.55, 12.55)	0.73 (0.52, 1.02)
GX	101	27 (65)	N.A. (13.40, N.A.)	21 (36)	11.10 (6.80, N.A.)	0.65 (0.37, 1.16)
Not Reported	2	0 (0)		0 (2)	N.A.	N.A.
Pathologic Lymph Node Status (CRF)						
ypN0	336	75 (227)	N.A. (29.37, N.A.)	48 (109)	27.04 (15.21, N.A.)	0.74 (0.51, 1.06)
>= ypN1	457	166 (305)	14.75 (10.94, 19.35)	106 (152)	7.59 (5.55, 9.26)	0.67 (0.53, 0.86)
Unknown	1	0 (0)		1 (1)	11.47 (N.A., N.A.)	N.A.
Pathologic Tumor Status (CRF)						
ypT0	47	11 (31)	34.00 (10.68, N.A.)	11 (16)	5.19 (2.76, N.A.)	0.35 (0.15, 0.82)
ypT1/ypT2	308	85 (202)	28.32 (16.66, N.A.)	68 (106)	9.26 (8.15, 13.83)	0.60 (0.44, 0.83)
ypT3/ypT4	436	142 (296)	18.89 (14.13, 29.37)	76 (140)	14.13 (8.38, 27.04)	0.84 (0.64, 1.11)
Unknown	3	3 (3)	5.36 (0.95, 16.49)	0 (0)		N.A.
Time From Beginning of Neoadjuvant CRT to Complete Resection						
< 6 Weeks	1	1 (1)	10.68 (N.A., N.A.)	0 (0)		N.A.
>= 6 Weeks	786	240 (526)	22.21 (16.49, 34.00)	154 (260)	11.04 (8.34, 14.32)	0.71 (0.58, 0.87)
Not Reported	7	0 (5)	N.A.	1 (2)	N.A. (5.55, N.A.)	N.A.



	N	Nivolumab N of Events (N of Subjects)	Nivolumab mDFS (95% CI)	Placebo N of Events (N of Subjects)	Placebo mDFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
Time From Complete Resection to Randomization (Weeks)						
< 10 Weeks	256	81 (182)	23.98 (13.73, N.A.)	41 (74)	14.13 (8.31, 26.25)	0.84 (0.57, 1.22)
>= 10 Weeks	538	160 (350)	21.42 (16.62, N.A.)	114 (188)	10.81 (7.59, 13.93)	0.66 (0.52, 0.84)
HER-2 Status (CRF)						
Positive	63	20 (41)	19.61 (5.52, N.A.)	14 (22)	7.56 (2.99, N.A.)	0.78 (0.40, 1.55)
Negative	207	58 (131)	21.42 (15.93, N.A.)	41 (76)	9.43 (5.88, N.A.)	0.69 (0.46, 1.03)
Unknown	2	1 (2)	18.99 (N.A., N.A.)	0 (0)		N.A.
Not Reported	522	162 (358)	23.98 (16.20, 34.00)	100 (164)	11.14 (8.31, 17.02)	0.70 (0.55, 0.90)
PD-L1 Status at Baseline (LAB) (1% Cut-Off)						
>= 1%	129	40 (89)	19.65 (11.33, N.A.)	24 (40)	14.13 (5.49, 22.80)	0.75 (0.45, 1.24)
< 1%	570	175 (374)	21.26 (16.30, 34.00)	118 (196)	11.10 (8.25, 15.21)	0.73 (0.57, 0.92)
Indeterminate / Non-evaluable	95	26 (69)	N.A. (13.31, N.A.)	13 (26)	9.49 (3.38, N.A.)	0.54 (0.27, 1.05)
PD-L1 Status at Baseline (LAB) (5% Cut-Off)						
>= 5%	88	26 (60)	28.32 (13.27, N.A.)	18 (28)	9.23 (3.25, 27.04)	0.60 (0.33, 1.10)
< 5%	611	189 (403)	19.65 (15.93, 34.00)	124 (208)	11.14 (8.34, 16.66)	0.75 (0.60, 0.94)
Indeterminate / Non-evaluable	95	26 (69)	N.A. (13.31, N.A.)	13 (26)	9.49 (3.38, N.A.)	0.54 (0.27, 1.05)
PD-L1 Status at Baseline (LAB) (10% Cut-Off)						
>= 10%	71	21 (47)	28.32 (13.27, N.A.)	16 (24)	8.31 (2.99, 22.80)	0.51 (0.27, 0.99)
< 10%	628	194 (416)	19.65 (15.93, 34.00)	126 (212)	11.14 (8.34, 16.66)	0.76 (0.61, 0.95)
Indeterminate / Non-evaluable	95	26 (69)	N.A. (13.31, N.A.)	13 (26)	9.49 (3.38, N.A.)	0.54 (0.27, 1.05)



Note: HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group. Race "Other" category includes "American Indian or Alaska Native", "Native Hawaiian or Other Pacific Islander" and "Not Reported" subjects. For the PD-L1 status at baseline categories, these values were based on central laboratory assessments and not the IRT.

Abbreviations: CI = confidence interval, CRF = case report form, CRT = chemoradiotherapy, ECOG = Eastern Cooperative Oncology Group, HER-2 = human epidermal growth factor receptor 2, LAB = laboratory value, mDFS = median disease-free survival per Investigator time (months), N.A. = not available, ROW = rest of world, US = United States

Source: Figure S.5.2.2

Efficacy by baseline tumour PD-L1 expression

The DFS benefit of nivolumab vs. placebo was observed regardless of tumour cell PD-L1 status (< 1%, ≥ 1%, < 5%, ≥ 5%, < 10%, ≥ 10%, and indeterminate/non-evaluable). However, at higher cut-offs of ≥ 5% and ≥ 10%, improved HR for DFS was observed (HR = 0.75 [95% CI: (0.45, 1.24)] in ≥ 1%, HR = 0.60 [95% CI: (0.33, 1.10)] in ≥ 5%, HR = 0.51 [95% CI: (0.27, 0.99)] in ≥ 10%).

The interaction test with a p-value of 0.9306 for the interaction of the tumour PD-L1 status (<1%, ≥ 1%) and treatment in addition to treatment and tumour PD-L1 status in the unstratified Cox proportional hazard model of DFS indicated that there was no interaction between baseline tumour cell PD-L1 status and treatment.

Figure 21: KM plot of DFS per investigator by PD-L1 status and treatment- All randomized subjects with evaluable PD-L1 expression ≥1%

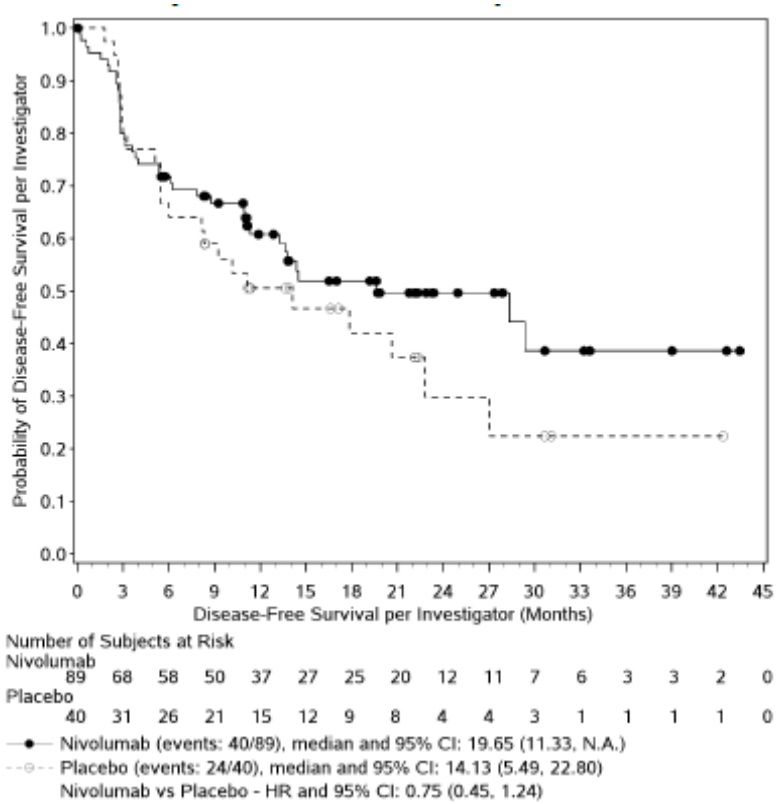
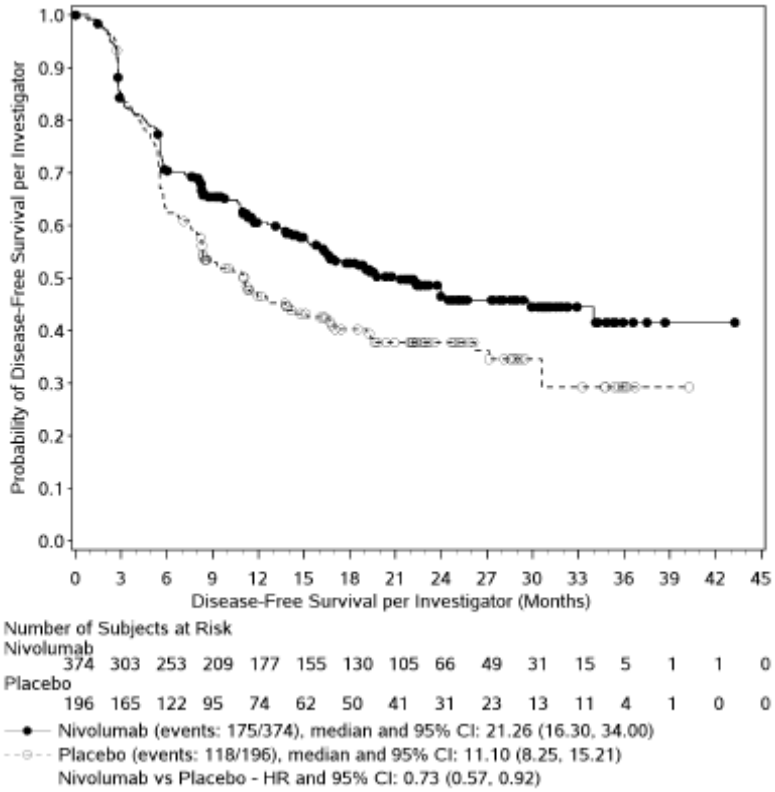


Figure 22: KM plot of DFS per investigator by PD-L1 status and treatment- All randomized subjects with evaluable PD-L1 expression <1%



Updated ad-hoc efficacy analysis (DBL 18-Feb-2021)

To further support clinical benefit of adjuvant nivolumab in the claimed indication, an ad hoc descriptive efficacy analysis of DFS, DMFS and PFS2 with longer follow-up have been provided. In this ad hoc analysis, the clinical data cut-off (last patient last visit [LPLV]) occurred on 04-Jan-2021, and the clinical DBL occurred on 18-Feb-2021. The minimum follow-up is 14.0 months and the median follow-up is 32.2 months (range: 14.0 to 52.7 months).

The updated results of DFS, DMFS and PFS2 in all randomized subjects (n=794), based on 18 Feb-2021 DBL, are presented in Table 6-1, side-by-side with the primary analysis data from the 03-Jul-2020 DBL.

Table 6-1: Overall Summary of Efficacy - All Randomized Subjects

	Primary Analysis 03-Jul-2020		Updated Analysis 18-Feb-2021	
	Nivolumab N= 532	Placebo N= 262	Nivolumab N= 532	Placebo N= 262
DFS (per Investigator)				
Events, n (%)	241 (45.3)	155 (59.2)	268 (50.4)	171 (65.3)
Median DFS (95% CI), mo.[a]	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)	22.41 (16.95, 33.64)	10.35 (8.31, 13.93)
HR[b]	0.69		0.67	
(96.4% CI)	(0.56, 0.86)		-	
(95% CI)	(0.56, 0.85)		(0.55, 0.81)	
p-value[c]	0.0003		-	
DMFS				
Events, n (%)	218 (41.0)	134 (51.1)	253 (47.6)	154 (58.8)
Median DMFS (95% CI), mo.[a]	28.32 (21.26, N.A.)	17.61 (12.45, 25.40)	29.37 (23.66, 36.63)	16.62 (11.37, 24.87)
HR[b]	0.74		0.71	
(95% CI)	(0.60, 0.92)		(0.58, 0.87)	
PFS2				
Events, n (%)	163 (30.6)	100 (38.2)	203 (38.2)	120 (45.8)
Median PFS (95% CI), mo.[a]	N.A. (34.00, N.A.)	32.07 (24.15, N.A.)	N.A. (36.63, N.A.)	30.72 (24.15, N.A.)
HR[b]	0.77		0.77	
(95% CI)	(0.60, 0.99)		(0.61, 0.96)	

Database lock: 03-Jul-2020; Minimum follow-up was 6.2 months. Median follow-up was 24.4 months (range: 6.2 to 44.9 months)

Database lock: 18-Feb-2021: Minimum follow-up was 14.0 months. Median follow-up was 32.2 months (range: 14.0 to 52.7 months)

[a] Based on Kaplan-Meier estimates.

[b] Stratified Cox proportional hazards model. Hazard Ratio is Nivolumab over Placebo. This model was stratified by PD-L1 status (≥1% vs <1% or indeterminate/non-evaluable), pathologic lymph node status (positive [≥ypN1] vs negative [ypN0]) and histology (squamous vs adenocarcinoma) as entered into the IRT.

[c] Log-rank test stratified by PD-L1 status (≥1% vs <1% or indeterminate/non-evaluable), pathologic lymph node status (positive [≥ypN1] vs negative [ypN0]) and histology (squamous vs adenocarcinoma) as entered into the IRT. 2-sided p-values from stratified log-rank test. Boundary for statistical significance p-value <0.036. Additional accuracy for p-value: 0.000339.

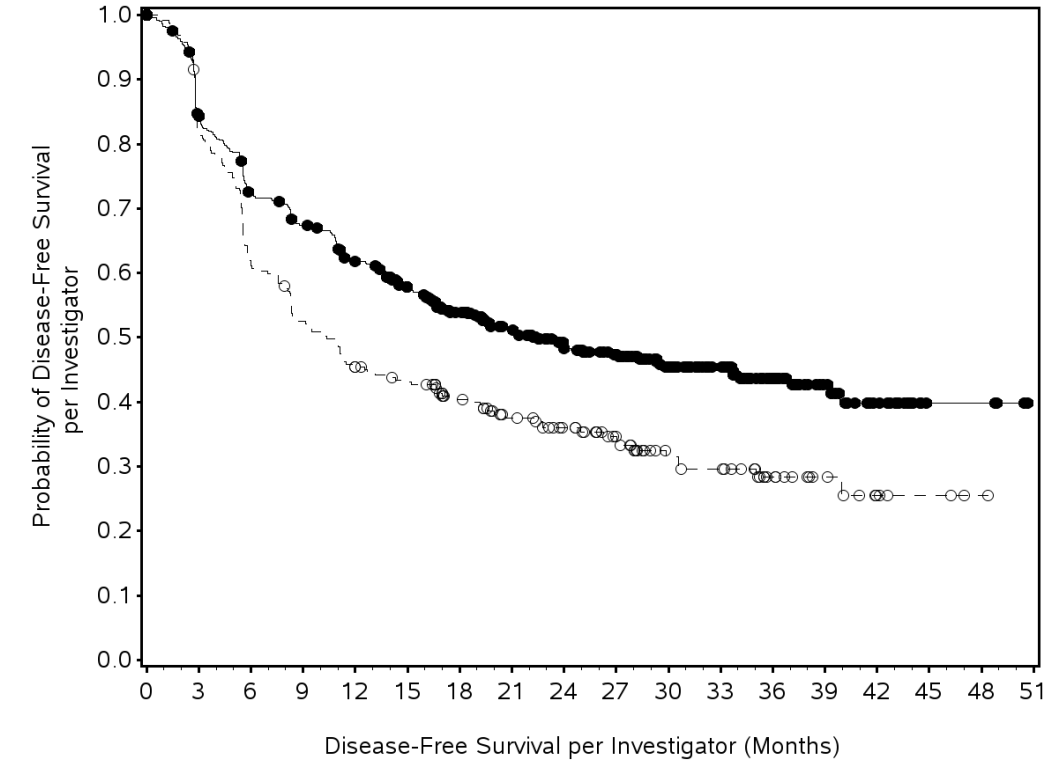
Abbreviations: CI = confidence interval; DFS = disease-free survival, n = number, DMFS = distant metastasis-free survival, mo = months, HR = hazard ratio; N.A. = not available, PFS2 = progression-free survival on subsequent systemic therapy

Source: Table 7.1-1 of CA209577 Primary CSR, Table S.5.22.1.1 (disease-free survival), Table S.5.22.2.1 (distant metastasis-free survival), Table S.5.23.1 (DFS rates), Table S.5.23.2 (DMFS rates), Table S.5.22.2.2 (progression-free survival on subsequent systemic therapy)

DFS

At the time of this ad-hoc analysis for DFS (18-Feb-2021), there were a total of 439 (55.3%) DFS events observed. The updated DFS HR for nivolumab vs placebo was 0.67 (95% CI: 0.55, 0.81) (Table 13, Figure 23).

Figure 23: Kaplan-Meier Plot of Disease-Free Survival per Investigator, Primary Definition - All Randomized Subjects (18-Feb-2021 DBL) -



Number of Subjects at Risk

Nivolumab

532 433 371 342 307 272 228 194 160 137 106 84 57 34 19 4 4 0

Placebo

262 211 158 134 114 107 88 73 62 50 33 30 18 11 5 3 1 0

Nivolumab (events: 268/532), median and 95% CI: 22.41 (16.95, 33.64)

Placebo (events: 171/262), median and 95% CI: 10.35 (8.31, 13.93)

Nivolumab vs. Placebo - hazard ratio and 95% CI: 0.67 (0.55, 0.81)

Table 13: Disease-Free Survival Rates per Investigator-All Randomized Subjects (18-Feb-2021 DBL)

Disease-Free Survival Rate (95% CI)	Nivolumab N = 532	Placebo N = 262
3-MONTH	84.3 (80.9, 87.2)	82.1 (76.9, 86.3)
6-MONTH	72.6 (68.5, 76.3)	61.5 (55.3, 67.1)
9-MONTH	67.3 (63.1, 71.2)	52.5 (46.2, 58.4)
12-MONTH	61.8 (57.4, 65.8)	45.5 (39.3, 51.4)
15-MONTH	57.9 (53.5, 62.0)	43.4 (37.3, 49.4)
18-MONTH	53.9 (49.5, 58.2)	40.4 (34.4, 46.4)
21-MONTH	51.1 (46.6, 55.5)	37.6 (31.5, 43.6)
24-MONTH	48.3 (43.7, 52.8)	36.0 (29.9, 42.0)

The updated sensitivity DFS analysis accounting for assessments on/after subsequent therapy was consistent with the primary definition for DFS with HR of 0.67 (95% CI: 0.55, 0.81).

Table 14: Disease-Free Survival, Sensitivity Analysis Accounting for Assessments on/after Subsequent Therapy - All Randomized Subjects (18-Feb-2021 DBL)

	Nivolumab N = 532	Placebo N = 262
# EVENTS / # SUBJECTS (%)	275/532 (51.7)	173/262 (66.0)
MEDIAN DFS (MONTHS) (1) (95% CI)	21.42 (17.05, 29.34)	10.35 (8.28, 13.93)
HR (95% CI)	0.67 (A) (0.55, 0.81)	

(1) Based on Kaplan-Meier Estimates
(A) Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab over Placebo.
Model stratified by PD-L1 Status (>=1% vs <1% / indeterminate / non-evaluable), Pathologic Lymph Node Status (positive >=ypN1 vs negative ypN0) and Histology (squamous vs adenocarcinoma) as entered into the IRT.
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DFS by stratification factors

DFS by Pathologic lymph node status

The results of the DFS by pathologic lymph node status, based on the 18-Feb-2021 DBL, are consistent with primary analyses (03-Jul-2020 DBL). In the subjects with ypN0 (n=337, 42.4%), the HR for DFS was 0.71 (95% CI: 0.51, 1.00) with median DFS not reached and 27.04 months (95% CI: 15.21, NA) for the nivolumab and placebo arms, respectively. In the subjects with ≥ypN1 (n=457, 57.6%), the HR for DFS was 0.65 (95% CI: 0.52, 0.83) with median DFS of 14.75 months (95% CI: 11.01, 19.32) and 7.59 months (95% CI: 5.55, 8.51) for the nivolumab and placebo arms, respectively.

DFS by Histology

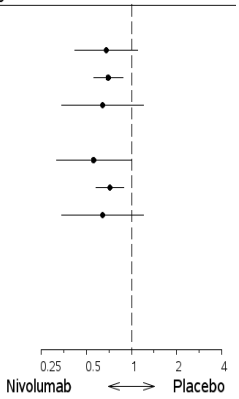
The results of the DFS by histology, based on the 18-Feb-2021 DBL is also consistent with primary analyses (03-Jul-2020 DBL). DFS benefit is observed regardless of histology. In the adenocarcinoma subgroup (n=563, 70.9%), the HR for DFS was 0.73 (95% CI: 0.58, 0.91) with median DFS of 19.61 months (95% CI: 16.00, 29.34) and 10.35 months (95% CI: 8.15, 16.66) for the nivolumab and placebo arms, respectively. In the squamous cell carcinoma subgroup (n=230, 29.0%), the HR for DFS was 0.60 (95% CI: 0.42, 0.86) with median DFS of 29.73 months (95% CI: 21.16, NA) and 10.60 months (95% CI: 6.05, 17.02) for the nivolumab and placebo arms, respectively.

DFS by PD-L1 status

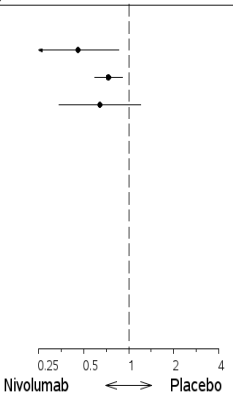
At the cutoff of 1%, HRs for DFS were similar between the tumor cell PD-L1 < 1% (n = 567; 0.70 [95% CI: 0.56, 0.87]) and ≥ 1% (n = 129; 0.68 [95% CI: 0.42, 1.10]) subgroups.

DFS was also analysed for different cut-offs (< 5%, ≥ 5%, < 10%, ≥ 10%, and indeterminate/non-evaluable).

	N	Nivolumab N of Events (N of Subjects)	Nivolumab mDFS (95% CI)	Placebo N of Events (N of Subjects)	Placebo mDFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
PD-L1 Status at Baseline (LAB) (1% Cut-Off)						
>= 1%	129	44 (89)	28.32 (13.27, N.A.)	27 (40)	10.15 (5.45, 22.80)	0.68 (0.42, 1.10)
< 1%	567	190 (371)	20.76 (16.00, 33.74)	130 (196)	11.04 (7.98, 15.11)	0.70 (0.56, 0.87)
Indeterminate / Non-evaluable	98	34 (72)	26.58 (14.09, N.A.)	14 (26)	9.92 (3.38, N.A.)	0.64 (0.34, 1.20)
PD-L1 Status at Baseline (LAB) (5% Cut-Off)						
>= 5%	88	29 (60)	28.32 (13.27, N.A.)	20 (28)	8.31 (3.25, 22.28)	0.56 (0.31, 0.99)
< 5%	608	205 (400)	20.76 (16.00, 33.74)	137 (208)	11.14 (8.31, 15.21)	0.72 (0.58, 0.89)
Indeterminate / Non-evaluable	98	34 (72)	26.58 (14.09, N.A.)	14 (26)	9.92 (3.38, N.A.)	0.64 (0.34, 1.20)



	N	Nivolumab N of Events (N of Subjects)	Nivolumab mDFS (95% CI)	Placebo N of Events (N of Subjects)	Placebo mDFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
PD-L1 Status at Baseline (LAB) (10% Cut-Off)						
>= 10%	71	23 (47)	29.34 (13.63, N.A.)	18 (24)	6.01 (2.92, 22.28)	0.46 (0.25, 0.86)
< 10%	625	211 (413)	20.76 (16.00, 33.74)	139 (212)	11.14 (8.31, 15.21)	0.73 (0.59, 0.91)
Indeterminate / Non-evaluable	98	34 (72)	26.58 (14.09, N.A.)	14 (26)	9.92 (3.38, N.A.)	0.64 (0.34, 1.20)



Abbreviations: CI = confidence interval, mDFS = median disease-free survival, PD-L1 = programmed death-ligand 1
mDFS - median Disease-Free Survival per Investigator time (months).
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Figure 4: Forest Plot of Treatment Effect on Disease-Free Survival per Investigator - in Subsets by PD-L1 (Lab) Status at Baseline - All Randomized Subjects (18-Feb-2021 DBL)

To evaluate the maturity of DFS in relation to the extent of follow-up in this updated efficacy analysis, DFS was also analysed in subsets of randomized subjects with 2-year and 2.5-year minimum follow up (defined as the time from randomization date to LPLV).

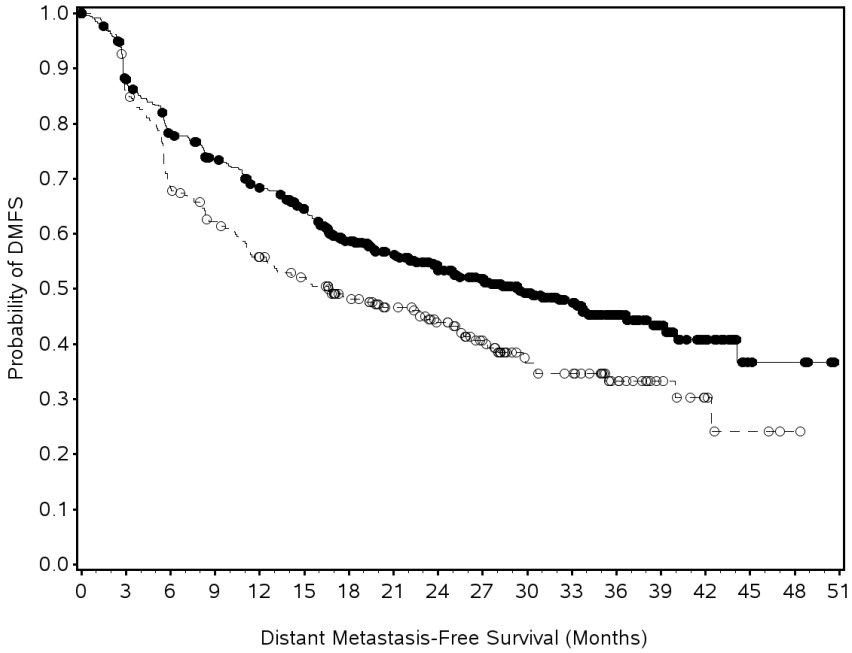
- Among the 794 randomized subjects, 596 (75.1%) randomized subjects had 2-year minimum follow-up, and 453 (57.1%) subjects had 2.5-year minimum follow-up.
- Treatment effect in terms of DFS HRs using un-stratified Cox model was consistent between the subset of subjects with either the 2-year or 2.5-year minimum follow up and all randomized subjects.
    - Subjects with 2-year minimum follow-up: HR = 0.67 (95% CI: 0.54, 0.84).
    - Subjects with 2.5-year minimum follow-up: HR = 0.67 (95% CI: 0.52, 0.86).
    - All randomized subjects (N = 794): HR = 0.68 (95% CI: 0.56, 0.83).
- The subset of subjects with 2.5-year minimum follow-up (57.1%) included more than half of the all randomized subjects, the 2.5-year minimum follow-up in this subset of subjects relative to the mDFS of 25.07 months in the nivolumab arm ensures that K-M curve of DFS is mature

and stable. Overlaid K-M curves show comparable K-M DFS curves among all randomized subjects and the subsets of subjects with 2-year and 2.5-year minimum follow up.

DMFS

Based on the 18-Feb-2021 DBL, there was a total of 407 (51.3%) DMFS events. The median DMFS is 29.37 months (95% CI: 23.66, 36.63) and 16.62 (95% CI: 11.37, 24.87) months, in nivolumab and placebo arms, respectively and the HR of DMFS was 0.71 (95% CI: 0.58, 0.87), consistent with the primary DMFS analysis reported from the 03-Jul-2020 DBL.

Figure 24: Kaplan-Meier Plot of Distant Metastasis-Free Survival - All Randomized Subjects (18-Feb-2021 DBL)



Number of Subjects at Risk

Nivolumab	532	453	400	369	339	307	252	219	181	157	123	93	61	38	22	6	5	0
Placebo	262	222	175	156	136	124	102	88	74	58	38	34	21	12	6	3	1	0

Nivolumab (events: 253/532), median and 95% CI: 29.37 (23.66, 36.63)

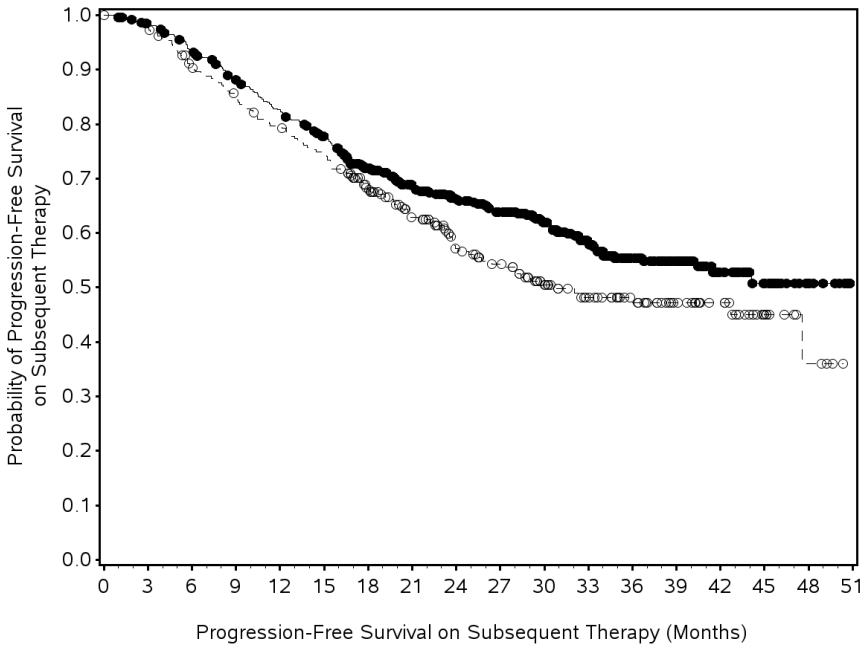
Placebo (events: 154/262), median and 95% CI: 16.62 (11.37, 24.87)

Nivolumab vs. Placebo - hazard ratio and 95% CI: 0.71 (0.58, 0.87)

PFS2

Based on the 18-Feb-2021 DBL, there were a total of 323 (40.7%) PFS2 events.

Figure 25: Kaplan-Meier Plot of Progression-Free Survival on Subsequent Systemic Therapy per Investigator - All Randomized Subjects (18-Feb-2021 DBL)



Number of Subjects at Risk

Nivolumab	532	517	488	453	424	391	335	276	248	222	180	145	102	72	45	23	10	0
Placebo	262	255	231	215	201	188	157	131	104	92	73	59	46	34	25	11	4	0

Nivolumab (events: 203/532), median and 95% CI: N.A. (36.63, N.A.)

Placebo (events: 120/262), median and 95% CI: 30.72 (24.15, N.A.)

Nivolumab vs. Placebo - hazard ratio and 95% CI: 0.77 (0.61, 0.96)

Summary of main study(ies)

The following table summarises 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).

Summary of Efficacy for trial CA209577

Title: Phase 3, randomized, double-blind, placebo-controlled study of adjuvant nivolumab in subjects with resected oesophageal cancer (OC) or gastro-oesophageal junction cancer (GEJC) who have received chemoradiotherapy (CRT) followed by surgery.	
Study identifier	CA209577 (CheckMate 577)
Design	Randomized, double-blind, placebo-controlled (adjuvant setting). Subjects (males or females ≥18 years) had Stage 2 or Stage 3 (per AJCC 7th edition) EC or GEJC (histologically confirmed [SCC or AC]) at the time of initial diagnosis. Subjects were required to complete pre operative (neoadjuvant) CRT followed by surgery prior to randomization. Subjects had to have complete resection (R0) and residual pathologic disease (i.e., non-pathologic complete response [non-pCR]) of their EC or GEJC with at least ypN1 or ypT1 listed in the pathology report of the resected specimens. Subjects were required to have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

	Duration of enrollment:		approximately 37 months from Jul-2016 to Aug-2019
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Objective	To compare DFS of nivolumab vs. placebo in subjects with resected OC or GEJC.		
Treatments groups	Nivolumab		Nivolumab 240 mg IV Q2W for 16 weeks (Cycles 1-8) followed by nivolumab 480 mg IV over 30 minutes Q4W beginning at Week 17 (2 weeks after the 8th dose) [Cycles 9 17] for a total duration of 1 year
	Placebo		30 min infusion, same duration
Endpoints and definitions	Primary endpoint	DFS	The time between randomization date and first date of recurrence or death, whichever occurred first.
	Secondary endpoint	OS	The time from randomization to the date of death from any cause.
	Exploratory endpoint	DMFS	The time between the date of randomization and the date of first distant recurrence or date of death (whatever the cause), whichever occurs first
	Exploratory endpoint	PFS2	The time from randomization to objectively documented progression, per investigator assessment, on the next systemic therapy or to death from any cause, whichever occurs first.
Database lock	03-Jul-2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All randomized subjects (N=794) – IA at 90% of the total planned events (396/440) Clinical cut-off date: 12-May-2020 Minimum follow-up: 6.2 months Median follow-up time was 24.4 months (range: 6.2 to 44.9 months)		
Descriptive statistics and estimate variability / Effect estimate per comparison	Treatment group	**Nivolumab**	**Placebo**
	Number of subject	**532**	**262**
	DFS (per investigator) (primary endpoint)		
	DFS Events, n (%)	241 (45.3)	155 (59.2)
	Median DFS (95% CI) months	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)
	HR (96.4% CI)	0.69 (0.56, 0.86)	
	6-month DFS rates (95% CI), %	72.3 (68.2, 76.0)	63.4 (57.2, 69.0)
	DMFS (exploratory endpoint)		
	DMFS Events, n (%)	218 (41.0)	134 (51.1)

	Median DFS (95% CI) months	28.32 (21.26, N.A.)	17.61 (12.45, 25.40)
	HR (95% CI)	0.74 (0.60, 0.92)	
	6-month DMFS rates (95% CI), %	78.1 (74.3, 81.5)	71.1 (65.1, 76.2)
	PFS2 (exploratory endpoint)		
	PFS2 Events, n (%)	163 (30.6)	100 (38.2)
	Median PFS2 (95% CI) months	N.A. (34.00, N.A.)	32.07 (24.15, N.A.)
	HR (95% CI)	0.77 (0.60, 0.99)	
Database lock	18-Feb-2021		
Results and Analysis			
Analysis description	**Ad-hoc Analysis**		
Analysis population and time point description	All randomized subjects (N=794) – ad-hoc descriptive efficacy analysis Clinical cut-off date: 04-Jan-2021 Minimum follow-up: 14 months Median follow-up time was 32.2 months (range: 14.0 to 52.7 months)		
Descriptive statistics and estimate variability / Effect estimate per comparison	Treatment group	**Nivolumab**	**Placebo**
	Number of subject	**532**	**262**
	DFS (per investigator) (primary endpoint)		
	DFS Events, n (%)	268 (50.4)	171 (65.3)
	Median DFS (95% CI) months	22.41 (16.95, 33.64)	10.35 (8.31, 13.93)
	HR (95% CI)	0.67 (0.55, 0.81)	
	12-month DFS rates (95% CI), %	61.8 (57.4, 65.8)	45.5 (39.3, 51.4)
	DMFS (exploratory endpoint)		
	DMFS Events, n (%)	253 (47.6)	154 (58.8)
	Median DFS (95% CI) months	29.37 (23.66, 36.63)	16.62 (11.37, 24.87)
	HR (95% CI)	0.71 (0.58, 0.87)	
	12-month DMFS rates (95% CI), %	68.4 (64.1, 72.2)	55.8 (49.5, 61.7)
	PFS2 (exploratory endpoint)		
	PFS2 Events, n (%)	203 (38.2)	120 (45.8)
	Median PFS2 (95% CI) months	N.A. (36.63, N.A.)	30.72 (24.15, N.A.)
	HR (95% CI)	0.77 (0.61, 0.96)	
	12-month PFS2 rates (95% CI), %	82.7 (79.1, 85.6)	79.7 (74.2, 84.1)

55.8 (49

Clinical studies in special populations

No specific studies have been performed in special populations. Patients ≥65 years old comprised 36.15% of the overall population. The table below shows the DFS results for the elderly population:

	Age ≥65 and <75		Age ≥75	
	Nivolumab	**Placebo**	**Nivolumab**	**Placebo**
N subjects/overall	175/245	70/245	24/42	18/42
N events (N subjects)	81 (175)	46 (70)	15 (24)	8 (18)
mDFS (95% CI) months	19.65 (11.70, NA)	11.14 (5.55, 17.84)	11.33 (3.45, 29.73)	22.80 (9.23, 27.04)
Unstratified HR (95% CI)	0.68 (0.47, 0.98)		1.64 (0.68, 3.91)	

Supportive study(ies)

Not applicable

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The randomised, double blind, placebo-controlled design of study CA209577 is considered adequate to evaluate the efficacy and safety of nivolumab in patients with oesophageal cancer (EC) or gastroesophageal junction cancer (GEJC) who have residual pathologic disease following (neoadjuvant) chemoradiotherapy and surgery (complete resection). In this disease setting there is no established standard of care and therefore the use of placebo as control is acceptable. Subjects randomized to the nivolumab treatment arm received nivolumab 240 mg intravenous (IV) infusion over 30 minutes every 2 weeks (Q2W) for 16 weeks (Cycles 1-8) followed by nivolumab 480 mg IV infusion over 30 minutes every 4 weeks (Q4W) beginning at Week 17 (2 weeks after the 8th dose) [Cycles 9-17] for a total duration of 1 year. Subjects randomized to the placebo arm received placebo IV infusion over 30 minutes with the same dosing schedule as nivolumab. It is noted that the infusion time for the 480 mg dose has been modified compared to the previously authorized for other indications (60 min). Although a sound justification for the selected treatment duration of one year in study CA209577 has not been provided, the approach proposed by the MAH can be considered acceptable and in line with that used in other adjuvant trials/settings such as melanoma (CA209238) and muscle invasive urothelial carcinoma (CA209274), although the latter is currently under review (EMEA/H/C/003985/II/0100).

The inclusion and exclusion criteria for study CA209577 are overall, acceptable. The enrolment of patients with resected grade II-III OC/GEJC who received CRT followed by surgery and still had residual pathologic disease is reflective of the applied indication and therefore considered acceptable. The study included patients with both adenocarcinoma and squamous cell histology which is considered reasonable bearing in mind the difficulties to conduct histology-specific trials. According to ESMO guidelines, both CRT and perioperative chemotherapy are considered standard for locally advanced adenocarcinoma tumours and there is not enough evidence to make a stronger recommendation of one regimen over the other option. Study CA209577 only included patients who had undergone surgery

after CRT and therefore, adenocarcinoma patients who receive perioperative chemotherapy as neoadjuvant regimen fall out of the scope of this indication, as already reflected in the PI. This requirement did however not impact the enrolment of adenocarcinoma patients in the study, i.e. 70.9% of participants presented this histology and were adequately balanced between arms (histology was a stratification factor). Recruitment was slow in the study which could have been caused by the difficulty to enrol subjects with ECOG PS 0-1, following the major surgery for complete resection, during the protocol-required window from surgery to randomization of 4 to 14 weeks (extended to up to 16 weeks in the revised protocol 02). Information about this time window is included in section 5.1 of the SmPC, see PI.

Overall, the primary and secondary endpoints are endorsed and in line with EMA guidelines (i.e. *Guideline on the evaluation of anticancer medicinal products in man* - EMA/CHMP/205/95 Rev.5). DFS is recognised as an acceptable primary endpoint in the adjuvant setting, as long as there is no detrimental effect observed for OS. No OS data were however submitted within the initial application, see comments below. In the adjuvant setting, the ultimate aim is to increase cure rate. However, to support an increase in the fraction of cured patients, DFS data with longer follow-up would be needed (beyond 36 months).

OS was changed from a dual primary endpoint to the first secondary endpoint, to be tested hierarchically. The CHMP noted, at the time when scientific advice was sought, that the change in the primary endpoint could be acceptable but advised against the first IA due to expected immature OS data at that time. At the time when the primary endpoint was changed, PFS2 was included as an additional exploratory endpoint, per EMA guidance. The study design includes OS and 1, 2 and 3-years survival rates as secondary endpoints. However, no data on OS data have been formally submitted within this application. Assessments for recurrence were planned to occur every 12 weeks between months 12 and 24, and then every 6 to 12 months between years 3 and 5. They could be done by imaging or biopsy. Criteria for recurrence by imaging are not mentioned. No (blinded) central evaluation of imaging was performed, which can be questioned even if the trial is double blind.

The stratification factors used (i.e. histology, pathologic lymph node status and tumour cell PD-L1 status) are acceptable, as they are documented prognostic factors for this kind of tumours. Analyses were performed in accordance to the SAP version 3.0 (approved 8-May-2020). SAP version 4.0 (6-Oct-2020) has been submitted, where the formula for the nivolumab relative dose intensity was corrected, considered to over-estimate its value in v 3.0.

At the time of the DFS IA, the OS data were not mature (49.6% of total OS events were observed vs. 65.0% planned OS events), and did not meet the pre-specified boundary for declaring the statistical significance of $p = 0.003$, so the OS efficacy results were not released to the sponsor by the DMC and no data were available within the initial submission.

The assumptions and operating characteristics of the sample size estimation are well described.

Major changes to the protocol (Revised Protocol 03) were made on 06-Jun-2019 when 700 subjects had been randomized at the time of this revision: DFS became the single primary endpoint in the study, and OS a secondary endpoint, to be tested hierarchically; PFS2 was added as exploratory endpoint; due to slow enrolment, the duration of enrolment was re-projected twice (revised protocol 02 and 03) from 15 to 36 months and, as consequence of the unexpected good results of CRT+ surgery arm in the CROSS LT trial, according to which the median DFS and OS in the placebo arm should be longer than the original assumption requiring the study to be modified to be adequately powered. The above changes, justified on the basis of external data, were already accepted at the time when scientific advice was sought from SAWP/CHMP and FDA.

Regarding protocol deviations, there were 8 classified as "process of diagnosis (CT/MRI and biopsy) of tumour recurrence was not followed". This was later corrected by the investigators and 5 were no longer considered to have a protocol deviation as their recurrences were diagnosed by PET (imaging method not originally included in the protocol) and this was considered a valid clinical diagnosis. All data were included in the analyses and no impact on the data integrity or on the interpretation of the results is expected.

Efficacy data and additional analyses

In total, 794 patients were randomized to receive either nivolumab (n = 532) or placebo (n = 262). Two patients from the placebo group were never treated. At the time of the data cut-off (12-May-2020), 50 patients were still on treatment: 31 (5.8%) in the nivolumab arm and 19 (7.3%) in the placebo arm. The main reasons for discontinuation were study treatment completion, 43% and 38.1% respectively, and disease recurrence (28% nivolumab and 43.5% placebo). There were 30 (5.6%) and 5 (1.9%) subjects, respectively, who requested to discontinue study treatment and 12 (2.3%) and 4 (1.5%) subjects who withdrew consent. These proportions were higher in the nivolumab treatment arm, along with discontinuations due to drug toxicity. At the time of the 18-Feb-2021 DBL, all subjects were off treatment and had completed the 100 days follow up period.

Median age was 62 years. Patients older than 65 years were well represented as they were 37.4% in the nivolumab arm and 33.6% in the placebo arm; however, only 4.5% and 6.9%, respectively, were ≥75 years, as widely observed in other immunotherapy studies. Most of the subjects were male (84.5%) and white (81.6%). By geographic location, 38.2% of subjects were from Europe and 32.1% from US/Canada, and this was well balanced between treatment arms. Baseline disease characteristics were, reasonably, well balanced between groups, but there were some exceptions. Proportion of patients with Stage II disease at initial diagnosis was slightly higher in the placebo arm (33.6% vs. 37.8%) so, stage III patients were 66% in the nivolumab arm and 62.2% in the placebo treatment arm, this could have been translated in a better prognosis for the placebo group subjects, although the difference between arms is considered small. Baseline tumour cell PD-L1 expression was an additional stratification factor. For the 1% cut-off point, subjects with <1% baseline tumour cell expression were 70.3% in the nivolumab arm and 74.8% in the placebo arm, subjects with ≥1% expression were balanced between both arms (16.7% vs. 15.3%) and there were also 13% of indeterminate/ non-evaluable subjects in the nivolumab group and 9.9% in the placebo group. Efficacy by PD-L1 expression was an exploratory objective and is described below.

The primary efficacy endpoint was DFS, assessed by the investigator. At the IA, with 396 DFS events (90% of the total number planned), 241 (45.3%) in the nivolumab arm and 155 (59.2%) in the placebo arm, a statistically significant improvement in DFS was reported: HR = 0.69 (96.4% CI: 0.56, 0.86), stratified 2-sided log-rank p value = 0.0003; significance level = 0.036. Median DFS was 22.41 (95% CI, 16.62-34) months for nivolumab and 11.04 (95%CI, 8.34-14.32) months for placebo. These data represent the final analysis for DFS. At that time the minimum follow-up time was 6.2 months and the median follow-up time was 24.4 months (range: 6.2 to 44.9 months). Fifty one percent of patients at that time had 2 years follow-up. There were 10 deviations due to "complete resection performed out of time window or did not have negative margins" and 6 classified as "subjects had a primary malignancy active within previous 3 years, was not disease free at study entry, or had a cancer type that did not meet inclusion criteria". An ad-hoc sensitivity analysis of DFS, excluding these 16 subjects, was performed and the results were consistent with the primary DFS analysis.

Different sensitivity analyses were performed for the primary endpoint which seemed to confirm the primary efficacy analysis results. Of note, the primary analysis of DFS included censoring for new anti-cancer treatment which is not in line with the EMA anticancer guideline (EMA/CHMP/205/95 Rev.5). A sensitivity analysis was performed for DFS without censoring for new anti-cancer treatment and

results, per both definitions, were consistent. This fact is reassuring and has been reflected in section 5.1 of the SmPC.

An updated ad-hoc descriptive efficacy analysis of DFS, DMFS and PFS2 in all randomized subjects (n=794) was provided (DBL 18-Feb-2021), with a minimum follow-up of 14 months and a median follow-up of 32.2 months, providing almost 8 additional months of follow-up for the included subjects. Based on the updated results, DFS HR for nivolumab vs placebo was 0.67 (95% CI: 0.55, 0.81). Median DFS was 22.41 (95% CI: 16.95, 33.64) months for nivolumab and 10.35 (95% CI: 8.31, 13.93) months for the placebo arm, i.e. consistent with the results reported in the previous DBL. Sensitivity analysis for DFS, accounting for assessments on/after subsequent therapy, was repeated and results were consistent with the previous ones and also with the updated results for DFS according to the new DBL.

DFS benefit was also reported in the pre-specified subgroups but with some limitations. Regarding histology, a HR=0.61 (95% CI: 0.42-0.88) was observed for squamous cell carcinoma (n=230) while the benefit was lower for adenocarcinoma (n=563), HR=0.75 (95% CI, 0.59-0.96). Based on the updated data, HR was 0.60 (95% CI: 0.42, 0.86) for SCC and 0.73 (95% CI: 0.58, 0.91) for adenocarcinoma, respectively. By pathologic lymph node status: positive (≥ ypN1) HR = 0.67 (95% CI: 0.53- 0.86) and negative (ypN0) HR = 0.74 (95% CI: 0.51- 1.06). The results for the updated analysis were consistent, i.e. HR = 0.65 (95% CI: 0.52, 0.83) and HR = 0.71 (95% CI: 0.51, 1.00), respectively. Patients with higher risk, based on positive lymph nodes, seem to derive higher benefit from adjuvant treatment with nivolumab. Improvements in DFS were overall consistently observed in other predefined subsets except for patients ≥75 years, in whom the effect of nivolumab in DFS is unclear and would appear as detrimental, HR=1.64 (95%, 0.68-3.91). However the data in this subgroup with only 42 subjects (24 in the nivolumab arm and 18 in the placebo arm), are too limited to draw conclusions (see section 5.1 of the SmPC).

As an exploratory objective, efficacy by tumour cell PD-L1 status was also assessed, to evaluate whether tumour cell PD-L1 status is a predictive biomarker for DFS and OS in subjects with resected OC or GEJC. The cut-off for stratification at the time of randomization was 1%. Tumour PD-L1 expression levels were balanced between the two treatment groups (nivolumab vs. placebo) at each of the predefined tumour PD-L1 expression levels. The following results were reported: PD-L1 ≥1% (HR = 0.75; 95% CI: 0.45, 1.24, n=129), PD-L1 <1% (HR = 0.73, 95% CI: 0.57, 0.92, n=570) [and indeterminate/non-evaluable tumour cell PD-L1 (HR = 0.54, 95% CI: 0.27, 1.05, n=95)]. With higher PD-L1 expression cut-offs, improved HR for DFS were observed, i.e. HR = 0.60 (95% CI: 0.33, 1.10) in PD-L1 ≥ 5% and HR = 0.51 (95% CI: 0.27, 0.99) in PD-L1 ≥ 10%. HRs for DFS corresponding to the DBL 18-Feb-2021 were similar between the tumour cell PD-L1 <1% [n = 567; HR = 0.70 (95% CI: 0.56, 0.87)] and ≥1% [n = 129; HR = 0.68 (95% CI: 0.42, 1.10) subgroups. Regarding the results with 5% and 10% cut-offs, results appear in favour of nivolumab in all subgroups, with an apparent higher benefit in patients with higher PD-L1 expression. For the 5% cut-off: HR=0.56 (95% CI: 0.31, 0.99) for ≥5% (n=88) and HR=0.72 (95% CI: 0.58, 0.89) for <5% (n=608). For the 10% cut-off: HR=0.46 (95% CI: 0.25, 0.86) for ≥10% (n=71) and HR=0.73 (95% CI: 0.59, 0.91) for <10% (n=625).

PD-L1 expression in GC and OC has been associated with depth of muscle invasion, tumour size, and lymph node metastasis and it appears that OS (and DFS) of patients with PD-L1 (or PD-L2) positive tumours tends to be worse than in those with PD-L1 non expressing tumours, indicating that PD-L1 positive tumours may have a poor prognosis. This appears in line with the reported results according to different PD-L1 expression cut-offs, acknowledging the limitations of the proposed comparison/interpretation based on data from subgroup analyses. Efficacy by PD-L1 expression assessed in tumour cells by IHC, PD-L1 by combined positive score (CPS), microsatellite instability

(MSI), tumour mutational burden (TMB), somatic mutations of selected genes, and inflammatory gene expression signature (GES) was investigated and available results were submitted. DFS was assessed in all the resulting subgroups and, although these are exploratory analyses and the study was not powered to reach any conclusions, benefit for nivolumab is observed for almost all of them. Some of the observed differences could likely be explained by unbalanced distribution of patients in terms of both patient and disease baseline characteristics.

Exploratory endpoints included distant metastasis free survival (DMFS), which was longer in the nivolumab arm compared with the placebo arm, 28.32 (21.26, N.A.) vs. 17.61 (12.45, 25.40) months, with a HR of 0.74 (95% CI: 0.60, 0.92), and PFS after subsequent systemic therapy (PFS2), where median PFS2 (assessed by the investigator) was not reached for the nivolumab arm and it was 32 (95% CI: 24.15, N.A.) months in the placebo arm; HR=0.77 (95% CI: 0.60, 0.99). These results are considered to give support to the primary efficacy analysis results. Based on the later DBL (18-Feb-2021), DMFS HR for nivolumab vs placebo was 0.71 (95% CI: 0.58, 0.87) and PFS2 HR was the same as previously reported in the primary analysis, HR = 0.77 (95% CI: 0.61, 0.96) with median PFS2 not reached for nivolumab and of 30.72 months in the placebo arm.

To evaluate the maturity of DFS in relation to the extent of follow-up, the MAH conducted post-hoc analyses for the subset of randomized subjects with 1-year and 2-year minimum follow-up. At the time of DFS IA, 683/794 (86.0%) randomized subjects had 1-year minimum follow-up and 406/794 (51.1%) subjects had 2-year minimum follow-up. Treatment effect (DFS HRs using un-stratified Cox model) seemed consistent between these different subgroups: 1-year minimum follow-up HR = 0.71 (95% CI: 0.57, 0.87) and 2-year minimum follow-up HR = 0.70 (95% CI: 0.53, 0.92). Based on the results from the latest DBL (Feb-2021), DFS was assessed for the subsets of patients with a 2-year and 2.5-year minimum follow-up. Among the 794 randomized subjects, 596 (75.1%) randomized subjects had a 2-year minimum follow-up, and 453 (57.1%) subjects had 2.5-year minimum follow-up. HR of nivolumab vs. placebo for both subsets of patients was 0.67 and, considering that more than half of the included subjects had more than 2.5 years of follow-up, DFS results seem to be mature enough to confirm the beneficial effect of nivolumab in the intended adjuvant setting.

The statistically significant improvement in DFS reported in study CA209577, with a median follow up of 24.4 months and more than 50% event rate in the placebo group, can be considered indicative of clinical benefit in the intended adjuvant setting also bearing in mind the short post-recurrence survival observed in the placebo arm; i.e. median DFS of 11.04 (95% CI: 8.34, 14.32) months. Results were indeed considered encouraging and an update of the DFS and DMFS results with longer follow-up, a summary of DFS event rates per three months for each study arm, separately, and updated PFS2 data were requested. Updated results for DFS and DMFS have been included above. DFS event rates, up to 48 months, seem to confirm the beneficial effect of nivolumab.

Regarding PFS2 results, only 27% of the study population had been treated with subsequent systemic therapy for relapsed disease at the initial DBL which is indicative of the relatively short follow-up time and prevents clear interpretation of PFS2 data and its value. The MAH provided updated data on subsequent systemic anti-cancer therapies based on the latest DBL (18-Feb-2021). At that time 255 (32.1%) subjects had received subsequent systemic therapy, which means a 5% increase in the number of patients receiving subsequent systemic therapy observed with additional 7-8 months of follow-up, 154 (28.9%) in the nivolumab arm and 101 (38.5%) in the placebo arm. Thirty-three (4.2%) subjects had received subsequent immunotherapy, 37 (4.7%) had received targeted therapy and 248 (31.2%) subjects had received other systemic therapy or chemotherapy. Per treatment line, 163 (20.5%) had received 1 subsequent line of treatment, 55 subjects (6.8%) 2 lines, 28 (3.5%) had received 3 subsequent treatment lines and 10 (1.3%) had received 4 or more subsequent lines. The reported updated PFS2 results, along with the number of subsequent treatment lines received, appear

to indicate that no lack of efficacy of further treatments is expected for patients who have received nivolumab in the adjuvant setting. Even if study CA209577 was double-blind, quality of life endpoints were included as exploratory (not alpha protected) and only descriptive analyses were conducted.

No data from the 49.6% OS events having accumulated at the July 2020 DBL (IA1) were provided in the initial submission, as the pre-specified boundary for declaring the statistical significance of p = 0.003 was not met. However, in view of the expected relatively short post recurrence survival time, and the known safety profile of nivolumab, a detrimental effect on OS is considered very unlikely and the provided updated DFS results are considered sufficient to support clinical benefit in the intended treatment setting. This having said, results of the planned second IA (planned at approximately 80% (~368) of OS events) and of the final analysis for OS will be provided, when available, to confirm DFS results. Both OS analyses and their due date have been included in the PI, as an annex 2 condition (PAES), and the results will be assessed when available.–

A slight rewording of the applied indication was proposed (the reference to resected cancer was removed), in order to provide clarity and in alignment with EMA guidance (EMA/CHMP/483022/2019) and already approved indications in the adjuvant setting. The proposed change has been implemented.

2.4.4. Conclusions on the clinical efficacy

In study CA209577 a statistically significant gain in DFS was shown for nivolumab as compared to placebo when given as adjuvant treatment in adult patients with grade II-III oesophageal or gastroesophageal junction cancer who had residual pathologic disease following prior neoadjuvant chemoradiotherapy and complete resection.

The observed improvement in DFS for nivolumab over placebo from a pre-planned IA, is consistent across most pre-defined subgroups including histology, lymph node status and PD-L1 tumour cell expression and results are supported by exploratory endpoints, e.g. DMFS and PFS2. Sensitivity analyses also confirmed the results from the primary efficacy analysis. Updated efficacy data (i.e. DFS, DMFS and PFS2) with a longer follow-up remained consistent with the primary analysis. No data on OS were however formally submitted during the procedure. Even if this constitutes a limitation in the context of an adjuvant treatment being proposed, in view of the expected relatively short post recurrence survival time, and the known safety profile of nivolumab, a detrimental effect on OS is considered very unlikely and the provided updated DFS results and additional analyses are considered sufficient to support clinical benefit in the intended treatment setting. Results of the planned second IA (planned at approximately 80% (~368) of OS events) and final analysis for OS should however be provided when available, as an annex 2 condition, to confirm DFS results.

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

Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer, the MAH should submit the OS data from the second interim analysis and the final OS analysis of the Phase III study CA209577 by 30 September 2024.

2.5. Clinical safety

Introduction

Safety data to support the use of adjuvant nivolumab in subjects with oesophageal cancer (EC), or gastroesophageal junction cancer (GEJC) who have received neoadjuvant chemoradiotherapy (CRT) followed by surgery is based on the results of Pivotal Study CA209577 (CheckMate 577).

This is a phase 3, multicenter, randomized, double-blind study of adjuvant nivolumab or placebo in subjects with resected esophageal, or gastroesophageal junction cancer. Subjects were randomized 2:1 between adjuvant nivolumab (nivolumab arm) and placebo (placebo arm). Randomization was stratified by: tumour cell PD-L1 status (≥1% vs. <1% indeterminate or non-evaluable), pathologic lymph node status (positive ≥ypN1 vs. negative ypN0) and histology (squamous vs. adenocarcinoma).

Patients in the nivolumab arm were to receive nivolumab 240 mg intravenous (IV) infusion over 30 minutes every 2 weeks (Q2W) for 16 weeks (Cycles 1-8) followed by nivolumab 480 mg IV infusion over 30 minutes every 4 weeks (Q4W) beginning at Week 17 (2 weeks after the 8th dose) (Cycles 9-17) for up to one year or, until disease recurrence or unacceptable toxicity, whichever occurred first.

Safety Analysis Set (SAS) consists of all randomized subjects who received, at least, one dose of any study treatment (N=792), 532 subjects in the nivolumab arm and 260 in the placebo treatment arm.

Patient exposure

CA209577 study was conducted at 170 sites in 29 countries. The last subject was randomized on 07-Nov-2019, the clinical cut-off occurred on 12 May 2020 (LPLV), and the DBL occurred on 03-Jul-2020.

At the time of the DBL, 755 (95.3%) subjects were continuing in the study, 50 (6.3%) subjects were still on treatment: 31 (5.8%) subjects in the nivolumab arm and 19 (7.3%) subjects in the placebo arm. The overall rates of discontinuation during the treatment period were 94.2% and 92.7% in the nivolumab and placebo arms, respectively (Table 15).

The most common reasons for not continuing in the treatment period were study treatment completion (41.4% overall; 43.0% with nivolumab and 38.1% with placebo), disease recurrence (33.1% overall; 28.0% with nivolumab and 43.5% with placebo), and study drug toxicity (8.2% overall; 10.7% with nivolumab and 3.1% with placebo). Overall, 18 (2.3%) subjects withdrew consent and did not complete the treatment period.

Table 15: Subject Disposition - All Enrolled, Randomized, and Treated Subjects

	Nivolumab	Placebo	Total
SUBJECTS ENROLLED			1085
SUBJECTS RANDOMIZED	532	262	794
SUBJECTS TREATED (%) (A)	532 (100.0)	260 (99.2)	792 (99.7)
SUBJECTS NOT TREATED (%) (A)	0	2 (0.8)	2 (0.3)
REASON FOR NOT BEING TREATED (%) (A)			
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	0	1 (0.4)	1 (0.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.4)	1 (0.1)
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%) (B)	31 (5.8)	19 (7.3)	50 (6.3)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%) (B)	501 (94.2)	241 (92.7)	742 (93.7)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%) (B)			

	Nivolumab	Placebo	Total
COMPLETED TREATMENT	229 (43.0)	99 (38.1)	328 (41.4)
DISEASE RECURRENCE	149 (28.0)	113 (43.5)	262 (33.1)
STUDY DRUG TOXICITY	57 (10.7)	8 (3.1)	65 (8.2)
DEATH	1 (0.2)	0	1 (0.1)
ADVERSE EVENT UNRELATED TO STUDY DRUG	15 (2.8)	9 (3.5)	24 (3.0)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	30 (5.6)	5 (1.9)	35 (4.4)
SUBJECT WITHDREW CONSENT	12 (2.3)	4 (1.5)	16 (2.0)
LOST TO FOLLOW-UP	0	1 (0.4)	1 (0.1)
POOR/NON-COMPLIANCE	1 (0.2)	0	1 (0.1)
OTHER	7 (1.3)	2 (0.8)	9 (1.1)
CONTINUING IN THE STUDY (C) (D)	507 (95.3)	248 (95.4)	755 (95.3)
NOT CONTINUING IN THE STUDY (C)	25 (4.7)	12 (4.6)	37 (4.7)
REASON FOR NOT CONTINUING IN THE STUDY			
DEATH	8 (1.5)	4 (1.5)	12 (1.5)
SUBJECT WITHDREW CONSENT	13 (2.4)	5 (1.9)	18 (2.3)
LOST TO FOLLOW-UP	3 (0.6)	2 (0.8)	5 (0.6)
OTHER	1 (0.2)	1 (0.4)	2 (0.3)

(A) Percentages based on subjects randomized
(B) Percentages based on subjects that were treated
(C) Subject status at end of treatment
(D) Includes subjects still on treatment and subjects off treatment continuing in the follow-up period
Source: Table 5.1-1 of the CA209577 Primary CSR

Up to the clinical cut-off date, the minimum and median follow-up was 6.2 months and 24.4 months, respectively. The median number of nivolumab doses received was 15, and the median number of placebo doses received was 14. The descriptive median duration of study therapy was 10.14 and 8.99 months in the nivolumab and placebo arms, respectively. The proportion of subjects in the nivolumab and placebo arms with more than 6 months of therapy was 61.1% and 61.5%, respectively. The proportion of subjects in the nivolumab and placebo arms with more than 9 months of therapy was 54.3% and 50.0%, respectively (Table 16).

Table 16: Cumulative Dose and Relative Dose Intensity Summary - All Treated Subjects

	Number of Subjects (%)	
	Nivolumab N = 532	Placebo N = 260
NUMBER OF DOSES RECEIVED		
MEAN (SD)	12.2 (5.4)	12.4 (4.8)
MEDIAN (MIN - MAX)	15.0 (1 - 17)	14.0 (1 - 18)
CUMULATIVE DOSE (MG)		
MEAN (SD)	4167.7 (2239.2)	N.A.
MEDIAN (MIN - MAX)	5280.0 (240 - 6240)	N.A.
RELATIVE DOSE INTENSITY (%)		
>= 110%	1 (0.2)	N.A.
90% TO < 110%	458 (86.1)	N.A.
70% TO < 90%	67 (12.6)	N.A.
50% TO < 70%	4 (0.8)	N.A.
< 50%	2 (0.4)	N.A.

Table 317: Duration of Study Therapy Summary - All Treated Subjects

	Nivolumab N = 532	Placebo N = 260	Total N = 792
DURATION OF THERAPY (MONTHS)			
MEAN (MIN, MAX)	7.58 (<0.1, 14.2)	7.64 (<0.1, 15.0)	7.60 (<0.1, 15.0)
MEDIAN	10.14	8.99	9.46
> 3 MONTHS (%)	392 (73.7)	208 (80.0)	600 (75.8)
> 6 MONTHS (%)	325 (61.1)	160 (61.5)	485 (61.2)
> 9 MONTHS (%)	289 (54.3)	130 (50.0)	419 (52.9)
> 12 MONTHS (%)	24 (4.5)	8 (3.1)	32 (4.0)

Adverse events

The overall frequencies of all-causality any-grade AEs and Grade 3-4 AEs were similar between the nivolumab and placebo arms. However, the overall frequencies of drug-related any grade AEs and Grade 3-4 AEs were higher with nivolumab compared with placebo (Table 17).

Common adverse events

Any-grade all-causality AEs were reported in 510 (95.9%) subjects in the nivolumab arm and 243 (93.5%) subjects in the placebo arm (Table 18). The most frequently reported all-causality AEs were:

- Nivolumab: diarrhoea (29.1%), fatigue (27.1%), nausea (22.7%), cough (18.4%), and vomiting (15.0%).
- Placebo: diarrhoea (29.2%), fatigue (24.2%), nausea (21.2%), cough (18.5%), dysphagia (16.5%), and vomiting (16.2%).

Grade 3-4 all-causality AEs were reported in 183 (34.4%) subjects in the nivolumab arm, and 84 (32.3%) subjects in the placebo arm (Table 18). The most frequently reported Grade 3-4 AEs were:

- Nivolumab: pneumonia (2.6%), amylase increased (2.3%), fatigue (1.3%), and aspartate aminotransferase increased, alanine aminotransferase increased, and hypertension (1.1% each).
- Placebo: dysphagia (3.5%), pneumonia (1.5%), and vomiting, abdominal pain, fatigue, and hypertension (1.2% each).

Table 18: Adverse Events by Worst CTC Grade in ≥ 10% of All Treated Subjects

	Nivolumab N = 532			Placebo N = 260		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	510 (95.9)	183 (34.4)	9 (1.7)	243 (93.5)	84 (32.3)	6 (2.3)
Gastrointestinal disorders	352 (66.2)	43 (8.1)	0	178 (68.5)	33 (12.7)	0
Diarrhoea	155 (29.1)	5 (0.9)	0	76 (29.2)	2 (0.8)	0
Nausea	121 (22.7)	4 (0.8)	0	55 (21.2)	0	0
Vomiting	80 (15.0)	3 (0.6)	0	42 (16.2)	3 (1.2)	0
Dysphagia	69 (13.0)	4 (0.8)	0	43 (16.5)	9 (3.5)	0
Abdominal pain	62 (11.7)	3 (0.6)	0	37 (14.2)	3 (1.2)	0
Constipation	61 (11.5)	0	0	32 (12.3)	0	0
Gastrooesophageal reflux disease	41 (7.7)	1 (0.2)	0	34 (13.1)	0	0
General disorders and administration site conditions	242 (45.5)	12 (2.3)	0	103 (39.6)	7 (2.7)	0
Fatigue	144 (27.1)	7 (1.3)	0	63 (24.2)	3 (1.2)	0
Respiratory, thoracic and mediastinal disorders	217 (40.8)	23 (4.3)	1 (0.2)	96 (36.9)	8 (3.1)	1 (0.4)
Cough	98 (18.4)	1 (0.2)	0	48 (18.5)	1 (0.4)	0
Dyspnoea	54 (10.2)	3 (0.6)	0	27 (10.4)	1 (0.4)	0
Skin and subcutaneous tissue disorders	202 (38.0)	8 (1.5)	0	63 (24.2)	1 (0.4)	0
Pruritus	68 (12.8)	2 (0.4)	0	16 (6.2)	0	0
Rash	63 (11.8)	4 (0.8)	0	17 (6.5)	1 (0.4)	0
Investigations	195 (36.7)	42 (7.9)	0	74 (28.5)	11 (4.2)	0
Weight decreased	69 (13.0)	2 (0.4)	0	23 (8.8)	0	0
Musculoskeletal and connective tissue disorders	156 (29.3)	6 (1.1)	0	80 (30.8)	3 (1.2)	0
Arthralgia	53 (10.0)	1 (0.2)	0	21 (8.1)	0	0
Metabolism and nutrition disorders	148 (27.8)	23 (4.3)	0	63 (24.2)	9 (3.5)	0
Decreased appetite	79 (14.8)	5 (0.9)	0	26 (10.0)	2 (0.8)	0
Nervous system disorders	122 (22.9)	14 (2.6)	1 (0.2)	66 (25.4)	2 (0.8)	0
Headache	41 (7.7)	1 (0.2)	0	29 (11.2)	0	0
Endocrine disorders	91 (17.1)	3 (0.6)	0	8 (3.1)	1 (0.4)	0
Hypothyroidism	56 (10.5)	0	0	4 (1.5)	0	0

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

Source: Table 8.5-1 of the CA209577 Primary CSR

Drug-related adverse events

Any-grade drug-related AEs were reported in 376 (70.7%) subjects in the nivolumab arm and 119 (45.8%) subjects in the placebo arm (Table 18). The most frequently reported drug-related AEs were:

- Nivolumab: fatigue (16.9%), diarrhoea (16.5%), and pruritus (10.0%).
- Placebo: diarrhoea (15.0%) and fatigue (11.2%).

Grade 3-4 drug-related AEs were reported in 71 (13.3%) subjects in the nivolumab arm and 15 (5.8%) subjects in the chemotherapy arm (Table 19). The most frequently reported Grade 3-4 drug-related AEs were:

- Nivolumab: amylase increased (1.7%), lipase increased (1.3%), and fatigue (1.1%).
- Placebo: diarrhoea, alanine aminotransferase increased, and lipase increased (0.8% each).

Table 19: Drug-Related Adverse Events by Worst CTC Grade in ≥ 5% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab N = 532			Placebo N = 260		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	376 (70.7)	71 (13.3)	1 (0.2)	119 (45.8)	15 (5.8)	0
Gastrointestinal disorders	150 (28.2)	7 (1.3)	0	61 (23.5)	4 (1.5)	0
Diarrhoea	88 (16.5)	2 (0.4)	0	39 (15.0)	2 (0.8)	0
Nausea	47 (8.8)	0	0	13 (5.0)	0	0
Skin and subcutaneous tissue disorders	145 (27.3)	8 (1.5)	0	33 (12.7)	1 (0.4)	0
Pruritus	53 (10.0)	2 (0.4)	0	9 (3.5)	0	0
Rash	52 (9.8)	4 (0.8)	0	10 (3.8)	1 (0.4)	0
General disorders and administration site conditions	139 (26.1)	7 (1.3)	0	36 (13.8)	1 (0.4)	0
Fatigue	90 (16.9)	6 (1.1)	0	29 (11.2)	1 (0.4)	0
Asthenia	28 (5.3)	0	0	4 (1.5)	0	0
Investigations	103 (19.4)	22 (4.1)	0	24 (9.2)	5 (1.9)	0
Aspartate aminotransferase increased	29 (5.5)	2 (0.4)	0	10 (3.8)	0	0
Endocrine disorders	82 (15.4)	3 (0.6)	0	6 (2.3)	0	0
Hypothyroidism	50 (9.4)	0	0	4 (1.5)	0	0
Hyperthyroidism	35 (6.6)	0	0	1 (0.4)	0	0
Musculoskeletal and connective tissue disorders	57 (10.7)	2 (0.4)	0	12 (4.6)	0	0
Arthralgia	30 (5.6)	1 (0.2)	0	4 (1.5)	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 8.5-2 of the CA209577 Primary CSR

Serious adverse events/deaths/other significant events

Deaths

At the time of this pre-specified interim analysis, the OS data were not mature and did not meet the pre-specified statistical boundary for the interim analysis. The Data Monitoring Committee (DMC) reviewed the death summary by treatment arm and recommended to not release this information to BMS in alignment with the DMC charter, which pre-specified to keep BMS blinded to OS efficacy results if the statistical boundary was not met. Following this recommendation, BMS remained blinded to the death summary by treatment arm and therefore, no death summary is included in this application.

Review of the drug-related SAEs and narratives showed only 1 Grade 5 drug-related SAE (cardiac arrest) reported in 1 subject in the nivolumab arm. This event was deemed not to be treatment-related by the investigator after the DBL. A brief narrative is provided below:

- A 43 year-old white male with GEJC died due to cardiac arrest, approximately 51 days after the first dose and 16 days after the last dose of nivolumab. He did not receive treatment for the event. There was no evidence of disease progression at the time of death. An autopsy was not performed. Prior to his death, Cycle 4 of treatment was delayed due to asthenia (Grade 2, drug-related) and worsening general status (Grade 2, unrelated). This event was reported as drug-related by the investigator at the time of the DBL. Post-clinical DBL, the investigator

amended the causality for cardiac arrest to unrelated to study drug based upon further evaluation of the fatal event (data on file).

Serious adverse events

Any-grade all-causality SAEs (within 30 days of last dose) were reported in 158 (29.7%) subjects in the nivolumab arm vs. 78 (30.0%) subjects in the placebo arm. Grade 3-4 SAEs were reported in 107 (20.1%) subjects in the nivolumab arm and 53 (20.4%) subjects in the placebo arm (Table 20). The most frequently reported all-causality SAEs were (Table 20):

- Nivolumab: pneumonia (3.0%), malignant neoplasm progression (2.3%), pneumonia aspiration (1.3%), and pneumonitis and dysphagia (1.1% each).
- Placebo: malignant neoplasm progression (3.1%), pneumonia and dysphagia (1.9% each), pleural effusion (1.5%), and pneumothorax, dyspnoea, and diaphragmatic hernia and oesophageal stenosis (1.2% each).

Any-grade drug-related SAEs (within 30 days of last dose) were reported in 40 (7.5%) subjects in the nivolumab arm and 7 (2.7%) subjects in the placebo arm. Grade 3-4 drug related SAEs were reported in 29 (5.5%) subjects in the nivolumab arm and 3 (1.2%) subjects in the placebo arm. The most frequently reported drug-related SAE was pneumonitis in both nivolumab (1.1%) and placebo (0.8%) arms (Table 21).

Table 20: Serious Adverse Events Reported in ≥ 1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab N = 532 Any Grade	Nivolumab N = 532 Grade 3-4	Nivolumab N = 532 Grade 5	Placebo N = 260 Any Grade	Placebo N = 260 Grade 3-4	Placebo N = 260 Grade 5
TOTAL SUBJECTS WITH AN EVENT	158 (29.7)	107 (20.1)	9 (1.7)	78 (30.0)	53 (20.4)	6 (2.3)
Gastrointestinal disorders	43 (8.1)	34 (6.4)	0	26 (10.0)	21 (8.1)	0
Dysphagia	6 (1.1)	4 (0.8)	0	5 (1.9)	4 (1.5)	0
Diaphragmatic hernia	4 (0.8)	4 (0.8)	0	3 (1.2)	2 (0.8)	0
Oesophageal stenosis	4 (0.8)	4 (0.8)	0	3 (1.2)	3 (1.2)	0
Infections and infestations	31 (5.8)	26 (4.9)	0	10 (3.8)	5 (1.9)	1 (0.4)
Pneumonia	16 (3.0)	13 (2.4)	0	5 (1.9)	3 (1.2)	0
Respiratory, thoracic and mediastinal disorders	29 (5.5)	16 (3.0)	1 (0.2)	15 (5.8)	4 (1.5)	1 (0.4)
Pneumonia aspiration	7 (1.3)	4 (0.8)	1 (0.2)	0	0	0
Pneumonitis	6 (1.1)	3 (0.6)	0	2 (0.8)	1 (0.4)	0
Pleural effusion	5 (0.9)	4 (0.8)	0	4 (1.5)	2 (0.8)	0
Pneumothorax	3 (0.6)	3 (0.6)	0	3 (1.2)	1 (0.4)	1 (0.4)
Dyspnoea	1 (0.2)	1 (0.2)	0	3 (1.2)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19 (3.6)	10 (1.9)	4 (0.8)	20 (7.7)	13 (5.0)	4 (1.5)
Malignant neoplasm progression	12 (2.3)	8 (1.5)	3 (0.6)	8 (3.1)	4 (1.5)	4 (1.5)

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 8.3-2 of the CA209577 Primary CSR

Table 21: Drug-Related Serious Adverse Events Reported in ≥ 1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab N = 532 Any Grade	Nivolumab N = 532 Grade 3-4	Nivolumab N = 532 Grade 5	Placebo N = 260 Any Grade	Placebo N = 260 Grade 3-4	Placebo N = 260 Grade 5

Table 21: Drug-Related Serious Adverse Events Reported in ≥ 1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab N = 532			Placebo N = 260		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	40 (7.5)	29 (5.5)	1 (0.2)	7 (2.7)	3 (1.2)	0
Respiratory, thoracic and mediastinal disorders	11 (2.1)	6 (1.1)	0	3 (1.2)	1 (0.4)	0
Pneumonitis	6 (1.1)	3 (0.6)	0	2 (0.8)	1 (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 8.3-2 of the CA209577 Primary CSR

Select adverse events

In order to characterize adverse events (AEs) of special clinical interest that are potentially associated with the use of nivolumab, BMS identified select AEs based on the following 4 guiding principles:

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

Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, 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. Events of special clinical interest that do not benefit from pooling of multiple terms were analysed outside of the context of the select AE categories.

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 characterization. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered select AEs.

The most frequently reported drug-related select AE categories (any grade) were as follows in each treatment arm (Table 22):

- Nivolumab: skin (24.4%), gastrointestinal (17.1%), and hepatic (9.2%).
- Placebo: gastrointestinal (15.4%), skin (10.8%), and hepatic (6.9%).

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

- Nivolumab: diarrhoea (16.5%), pruritus (10.0%), rash (9.8%), aspartate aminotransferase (AST) increased (5.5%), alanine aminotransferase (ALT) increased (4.7%).
- Placebo: diarrhoea (15.0%), rash (3.8%), and AST increased (3.8%).

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

- Nivolumab: pneumonitis (1.1%), colitis (0.4%), diarrhea (0.4%), and interstitial lung disease (0.4%).
- Placebo: pneumonitis (0.8%), ALT increased (0.4%), and cholangitis (0.4%).

The majority of select AEs were Grade 1-2, and most were considered drug-related by the investigator. Across the select AE categories, the majority of events in the nivolumab arm were manageable using the established algorithms, with resolution occurring when IMMs (mainly systemic corticosteroids) were administered (Table 22). Except for endocrine events, most drug-related select AEs with nivolumab had resolved (ranging from 65.4% to 100% across categories) at the time of the DBL. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Table 22: Onset, Management, and Resolution of Drug-Related Select Adverse Events – Nivolumab Treated Subjects (N = 532)

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AEs	Median Time to Onset of Drug-related Select AEs (range), wks	% Treated Subj. with Drug-related Select AEs Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median[b] Time to Resolution of Drug-related Select AEs[c,d] (range[e]), wks	% Subj. with Drug-related Select AEs that Resolved[c,d]
Endocrine	17.5 / 0.9	9.71 (1.7 - 52.4)	0.9	10.8 / 4.3	21.14 (2.0 - 150.0+)	66.7
Gastrointestinal	17.1 / 0.8	7.43 (0.1 - 49.3)	0.8	9.9 / 8.8	3.50 (0.1 - 84.1+)	94.3
Hepatic	9.2 / 1.1	6.14 (1.1 - 49.3)	0.6	14.3 / 14.3	7.57 (0.4+ - 126.4+)	80.4
Pulmonary	4.3 / 1.1	12.71 (4.0 - 47.9)	2.3	73.9 / 60.9	5.86 (0.7 - 65.0)	73.9
Renal	1.3 / 0.2	12.14 (1.9 - 37.1)	0	28.6 / 28.6	2.64 (0.7 - 17.0)	100
Skin	24.4 / 1.3	6.07 (0.1 - 49.0)	1.5	38.5 / 3.1	17.86 (0.1 - 163.1+)	65.4
Hypersensitivity/ Infusion Reaction	1.9 / 0	10.64 (0.1 - 48.4)	0	20.0 / 10.0	3.14 (0.1 - 36.1)	100

Other events of special interest (OESIs)

OESIs (regardless of causality or IMM treatment, with extended follow up) were infrequent in the nivolumab treatment arm (Table 23). Overall, OESIs were reported in 5/532 (0.9%) subjects in the nivolumab arm and no subjects in the placebo arm. 3/5 subjects with OESIs in the nivolumab arm were resolved with IMM treatment at the time of database lock. Safety narratives for OESIs for the nivolumab treatment arm have been provided.

In the nivolumab arm, the OESIs reported were myocarditis (3 subjects [1 Grade 4 event each]), pancreatitis (1 subject [1 Grade 3 event]), and Guillain-Barré syndrome (1 subject [1 Grade 4 event]). All 5 OESIs were reported as drug-related SAEs. Prior to enrolment, the 3 subjects with grade 4 myocarditis had received neoadjuvant CRT with carboplatin/paclitaxel with radiation directed to the chest followed by esophagectomy, and had cardiovascular risk factors in their medical history. Nivolumab treatment was discontinued due to myocarditis in all 3 subjects. At the time of DBL, 2 events (Guillain-Barré syndrome and myocarditis) were not resolved; other events were resolved with IMM treatment.

Table 23: Treatment, Onset, and Resolution Information for Other Events of Special Interest by Subject - All Treated Subjects

PID	Event Description	Immune-modulating Medication	Onset Date (Study Day)	Duration of Event (Days)	Resolution (Yes/No)
Nivolumab					
Guillain-Barré Syndrome:					
CA209577-xx-xxx	Grade 4 drug-related SAE of Guillain-Barré syndrome	Gamma globulin, meprednisone, methylprednisolone	23-Mar-2019 (17)	Continuing	No
Pancreatitis:					
CA209577-xx-xxx	Grade 3 drug-related SAE of pancreatitis	Prednisolone	03-Nov-2018 (88)	5	Yes
Myocarditis:					
CA209577-xx-xxx	Grade 4 drug-related SAE of myocarditis	Methylprednisolone, infliximab, prednisone	17-Jul-2018 (21)	Continuing	No
CA209577-xx-xxx	Grade 4 drug-related SAE of myocarditis	Hydrocortisone, methylprednisolone, antilymphocyte immunoglobulin, hydrocortisone, prednisolone (systemic and topical), mycophenolic acid	27-May-2017 (39)	24	Yes
CA209577-xx-xxx	Grade 4 drug-related SAE of myocarditis	Methylprednisolone	13-Sep-2018 (35)	22	Yes

Abbreviations: AE = adverse event; OESI = other event of special interest; PID = patient identification number; SAE = serious adverse event

Immune-mediated adverse events (IMAEs)

Additional analyses of immune-mediated adverse events (IMAEs) were conducted in order to further characterize AEs of special clinical interest. IMAEs are specific events (or groups of PTs describing specific events) that include diarrhoea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, hypersensitivity/infusion reactions, and endocrine (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus). IMAE analyses included:

- Events occurring within 100 days of the last dose.
- Events regardless of causality.
- Events treated with immune-modulating medication (IMM) [of note, endocrine AEs such as adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, hyperthyroidism,

diabetes mellitus, and hypophysitis were considered IMAEs regardless of IMM use, since endocrine drug reactions are often managed without IMM].

- Events with no clear alternate aetiology based on investigator assessment, or with an immune mediated component.

The most frequently reported IMAE categories (any grade) were as follows in each treatment arm (Table 23):

- Nivolumab: hypothyroidism/thyroiditis (11.1%), rash (7.9%), hyperthyroidism (6.6%), and pneumonitis (4.5%).
- Placebo: pneumonitis (1.5%), rash (1.5%), hepatitis (1.2%), and hypothyroidism/thyroiditis (1.2%).

Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution occurring when IMMs (mostly systemic corticosteroids) were administered (Table 17). Some endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

Re-challenge information was also summarized for subjects who continued to receive nivolumab treatment after the onset of an IMAE (Table 23). 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. 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.

Overall, the majority of IMAEs were Grade 1-2. Safety narratives for nivolumab treated subjects with any-grade IMAEs within 100 days of last dose, excluding rash treated only with topical steroids, have been provided.

Table 24: Onset, Management and Resolution of All-Causality Immune-Mediated Adverse Events within 100 Days of Last Dose – Nivolumab Treated Subjects (N = 532)

IMAE Category	% Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAE leading to DC / Dose Delay	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE[b,c,d]	Median[e] Time to Resolution (range[f]), wks	% Subj. with Recurrence after Reinitiation[g]
Pneumonitis	4.5 / 1.7	23.00 (4.0 - 55.0)	3.4 / 1.3	100 / 87.5	10.14 (0.7 - 75.0)	70.8	17.57 (0.7 - 101.6+)	33.3 (1 / 3)
Diarrhea/Colitis	1.9 / 0.8	18.07 (6.9 - 39.3)	0.8 / 0.4	100 / 90.0	3.86 (0.3 - 7.3)	100	2.71 (0.9 - 15.7)	0 (0 / 1)
Hepatitis	1.1 / 0.8	5.43 (1.1 - 14.1)	0.6 / 0.2	100 / 100	5.14 (1.3 - 18.1)	83.3	7.50 (0.9 - 35.7+)	100 (1 / 1)
Nephritis/Renal Dysfunction	0.4 / 0.2	6.07 (2.1 - 10.0)	0 / 0.2	100 / 100	1.79 (0.4 - 3.1)	100	3.07 (0.9 - 5.3)	0 (0 / 1)
Rash	7.9 / 0.9	7.43 (0.3 - 40.1)	0.9 / 0.9	100 / 9.5	18.64 (0.4 - 163.1)	57.1	21.14 (1.1 - 163.1+)	75.0 (3 / 4)
Hypersensitivity	0.2 / 0	48.43 (48.4 - 48.4)	0 / 0	100 / 100	0.14 (0.1 - 0.1)	100	0.14 (0.1 - 0.1)	0 (0 / 0)
Adrenal Insufficiency	0.9 / 0.4	24.71 (8.9 - 36.1)	0.4 / 0.4	100 / 40.0	13.71 (2.1 - 36.6)	80.0	1.43 (0.6 - 48.6)	0 (0 / 1)
Hypophysitis	0.2 / 0	11.00 (11.0 - 11.0)	0 / 0	0 / 0	N.A.	100	1.14 (1.1 - 1.1)	0 (0 / 0)
Hypothyroidism/ Thyroiditis	11.1 / 0.4	12.00 (2.1 - 52.4)	0.4 / 1.5	3.4 / 1.7	8.43 (3.1 - 13.7)	49.2	73.14 (1.3 - 155.3+)	33.3 (1 / 3)
Hyperthyroidism	6.6 / 0	6.14 (2.0 - 22.1)	0.4 / 0.8	8.6 / 5.7	2.86 (2.7 - 6.9)	91.4	8.57 (1.7 - 47.0+)	0 (0 / 1)
Diabetes Mellitus	0.6 / 0.4	6.57 (1.9 - 16.4)	0.2 / 0	33.3 / 0	40.14 (40.1 - 40.1)	66.7	4.14 (3.6 - 64.7+)	0 (0 / 0)

MedDRA Version: 23.0. CTC Version 4.0. Includes events reported between first dose and 100 days after last dose of study therapy.

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

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

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

For each subject, the longest duration of immune-mediated AEs where immune modulation is considered.

From Kaplan-Meier estimation.

Symbol + indicates a censored value.

Percentages are based on subjects who were re-challenged.

Abbreviations: DC = discontinuation; IMAE = immune-mediated adverse event; IMM = immune-modulating medication; N.A. = not applicable; Subj. = subject; wks = weeks

Source: Table S.6.2.03.2 (non-endocrine IMAEs), Table S.6.2.03.1 (endocrine IMAEs), Table S.6.217.2 (time to onset of non-endocrine IMAEs), Table S.6.217.1 (time to onset of endocrine IMAEs), Table S.6.2.02.3 (non-endocrine IMAEs leading to DC), Table S.6.2.02.4 (non-endocrine IMAEs leading to dose delay or reduction), Table S.6.2.02.1 (endocrine IMAEs leading to DC), Table S.6.2.02.2 (endocrine IMAEs leading to dose delay), Table S.6.12.91.1 (duration of IMM for IMAE management), Table S.6.219.2 (time to resolution of non-endocrine IMAEs), Table S.6.219.1 (time to resolution of endocrine IMAEs), Table S.6.223 (re-challenged with nivolumab by IMAEs category)

Adverse Drug Reactions (ADRs)

For labelling purposes, drug-related AEs data across completed studies in multiple indications (approved and under review) for the intended dose and regimen of nivolumab monotherapy (3 mg/kg Q2W or 240 mg IV Q2W) were integrated. MedDRA PTs representing the same or similar clinical conditions for the integrated AE data were re-mapped to generate summary tables where resulting clinically relevant events, by SOC and frequency, were included in the final ADR table (Table 6 in Section 4.8 of the SmPC).

Comparative safety data from study CA209577 with pooled data from other nivolumab monotherapy studies (excluding study CA209577) were provided. Results seemed consistent and the pooling strategy was considered acceptable. The frequencies of any grade, all-causality, and drug-related AEs were comparable or numerically lower in nivolumab treated subjects in CA209577 when compared with the pooled nivolumab monotherapy studies (included studies with more advanced disease settings and excluding study CA209577), except the following differences:

- Any grade all-causality AEs were higher in nivolumab monotherapy treated subjects in CA209577 vs the pooled nivolumab monotherapy studies, excluding CA209577 for; diarrhea

(29.1% vs 25.2%), dyspepsia (11.7% vs 5.6%), dysphagia (13.0% vs 2.7%), weight decreased (13.0% vs 7.1%), transaminases increased (10.9% vs 8.1%), hypothyroidism (10.5% vs 8.8%), respectively.

- Drug-related AEs were higher in nivolumab monotherapy treated subjects in CA209577 vs the pooled nivolumab monotherapy studies, excluding CA209577 for; diarrhea (16.5% vs 14.2%), transaminases increased (7.0% vs 5.0%), hypothyroidism (9.4% vs 7.3%), hyperthyroidism (6.8% vs 3.1%), respectively.

Laboratory findings

Haematology

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

The following Grade 3 hematologic abnormalities were reported in ≥ 5% of treated subjects with on-treatment laboratory results:

- Nivolumab: lymphocytes decreased (21.8% Grade 3).
- Placebo: lymphocytes decreased (17.5% Grade 3).

Serum chemistry

Liver tests

During the treatment period, abnormalities in hepatic parameters (all increases) were primarily Grade 1 or 2 in severity.

A total of 2/525 (0.4%) subjects in the nivolumab arm and no subjects in the placebo arm had concurrent ALT or AST >3 x ULN with total bilirubin >2 x ULN within 1 day and within 30 days, based on laboratory results reported after the first dose and within 30 days of last dose of study therapy (Table 25).

Table 25: Summary of Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects

Abnormality (%)	Nivolumab N = 532	Placebo N = 260	Total N = 792
	N = 526	N = 257	N = 783
ALT OR AST > 3XULN	38 (7.2)	9 (3.5)	47 (6.0)
ALT OR AST > 5XULN	15 (2.9)	4 (1.6)	19 (2.4)
ALT OR AST > 10XULN	5 (1.0)	1 (0.4)	6 (0.8)
ALT OR AST > 20XULN	1 (0.2)	1 (0.4)	2 (0.3)
	N = 525	N = 257	N = 782
TOTAL BILIRUBIN > 2XULN	7 (1.3)	2 (0.8)	9 (1.2)
	N = 525	N = 257	N = 782
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	2 (0.4)	0	2 (0.3)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	2 (0.4)	0	2 (0.3)

Notes: 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

Narratives were provided for subjects who had concurrent (within 1 day) ALT or AST >3 x upper limit of normal (ULN) and total bilirubin >2 x ULN within 100 days of the last dose.

Kidney function tests

Abnormalities in creatinine (increased) were primarily Grade 1 or 2 in severity. 689 (88.1%) subjects with, at least, 1 on-treatment measurement had normal creatinine values during the treatment reporting period. No subjects in the nivolumab arm or placebo arm had a Grade 3 or 4 increased creatinine level.

Thyroid function test

TSH increases (> ULN) from baseline (≤ ULN) were reported in 100/502 (19.9%) subjects in the nivolumab arm, and 19/253 (7.5%) subjects in the placebo arm (Table 26). Decreases (< lower limit of normal [LLN]) from baseline (≥ LLN) were reported in 110/502 (21.9%) subjects in the nivolumab arm, and 16/253 (6.3%) subjects in the placebo arm.

Table 26: Summary of Laboratory Abnormalities in Specific Thyroid Tests (SI Units) - All Treated Subjects with at Least One On-Treatment TSH Measurement

Abnormality (%)	Nivolumab N = 502	Placebo N = 253	Total N = 755
TSH > ULN	117 (23.3)	30 (11.9)	147 (19.5)
TSH > ULN			
WITH TSH <= ULN AT BASELINE	100 (19.9)	19 (7.5)	119 (15.8)
TSH > ULN			
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	71 (14.1)	5 (2.0)	76 (10.1)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	37 (7.4)	21 (8.3)	58 (7.7)
WITH FT3/FT4 TEST MISSING (A) (B)	9 (1.8)	4 (1.6)	13 (1.7)
TSH < LLN	145 (28.9)	30 (11.9)	175 (23.2)
TSH < LLN			
WITH TSH >= LLN AT BASELINE	110 (21.9)	16 (6.3)	126 (16.7)
TSH < LLN			
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	68 (13.5)	10 (4.0)	78 (10.3)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	56 (11.2)	15 (5.9)	71 (9.4)
WITH FT3/FT4 TEST MISSING (A) (B)	21 (4.2)	5 (2.0)	26 (3.4)

Note: 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

Pancreas function tests

Most subjects had normal amylase and lipase levels during the treatment reporting period. Abnormalities in amylase and lipase during treatment were primarily Grade 1 to 2 in severity. Grade 3 or 4 abnormalities in amylase or lipase were reported in <5% of treated subjects with on treatment laboratory results.

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 abnormalities in electrolytes were reported in ≥5% of treated subjects with on-treatment laboratory results:

- Nivolumab: hypocalcaemia (N=8, 12.5% Grade 4).

Vital signs and physical findings

Vital signs 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.

Safety in special populations

Overall, the safety profile of nivolumab among subgroups of age, gender, race and geographic region was generally similar to the total nivolumab treated population.

The following numerical differences were observed:

- In the Endocrine Disorder SOC, more all-causality and drug-related AEs were reported in female subjects compared with male subjects in the nivolumab arm:
    - Any grade all-causality AEs were reported in 28.9% female subjects and 14.9% male subjects.
    - Any grade drug-related AEs were reported in 24.1% female subjects and 13.8% male subjects.
- In the Metabolism and Nutrition Disorders SOC, more all-causality and drug-related AEs were reported in male subjects compared with female subjects in the nivolumab arm:
    - Any grade all-causality AEs were reported in 28.7% male subjects and 22.9% female subjects.
    - Any grade drug-related AEs were reported in 9.4% male subjects and 4.8% female subjects.

For subgroups based on race, most participants were in a single category (White) which limited the interpretability of potential differences.

For subgroups based on geographical region, the frequencies of all-causality and drug-related AEs in the nivolumab arm and placebo arm, US/Canada, Europe, Asia were comparable to the AE frequencies reported in the rest of the world.

No overall differences in safety (all-causality and drug-related AEs) were observed in older subjects (≥65 and <75, and ≥75 and <85 years old) compared with younger subjects (< 65 years old).

Inmunogenicity

Of the 464 nivolumab ADA evaluable subjects in the nivolumab arm, 20 (4.3%) subjects were nivolumab ADA positive at baseline, and 21 (4.5%) subjects were nivolumab ADA positive after the start of treatment (Table 27).

- No subjects were considered persistent positive, and 1 (0.2%) subject was neutralizing ADA positive.
- The highest titer value observed in nivolumab ADA positive subjects was 32, which occurred in 2 subjects. All other titers were low, ranging from 1 to 16.
- A NAb result from 1 evaluable subject was not available at the time of the DBL. However, after the DBL, the result was reported as neutralizing ADA negative. Therefore, this had no impact on the immunogenicity data interpretation.

Table 27: Anti-Drug Antibody Assessments Summary - All Nivolumab Treated Subjects with Baseline and at Least One Post-Baseline Assessment

	Nivolumab
	Nivolumab ADA
Subject ADA Status (%)	N = 464
BASELINE ADA POSITIVE	20 (4.3)
ADA POSITIVE	21 (4.5)
PERSISTENT POSITIVE (PP)	0
NOT PP - LAST SAMPLE POSITIVE	3 (0.6)
OTHER POSITIVE	18 (3.9)
NEUTRALIZING POSITIVE	1 (0.2)
ADA NEGATIVE	442 (95.3)

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (≥) than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart;
Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling time point;
Other Positive: Not persistent but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Note: Post-baseline assessments are assessments reported after initiation of treatment. 1 subject who had baseline and at least one post-baseline assessment was neither ADA positive nor ADA negative.
Abbreviations: ADA = anti-drug antibody, PP = persistent positive

Source: Table 11.1-1 of the CA209577 Primary CSR

Effect of immunogenicity on Safety

The effect of immunogenicity on safety was assessed in the nivolumab arm. Overall, the incidence of nivolumab ADA was 4.5% (Table 27) and did not appear to have an effect on safety of the tested regimen.

Of all the nivolumab treated subjects who were evaluable for ADA, hypersensitivity/infusion reaction select AEs were experienced by 14 (3.2%) nivolumab ADA negative subjects, and no nivolumab ADA-positive subjects (Table 28).

Table 28: Select Adverse Events of Hypersensitivity/Infusion Reaction by ADA Status (Positive, Negative) - All Nivolumab Treated Subjects with ADA Positive or ADA Negative

	Nivolumab	
Preferred Term (%)	Nivolumab ADA Positive N = 21	Nivolumab ADA Negative N = 442
TOTAL SUBJECTS WITH AN EVENT	0	14 (3.2)
Bronchospasm	0	2 (0.5)
Hypersensitivity	0	4 (0.9)
Infusion related reaction	0	8 (1.8)

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

Abbreviation: ADA = anti-drug antibody

Source: Table 11.1.2-1 of the CA209577 Primary CSR

Concomitant therapies

Immune-Modulating Concomitant Medications for Management of Adverse Events

IMMs were recommended for the treatment of certain AEs. The list of IMMs was derived from the World Health Organization (WHO) Drug Dictionary, and included all drugs belonging to the following categories: corticosteroids, immune-modulating agents, immunosuppressive agents, and glucocorticoids.

Among all treated subjects in this study, immune-modulating concomitant medications were administered to 41.4% of subjects in the nivolumab arm and 31.2% of subjects in the placebo arm. The proportion of treated subjects with an AE that required immune-modulating concomitant medications was 34.2% in the nivolumab arm and 17.7% in the placebo arm.

The most frequently reported AEs (> 1% of treated subjects) that required IMM included the following (Table S.6.1.4):

- Nivolumab arm: rash (5.1%), pneumonitis (3.0%), pruritus (2.3%), rash maculopapular (1.7%), pneumonia (1.3%), and rash pruritic (1.1%)
- Placebo arm: pneumonitis and pneumonia (1.2% each)

Discontinuation due to adverse events

Adverse events leading to discontinuation of study treatment

Any-grade all-causality AEs leading to discontinuation were reported in 68 (12.8%) subjects in the nivolumab arm and 20 (7.7%) subjects in the placebo arm. Grade 3 4 AEs leading to discontinuation were reported in 38 (7.1%) subjects in the nivolumab arm and 16 (6.2%) subjects in the placebo arm. The most frequently reported all-causality AEs leading to discontinuation were (Table 29):

- Nivolumab: pneumonitis (1.9%), malignant neoplasm (0.9%), rash (0.6%), and myocarditis (0.6%).

- Placebo: malignant neoplasm (1.5%) and pneumonitis (0.8%).

Table 29: Adverse Events Leading to Discontinuation in ≥ 2 Subjects - All Treated Subjects

System Organ Class (%) / Preferred Term (%)	Nivolumab N = 532			Placebo N = 260		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	68 (12.8)	38 (7.1)	3 (0.6)	20 (7.7)	16 (6.2)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	19 (3.6)	5 (0.9)	1 (0.2)	4 (1.5)	1 (0.4)	1 (0.4)
Pneumonitis	10 (1.9)	3 (0.6)	0	2 (0.8)	1 (0.4)	0
Pleural effusion	2 (0.4)	1 (0.2)	0	1 (0.4)	0	0
Pneumonia aspiration	2 (0.4)	0	1 (0.2)	0	0	0
Skin and subcutaneous tissue disorders	8 (1.5)	3 (0.6)	0	0	0	0
Rash	3 (0.6)	1 (0.2)	0	0	0	0
Pruritus	2 (0.4)	1 (0.2)	0	0	0	0
Psoriasis	2 (0.4)	1 (0.2)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.3)	6 (1.1)	1 (0.2)	8 (3.1)	7 (2.7)	0
Malignant neoplasm progression	5 (0.9)	4 (0.8)	1 (0.2)	4 (1.5)	4 (1.5)	0
Cardiac disorders	6 (1.1)	4 (0.8)	1 (0.2)	1 (0.4)	1 (0.4)	0
Myocarditis	3 (0.6)	3 (0.6)	0	0	0	0
Infections and infestations	6 (1.1)	3 (0.6)	0	0	0	0
Pneumonia	2 (0.4)	1 (0.2)	0	0	0	0
Sepsis	2 (0.4)	2 (0.4)	0	0	0	0
Hepatobiliary disorders	4 (0.8)	3 (0.6)	0	2 (0.8)	2 (0.8)	0
Autoimmune hepatitis	2 (0.4)	1 (0.2)	0	0	0	0
Investigations	3 (0.6)	2 (0.4)	0	1 (0.4)	1 (0.4)	0
Alanine aminotransferase increased	2 (0.4)	0	0	1 (0.4)	1 (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 8.4-1 of the CA209577 Primary CSR

Any-grade drug-related AEs leading to discontinuation were reported in 48 (9.0%) subjects in the nivolumab arm and 8 (3.1%) subjects in the placebo arm. Grade 3 4 AEs leading to discontinuation were reported in 26 (4.9%) subjects in the nivolumab arm and 7 (2.7%) subjects in the placebo arm. The most frequently reported drug-related AEs leading to discontinuation were (Table 30):

- Nivolumab: pneumonitis (1.9%), rash (0.6%), and myocarditis (0.6%).
- Placebo: pneumonitis (0.8%).

Table 30: Drug-Related Adverse Events Leading to Discontinuation in ≥ 2 Subjects - All Treated Subjects

System Organ Class (%) / Preferred Term (%)	Nivolumab N = 532			Placebo N = 260		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	48 (9.0)	26 (4.9)	1 (0.2)	8 (3.1)	7 (2.7)	0
Respiratory, thoracic and mediastinal disorders	14 (2.6)	4 (0.8)	0	2 (0.8)	1 (0.4)	0
Pneumonitis	10 (1.9)	3 (0.6)	0	2 (0.8)	1 (0.4)	0

Table 30: Drug-Related Adverse Events Leading to Discontinuation in ≥ 2 Subjects - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab N = 532 Any Grade	Nivolumab N = 532 Grade 3-4	Nivolumab N = 532 Grade 5	Placebo N = 260 Any Grade	Placebo N = 260 Grade 3-4	Placebo N = 260 Grade 5
Skin and subcutaneous tissue disorders	8 (1.5)	3 (0.6)	0	0	0	0
Rash	3 (0.6)	1 (0.2)	0	0	0	0
Pruritus	2 (0.4)	1 (0.2)	0	0	0	0
Psoriasis	2 (0.4)	1 (0.2)	0	0	0	0
Cardiac disorders	4 (0.8)	3 (0.6)	1 (0.2)	0	0	0
Myocarditis	3 (0.6)	3 (0.6)	0	0	0	0
Infections and infestations	4 (0.8)	3 (0.6)	0	0	0	0
Pneumonia	2 (0.4)	1 (0.2)	0	0	0	0
Sepsis	2 (0.4)	2 (0.4)	0	0	0	0
Hepatobiliary disorders	3 (0.6)	2 (0.4)	0	2 (0.8)	2 (0.8)	0
Autoimmune hepatitis	2 (0.4)	1 (0.2)	0	0	0	0
Investigations	2 (0.4)	1 (0.2)	0	1 (0.4)	1 (0.4)	0
Alanine aminotransferase increased	2 (0.4)	0	0	1 (0.4)	1 (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 8.4-2 of the CA209577 Primary CSR

Adverse events leading to dose delay

Any-grade all-causality AEs leading to dose delay were reported in 148 (27.8%) subjects in the nivolumab arm and 62 (23.8%) subjects in the placebo arm. Grade 3-4 AEs leading to discontinuation were reported in 61 (11.5%) subjects in the nivolumab arm and 20 (7.7%) subjects in the placebo arm. The most frequently reported all-causality AEs leading to dose delay were (Table 31):

- Nivolumab: pneumonia (3.0%), pneumonitis (2.1%), alanine aminotransferase increased (1.7%), and aspartate aminotransferase increased (1.5%).
- Placebo: diarrhoea (2.3%), and pneumonia and fatigue (1.9% each).

Table 31: Adverse Events Leading to Dose Delay in ≥ 1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab N = 532			Placebo N = 260		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	148 (27.8)	61 (11.5)	0	62 (23.8)	20 (7.7)	0
Infections and infestations	37 (7.0)	16 (3.0)	0	16 (6.2)	1 (0.4)	0
Pneumonia	16 (3.0)	7 (1.3)	0	5 (1.9)	1 (0.4)	0
Herpes zoster	6 (1.1)	1 (0.2)	0	2 (0.8)	0	0
Lower respiratory tract infection	0	0	0	3 (1.2)	0	0
Respiratory, thoracic and mediastinal disorders	29 (5.5)	8 (1.5)	0	13 (5.0)	1 (0.4)	0
Pneumonitis	11 (2.1)	0	0	2 (0.8)	0	0
Cough	1 (0.2)	0	0	3 (1.2)	0	0
Investigations	28 (5.3)	9 (1.7)	0	12 (4.6)	4 (1.5)	0
Alanine aminotransferase increased	9 (1.7)	0	0	2 (0.8)	1 (0.4)	0
Aspartate aminotransferase increased	8 (1.5)	2 (0.4)	0	3 (1.2)	0	0
Gastrointestinal disorders	25 (4.7)	9 (1.7)	0	21 (8.1)	7 (2.7)	0
Diarrhoea	5 (0.9)	0	0	6 (2.3)	0	0
Diaphragmatic hernia	1 (0.2)	1 (0.2)	0	3 (1.2)	2 (0.8)	0
Dysphagia	1 (0.2)	0	0	4 (1.5)	1 (0.4)	0
General disorders and administration site conditions	17 (3.2)	3 (0.6)	0	6 (2.3)	1 (0.4)	0
Fatigue	7 (1.3)	1 (0.2)	0	5 (1.9)	1 (0.4)	0
Endocrine disorders	15 (2.8)	2 (0.4)	0	0	0	0
Hypothyroidism	7 (1.3)	0	0	0	0	0
Hyperthyroidism	6 (1.1)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	9 (1.7)	1 (0.2)	0	4 (1.5)	0	0
Arthralgia	6 (1.1)	1 (0.2)	0	1 (0.4)	0	0

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

Source: Table 8.4.1-1 of the CA209577 Primary CSR

Any-grade drug-related AEs leading to dose delay were reported in 73 (13.7%) subjects in the nivolumab arm and 25 (9.6%) subjects in the placebo arm. Grade 3-4 AEs leading to discontinuation were reported in 23 (4.3%) subjects in the nivolumab arm and 4 (1.5%) subjects in the placebo arm. The most frequently reported drug-related AEs leading to dose delay were (Table 32):

- Nivolumab: pneumonitis (1.3%), and alanine aminotransferase increased, hyperthyroidism, and hypothyroidism (1.1% each).
- Placebo: diarrhoea (1.5%) and fatigue (1.2%).

Table 32: Drug-Related Adverse Events Leading to Dose Delay in ≥ 1% of All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivolumab N = 532			Placebo N = 260		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade5
TOTAL SUBJECTS WITH AN EVENT	73 (13.7)	23 (4.3)	0	25 (9.6)	4 (1.5)	0
Investigations	19 (3.6)	6 (1.1)	0	5 (1.9)	2 (0.8)	0
Alanine aminotransferase increased	6 (1.1)	0	0	2 (0.8)	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	15 (2.8)	2 (0.4)	0	5 (1.9)	0	0
Pneumonitis	7 (1.3)	0	0	2 (0.8)	0	0
Endocrine disorders	14 (2.6)	2 (0.4)	0	0	0	0
Hyperthyroidism	6 (1.1)	0	0	0	0	0
Hypothyroidism	6 (1.1)	0	0	0	0	0
Gastrointestinal disorders	12 (2.3)	1 (0.2)	0	6 (2.3)	0	0
Diarrhoea	4 (0.8)	0	0	4 (1.5)	0	0
General disorders and administration site conditions	8 (1.5)	2 (0.4)	0	4 (1.5)	1 (0.4)	0
Fatigue	5 (0.9)	1 (0.2)	0	3 (1.2)	1 (0.4)	0

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

Source: Table 8.4.1-2 of the CA209577 Primary CSR

Infusion interruptions

Ten (1.9%) subjects in the nivolumab arm and 3 (1.2%) subjects in the placebo arm had an infusion interruption. All subjects who required an infusion interruption only had 1 infusion interrupted. Of the subjects who required an infusion interruption by treatment arm, the most common reasons were 'other' (5 [50.0%] infusions interrupted) and 'hypersensitivity reaction' (3 [30.0%] infusions interrupted) in the nivolumab arm, and 'infusion administration issues' (2 [66.7%] infusions interrupted) and 'other' (1 [33.3%] infusions interrupted) in the placebo arm.

Infusion rate reductions

Seven (1.3%) subjects in the nivolumab arm and 8 (3.1%) subjects in the placebo arm had an infusion rate reduction. Of the subjects who required an infusion rate reduction, most (14 [1.8%]) had only 1 infusion rate reduction. Of the subjects who required an infusion rate reduction by treatment arm, the most common reasons were 'infusion administration issues' (5 [71.4%] and 4 [40.0%] infusion rate reductions in the nivolumab arm and placebo arm, respectively) and 'other' (2 [28.6%] and 6 [60.0%], respectively).

Updated safety data (DBL 18-Feb-2021)

Updated safety data based on the latest cut-off (DBL Feb-2021), with a minimum follow-up of 14 months and a median follow-up time of 32.2 months have been provided (Table 33, 34, 35 and 36).

Table 33: Summary of Safety in Subjects Treated with Nivolumab - Primary and Updated Analysis - CA209577

	Number (%) Subjects			
	Primary Analysis: 03-Jul-2020 DBL N = 532		Updated Analysis: 18-Feb-2021 DBL N = 532	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	158 (29.7)	107 (20.1)	160 (30.1)	109 (20.5)
Drug-related SAEs	40 (7.5)	29 (5.5)	41 (7.7)	31 (5.8)
All-causality AEs leading to DC	68 (12.8)	38 (7.1)	71 (13.3)	39 (7.3)
Drug-related AEs leading to DC	48 (9.0)	26 (4.9)	49 (9.2)	26 (4.9)
All-causality AEs	510 (95.9)	183 (34.4)	513 (96.4)	186 (35.0)
Drug-related AEs	376 (70.7)	71 (13.3)	379 (71.2)	74 (13.9)
All-causality Select AEs				
Skin	169 (31.8)	7 (1.3)	170 (32.0)	7 (1.3)
Gastrointestinal	157 (29.5)	6 (1.1)	158 (29.7)	6 (1.1)
Endocrine	101 (19.0)	5 (0.9)	104 (19.5)	5 (0.9)
Hepatic	79 (14.8)	14 (2.6)	80 (15.0)	14 (2.6)
Pulmonary	29 (5.5)	6 (1.1)	29 (5.5)	6 (1.1)
Hypersensitivity/Infusion Reactions	15 (2.8)	1 (0.2)	16 (3.0)	1 (0.2)
Renal	12 (2.3)	1 (0.2)	12 (2.3)	1 (0.2)
Drug-Related Select AEs				
Skin	130 (24.4)	7 (1.3)	131 (24.6)	7 (1.3)
Endocrine	93 (17.5)	5 (0.9)	94 (17.7)	5 (0.9)
Gastrointestinal	91 (17.1)	4 (0.8)	92 (17.3)	4 (0.8)
Hepatic	49 (9.2)	6 (1.1)	50 (9.4)	6 (1.1)
Pulmonary	23 (4.3)	6 (1.1)	23 (4.3)	6 (1.1)
Hypersensitivity/Infusion Reactions	10 (1.9)	0	11 (2.1)	0
Renal	7 (1.3)	1 (0.2)	7 (1.3)	1 (0.2)

Primary analysis: MedDRA version 23.0 CTCAE version 4.0.

Updated analysis: MedDRA Version: 23.1 CTC Version 4.0

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

Abbreviations: DBL, database lock, AE = adverse event, CTC = Common Toxicity Criteria, DC = discontinuation, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event

Source: Table S.6.3.1.2.1 (all-causality SAEs - primary analysis), Table S.6.3.1.2.2 (drug-related SAEs- primary analysis), Table S.6.4.2.1 (all-causality AEs leading to DC- primary analysis), Table S.6.4.2.2 (drug-related AEs leading to DC- primary analysis), Table S.6.1.31.1 (all-causality AEs- primary analysis); Table S.6.1.32.1 (drug-related AEs- primary analysis), Table S.6.5.1.3.1 (all-causality select AEs- primary analysis), Table S.6.5.1.3.5 (all-causality endocrine select AEs- primary analysis), Table S.6.5.1.3.2 (drug-related select AEs- primary analysis), Table S.6.5.1.3.6 (drug-related endocrine select AEs- primary analysis) of the CA209577 CSR[iii]; Table S.4.1.3 (all-causality SAEs - updated analysis), Table S.4.1.4 (drug-related SAEs- updated analysis), Table S.4.1.5 (AEs leading to DC- updated analysis), Table S.4.1.6 (drug-related AEs leading to DC- updated analysis), Table S.4.1.1 (AEs- updated analysis), Table S.4.1.2 (drug-related AEs- updated analysis), Table S.4.2.1 (select AEs- updated analysis), Table S.4.2.2 (drug-related select AEs- updated analysis), Table S.4.2.3 (select endocrine AEs- updated analysis), Table S.4.2.4 (drug-related endocrine select AEs- updated analysis)

Table 34: Summary of Safety - All Treated Subjects (Updated Analysis: 18-Feb-2021 DBL)

Safety Parameters	No. of Subjects (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	160 (30.1)	109 (20.5)	80 (30.8)	53 (20.4)
Drug-related SAEs	41 (7.7)	31 (5.8)	7 (2.7)	3 (1.2)
All-causality AEs leading to DC	71 (13.3)	39 (7.3)	21 (8.1)	16 (6.2)
Drug-related AEs leading to DC	49 (9.2)	26 (4.9)	8 (3.1)	7 (2.7)
All-causality AEs	513 (96.4)	186 (35.0)	243 (93.5)	84 (32.3)
Most Frequent AEs (≥ 10% of Any Grade in any Treatment Arm)				
Diarrhea	156 (29.3)	5 (0.9)	77 (29.6)	2 (0.8)
Fatigue	146 (27.4)	7 (1.3)	64 (24.6)	3 (1.2)
Nausea	124 (23.3)	4 (0.8)	56 (21.5)	0
Cough	103 (19.4)	1 (0.2)	50 (19.2)	1 (0.4)
Vomiting	83 (15.6)	3 (0.6)	42 (16.2)	3 (1.2)
Decreased appetite	79 (14.8)	5 (0.9)	26 (10.0)	2 (0.8)
Dysphagia	67 (12.6)	3 (0.6)	43 (16.5)	9 (3.5)
Weight decreased	70 (13.2)	2 (0.4)	23 (8.8)	0
Pruritus	67 (12.6)	2 (0.4)	16 (6.2)	0
Rash	62 (11.7)	4 (0.8)	17 (6.5)	1 (0.4)
Abdominal pain	63 (11.8)	3 (0.6)	37 (14.2)	3 (1.2)
Constipation	62 (11.7)	0	32 (12.3)	0
Hypothyroidism	59 (11.1)	0	4 (1.5)	0
Dyspnoea	55 (10.3)	3 (0.6)	26 (10.0)	1 (0.4)
Arthralgia	65 (12.2)	1 (0.2)	29 (11.2)	0
Gastroesophageal reflux disease	43 (8.1)	1 (0.2)	34 (13.1)	0
Headache	43 (8.1)	1 (0.2)	29 (11.2)	0
Drug-related AEs	379 (71.2)	74 (13.9)	122 (46.9)	16 (6.2)
≥ 5% of Subjects in any Treatment Arm				
Fatigue	92 (17.3)	6 (1.1)	29 (11.2)	1 (0.4)
Diarrhoea	89 (16.7)	2 (0.4)	39 (15.0)	2 (0.8)
Pruritus	53 (10.0)	2 (0.4)	9 (3.5)	0
Rash	51 (9.6)	4 (0.8)	10 (3.8)	1 (0.4)
Hypothyroidism	51 (9.6)	0	4 (1.5)	0
Nausea	48 (9.0)	0	13 (5.0)	0
Hyperthyroidism	35 (6.6)	0	1 (0.4)	0
Arthralgia	33 (6.2)	1 (0.2)	5 (1.9)	0
Aspartate aminotransferase increased	29 (5.5)	2 (0.4)	10 (3.8)	0
Asthenia	28 (5.3)	0	4 (1.5)	0
All-causality Select AEs				
Skin	170 (32.0)	7 (1.3)	48 (18.5)	1 (0.4)
Gastrointestinal	158 (29.7)	6 (1.1)	78 (30.0)	3 (1.2)
Endocrine	104 (19.5)	5 (0.9)	8 (3.1)	0
Hepatic	80 (15.0)	14 (2.6)	31 (11.9)	6 (2.3)
Pulmonary	29 (5.5)	6 (1.1)	5 (1.9)	1 (0.4)
Hypersensitivity/Infusion Reactions	16 (3.0)	1 (0.2)	5 (1.9)	0
Renal	12 (2.3)	1 (0.2)	7 (2.7)	0
Drug-Related Select AEs				

Table 34: Summary of Safety - All Treated Subjects (Updated Analysis: 18-Feb-2021 DBL)

Safety Parameters	No. of Subjects (%)			
	Nivolumab (N = 532)		Placebo (N = 260)	
	Adverse Event Grades			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Skin	131 (24.6)	7 (1.3)	28 (10.8)	1 (0.4)
Endocrine	94 (17.7)	5 (0.9)	6 (2.3)	0
Gastrointestinal	92 (17.3)	4 (0.8)	40 (15.4)	3 (1.2)
Hepatic	50 (9.4)	6 (1.1)	18 (6.9)	4 (1.5)
Pulmonary	23 (4.3)	6 (1.1)	4 (1.5)	1 (0.4)
Hypersensitivity/Infusion Reactions	11 (2.1)	0	3 (1.2)	0
Renal	7 (1.3)	1 (0.2)	2 (0.8)	0
All-causality OESIs within 100 days of last dose				
With or without immune modulating medication				
Myocarditis	3 (0.6)	3 (0.6)	0	0
Pancreatitis	1 (0.2)	1 (0.2)	0	0
Guillain-Barré Syndrome	1 (0.2)	1 (0.2)	0	0

MedDRA version 23.1 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise specified.

Abbreviations: DBL = database lock, AE = adverse event, CTC = Common Toxicity Criteria, DC = discontinuation, MedDRA = Medical Dictionary for Regulatory Activities, OESI = other event of special interest, SAE = serious adverse event

Source: Table S.4.1.3 (all-causality SAEs), Table S.4.1.4 (drug-related SAEs), Table S.4.1.5 (AEs leading to DC), Table S.4.1.6 (drug-related AEs leading to DC), Table S.4.1.1 (all-causality AEs), Table S.4.1.2 (drug-related AEs), Table S.4.2.1 (select AEs), Table S.4.2.2 (drug-related select AEs), Table S.4.2.3 (select endocrine AEs), Table S.4.2.4 (drug-related endocrine select AEs), and Table S.4.3.1 (OESI)

Table 35: All-causality and Drug-related AEs Leading to Death - All Treated Subjects who Died during the On-Treatment or Post-Treatment Follow-up Period in CA209577 (Feb-2021 Database Lock)

All Treated Subjects	Nivolumab N = 532	Placebo N = 260
All-causality AEs Leading to Death, n (%)	35 (6.6)	21 8.1)
Grade 5 AEs, n (%)[a]	28 (5.3)	18 (6.9)
Drug-related AEs Leading to Death, n (%)	0	0

Table 36: Onset, Management, and Resolution of Drug-Related Select Adverse Events - Nivolumab Treated Subjects (Updated Analysis: 18-Feb-2021 DBL)

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AEs	Median Time to Onset of Drug-related Select AEs (range), wks	% Treated Subj. with Drug-related Select AEs Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median[b] Time to Resolution of Drug-related Select AEs[c,d] (range[e]), wks	% Subj. with Drug-related Select AEs that Resolved[c,d]
Endocrine	17.7 / 0.9	9.71 (1.7 - 52.4)	0.9	10.6 / 4.3	22.79 (2.0 - 183.9+)	70.2
Gastrointestinal	17.3 / 0.8	7.21 (0.1 - 49.3)	0.8	9.8 / 8.7	3.00 (0.1 - 114.7+)	95.5
Hepatic	9.4 / 1.1	6.21 (1.1 - 49.3)	0.9	14.0 / 14.0	8.00 (0.6 - 159.1+)	78.7
Pulmonary	4.3 / 1.1	12.71 (4.0 - 47.9)	2.4	73.9 / 60.9	6.29 (0.7 - 99.0+)	78.3
Renal	1.3 / 0.2	12.14 (1.9 - 37.1)	0	28.6 / 28.6	2.64 (0.7 - 17.0)	100
Skin	24.6 / 1.3	6.00 (0.1 - 49.0)	1.5	38.9 / 3.1	17.14 (0.1 - 197.0+)	70.2
Hypersensitivity/ Infusion Reaction	2.1 / 0	10.00 (0.1 - 48.4)	0	18.2 / 9.1	4.14 (0.1 - 36.1)	100

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 European Union (EU), and for other indications as monotherapy (eg, metastatic non-small cell lung cancer [NSCLC], advanced renal cell carcinoma [RCC], classical Hodgkin lymphoma [cHL], squamous cell carcinoma of the head and neck [SCCHN], urothelial carcinoma [UC], and esophageal squamous cell carcinoma (ESCC). In US, nivolumab monotherapy was also approved for hepatocellular carcinoma [HCC], microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR] metastatic colorectal cancer [CRC], and small cell lung cancer [SCLC]).

Based on pharmacovigilance activities conducted by Bristol Myers Squibb (BMS) World Wide Patient Safety, review of postmarketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab. The safety profile of nivolumab in the postmarketing setting remains favourable. Postmarketing data for nivolumab are subject to continued 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.

2.5.1. Discussion on clinical safety

Safety data to support the positive benefit/risk of adjuvant nivolumab in subjects with oesophageal cancer (EC), or gastro-oesophageal junction cancer (GEJC) who have received neoadjuvant chemoradiotherapy (CRT) followed by surgery is based on the results of Study CA209577.

All patients presented with ECOG 1-2, Stage II or III disease with confirmed adenocarcinoma or squamous cell histology and should have completed neoadjuvant platinum-based chemoradiotherapy and complete resection 4-16 weeks prior to randomization.

Patients were randomized 2:1 to receive nivolumab (N=532) or placebo (N=262) until disease recurrence or unacceptable toxicity for a maximum treatment duration of one year. Up to the cut-off date (3-Jul-2020), 50 patients were still on treatment (31 subjects in the nivolumab arm and 19 in the placebo arm) and 328 (41.4%) subjects had completed treatment. From these 328 patients, 229 (43%) from the nivolumab group and 99 (38.1%) from the placebo group had completed one year treatment. On the other hand, 149 (28%) subjects from the nivolumab arm and 113 (43.5%) from the placebo arm had discontinued treatment due to disease recurrence. Study drug toxicity was the reason for not continuing in the treatment period for 57 (10.7%) patients in the nivolumab group and 8 (3.1%) patients in the placebo group. Median duration of study treatment was 10.14 months for the nivolumab arm and 8.99 months for the placebo arm.

As there is not any licensed treatment in the adjuvant setting, placebo as comparator is acceptable but some consideration must be given to the fact that any toxicity, even mild, is added to, otherwise, subjects whose care would be limited to observation and a strict clinical follow-up.

Minimum and median follow-up was 6.2 months and 24.4 months, respectively. Bearing in mind that clinical cut-off was May 2020 and 50 patients were still on treatment, the MAH was requested to provide updated safety data in order to review this assessment with longer follow-up for all patients, especially important with immunotherapy treatment, as long-term and delayed toxicities are quite common.

Regarding baseline disease characteristics, initial performance status was well balanced between both arms, with 308 (57.9%) subjects in the nivolumab group and 156 (59.5%) in the placebo group reported ECOG 0 and the rest of patients ECOG 1. In addition, median baseline weight was 70.90 kg in the nivolumab group and 73.60 kg in the placebo group. According to ESMO clinical guidelines, the nutritional status and body mass index (BMI) should be recorded for all patients so the MAH was asked to provide data from subjects BMI to give an idea of the nutritional status which, along with weight loss, confers not only an increased operative risk but, also, worsens a patient's quality of life and is associated with poor survival in advanced disease (Lordick F. et al. 2016). No relevant differences regarding BMI or weight, from baseline to the end of follow-up, were identified.

Any grade AEs were reported in 510 (95.9%) subjects in the nivolumab arm and 243 (93.5%) subjects in the placebo arm. The most common AEs were: diarrhoea (29.1% nivolumab vs. 29.2% placebo), fatigue (27.1% vs. 24.2%), and nausea (22.7% vs. 21.2%). Grade 3-4 AEs were reported in 183 (34.4%) subjects in the nivolumab arm, and 84 (32.3%) subjects in the placebo arm. The most frequently reported Grade 3-4 AEs were pneumonia (2.6% vs. 1.5%), fatigue (1.3% vs. 1.2%) and hypertension (1.1% vs. 1.2%).

Drug-related AEs were reported more frequently with nivolumab than placebo (70.7% vs. 45.8%), being the most commonly reported: diarrhoea (16.5% vs. 15%), fatigue (16.9% vs. 11.2%) and pruritus (1% vs. 3.5%); with Grade 3-4 drug-related AEs reported by 13.3% and 5.8% of subjects, respectively.

Due to the immaturity of OS data at the time of this IA, the MAH remained blinded to deaths by treatment arm so no information about these events has been included in this submission but, based on the review of SAEs, one Grade 5 drug-related SAE was reported in the nivolumab group. The identified PT was cardiac arrest but the causality of this event was amended by the investigator, after the data cut-off, and labelled as not-related to treatment. Also, there was a Grade 5 reported SAE of

pneumonia aspiration. It is expected that, with a later OS IA, deaths, especially those related to AEs, can be properly assessed.

Serious adverse events were reported in 158 (29.7%) subjects in the nivolumab arm vs. 78 (30.0%) subjects in the placebo arm. Similar incidences were reported in both groups for Grade 3-4 SAEs (20.1% vs. 20.4%). Pneumonia (any grade) was reported in 3% of subjects in the nivolumab group and 1.9% in the placebo group and Grade 3-4 pneumonia in 2.4% of patients in the nivolumab arm and 1.2% in the placebo treatment arm. Gastrointestinal disorders of dysphagia, diaphragmatic hernia and oesophageal stenosis were reported as SAEs with similar incidences in both treatment groups, as could be expected due to the disease nature and post-operative complications.

Regarding AEs leading to treatment discontinuation, these were reported in 68 (12.8%) subjects in the nivolumab arm and 20 (7.7%) in the placebo arm. The most commonly reported AEs leading to discontinuation in both groups were pneumonitis (1.9% nivolumab vs. 0.8% placebo), malignant neoplasm progression (0.9% vs. 1.5%), pleural effusion and ALT increased (0.4% both). There were also some causes for discontinuation in the nivolumab arm that were not reported for the placebo arm: rash (0.6%), myocarditis (0.6%), sepsis, pruritus and autoimmune hepatitis (0.4%). There were also some dose delays due to AEs. Three subjects discontinued treatment due to grade 4 myocarditis but all 3 had cardiovascular risk factors and have received neoadjuvant chemotherapy and chest radiotherapy, which could have impacted on this AE.

Updated safety data, based on a later DBL (Feb-2021) was provided, upon request. Overall, safety results remain quite similar to the ones previously reported (DBL Jul-2020). There were slight increases in the number of patients who reported some drug-related select AEs, expected with longer follow-up, but no new remarkable safety information has emerged. No changes in most common AEs or drug-related AEs have been observed, keeping the same order in incidence. With the updated safety data submitted, no changes in the nivolumab safety profile have been identified in this adjuvant setting.

As seen in other nivolumab studies, some select AEs have been identified based on their causality (not seen with non-immunotherapies), management (corticosteroids) and the fact that early recognition and treatment might prevent severe toxicity. This selection included endocrine, gastrointestinal, hepatic, pulmonary, renal, skin and hypersensitivity. It is acknowledged that most of these events are widely known from other immunotherapy studies, but it is remarkable how, in this study, only 66.7% of subjects with endocrine events, 73.9% for pulmonary and 65.4% with skin events were considered resolved, meaning that patients still needed corticosteroids treatment or presented long-term toxicity symptoms. According to the MAH, some endocrine select AEs were not considered resolved due to continuous need for hormone replacement therapy and the MAH was asked to provide further information about the management of these patients with unresolved toxicity, including the concomitant medications used. Based on the updated safety data, a total of 86 subjects reported unresolved drug-related select AEs, including 28 in category of endocrine, 4 gastrointestinal, 10 hepatic, 5 pulmonary, and 39 skin. Seven subjects reported Grade 3 or 4 unresolved drug-related selected AEs, including one of each for type 1 diabetes mellitus, increased blood alkaline phosphatase (ALP), increased AST, increased ALT, pneumonitis, psoriasis, and rash. As originally assessed, there were 21 subjects with unresolved hypothyroidism, most of them treated and 4 with unresolved pneumonitis. Quite remarkable are also figures for skin AEs, with several patients presenting unresolved rash and pruritus, most of them needing concomitant treatment. Overall, nivolumab safety profile in this new setting remains the same as observed with other indications but prescribers need to be aware of some long-term toxicities which may occur.

Some Grade 3-4 electrolytes abnormalities were reported for subjects in the nivolumab group. Data about subjects who reported Grade 3-4 electrolytes abnormalities were provided to see if they had

reported AE of diarrhoea. Only 7/19 subjects reported diarrhoea and all of them were Grade 1-2. Apparently, no cases of electrolytes abnormalities were caused by diarrhoea. Overall, reported electrolytes abnormalities did not have a relevant clinical impact. Most of them were resolved without medical intervention and only two of the events led to a delay in the administration of nivolumab.

The most commonly reported immune-mediated AEs (treated with immunosuppression) were hypothyroidism/thyroiditis (11.1%), rash (7.9%), hyperthyroidism (6.6%) and pneumonitis (4.5%) in the nivolumab arm. No new IMAE were identified in this study.

An infusion time of 30 min for the 480 mg Q4W dose has been used in study CA209577 while, for previous indications, the infusion time was 60 min. Infusion interruptions and infusion rate reductions were reported in a low percentage of patients, suggesting that tolerability of this reduced infusion rate was acceptable.

A comparison between safety results from Study CA209577 and results across pooled monotherapy studies in different indications and posologies have been provided, also as a justification for adverse reactions included in Section 4.8 of the SmPC. Overall, AEs incidences were comparable although some differences were found. In Study CA209577, any grade AEs were reported for the 95.9% of subjects while this was reported for 97.2% of the monotherapy pooled subjects. In the same way, Grade 3-4 AEs were reported for 34.4% vs. 43.8% respectively. Using re-mapped terms (occurring in at least 10% of subjects), most of them were reported in a slightly higher incidence in monotherapy pooled studies and this could be related to the fact that most of the studies were performed in advanced or metastatic settings where patients' general status could be worse than in the adjuvant setting. The incidences of drug-related diarrhoea, transaminases increased, hypothyroidism, and hyperthyroidism are numerically higher in CA209577 nivolumab group compared to nivolumab pooled monotherapy group. Also, for all-causality AEs, incidence was higher in Study CA209577 for dysphagia (13.0% vs. 4.6%) and weight decreased (13.0% vs. 8.7%), which could be related to the disease nature, as already discussed. In fact, as the pooled monotherapy studies included safety results from study CA209577, and due to these differences above detailed, the MAH provided the same comparison between safety data from this study and the pooled monotherapy studies, excluding study CA209577, in order to properly assess if these results can indeed be presented pooled in the PI. Similar results than the above discussed were observed and the approach proposed by the MAH is considered acceptable.

2.5.2. Conclusions on clinical safety

Overall, the safety data from Study CA209577 are consistent with the already known safety profile of nivolumab and no new risks have been identified. However, this study has been performed in a new clinical scenario: oesophagus or GEJ carcinoma adjuvant setting, where no other treatments have been licensed yet, so nivolumab toxicity, although known and relatively manageable, is not minor and long-term follow-up is considered necessary for these patients.

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 22.2 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

The CHMP endorsed the Risk Management Plan version 22.2 with the following content:

Safety concerns

Table 37: 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 38: 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				

Table 38: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
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, solid organ transplant rejection, and VKH), and infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCT Ongoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission	With PSUR starting at DLP 03-Jul-2017 06-2019 4Q2022

Risk minimisation measures

Table 39: Summary of Risk Minimization Measures

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

Table 39: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Other immune-related ARs		
Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse

Table 39: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
and/or renal impairment	SmPC Sections 4.2 and 5.2	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. Update of the Product information

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

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

OPDIVO (nivolumab) is a programmed death receptor-1 (PD-1) blocking antibody. Nivolumab as a single agent has been approved in the United States (US), European Union (EU), Japan, and several other countries. Initial and subsequent approvals have resulted in indications for the treatment of patients with melanoma, non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), and oesophageal squamous cell carcinoma (OSCC).

3.1.1. Disease or condition

EC is the seventh most common cancer globally in terms of incidence with over 572,000 new cases annually. It is the sixth most common cause of deaths, accounting for over 500,000 deaths annually worldwide (see Section 1.2 for references). The appropriate management of locally advanced disease has been contentious for a number of years, and no standard of care worldwide has been clearly defined.

3.1.2. Available therapies and unmet medical need

Neoadjuvant CRT followed by surgery (trimodality therapy) is the mainstay in the curative treatment of resectable locally advanced EC or GEJC and is a widely accepted standard of care in these patients. However, the risk of disease recurrence following trimodality therapy remains high, with 70% - 75% of patients failing to achieve pathologic complete response (pCR) after trimodality therapy, and a prognosis worse than that for patients with pCR.

There is a medical need for novel treatment strategies in both EC and GEJC. Anti-PD-L1 immunotherapy, nivolumab, is being investigated for the treatment of patients with advanced GC, including OC and GEJC. Nivolumab monotherapy has been approved for previously treated OSCC in the EU, US, Japan, and Brazil, as well as previously treated GC in Japan and China.

3.1.3. Main clinical studies

In support of this application, the MAH has submitted efficacy and safety results from Study CA209577: a phase 3, ongoing, randomized, double-blind, placebo controlled study comparing nivolumab versus placebo in adults subjects with Grade II-III oesophageal or GEJ cancer (squamous cell carcinoma or adenocarcinoma) who underwent CRT followed by complete resection and who have residual pathologic disease.

A total of 794 patients were randomized in a 2:1 ratio to receive either nivolumab 240 mg IV Q2W for 16 weeks (Cycles 1 8), followed by nivolumab 480 mg IV Q4W until recurrence or discontinuation from study up to 1 year or placebo with the same dosing schedule and treatment duration. Subjects were stratified by histology [squamous cell carcinoma (SCC) vs. adenocarcinoma (AC)], pathologic lymph node status (positive ≥yN1 vs. negative ypN0) and tumour cell PD-L1 status (≥1% vs. <1% or indeterminate or non-evaluable).

The primary endpoint was DFS, assessed by the investigator and, as exploratory endpoints, DMFS and PFS2 were also assessed. Prognostic value of PD-L1 expression, safety and PROs were also analysed in this study. OS was a secondary endpoint, to be tested hierarchically after DFS.

3.2. Favourable effects

The primary endpoint of DFS was statistically significant for nivolumab vs. placebo (HR = 0.69 [96.4% CI: 0.56, 0.86], stratified log-rank test p-value = 0.0003; significance level = 0.036) in subjects with resected OC or GEJC who received CRT prior to surgery and had residual pathologic disease (see Section 4.3), based on results from the primary analysis (DBL 03-Jul-2020). Median DFS was significantly higher in the nivolumab arm compared with placebo: 22.41 (95% CI: 16.62, 34.00) vs. 11.04 (95% CI: 8.34, 14.32) months.

Subgroup analyses of DFS also favoured nivolumab:

- Histology: SCC (n=230), HR=0.61 (95% CI: 0.42, 0.88) and AC (n=563), HR=0.75 (95% CI: 0.59, 0.96).
- Pathologic lymph node status: positive (≥ypN1) (n = 457): HR=0.67 (95% CI: 0.53, 0.86) and negative (ypN0) (n = 336): HR=0.74 (95% CI: 0.51, 1.06).
- PD-L1 status: PD-L1 ≥1% (n = 129): HR = 0.75 (95% CI: 0.45, 1.24), PD-L1 <1% (n = 570): HR = 0.73 (95% CI: 0.57, 0.92) and Indeterminate/non-evaluable PD-L1 (n = 95): HR = 0.54 (95% CI: 0.27, 1.05).

Exploratory endpoints (DMFS and PFS2) showed benefit for nivolumab over placebo. Median DMFS (95% CI) was numerically longer in the nivolumab arm compared with the placebo arm: 28.32 (21.26, N.A.) vs. 17.61 (12.45, 25.40) months, with a HR of 0.74 (95% CI: 0.60, 0.92). A total of 263 PFS2 events were reported for 163 (30.6%) subjects in the nivolumab arm and 100 (38.2%) subjects in the placebo arm. PFS2 HR: 0.77 (95% CI: 0.60, 0.99) favoured nivolumab over placebo. Median PFS2 was not reached in the nivolumab arm and was 32.07 (95% CI: 24.15, N.A.) months in the placebo arm.

Sensitivity analyses of the primary endpoint confirmed the above-mentioned results. Since the primary analysis of DFS included censoring for new anti-cancer treatment, which is not in line with the EMA anticancer guideline (EMA/CHMP/205/95 Rev.5), a sensitivity analysis was performed for DFS without censoring for new anti-cancer treatment. Results per both definitions were consistent, which is reassuring. In addition, a post-hoc analysis of DFS by extent of follow-up was performed in subsets of randomized subjects with 1 and 2-year minimum follow-up that also concurred with the main analysis.

An updated descriptive efficacy analysis of DFS, DMFS and PFS2 was performed, based on data from a later cut-off (DBL 18-Feb-2021), with a minimum follow-up of 14 months and a median follow-up of 32.2 months. DFS HR for nivolumab vs. placebo was 0.67 (95% CI: 0.55, 0.81), median DFS (Feb-2021) was 22.41 (95% CI: 16.95, 33.64) months for nivolumab and 10.35 (95% CI: 8.31, 13.93) months for the placebo arm. DMFS HR for nivolumab vs. placebo was 0.71 (95% CI: 0.58, 0.87). PFS2 HR was the same as previously reported in the primary analysis, HR = 0.77 (95% CI: 0.61, 0.96) and median PFS2 was not reached for nivolumab in either case and was of 30.72 months for the placebo arm according to the latest analysis. Sensitivity analysis for the primary endpoint (DFS) accounting for assessments on/after subsequent therapy was repeated and its results were consistent with the previous ones and also with the updated results for DFS in this new DBL.

Updated subgroup analyses of DFS also favoured nivolumab and were consistent with data previously reported.

3.3. Uncertainties and limitations about favourable effects

The statistically significant improvement in DFS reported in study CA209577, with a median follow up of 24.4 months and more than 50% event rate in the placebo group, was considered indicative of clinical benefit in the intended adjuvant setting, but an update of the DFS and DMFS results with longer follow-up, a summary of DFS event rates per three months for each study arm, separately, and any other relevant efficacy results that may be available (e.g. updated PFS2 data) was requested. Updated efficacy data (i.e. DFS, DMFS and PFS2) with a longer follow-up remained consistent with the primary analysis.

OS data are immature and no data from the 49.6% OS events having accumulated at the July 2020 DBL (IA1) were provided in the initial submission, as the pre-specified boundary for declaring the statistical significance of p = 0.003 was not met. Even if the absence of formally submitted OS data constitutes a limitation in the context of an adjuvant treatment being proposed, in view of the expected relatively short post recurrence survival time, and the known safety profile of nivolumab, a

detrimental effect on OS is considered very unlikely and the provided updated DFS results are considered sufficient to support clinical benefit in the intended treatment setting. This having said, results of the planned second IA (planned at approximately 80% (~368) of OS events) and final analysis for OS should be provided when available, as an annex 2 condition, to confirm DFS results.

Although a sound justification for the selected treatment duration in study CA209577 has not been provided, the approach proposed by the MAH can be considered acceptable and in line with that used in other adjuvant trials/settings such as melanoma (CA209238) and muscle invasive urothelial carcinoma (CA209274), although the latter is currently under review (EMEA/H/C/003985/II/0100).

In line with what observed with nivolumab in other development programs the benefit/risk in older patients (≥75 years) is less clear, with few patients pertaining to this subgroup enrolled in the study. The limited evidence available precludes any definitive recommendation in this particular population.

3.4. Unfavourable effects

In study CA209577, any grade AEs were reported in 510 (95.9%) subjects in the nivolumab arm and 243 (93.5%) subjects in the placebo arm. The most common AEs were: diarrhoea (29.1% nivolumab vs. 29.2% placebo), fatigue (27.1% vs. 24.2%), and nausea (22.7% vs. 21.2%). Grade 3-4 AEs were reported in 183 (34.4%) subjects in the nivolumab arm, and 84 (32.3%) subjects in the placebo arm. One Grade 5 AE was reported in the nivolumab arm for the PT: cardiac arrest.

Drug-related AEs were reported more frequently with nivolumab than placebo (70.7% vs. 45.8%), being the most commonly reported: diarrhoea (16.5% vs. 15%), fatigue (16.9% vs. 11.2%) and pruritus (1% vs. 3.5%); with Grade 3-4 drug-related AEs reported by 13.3% and 5.8% of subjects, respectively.

Grade 5 AEs were reported for 9 (1.7%) subjects in the nivolumab group and 6 (2.3%) in the placebo group.

Serious adverse events were reported in 158 (29.7%) subjects in the nivolumab arm vs 78 (30.0%) subjects in the placebo arm. Similar incidences were reported in both groups for Grade 3-4 SAEs (20.1% vs. 20.4). Pneumonia (any grade) was reported in 3% of subjects in the nivolumab group and 1.9% in the placebo group and Grade 3-4 pneumonia in 2.4% of patients in the nivolumab arm and 1.2% in the placebo treatment arm.

Regarding AEs leading to treatment discontinuation, these were reported in 68 (12.8%) subjects in the nivolumab arm and 20 (7.7%) in the placebo arm. The most commonly reported AEs leading to discontinuation in both groups were pneumonitis (1.9% nivolumab vs. 0.8% placebo), malignant neoplasm progression (0.9% vs. 1.5%), pleural effusion and ALT increased (0.4% both). There were also some causes for discontinuation in the nivolumab arm that were not reported for the placebo arm: rash (0.6%), myocarditis (0.6%), sepsis, pruritus and autoimmune hepatitis (0.4%). There were also some dose delays due to AEs.

As seen with other nivolumab studies, some select AEs have been identified based on their causality (not seen with non-immunotherapies), management (corticosteroids) and the fact that early recognition and treatment might prevent severe toxicity. This selection included endocrine, gastrointestinal, hepatic, pulmonary, renal, skin and hypersensitivity.

Some Grade 3-4 electrolytes abnormalities were reported for subjects in the nivolumab group: hyponatremia G3 7 subjects and G4 2 subjects, hyperkalemia G3 3 subjects, hypokalemia G4 2 subjects, hypocalcemia G4 one subject.

The most commonly reported immune-mediated AEs (treated with immunosuppression) were hypothyroidism/thyroiditis (11.1%), rash (7.9%), hyperthyroidism (6.6%) and pneumonitis (4.5%) in the nivolumab arm.

A comparison between safety results from Study CA209577 and results across pooled monotherapy studies in different indications and posologies have been provided. Overall, AEs incidences were comparable, although some differences were found. Any grade AEs were reported for the 95.9% of subjects while this was reported for 97.2% of the monotherapy pooled subjects. In the same way, Grade 3-4 AEs were reported for 34.4% vs. 43.8% respectively. Using re-mapped terms (occurring in at least 10% of subjects), most of them were reported in a slightly higher incidence in monotherapy pooled studies and this could be related to the fact that most of the studies were performed in advanced or metastatic settings where patients' general status could be worse than in the adjuvant setting. The incidences of drug-related diarrhoea, transaminases increased, hypothyroidism, and hyperthyroidism are numerically higher in CA209577 nivolumab group compared to nivolumab pooled monotherapy group. Also, for all-causality AEs, incidence was higher in Study CA209577 for dysphagia (13.0% vs. 4.6%) and weight decreased (13.0% vs. 8.7%).

3.5. Uncertainties and limitations about unfavourable effects

Minimum and median follow-up was 6.2 months and 24.4 months, respectively. Bearing in mind that clinical cut-off was May 2020, treatment is recommended up to 12 months and 50 patients were still on treatment, this follow-up is still considered low, especially with immunotherapy treatment, as long-term and delayed toxicities are quite common. Updated safety data, with a minimum follow-up of 14 months and a median follow-up time of 32.2 months was provided and no changes in the nivolumab safety profile were identified which is reassuring.

No deaths data have been provided due to the immaturity of the OS data in this IA, only a review of reported Grade 5 AEs has been included.

In this study, there were relatively high percentage of endocrine, pulmonary and skin AEs which were not considered resolved, meaning that those patients still needed concomitant treatment or presented long-term toxicity symptoms after the end of the treatment period. Overall, nivolumab safety profile in this new setting remains the same as observed with other indications but prescribers need to be aware of some long-term toxicities which may occur.

3.6. Effects Table

Table 40: Effects Table for Nivolumab for adjuvant treatment of patients with resected EC or GEJC (data cut-off: 03-Jul-2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
			Nivolumab (N=532)	**Placebo (N=262)**		
Primary endpoint						
DFS	Disease Free Survival	Median months (95% CI)	22.41 (16.62, 34.00)	11.04 (8.34, 14.32)	HR=0.69 (96.4% CI: 0.56, 0.86) p-value = 0.0003	CSR

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
6-month DFS rate		% (95% CI)	72.3 (68.2, 76)	63.4 (57.2, 69)		CSR
Secondary endpoint						
Overall survival data – not available						
Exploratory endpoints						
DMFS	Distant Metastasis Free Survival	Median months (95% CI)	28.32 (21.26, N.A.)	17.61 (12.45, 25.40)	HR=0.74 (95% CI: 0.60, 0.92)	CSR
PFS2	Progression-Free Survival on Subsequent Systemic Therapy	Median months	N.A.	32.07	HR=0.77 (95% CI:0.60, 0.99)	CSR
Unfavourable Effects						
			Nivolumab (N=532)	**Placebo (N=260)**		
AEs		N (%)	510 (95.9%)	243 (93.5%)		
Drug-related AE		N (%)	376 (70.7%)	119 (45.8%)		
Grade 3-4		N (%)	183 (34.4%)	84 (32.3%)		
Drug-related G3-4 AEs		N (%)	71 (13.3%)	15 (5.8%)		
Grade 5		N (%)	9 (1.7%)	6 (2.3%)		
SAEs		N (%)	158 (29.7%)	78 (30.0%)		
Drug-related SAEs		N (%)	40 (7.5%)	7 (2.7%)		
AEs leading to discontinuations		N (%)	68 (12.8%)	20 (7.7%)		
Drug-related AEs leading to discontinuation		N (%)	48 (9.0%)	8 (3.1%)		

Abbreviations: DFS=disease free survival, DMFS=distant metastasis free survival, PFS2=progression-free survival after subsequent systemic therapy, OS=overall survival, HR= hazard ratio, CI= confidence interval, CSR= clinical study report, AE= adverse event, SAE= serious adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Adult patients with grade II-III oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy and complete resection of the tumour are at risk of disease recurrence and are therefore considered candidates for adjuvant treatment.

The reported DFS results in study CA209577 showed an advantage for nivolumab compared to placebo in the intended adjuvant setting. The reported DFS benefit was observed in almost all the predefined subgroups and subsets, and was confirmed by multiple sensitivity analyses. The results are also supported by exploratory endpoints (DMFS and PFS2), although it is acknowledged that only 32.1% of the study population had been treated with subsequent systemic therapy, so the value of PFS2 results is limited at this point.

Nivolumab safety profile is widely known and no additional important risks have been identified in this study.

Updated safety data as well as an update of the efficacy results with longer follow up were requested in order to update this benefit/risk assessment. Unfortunately, OS data are still immature so they cannot support this assessment. Even if this constitutes a limitation in the context of an adjuvant treatment being proposed, in view of the expected relatively short post recurrence survival time, and the known safety profile of nivolumab, a detrimental effect on OS is considered very unlikely and the provided updated DFS results and additional analyses are considered sufficient to support clinical benefit in the intended treatment setting. Results of the planned second IA and final analysis for OS will be provided when available, as an annex 2 condition, to confirm DFS results.

3.7.2. Balance of benefits and risks

The statistically significant improvement in DFS initially reported in study CA209577 has been confirmed by updated efficacy data with a longer follow-up submitted during the procedure and that remained consistent with the primary analysis. The observed improvement in DFS is consistent across most pre-defined subgroups including histology, lymph node status and PD-L1 tumour cell expression and results are supported by exploratory endpoints, e.g. DMFS and PFS2. Updated data for these endpoints have also been provided supporting the initial findings. Even if lack of OS data to support this assessment constitutes a limitation, in view of the expected relatively short post recurrence survival time (and the known safety profile of nivolumab) a detrimental effect on OS is considered very unlikely and the provided updated DFS results and additional analyses are considered sufficient to support clinical benefit in the intended treatment setting.

Overall, the safety data from study CA209577 are consistent with the already known safety profile of nivolumab and no new risks have been identified.

3.8. Conclusions

Based on the above, the overall B/R of OPDIVO for the applied indication is considered positive.

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

Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as

adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer, the MAH should submit the OS data from the second interim analysis and the final OS analysis of the Phase III study CA209577 by 30 September 2024.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication to include adjuvant treatment of adult patients with oesophageal, or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy for OPDIVO (study CA209577) as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 22.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics, Annex II 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, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer, the MAH should submit the OS data from the second interim analysis and the final OS analysis of the Phase III study CA209577.	By 30th September 2024

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-0095'

[i] A Randomized, Multicenter, Double-Blind, Phase III Study of Adjuvant Nivolumab or Placebo in Subjects with Resected Esophageal, or Gastroesophageal Junction Cancer (Study CA209577); Primary Clinical Study Report. Bristol-Myers Squibb Company; 2020. Document Control No. 930160038.

[ii] Liu C, Yu J, Li H, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. Clin Pharmacol Ther 2017;101:657-66.

[iii] Primary Clinical Study Report for Study CA209577: A Phase 3, randomized, double-blind, placebo-controlled study of adjuvant nivolumab in subjects with resected esophageal cancer (EC), or gastroesophageal junction (GEJ) cancer who have received chemoradiotherapy (CRT) followed by surgery. Bristol Myers Squibb; 2020. Document Control No. 930160038.