26 April 2018
EMA/CHMP/634022/2018

Withdrawal assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0039

Note

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

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Assessment Timetable

Timetable	Planned dates	Actual dates
Start of procedure:	16 September 2017	16 September 2017
CHMP Co-Rapporteur Assessment Report	10 November 2017	14 November 2017
CHMP Rapporteur Assessment Report	10 November 2017	15 November 2017
PRAC Rapporteur Assessment Report	17 November 2017	22 November 2017
PRAC members comments	22 November 2017	N/A
Updated PRAC Rapporteur Assessment Report	23 November 2017	N/A
PRAC Outcome	30 November 2017	30 November 2017
CHMP members comments	4 December 2017	4 December 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 December 2017	7 December 2017
1st Request for Supplementary Information	14 December 2017	14 December 2017
Submission:	23 February 2018	20 February 2018
Re-start:	26 February 2018	26 February 2018
CHMP Rapporteur Assessment Report	26 March 2018	26 March 2018
PRAC Rapporteur Assessment Report	28 March 2018	28 March 2018
PRAC members comments	4 April 2018	4 April 2018
Updated PRAC Rapporteur Assessment Report	5 April 2018	n/a
PRAC Outcome	12 April 2018	12 April 2018
CHMP members comments	16 April 2018	16 April 2018
Updated CHMP Rapporteur Assessment Report	19 April 2018	20 April 2018
2nd Request for Supplementary Information	26 April 2018	26 April 2018
Submission:	29 May 2018	29 May 2018
Re-start:	30 May 2018	30 May 2018
PRAC Rapporteur Assessment Report	4 June 2018	4 June 2018
PRAC members comments	6 June 2018	6 June 2018
Updated PRAC Rapporteur Assessment Report	7 June 2018	7 June 2018
CHMP Rapporteur Assessment Report	13 June 2018	13 June 2018
PRAC Outcome	14 June 2018	14 June 2018
CHMP members comments	18 June 2018	18 June 2018
Updated CHMP Rapporteur Assessment Report	21 June 2018	22 June 2018
OE/Opinion	28 June 2018	28 June 2018

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List of abbreviations

ADA	anti-drug-antibody
ADR	Adverse Drug Reaction
AE	adverse event
ASR	age-standardized incidence rate
BMS	Bristol-Myers Squibb
BSC	best supportive care
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CTLA	cytotoxic T-lymphocyte antigen
DOR	duration of response
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
GEJ	gastro-esophageal junction
GC	gastric cancer
GCP	Good Clinical Practice
GI	gastrointestinal
HCC	hepatocellular carcinoma
HLGT	High-level Group Term
HR	hazard ratio
ICH	International Conference on Harmonisation
IMM	immune-modulating medication
IND	Investigational New Drug
I-O	immuno-oncology
ITT	intention to treat
IV	intravenous(ly)
LDH	lactate dehydrogenase
MAA	Marketing Authorization Application
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	high-level microsatellite instability
MSI-L	low-level microsatellite instability

MSI-S	microsatellite stable
NIH	National Institutes of Health
NSCLC	non-small cell lung cancer
Ono	ONO Pharmaceutical Co. Ltd
ORR	objective response rate
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PI	product information
PK	pharmacokinetic
PPK	population pharmacokinetic
PR	partial response
PRAC	Pharmacovigilance Risk Assessment Committee
PS	performance status
PSUR	Periodic Safety Update Report
PT	preferred term
OS	overall survival
Q2W	every 2 weeks
RCC	renal cell carcinoma
RMP	Risk Management Plan
S-1	tegafur/gimeracil/oteracil potassium
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy
SCLC	small cell lung cancer
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	standard of care
TCGA	The Cancer Genome Atlas
TNM	Tumor Node Metastasis
US	United States
VAS	visual analogue scale
WHO	World Health Organization

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 23 August 2017 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, II and IIIB

Extension of Indication to include treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer after two or more prior systemic therapies, based on data from study ONO-4538-12. As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated.

The Annex II and Package Leaflet are updated in accordance. The RMP version 11.0 has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0064/2014 on the agreement of a paediatric investigation plan (PIP) and on the granting of a deferral and on the granting of a waiver for nivolumab.

Information relating to orphan market exclusivity

N/A

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP nor at national agencies for this indication.

2. Scientific discussion

2.1. Introduction

Nivolumab (Opdivo, BMS-936558, MDX-1106, ONO-4538) is a human immunoglobulin G4 monoclonal antibody that binds to the programmed death-1 (PD-1) T-cell membrane receptor and thereby blocks its interaction with PD-1 ligand 1 (PD-L1 or B7-H1) and PD-1 ligand 2 (PD-L2). PD-1 functions as an immune checkpoint and is a negative regulator of T cell activity which has been shown to control T cell immune response. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by 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, by blocking binding of PD-L1 and

PD-L2 ligands to PD-1 receptor, potentiates T cell responses, including anti-tumour response, in a proportion of patients.

GC/GEJ Cancer

GC is the third most common cause of cancer death worldwide. In 2012, there were nearly 1 million (952,000) new cases of GC and 723,000 deaths from GC reported globally. The geographic distribution, however, is varied across the globe, with the highest burden of disease seen in Eastern and Western Asia, Central and Eastern Europe, South America, and Central America.

GEJ cancer anatomically straddles the distal esophagus and proximal stomach. Due to its location and given that, like GC, the majority of GEJ tumors are adenocarcinomas, GEJ tumors are frequently grouped together with GC in advanced settings.

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

The vast majority of GC and GEJ cancers are adenocarcinomas, which are most frequently classified based on Lauren's criteria as either intestinal subtype or diffuse subtype. The intestinal subtype most commonly occurs in elderly men, affects the gastric antrum, and has a better prognosis. In contrast, the diffuse subtype is associated with younger age and exhibits a predilection for females, it usually affects the body of the stomach, and has worse prognosis compared to the intestinal type. The 2 subtypes share common dietary and environmental factors; however, the intestinal type is associated with more environmental factors and the diffuse type usually has a genetic etiology. The prognostic significance has been described in the 2 subtypes, but the treatments in patients are the same regardless of classification.

The Cancer Genome Atlas (TCGA) Research Network evaluated the molecular characteristics in 295 Western GC patients, and proposed 4 different sub-types: tumors positive for Epstein–Barr virus, microsatellite unstable tumors (MSI), genomically stable tumors, and tumors with chromosomal instability. Similarly, the Asian Cancer Research Group analyzed the molecular characteristics in 300 Asian patients with primary GC disease with MSS based different subtypes. While some differences in the nature of molecular characteristics are observed between Asian and Western patients, for well-defined subsets including MSI, the frequency in both populations is generally similar.

GC often presents as advanced disease upon diagnosis, comprising approximately 40% of newly diagnosed cases in the US and Europe and approximately 20% in Japan and Korea, where early detection is common. At the time of diagnosis the reported 5-year survival is approximately 30% for those with advanced disease. Patients with localized disease are candidates for multimodality therapy such as surgery, radiation, and chemotherapy, which has offered a survival advantage over curative surgery alone. Unfortunately, however, more than 60% of patients will develop locally recurrent or metastatic disease.

Standard Treatments for Advanced or Recurrent Gastric and GEJ Cancer

Advanced metastatic or recurrent GC or GEJ cancer, regardless of region or ethnicity, is an aggressive disease and is associated with poor prognosis. Currently approved standard of care (SOC) systemic therapies are similar across regions and offer limited benefit in metastatic disease:

Table 1. Currently Approved Classes of Agents in Gastric/Gastro-esophageal Junction Cancer

Gastric/Gastro-esophageal Junction Cancer Guidelines	1L Treatment	2L Treatment	3L Treatment
ESMO/Japanese Guidelines	Platinum/fluoropyrimidine[a] ± Taxane or Epirubicin Trastuzumab for HER2 positive tumor	• Taxane ± Ramucirumab • Irinotecan	No recommended therapies
NCCN	Platinum/fluoropyrimidine ± Taxane or Epirubicin Trastuzumab for HER2-positive tumors	• Taxane ± Ramucirumab • Irinotecan	No recommended therapies

Abbreviations: 1L = first line; 2L = second line; 3L = third line; NCCN = National Comprehensive Cancer Network; ESMO = European Society For Medical Oncology.

[a] Includes tegafur/gimeracil/oteracil potassium (S-1).

Globally, palliative therapy (systemic therapy, clinical trial, or best supportive care [BSC]) is recommended for patients with unresectable, recurrent, or metastatic GC or GEJ cancer. The choice of 2 or 3 drug-cytotoxic regimens is made in the context of the performance status (PS), comorbid conditions, and toxicity profile. Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur/gimeracil/oteracil potassium [S-1]), and the addition of trastuzumab for HER2-positive tumors, are generally considered as first-line, SOC treatment options in metastatic GC and GEJ cancer across geographic regions. While 1L chemotherapy is associated with improvement in OS, PFS, and response rate, most patients will ultimately progress, and the overall prognosis remains poor with median survival between 7 and 10 months. The selection of a second-line (2L) therapy for these patients is highly dependent on prior therapy and PS and for select patients, best SOC is an acceptable option. For those medically fit to receive 2L therapy, treatment options include single-agent taxane (paclitaxel, docetaxel), irinotecan, or ramucirumab, or ramucirumab in combination with paclitaxel. There are no approved therapies in the third-line (3L) and beyond across regions.

Once patients progress to the 3L salvage setting, there are no approved therapies in the US or EU and in other regions, and treatment decisions are made in the absence of randomized controlled trials or recommendations from treatment guidelines. There are no established standards or approved therapies across regions, except in China where apatinib has been approved in 3L treatment. Toxicities associated with therapies must be carefully considered and balanced with the patient's quality of life.

Available palliative chemotherapies provide very modest improvements in outcomes and survival remains dismal, reflecting the aggressive nature of the disease and its associated poor prognosis

Advanced GC/GEJ Cancer Medical Practice in Asian and Non-Asian Patients

Geographic differences in survival outcomes have been well documented in randomized controlled trials with chemotherapy and targeted therapies for 1L and 2L treatments of advanced GC. Longer OS has generally been observed in patients from Asia, specifically Japan, relative to Non-Asian patients, likely impacted by several factors:

- Asian patients have greater use of subsequent treatment compared with Non-Asian patients even in the absence of approved therapies. Up to 70% of Japanese patients and 66% of Asian patients received chemotherapy following failure of 1L therapy compared with 21% of Pan-American patients

and 31% of European patients. Similarly, up to 69% of Asian patients received chemotherapy following failure of 2L therapy compared with 38% of non-Asian patients. As a result, there appears to be a higher threshold for demonstrating survival benefit in the Asian population against standard of care.

- In the RAINBOW trial a Phase 3, randomized, placebo-controlled trial in advanced gastric or GEJ cancer, evaluating a VEGFR-2 antagonist, ramucirumab + paclitaxel as 2L treatment, no survival benefit was demonstrated in Asian patients although the longer median OS was longer compared with the overall population (11.4 vs 8.6 months) due to high frequencies of subsequent therapy.
- Asian patients treated in the earlier setting differ on some disease characteristics:
  - Trials conducted in Asia often include patients with better baseline prognostic factors than those trials conducted outside of Asia, with Asians presenting with better ECOG PS, less number of metastatic sites, and longer time to progression in 1L treatment, which might contribute to longer survival.
  - REGATE, a registry established to examine how baseline characteristics and treatment patterns vary between regions, reported a meta-analysis and meta-regression on 25 trials (8 Asian, 13 Western, 4 international) exploring systemic chemotherapy as 1L treatment for advanced or metastatic GC or gastroesophageal cancer. The rate of GC surgery was highest in the Asia-Pacific region at 73.9% compared with 63.4% in Europe, 50.8% in Latin America, and 49.8% in North Africa. Per the meta-regression analysis, the increased percentage of non-Asian patients with GEJ cancer was associated with poor PFS rate; however, the analysis did not identify geographic region as an independent predictor of 1-year OS or 6-month PFS rates.**1** Of note, in other analyses PFS and OS were very similar between GC and GEJ cancer. Thus, treatment effects in GC and GEJ cancers should be interpreted with caution.

Geographic variability alone cannot fully explain differences in clinical outcomes as Asian patients treated in the West still show superior outcomes compared to non-Asian patients. There are other factors that may impact clinical outcomes aside from regional variability in clinical practice and baseline disease factors. Molecular comparison of gene expression profiles of > 1600 GCs from Asian and non-Asian cohorts have identified differential gene signatures related to immune function and inflammation. Non-Asian GCs and GEJ cancers were associated with enrichment of tumor infiltrating T-cells as well as T-cell gene expression signatures, such as cytotoxic T-lymphocyte antigen (CTLA)-4 signaling. These data suggest that non-Asian patients may have an enhanced underlying tumoral immune biology and that immuno-oncology (I-O) agents should have at least similar activity as in Asians.

While distinct characteristics are observed between Asian and non-Asian patients with GC/GEJ cancer, in the clinical setting analysis of data on later-line therapy with I-O agents suggests comparable efficacy profiles between Asian and non-Asian patients. Two I-O agent programmed cell death 1 (PD-1) inhibitors, nivolumab and pembrolizumab, have reported data in 3L and later settings across global patient populations. No differences in OS or PFS were observed between Asians and Non-Asians in KEYNOTE-012, a global, Phase 1b trial that evaluated pembrolizumab in PD-L1-positive advanced GC and in KEYNOTE-059, a Phase 2 trial that evaluated pembrolizumab in 259 patients with $\geq$ 2 prior lines of therapy in advanced GC and GEJ cancer:

Table 2. Efficacy in KEYNOTE-012 and KEYNOTE-059 Trials

	KEYNOTE-012 Subjects with PD-L1+ and GC/GEJ Cancer			KEYNOTE-0594 All-comers with GC/GEJ Cancer	
	All Subjects[a] N = 36	Asian Subjects[a] n = 17	ROW Subjects[a] n = 19	All Subjects[a] n = 259	All PD-L1 Positive Subjects n = 148
ORR (95% CI)	22% (10, 39)	24% (7, 50)	21% (6, 46)	11.6% (8.0, 16.1)[b]	15.5% (10.1, 22.4)[b]
Complete response, %	0	0	0	2.3	2.0
Partial response, %	22	24	21	9.3	13.5
mPFS[c], months (95% CI)	1.9 (1.8, 3.5)	1.9 (1.8, 5.7)	1.8 (1.6, 5.8)	2.0 (2.0, 2.1)	NA
mOS, months (95% CI)	11.4 (5.7, NR)	11.4 (3.1, NR)	NR (3.5, NR)	5.6 (4.3, 6.9)	NA

Abbreviations: CI = confidence interval; GC = gastric cancer; GEJ = gastro-esophageal junction; mOS = median overall survival; mPFS = median progression-free survival; NA = not available; NR = not reached; ROW = rest of the world.

[a] Only PD-L1 positive subjects were enrolled in KEYNOTE-012.

[b] Includes 3L and 4L+ subjects.

c Per Central review, RECIST 1.1.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The active substance, nivolumab is a protein and therefore no environmental risk assessment studies have been submitted, in line with guidelines.

2.2.2. Discussion on non-clinical aspects

NA

2.2.3. Conclusion on the non-clinical aspects

NA

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

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

- Tabular overview of clinical studies

Table 3: Summary of Studies in Subjects Supporting this Submission

	Primary Study	Supportive Study
Study Number	ONO-4538-12/CA209316	CA209032[a]
Study Title	A multicenter, double-blind, randomized study in subjects with unresectable advanced or recurrent GC and GEJ cancer	A Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors
Study Design	Phase 3, multicenter, double-blind, placebo- controlled, randomized study	Phase 1/2, multicenter, dose-ranging, and extension study with multiple arms: Nivolumab monotherapy treated subjects in the GC Cohort
Treatment	Nivolumab 3 mg/kg IV Q2W[b] or placebo Q2W	Nivolumab 3 mg/kg IV Q2W
Study Population	Subjects with previously treated advanced or recurrent GC (including esophagogastric junction cancer). Subjects were required to have histologically confirmed advanced or recurrent GC or GEJ adenocarcinoma, refractory to or intolerant of standard therapy, with ≥ 2 prior treatments, and were not planned to newly receive any antineoplastic treatments including antibody products.	GC (gastric monotherapy) cohort: Subjects with previously treated, advanced or metastatic GC. Subjects were required to have histologically confirmed gastric or GEJ carcinoma, including adenocarcinoma arising from the lower esophagus, with tumor progression or refractory disease and at least 1 prior chemotherapy regimen, or actively refused chemotherapy, for the treatment of metastatic (stage IV) or locally advanced disease. Subjects with HER-2 positive tumors must have had previous treatment with trastuzumab.
Geographic Location/ Subjects	49 sites in 3 countries Randomized subjects: Japan, n = 226 Korea, n = 220 Taiwan, n = 47	18 sites in 6 countries Treated subjects: US, n = 32 EU, n = 27: including Finland, Germany, Italy, Spain, and the United Kingdom
Primary Endpoint	OS	Confirmed ORR based on BICR and investigator assessment (using RECIST v1.1)
Additional Efficacy Endpoints	Investigator-assessed PFS, ORR, DOR, TTR, DCR, BOR, maximum percent changes from baseline in the sum of diameters of target lesions	OS; DOR and PFS based on BICR and investigator assessments; association between baseline tumor PD-L1 expression and efficacy
Number of Subjects	N = 493 randomized (n = 330 nivolumab; n = 163 placebo [161 of these subjects received at least 1 dose])	N = 59; n = 42 with GC or GEJ cancer previously treated with at least 2 prior regimens, which mostly matches the population studied in ONO-4538-12
Study Status	13-Aug-2016 (date of last subject's last observation prior to data cut-off); as of the data cutoff, 187 (56.7%) and 75 (46.0%) subjects in the nivolumab group and placebo group, respectively, were continuing study treatment.	The study is ongoing. An interim CSR is available based on 24-Mar-2016 database lock. The BICR review was performed on 19-Jul-2016 based on the 24-Mar-2016 DBL. As of the DBL on 24-Mar-2016, 3 (5.1%) subjects were continuing with study treatment.

Abbreviations: BICR = blinded independent central review; BOR = best overall response; CSR = clinical study report; DCR = disease control rate; DOR = duration of response; EU = European Union; GC = gastric cancer; GEJ = gastro-esophageal junction; IV = intravenous(ly); ORR = overall response rate; OS = overall survival; PD-L1 = programmed cell death ligand-1; PFS = progression-free survival; Q2W = every 2 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to response.

[a] Information summarized is for nivolumab monotherapy treated GC subjects.

[b] In the study protocol for ONO-4538-12, nivolumab treatment is referred to as ONO-4538.

Study CA209032 used nivolumab product from the same process that is used for marketed product. Nivolumab injection manufactured by Ono and by BMS uses the same drug substance with the same composition that is made by the same manufacturing process at Lonza Biologics, Inc., an approved drug substance manufacturing site. The drug product used in ONO-4538-12 was manufactured by Ono in a process that according to the applicant can be considered comparable to the BMS process. However, only BMS is an approved drug product manufacturing site. Thus, considering that Ono is not included as a manufacturing site for drug product in the marketing authorisation, comparability cannot be granted between drug products manufactured in both manufacturing sites with the limited data provided by the applicant (Please refer to RSI).

2.3.2. Pharmacokinetics

Absorption

N/A

Distribution

N/A

Elimination

N/A

Dose proportionality and time dependencies

N/A

Special populations

The PPK analysis was conducted in order to characterize nivolumab PK in subjects with GC/GEJ, and was based on a previously established nivolumab PPK model using time-varying clearance (CL).

The objective of the present analysis was to characterize the PK of nivolumab in subjects with GC/GEJ, and to determine the effect of key covariates (in particular, tumor type and race) on nivolumab PK and exposure. The effect of tumor type on nivolumab CL was assessed relative to NSCLC 2L+ subjects in the full model along with several other covariates.

The PPK analysis was performed using data from 1302 subjects with multiple tumor types including GC/GEJ and NSCLC 2L+. The analysis population consisted of all subjects enrolled who received at least one dose of nivolumab, and for whom nivolumab concentration values were available following nivolumab monotherapy from: 3 Phase 1 studies (MDX-1106-01, MDX-1106-03, and ONO-4538-01), 1 Phase 1/2 study (CA209032), 2 Phase 2 studies (CA209063 and ONO-4538-02), and 3 Phase 3 studies (ONO-4538-12, CA209017 and CA209057). These studies were selected either because they had intensive PK samples collected to allow characterization of nivolumab PK (MDX-1106-01 and MDX 1106 03) or because they were used as a reference tumor type in the PPK analysis (NSCLC 2L+ subjects from studies CA209063, CA209017, and CA209057). Data from ONO-4538-01 and ONO-4538-02 allowed assessment of nivolumab PK in Japanese subjects with multiple tumor types. Data from CA209032 and ONO- 4538-12 were further added to enable assessment of nivolumab PK in subjects with GC/GEJ.

PPK Model Development

The PPK model was developed in 3 steps: base, full and final model development. A previously developed final PPK model was used as a base model, with model parameters re-estimated with the current dataset. The base model was a two-compartment, zero-order IV infusion and timevarying CL (sigmoidal-Emax function) with a proportional residual error model, with random effect on CL, VC, volume of distribution of peripheral compartment (VP) and Emax and correlation of random effect between CL and VC.

The full model was intended to assess the tumor type effects on various nivolumab PK parameters. This was achieved by simultaneously incorporating all pre-specified covariate parameter relationships of interest into the model.

The pre-specified covariate-parameter effects of interest assessed in the full model were baseline albumin, LDH, tumor size, and gastrectomy (GC/GEJ subjects only). The final PPK model, given the data, contained baseline BWT, eGFR, PS, sex, race and tumor type (GC/GEJ or OTHER) on CL and baseline BWT and sex on VC.

The effects of baseline albumin, LDH, tumor size and gastrectomy relative to the CL parameter value of a reference subject (tumor type category of NSCLC_2L) were given by the following expression:

$$CL_{TV,i} = CL_{REF} \times (e^{CLgs})^{IGS_i * IGC_i} \times \left(\frac{BALB_i}{BALB}\right)^{CL_{BALB}} \times \left(\frac{BTSIZE_i}{BTSIZE}\right)^{CL_{BTSIZE}} \times \left(\frac{BLDH_i}{BLDH}\right)^{CL_{BLDH}}$$

$$CL_{TV,i} = CL_{REF} \times \left(\frac{BALB_i}{BALB}\right)^{CL_{BALB}} \times \left(\frac{BTSIZE_i}{BTSIZE}\right)^{CL_{BTSIZE}} \times \left(\frac{BLDH_i}{BLDH}\right)^{CL_{BLDH}}$$

where *CLREF* is the value of the parameter for the reference subject; *CLgs* is the estimated model parameter for the effect of gastrectomy on CL; *IGS*i is the indicator variable for gastrectomy of subject i, respectively (1=yes, and 0=no); *IGC*i is the indicator variable for the GC/GEJ tumor type of subject i, respectively (1=yes, and 0=no); *BALB*i is the value of the baseline albumin of subject i, *BALB* is the reference value of baseline albumin (4 gm/dL), and *CLBALB* is the estimated model parameter for the effect of baseline albumin; *BTSIZE*i is the value of the baseline tumor burden of subject i, *BTSIZE* is the reference value of baseline tumor burden (7.5 cm), *CLBTSIZE* is the estimated model parameter for the effect of baseline tumor burden, and BLDHi is the value of the baseline LDH in subject i, and BLDH is the reference value of baseline LDH (200 IU/mL).

The effects of GC/GEJ and OTHER tumor types relative to the Emax parameter value of a reference subject (tumor type category of NSCLC_2L) were given by the following expression:

$$EMAX_{TV,i} = EMAX_{REF} \times (e^{EMAX_{GC}})^{IGC_i} \times (e^{EMAX_{OTHER}})^{IOTHER_i}$$

where *EMAXREF* is the value of the parameter for the reference subject (NSCLC 2L); *EMAXGC* is the estimated model parameter for the effect of GC/GEJ tumor type; *IGC*i is the indicator variable for the GC/GEJ tumor type of subject i, respectively (1=yes, and 0=no); *EMAXOTHER* is the estimated model parameter for the effect of other tumor types (not NSCLC_2L or GC/GEJ); and *IOTHER*i is the indicator variable for the OTHER tumor type of subject i, respectively (1=yes, and 0=no).

The effect of tumor burden relative to the VC parameter value of a reference subject was given by the following expression:

$$VC_{TV,i} = VC_{REF} \times \left(\frac{BTSIZE_i}{BTSIZE}\right)^{VC_{BTSIZE}}$$

where *VCREF* is the value of the parameter for the reference subject; *BTSIZE*i is the value of the baseline tumor burden of subject i, *BTSIZE* is the reference value of baseline tumor burden (7.5 cm), and *VCBTSIZE* is the estimated model parameter for the effect of baseline tumor burden.

The final model was developed by backward elimination of the covariates in the full PPK model, based on BIC. The final PPK model contained baseline BW, eGFR, sex, race, PS, baseline ALB, baseline LDH, baseline tumor size and tumor type (other and GC/GEJ) on CL and baseline BW and sex on VC. Parameter estimates from the final model are presented in Table 4.

The PPK model parameters were estimated with good precision and the model evaluation demonstrated that there was good agreement between model predictions and observations.

Table 4: PPK Model Parameter Estimates (Final Model)

Name[a] [Units]	Symbol	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
Fixed Effects				
CL [L/h]	θ_1	0.0106	0.00041 (3.87)	0.00972-0.0116
VC [L]	θ_2	4.46	0.0563 (1.26)	4.35-4.57
Q [L/h]	θ_3	0.0262	0.00265 (10.1)	0.0212-0.0351
VP [L]	θ_4	2.52	0.119 (4.72)	2.27-2.79
CL_BBWT	θ_7	0.498	0.0573 (11.5)	0.374-0.604
CL_GFR	θ_8	0.151	0.043 (28.5)	0.0649-0.239
CL_SEX	θ_9	-0.134	0.028 (20.9)	-0.197--0.0863
CL_PS	θ_{10}	0.117	0.0236 (20.2)	0.0650-0.166
CL_OTH	θ_{11}	0.128	0.0353 (27.6)	0.0500-0.195
CL_GC	θ_{12}	0.31	0.0491 (15.8)	0.201-0.399
CL_RAAA	θ_{13}	-0.0487	0.051 (105)	-0.168-0.0540
CL_RAAS	θ_{14}	-0.201	0.0399 (19.9)	-0.279--0.120
VC_BBWT	θ_{15}	0.428	0.0403 (9.42)	0.351-0.507
VC_SEX	θ_{16}	-0.189	0.0244 (12.9)	-0.240--0.141
CL_EMAX	θ_{17}	-0.285	0.0514 (18)	-0.408--0.177
CL_T50	θ_{18}	1510	251 (16.6)	1040-2180
CL_HILL	θ_{19}	2.02	0.624 (30.9)	1.30-5.24
CL_BALB	θ_{20}	-0.869	0.088 (10.1)	-1.04--0.698
CL_BLDH	θ_{21}	0.379	0.106 (28)	0.165-0.577
CL_BTSIZE	θ_{22}	0.0887	0.0171 (19.3)	0.0570-0.122
CL_CASG	θ_{23}	-0.193	0.0404 (20.9)	-0.281--0.110
CL_CASG_MIS	θ_{24}	-0.112	0.089 (79.5)	-0.278-0.0661
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.0942 (0.307)	0.00855 (9.08)	0.0773 - 0.114
ZVC [-]	$\omega_{2,2}$	0.108 (0.329)	0.016 (14.8)	0.0800 - 0.141
ZVP [-]	$\omega_{3,3}$	0.314 (0.56)	0.0424 (13.5)	0.237 - 0.422
ZEMAX [h]	$\omega_{4,4}$	0.118 (0.344)	0.0371 (31.4)	0.0610 - 0.213
ZCL:ZVC [-]	$\omega_{1,2}$	0.0385 (0.382)	0.00684 (17.8)	0.0241 - 0.0534
Residual Error				
PERR [-]	θ_6	0.219	0.00893 (4.08)	0.202-0.239

[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 ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

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

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

Note: BBWT indicates baseline body weight, GFR indicates baseline eGFR, PS indicates performance status, OTH indicates other tumor types, GC indicates gastric cancer, RAAA indicates race (African American), RAAS indicates race (Asian), CLEMAX, CLT50 and CLHILL are the parameters that govern the time-varying CL, BALB indicates baseline albumin, BLDH indicates baseline LDH, BTSIZE indicates baseline tumor size, CASG indicates prior gastrectomy (Yes) and CASG_MIS indicates prior gastrectomy (Missing).

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/nm/e-final1.ctl

Source: Analysis Directory/nm/e-final1/e-final1.rtf

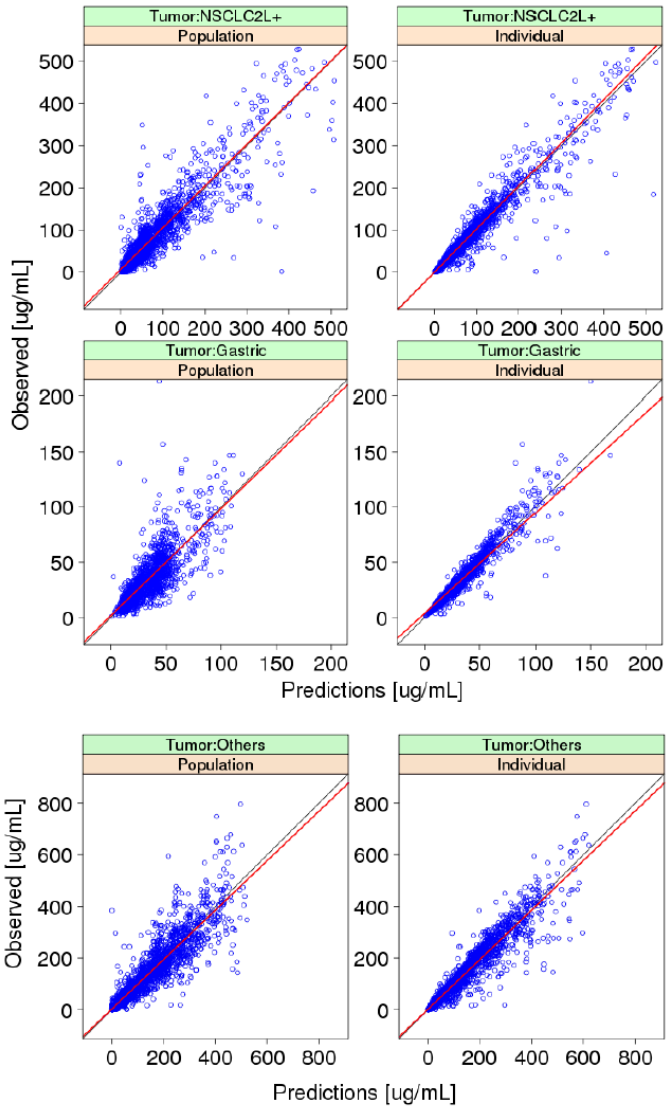
The shrinkage of the random effects for CL (18.9%) and VC (14.3%) was below 30%, while the shrinkage for VP and EMAX were 40.6% and 48.6%.

The PPK model was used to obtain summary measures of exposure for each subject in the analysis dataset. In addition, a graphical assessment of the effect of tumor type and Asian race on nivolumab exposure was conducted.

Model Evaluation

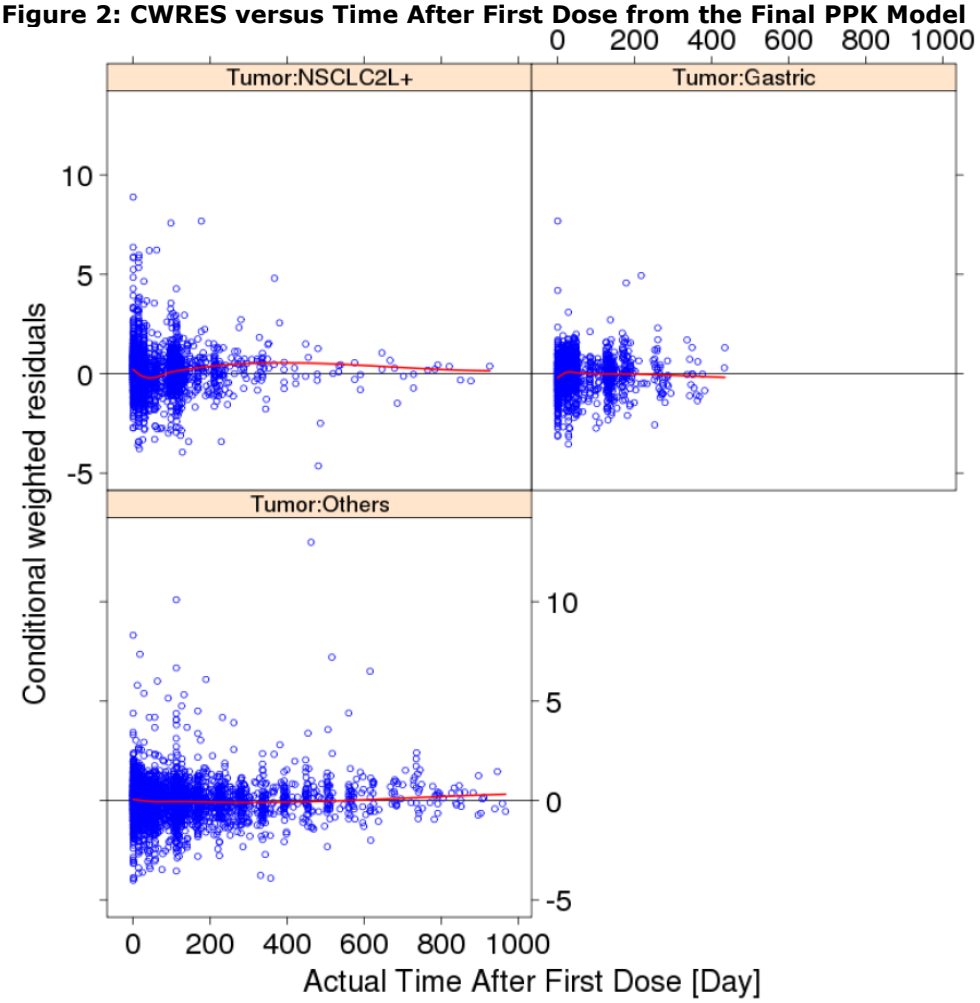
The diagnostic plots for the final model are provided in Figure 1, Figure 2, Figure 3 and Figure 4.

Figure 1: Observed versus Predicted Population Average and Individual Concentration (Final PPK Model)



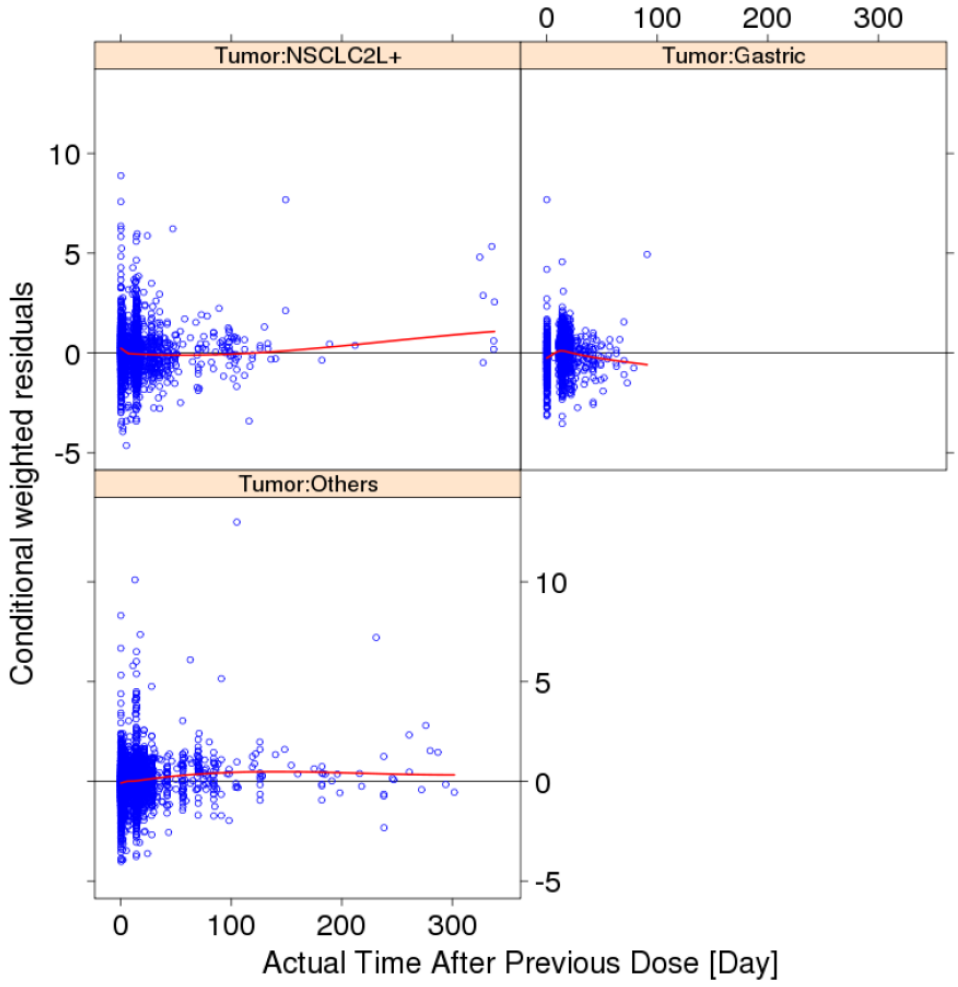
Note: Solid line represents line of identity. Fitted red line represents a linear regression line.
Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final
Program Source: Analysis Directory/R/scripts/diagnostic-plots.r
Source: Analysis Directory/nm/e-final1/plots/dv-vs-pred-ipred01.png
Source: Analysis Directory/nm/e-final1/plots/dv-vs-pred-ipred02.png

Figure 2: CWRES versus Time After First Dose from the Final PPK Model



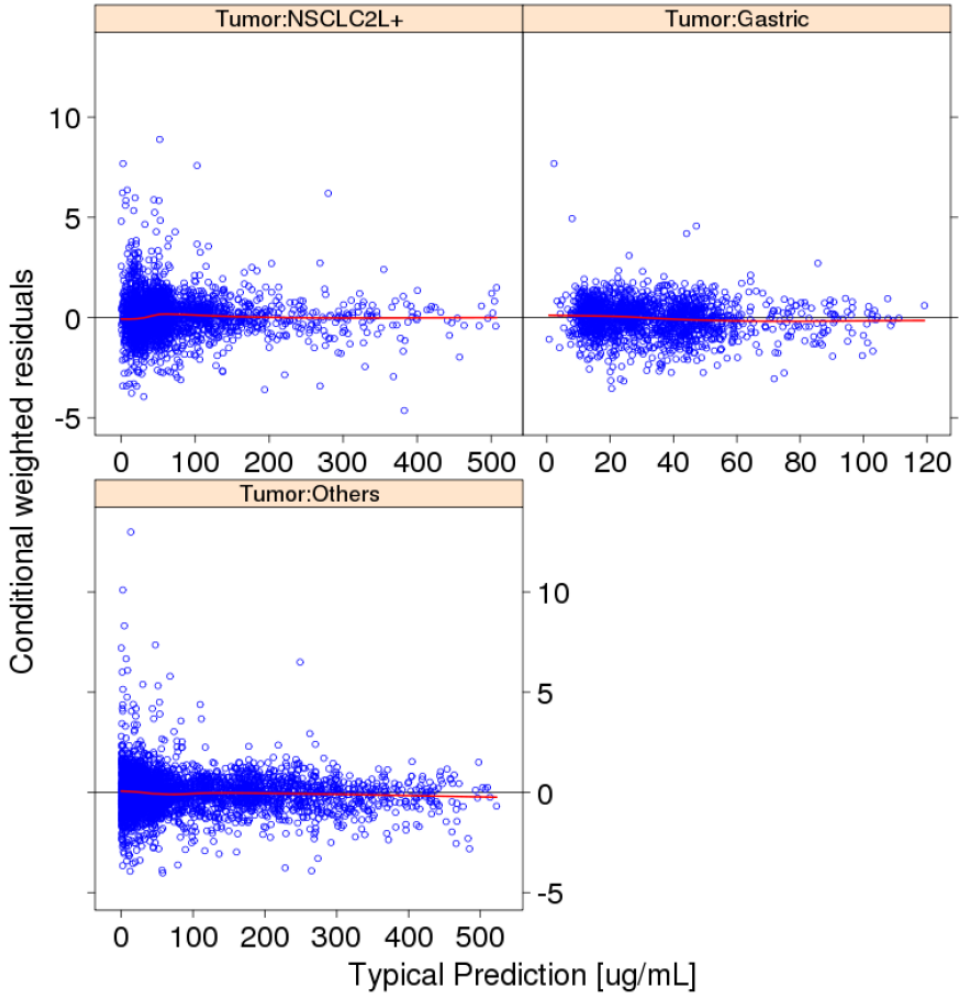
Note: Fitted red line represents locally weighted smooth line.
Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final
Program Source: Analysis Directory/R/scripts/diagnostic-plots.r
Source: Analysis Directory/nm/e-final1/plots/cwres-vs-ATAFD.png

Figure 3: CWRES versus Time After Previous Dose from the Final PPK Model



Note: Fitted red line represents locally weighted smooth line.
Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final
Program Source: Analysis Directory/R/scripts/diagnostic-plots.r
Source: Analysis Directory/nm/e-final1/plots/cwres-vs-ATAPD.png

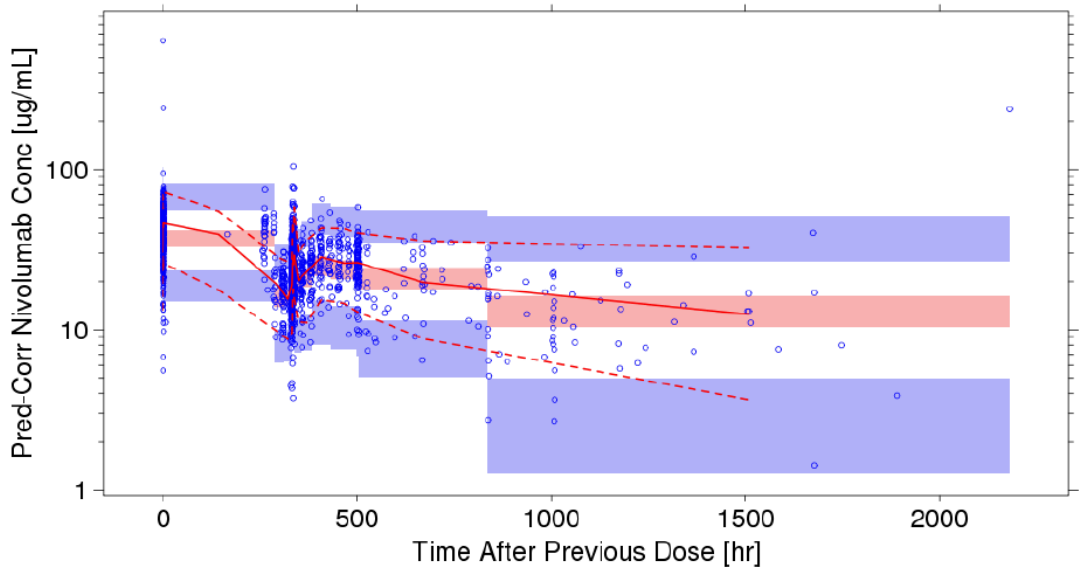
Figure 4: CWRESI versus Predicted (Typical) Serum Concentration from the Final PPK Model



Note: Fitted red line represents locally weighted smooth line.
Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final
Program Source: Analysis Directory/R/scripts/diagnostic-plots.r
Source: Analysis Directory/nm/e-final1/plots/cwres-vs-pred.png

The pcVPC with all available concentrations from GC subjects versus time after the previous dose are presented in Figure 5. The pcVPC with only trough concentrations from GC subjects versus time after the first dose are presented in Figure 6.

Figure 5: Visual Predictive Check of All Concentrations versus Actual Time After Previous Dose for Data from GC Subjects (Final PPK Model)



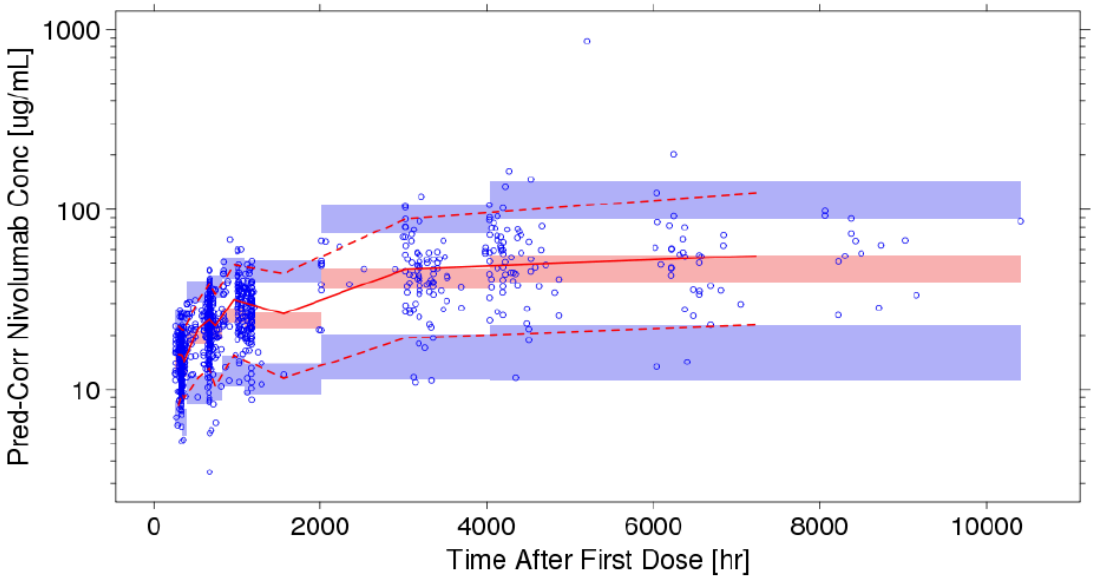
Note: Blue circles are observed data. The red lines represent the 5th, 50th and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 95% confidence intervals for the 5th, 50th and 95th percentiles of the predicted data.

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/nm/e-final1/e-final1.GC.ctl

Source: Analysis Directory/nm/e-final1/vpc_e-final1_gc_atapd/VPC-plots 1.png

Figure 6: Visual Predictive Check of Trough Concentrations versus Actual Time After First Dose from GC Subjects (Final PPK Model)



Note: Blue circles are observed data. The red lines represent the 5th, 50th and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 95% confidence intervals for the 5th, 50th and 95th percentiles of the predicted data.

Analysis Directory: /global/pkms/data/CA/209/C19/prd/ppk/final

Program Source: Analysis Directory/nm/e-final1/e-final1.vpc.GC.trough.ctl

Source: Analysis Directory/nm/e-final1/vpc_e-final1_gc_trough/VPC-plots 1.png

Analyses of Covariate Effects

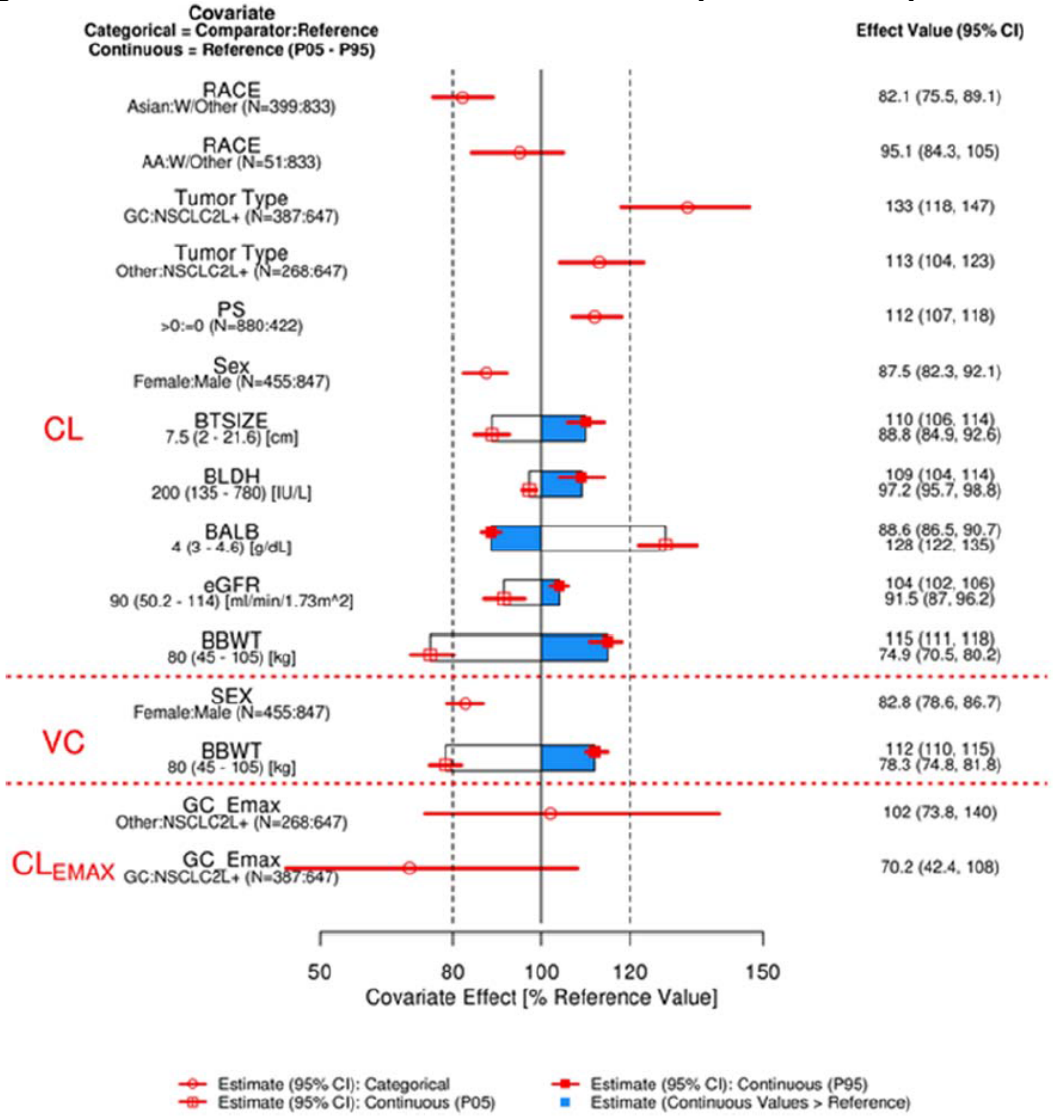
The effect of categorical and continuous covariates on the typical value of the structural model parameters of CL and VC and the estimated covariate effects (and 95% confidence intervals) are presented in Figure 7.

The magnitude of the effect of covariates on CL, accounting for uncertainty, was within the ± 20% boundaries for PS, sex, baseline tumor size, baseline LDH, and eGFR, but outside the ± 20% boundaries for body weight (BWT), GC/GEJ tumor type, and Asian race. CL was ~33% greater in subjects with GC/GEJ relative to that of subjects with NSCLC 2L+ as shown in Figure 3.1.2-1. Nivolumab CL and VC were higher in subjects with higher body weight. Nivolumab CL was higher in subjects with lower baseline ALB. The effect GC/GEJ tumor type on Emax was lower than that of NSCLC 2L+ on Emax, however the CI was wide and included 1, which suggested that it was not of clinical relevance. Race, sex, PS, baseline tumor size, baseline LDH, baseline eGFR also were not clinically relevant predictors of nivolumab CL (< 20% effect). The magnitude of the effect of PS, body weight, sex and GFR on CL, and the effect of sex and body weight on central volume of distribution in this population of GC/GEJ subjects are comparable to what was previously reported in the nivolumab comprehensive PPK analysis that included more tumor types.

The population mean CL in GC/GEJ subjects was 33% higher, calculated as [exp(CL_GC)- 1]*100, relative to that of NSCLC 2L+ subjects. Based on the full model, over time the population mean CL of GC/GEJ subjects will decrease by 20%, calculated as [1 exp(EMAX*exp(CL_GC_Emax))]*100, from baseline CL compared to ~27% in subjects with tumor type of either NSCLC 2L+ or Others. The effect of GC/GEJ on Emax was lower than that of NSCLC 2L+ on Emax, however, the CI was wide and included 1 for each, which suggested that tumor type was not of clinical relevance.

The magnitude of the effect of baseline BWT and sex were within the ± 20% boundaries for VC and not considered clinically relevant.

Figure 7: Covariate Effects on PPK Model Parameters (Full PPK Model)



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal red 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 red lines). Open/Blue 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 white/other race male, PS=0, eGFR=90 mL/min/1.73m^2, body weight=80kg, NSCLC tumor type. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/cov-eff-plot-full1.r

Source: Analysis Directory/R/plots/e-full1-ppk-cov-eff-plot-BS.png.

Estimates of Individual Exposure

A summary of the individual PK parameter estimates with all the studies obtained from the full PPK model is provided in Table 5. Summaries of the PK parameters from GC/GEJ subjects only are provided in Table 6. A summary of the individual measures of exposure for subjects who received 3 mg/kg Q2W is provided in Table 7. Summaries of the individual measures of exposure for GC/GEJ subjects only (receiving 3 mg/kg Q2W) are provided in Table 8.

Table 5: Summary Statistics of Individual PK Parameters (n=1302)

Parameter	Mean	Geometric Mean	Median (Min, Max)	SD	CV(%)
Baseline CL (L/h)	0.0116	0.0108	0.0107(0.00216,0.0414)	0.00449	38.8
CLSS (L/h)	0.00901	0.00818	0.0082(0.000475,0.113)	0.00495	55
VC (L)	4.04	3.85	3.88(0.206,9.76)	1.22	30.1
VP (L)	2.7	2.54	2.52(0.623,23)	1.22	45.2
VSS (L)[a]	6.74	6.53	6.49(2.11,26.6)	1.79	26.6
T-HALFα (hr)	37.8	36.7	37.1(4.67,85.6)	8.83	23.4
T-HALFβ (day)	19.7	18.8	18.7(6.74,157)	8.14	41.3

[a] VSS = VC + VP

Abbreviations: % = percent, geo. mean = geometric mean, CV% = coefficient of the variation expressed as a percentage, CL = clearance, CLSS = clearance at steady state, VC = volume of the central compartment, VP = volume of distribution of peripheral compartment, VSS = volume of distribution at steady state, T-HALF = geometric mean of terminal half-life

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/ summarize-model-application.r

Source: Analysis Directory/R/export/stats.para.csv

Table 6: Summary Statistics of Individual PK Parameters for GC/GEJ Subjects (n=387 including Subjects from CA209032 and ONO-4538-12)

Parameter	Mean	Geometric Mean	Median (Min, Max)	SD	CV(%)
Baseline CL (L/h)	0.0114	0.0107	0.0105(0.00362,0.0294)	0.00412	36.2
CLSS (L/h)	0.00897	0.00829	0.00815(0.000901,0.0243)	0.00367	40.9
VC (L)	4.08	3.92	3.94(0.378,8.29)	1.13	27.7
VP (L)	2.51	2.41	2.41(1.19,10.6)	0.857	34.1
VSS (L)[a]	6.59	6.44	6.33(3.38,13.1)	1.44	21.9
T-HALFα (hr)	36.8	36.1	36.1(7.78,59.9)	7.08	19.2
T-HALFβ (day)	19.3	18.6	18.5(7.8,66.8)	5.58	28.9

[a] VSS = VC + VP

Abbreviations: % = percent, geo. mean = geometric mean, CV% = coefficient of the variation expressed as a percentage, CL = clearance, CLSS = clearance at steady state, VC = volume of the central compartment, VP = volume of distribution of peripheral compartment, VSS = volume of distribution at steady state T-HALF = geometric mean of terminal half-lifeAnalysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/ summarize-model-application.r

Source: Analysis Directory/R/export/stats.para.ttypef2.csv

Table 7: Summary Statistics of Individual Measures of Nivolumab Exposure (3 mg/kg Q2W, n=971)

Parameter	Mean	Geometric Mean	Median (Min, Max)	SD	CV(%)
Cmin1 (µg/mL)	16.4	15.6	15.6(5.21,56.6)	5.17	31.5
Cmax1 (µg/mL)	56.4	52.7	52.4(24.5,780)	34.4	61.1
Cavg1 (µg/mL)	25.6	24.8	24.9(11.9,76.1)	6.79	26.5
Cminss (µg/mL)	42.3	38.9	40(7.77,290)	18.6	43.9
Cmaxss (µg/mL)	98.4	93	91.8(40,894)	44.3	45
Cavgss (µg/mL)	59.6	56.2	57(19.5,333)	22.1	37

Abbreviations: % = percent, geo. mean = geometric mean, CV% = coefficient of the variation expressed as a percentage, Cavg1 = post-dose 1 time-averaged serum concentration, Cavgss = Time-averaged serum concentration at steady-state, Cmax1 = post-dose 1 peak serum concentration, Cmaxss = peak serum concentration at steady-state, Cmin1 = post-dose 1 trough serum concentration, Cminss = trough serum concentration at steady-state, ug/mL = microgram per milliliter

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/export/stats.exp.real.3mgkg.csv

Table 8: Summary Statistics of Individual Measures of Nivolumab Exposure for Subjects with GC/GEJ Enrolled in CA209032 and ONO-4538-12 (3 mg/kg Q2W, n=387)

Parameter	Mean	Geometric Mean	Median (Min, Max)	SD	CV(%)
Cmin1 (µg/mL)	13.9	13.5	13.5(5.21,26.2)	3.63	26.1
Cmax1 (µg/mL)	45.2	43.4	43.3(24.5,350)	19.4	42.8
Cavg1 (µg/mL)	21.5	21.1	21.1(11.9,40.2)	4.37	20.3
Cminss (µg/mL)	35.9	33.3	34.3(9.91,132)	14.2	39.7
Cmaxss (µg/mL)	80.9	78.2	78.4(40,399)	25.9	31.9
Cavgss (µg/mL)	50.3	48	48(19.5,154)	16.1	32

Abbreviations: % = percent, geo. mean = geometric mean, CV% = coefficient of the variation expressed as a percentage, Cavg1 = post-dose 1 time-averaged serum concentration, Cavgss = Time-averaged serum concentration at steady-state, Cmax1 = post-dose 1 peak serum concentration, Cmaxss = peak serum concentration at steady-state, Cmin1 = post-dose 1 trough serum concentration, Cminss = trough serum concentration at steady-state, ug/mL = microgram per milliliter

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/export/stats.exp.real.3mgkg.ttypef2.csv

Effect of Tumor Type on Nivolumab PK

In addition to examining the effect of tumor type on CL and VC in the PPK structural model, an additional analysis was performed to examine the relationship between the summary measures of nivolumab exposure and tumor type (NSCLC 2L+ vs GC/GEJ vs OTHER). Nivolumab exposure estimates (Cmin1, Cmax1, Cavg1, Cminss, Cmaxss and Cavgss) for GC/GEJ subjects were lower compared to subjects with NSCLC2L+ as presented in Table 9. The largest difference was observed in the Cmax1 of which the geometric mean was 28% lower than NSCLC2L+ subjects, which is consistent with the trend observed in the full model. Graphical displays of nivolumab Cavg1 is presented in Figure 8.

Although a maximum of a 28% difference in exposure (Cmax 1) was observed in GC/GEJ subjects relative to NSCLC 2L+ subjects, this is not considered clinically relevant as the results of the ONO-4538-12 study demonstrated that nivolumab 3 mg/kg Q2W significantly reduced the risk of death by 37% (hazard ratio

[HR] = 0.63; P < 0.0001) in GC/GEJ subjects, suggesting that this dosing regimen was beneficial to this population regardless of the lower exposures versus NSCLC 2L+. Further, in other tumor types, e.g. RCC and melanoma, nivolumab ER relationships have been demonstrated to be flat over a dose range that includes nivolumab 3 mg/kg Q2W, suggesting that these lower exposures would not be clinically relevant. Finally, similar effects of GC/GEJ tumor type on PK have been demonstrated previously for other monoclonal antibodies used in the treatment of GC/GEJ.

Table 9: Exposure Comparison (3 mg/kg Q2W) Between Tumor Types

Exposure Parameter	Geometric Mean (CV%)		GM Diff Percent(%)[a]
	NSCLC2L+ (N=557)	GC/GEJ (N=387)	GC/GEJ vs NSCLC2L+
Cmin1 (µg/mL)	17.4(29.8)	13.5(26.1)	-22.4
Cmax1 (µg/mL)	60.3(63.2)	43.4(42.8)	-28
Cavg1 (µg/mL)	27.7(23.7)	21.1(20.3)	-23.8
Cminss (µg/mL)	43.4(42.6)	33.3(39.7)	-23.3
Cmaxss (µg/mL)	105(45.8)	78.2(31.9)	-25.5
Cavgss (µg/mL)	62.7(35.4)	48(32)	-23.4

a GM Diff Percent is the geometric mean difference in percentage, calculated as [(GC - NSCLC2L+) / NSCLC2L+] * 100

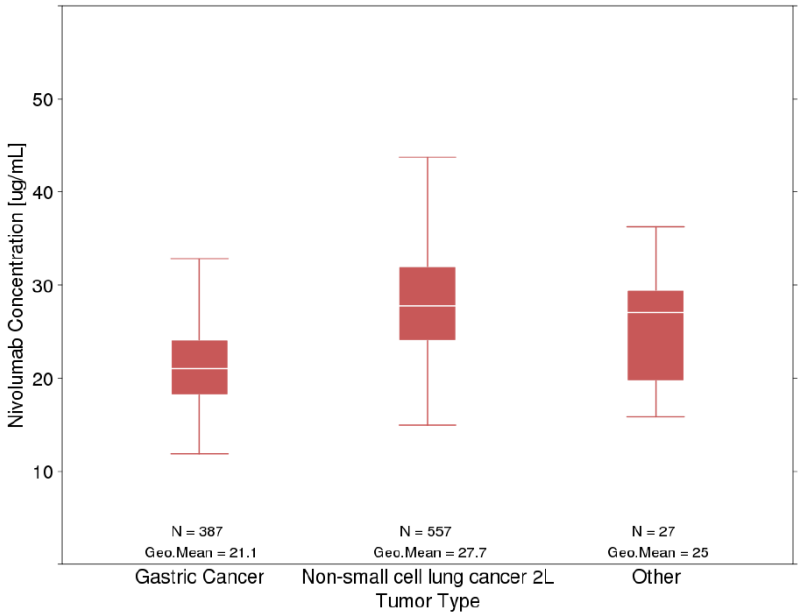
Abbreviations: % = percent, geo. mean = geometric mean, CV% = coefficient of the variation expressed as a percentage, Cavg1 = post-dose 1 time-averaged serum concentration, Cavgss = Time-averaged serum concentration at steady-state, Cmax1 = post-dose 1 peak serum concentration, Cmaxss = peak serum concentration at steady-state, Cmin1 = post-dose 1 trough serum concentration, Cminss = trough serum concentration at steady-state, ug/mL = microgram per milliliter

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/export/compare.exp.3mgkg.csv

Figure 8: Distribution of Nivolumab Cavg1 Estimates by Tumor Type (Nivolumab 3 mg/kg Q2W)



Note: The boxes represent the 25th, 50th, and 75th percentiles of the distribution. The whiskers extend to 1.5 times the interquartile range.

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/plots/Cavg1-3mgkg-ttypef2.png

The model estimated (typical value) of Emax (CLEMAX, -0.285, Table 4) indicated that nivolumab CL decreased with time, and that the maximal decrease was approximately 25% from baseline [calculated as: 1-exp(Emax)]. Since the tumor type effect on Emax was not statistically significant, the magnitude of CL change was similar in all tumor types as shown in Figure 9. The change in CL is estimated to occur soon after initiation of treatment, with the half-maximal change estimated to occur at approximately 2 months (T50 = 1500 h).

Table 10: Summary Statistics of Individual Percentage of Maximal Clearance Change from Baseline

		EMAXP(%)[a]		
Tumor Type	**cv**	**N**	**Mean(Sd)**	**Median(Min,Max)**
NSCLC2L+	57.7	647	24.3(14)	24.8(-192,78)
Others	102	268	21.8(22.1)	24.5(-198,74.8)
Gastric Cancer	58	387	21.8(12.6)	24.4(-73.4,75.1)

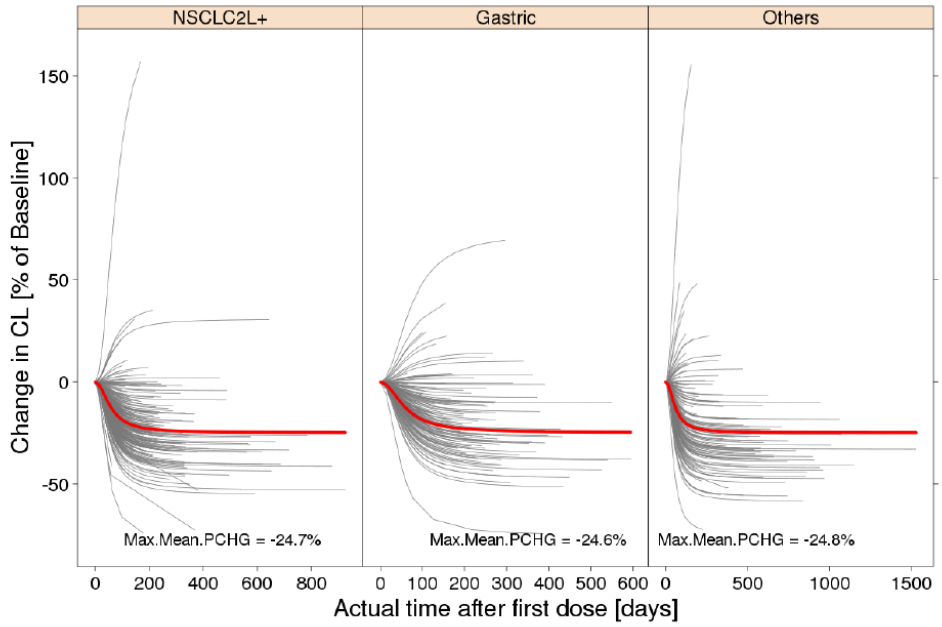
[a] EMAXP, a percentage of theoretical maximal CL change from baseline, was calculated as (1-exp(EMAX))*100. Positive numbers indicate CL reduction over time, negative numbers indicate CL increase over time.

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/export/EMAXP-ttype.csv

Figure 9: Model-Estimated Change in Clearance versus Time (Final Model)



%Change in CL = 100 * ((CLt - CLt=0)/CLt=0)

Max.Mean.PCHG is the population mean percentage change of CL from baseline at the maximal observation time

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/plots/CL.PCHG-vs-time-by-ttype.png

Effect of Asian Race on Nivolumab Exposure

In addition to examining the effect of race on CL and VC in the PPK structural model, an additional analysis was performed to examine the relationship between the summary measures of nivolumab exposure and race (Asian vs non-Asian). Nivolumab exposure measurements (Cmin1, Cmax1, Cavg1, Cminss, Cmaxss and Cavgss with 3 mg/kg at Q2W) in GC/GEJ subjects appeared to be similar among Asian and non-Asian subjects as presented in Table 11. Nivolumab exposures after the first dose were approximately 8% to

14% lower in Asians subjects, and the magnitude of differences were smaller after reaching steady state (up to 6% different). Nivolumab Cavg1 by race is presented in Figure 10. These data suggest that the effect of race is not clinically relevant. Further, the similar exposures in non-Asian and Asian GC/GEJ subjects demonstrates the lack of race effect and supports the ability to extrapolate the clinical findings in Asian to non-Asian GC/GEJ patients.

Table 11: Summary of Nivolumab Exposures in GC/GEJ Subjects by Race (Asian and Non-Asian)

Exposure Parameter(µg/mL)	Geometric Mean [CV%]		GM Diff[a] Percent (%)
	Non-Asian	Asian	
Cmin1	14.5(25.4)	13.3(26)	-8.28
Cmax1	49.4(32.2)	42.4(44.5)	-14.2
Cavg1	23.7(19.9)	20.6(19.6)	-13.1
Cminss	32.5(38.3)	33.4(39.9)	2.77
Cmaxss	82.7(29.5)	77.4(32.4)	-6.41
Cavgss	49.1(30.8)	47.8(32.2)	-2.65

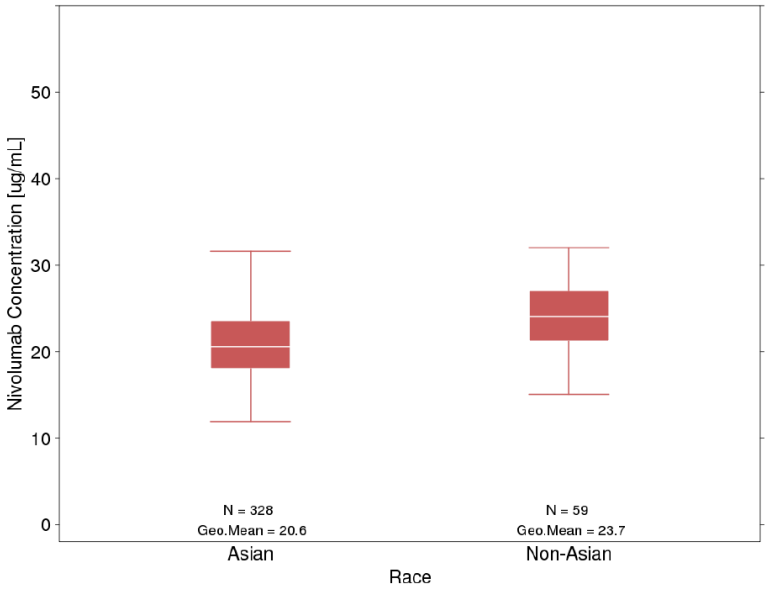
a GM Diff Percent = [(Geometric mean of Asian - Geometric mean of Non-Asian) / Geometric mean of Non-Asian] * 100

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/export/ compare.exp.gomy.csv

Figure 10: Distribution of Nivolumab Cavg1 Estimates in Asian and non-Asian GC/GEJ subjects (3 mg/kg Q2W)



Note: The boxes represent the 25th, 50th, and 75th percentiles of the distribution. The whiskers extend to 1.5 times the interquartile range.

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/plots/Cavg1-3mgkg-gc-race.png

Assessment of prior gastrectomy on exposure

The impact of gastrectomy on CL was assessed by handling missing values (N = 13) as "Missing" instead of imputing as the mode value (YES). This methodology enabled a robust estimation of parameters without bias. The CL in GC subjects with gastrectomy was lower by 18.1%, calculated as [exp(CL_CASG)-1]*100, compared to subjects without gastrectomy. Distributions of nivolumab exposure

measurements (Cmin1, Cmax1, Cavg1, Cminss, Cmaxss and Cavgss receiving 3 mg/kg at Q2W) in GC subjects were similar in subjects with and without prior gastrectomy as presented in Table 12. The differences observed in nivolumab exposures were greater (8.51% to 33.2%) at steady state compared to those observed after the first dose (1.4% to 11.2%). Graphical displays of nivolumab Cminss (the largest difference) is presented in Figure 11.

These findings for the effect of gastrectomy on PK in subjects with GC are consistent with previously reported analyses of other mAbs. Currently the reason(s) for this finding is unknown, but it has been postulated that subjects who have had gastrectomy are generally healthier versus those who have not had gastrectomy, which is consistent with findings that subjects who are generally healthier, as determined by baseline PS (ECOG or KPS), have slower CL versus those in worse health state. An interesting finding was that the differences observed in nivolumab exposures were greater (8.51% to 33.2%) at steady state compared to those observed after the first dose (1.4% to 11.2%). The reason for this finding is unknown, but could be explained by the relative health of those individuals and/or response to nivolumab treatment, where the greater reduction in CL occurs in those who are responding to treatment.

Table 12: Summary of Nivolumab Exposures in GC Subjects by Prior Gastrectomy Experience

Exposure Parameter(μg/mL)	Geometric Mean [CV%]		GM Diff[a] Percent (%)
	No	Yes	
Cmin1	12.5(30.6)	13.9(23.4)	11.2
Cmax1	45(21.9)	42.1(52.3)	-6.44
Cavg1	20.8(21.9)	21.1(19.4)	1.44
Cminss	27.7(42.5)	36.9(36.3)	33.2
Cmaxss	74(24.7)	80.3(35)	8.51
Cavgss	42.4(33.7)	51.3(30.1)	21

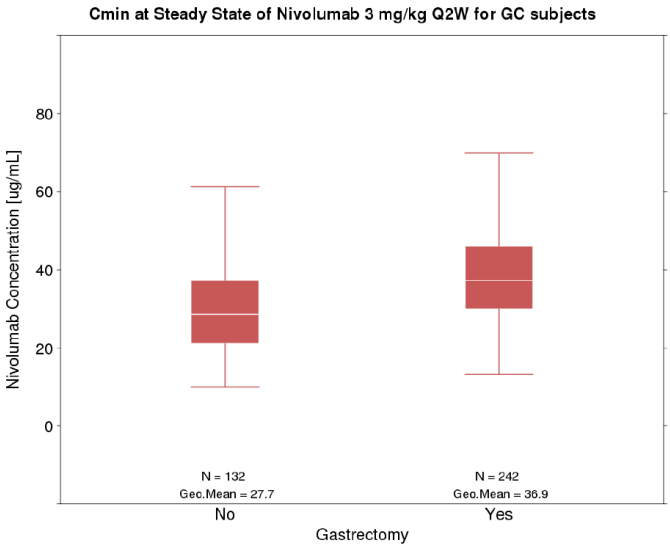
[a] GM Diff Percent = [(Geometric mean of gastrectomy Yes - Geometric mean of gastrectomy No) / Geometric mean of gastrectomy No] * 100

Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final

Program Source: Analysis Directory/R/scripts/summarize-model-application.r

Source: Analysis Directory/R/export/ compare.exp.gomy.csv

Figure 11: Distribution of Nivolumab Cminss Estimates by Prior Gastrectomy Experience in GC Subjects (3 mg/kg Q2W)



Analysis Directory: /global/pkms/data/CA/209/C18/prd/ppk/final
Program Source: Analysis Directory/R/scripts/summarize-model-application.r
Source: Analysis Directory/R/plots/Cminss-3mgkg-gc-gomy.png

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Dose Rationale

Nivolumab 3 mg/kg Q2W was selected as the dose anticipated to achieve an appropriate balance of benefit and risk in subjects with GC/GEJ in Studies ONO-4538-12 and CA209032 based upon the collective clinical experience of nivolumab monotherapy across multiple tumor types, including melanoma, NSCLC, and RCC. The analysis of safety, efficacy, and E-R analyses in melanoma, NSCLC, and RCC showed that the probability of a tumor response approached a plateau for nivolumab trough concentrations achieved following administration of nivolumab 3 mg/kg Q2W and nivolumab 10 mg/kg Q2W. In an E-R analysis of the relationship between nivolumab exposure (Cavgss) and OS over the nivolumab 1 mg/kg Q2W to nivolumab 10 mg/kg Q2W dose range, including nivolumab 3 mg/kg Q2W, Cavgss was not a significant predictor of hazard of death in NSCLC, melanoma and RCC, indicating a flat E-R relationship over the dose range. Therefore, nivolumab 3 mg/kg Q2W was used to assess nivolumab in the treatment of GC/GEJ. Results from ONO-4538-12 demonstrated that subjects with unresectable advanced or recurrent GC/GEJ refractory to or intolerant of standard therapy treated with nivolumab 3 mg/kg Q2W had an acceptable safety profile and a clinically meaningful response, with a median overall survival (OS) of 5.26 months for the nivolumab group compared to 4.14 months for placebo and a hazard ratio of 0.63 (95% CI: 0.51, 0.78) for the nivolumab group relative to the placebo group. Similarly, results from CA209032 demonstrated that subjects with GC/GEJ treated with nivolumab 3 mg/kg Q2W had an acceptable safety profile and a clinically meaningful response, with an ORR of 6.8% by a blinded independent central review (BICR) assessment.

A PPK model was developed to characterize the effect of race and GC/GEJ tumor type on the PK of nivolumab. Results demonstrated that Asian race, relative to White, did not affect the PK of nivolumab, supporting extrapolation of the findings from Asian to non-Asian GC/GEJ subjects. Further, the clinical response rates are similar in the Asian and non-Asian populations from ONO- 4538-12 and CA209032, respectively. PPK results showed that the nivolumab exposures in subjects with GC/GEJ were lower than that of subjects with NSCLC 2+; however, this finding is not considered clinically meaningful, as the robust response data in GC/GEJ demonstrates that these reductions do not preclude activity. Because

GC/GEJ tumor type does not have clinically meaningful effects on the PK of nivolumab, a similar safety profile across exposure levels and weight bands would be expected in the GC/GEJ population.

Collectively, the clinical data from studies ONO-4538-12 and CA209032 as well as the PPK analyses support the recommended dose of nivolumab 3 mg/kg Q2W in the treatment of adult patients with advanced or recurrent GC/GEJ cancer after two or more prior systemic therapies.

Immunogenicity

The immunogenicity following the administration of nivolumab 3 mg/kg Q2W monotherapy has been well characterized in the nivolumab development program across multiple tumor types. Updated immunogenicity analysis from studies ONO-4538-12 and CA209032 has been provided under this variation.

Immunogenicity Analysis

During the clinical development of nivolumab, three assays were used to detect the presence of nivolumab ADA. The CA209032 and ONO-4538-12 studies used in this submission and all of the studies included in the integrated summary of immunogenicity used the current sensitive and drug tolerant assay (ICDIM 140) for immunogenicity analysis, and a cell-based assay (15400) for the neutralizing antibody analysis.

Immunogenicity Results from Study ONO-4538-12

A summary of the ADA assessments for subjects on Study ONO-4538-12 who had evaluable ADA data at baseline and on treatment is presented in Table 13.

Table 13: Summary of ADA Assessments in Study ONO-4538-12 -Nivolumab Treated Subjects with Baseline and at Least One Post-Baseline Assessment

	Number of Subjects (%)
	Nivolumab 3 mg/kg (N=307)
Baseline ADA Positive	21 (6.8)
ADA Positive	36 (11.7)
Persistent Positive	1 (0.3)
Not PP - Last Sample Positive	18 (5.9)
Other Positive	17 (5.5)
Neutralizing ADA Positive[a]	-
ADA Negative	271 (88.3)

[a] Neutralizing antibodies were not assessed.

Baseline ADA Positive Subject: A subject with Baseline ADA positive sample; ADA Positive Subject: A subject with at least one ADA positive sample relative to baseline at any time after initiation of treatment; Persistent Positive Subject: ADA positive sample at 2 or more consecutive timepoints, with first and last ADA positive samples at least 16 weeks apart; Not PP - Last Sample Positive : Not persistent but ADA positive sample in the last sampling timepoint; Other Positive: Not persistent but some ADA positive samples with the last sample being negative; Neutralizing ADA 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. Post-baseline assessments are assessments reported after initiation of treatment.

Source: Table 11.4-11 of the ONO-4538-12 CSR[11]

Of the 307 GC/GEJ subjects treated with 3 mg/kg Q2W, 36 subjects (11.7%) were ADA positive. Of the 36 subjects, 1 subject had two or more consecutive positive samples, 18 subjects had a positive sample at the last sampling time point, and 17 subjects had some positive samples after the first administration but a negative result for the last sample.

Of the 5 subjects, who had infusion related and hypersensitivity reactions, 2 were ADA positive, while 3 were ADA negative. Of the 2 ADA positive subjects, only one had an infusion reaction related to drug administration, while 2 of the 3 ADA negative sub had hypersensitivity and infusion related reactions related to drug administration. These data suggest a lack of effect of ADA on safety.

Among the 36 ADA positive subjects, 6 had PR, 11 had SD, and 10 had PD . Thus, the ORR was 16.7% (6/36) in these ADA positive subjects, which is greater than the overall population, suggesting a lack of effect of ADA on efficacy. Further, a clear causal relationship between the time of ADA onset and/or persistence of ADA and response status and OS was not evident. Thus, the incidence of ADA did not appear to have an effect on efficacy of nivolumab.

At the time of the preparation of the ONO-4538-12 CSR, results from the neutralizing antibody assessments were not available. However, these data were subsequently become available and are briefly summarized as follows, out of the 307 subjects evaluable for immunogenicity assessment, 10 (3.25%) had detectable neutralizing antibodies while on treatment or during follow-up, all at only a single time point. There was not a consistent pattern across all neutralizing antibody positive subjects to when the presence of neutralizing antibodies were detected, as 6 (60%) had neutralizing antibodies detected on treatment, while 4 (40%) were detected after conclusion of treatment. There also is not a consistent pattern for the number of samples that were ADA, and neutralizing antibodies were detected versus the total number of post-baseline ADA samples tested for the presence of ADA. Further, the presence of neutralizing antibodies did not appear to have an effect on efficacy, as 1 (10%) subject had PR, 5 (50%) had SD, 2 (20%) had PD, and 2 (20%) were not evaluable (NE)(Table 14).

Table 14: ONO-4538-12 ADA positive subjects who have detectable neutralizing antibodies[a]

Subject ID	Visit (Day)	Scheduled Visit Code	Total Number of Post Baseline ADA Samples Collected	Number of ADA Positive Samples	Clinical Response
	21	CYCLE 2 DAY 1	4	3	SD
	71	CYCLE 7 DAY 1	8	1	SD
	-	END OF STUDY EXTENSION	4	3	PD
	13	CYCLE 1 DAY 15	7	2	PR
	-	FOLLOW UP 2	4	1	PD
	-	END OF STUDY EXTENSION	5	3	SD
	-	END OF STUDY EXTENSION	2	1	NE
	13	CYCLE 1 DAY 15	3	1	SD
	13	CYCLE 1 DAY 15	3	1	SD
	13	CYCLE 1 DAY 15	1	1	NE

[a] Source: Refer to the ONO-4538-12 Serum NAB Report[3]; Refer to Figure 4.1.2-1 in the Module 2.7.2 Summary of Clinical Pharmacology;[4] Refer to List_0035_Listing of All Anti Drug Antibody Assessments in the ONO-4538-12 CSR.[2]

Immunogenicity Results from Study CA209032 (GC/GEJ Cohort)

All Nivolumab-Treated GC/GEJ Subjects

A summary of the ADA assessments for all nivolumab treated GC/GEJ subjects on Study CA209032 who had evaluable ADA data at baseline and on treatment is presented in Table 15.

Table 15: Summary of Anti-Drug Antibody Assessments in Study CA209032 - All Nivolumab Treated GC/GEJ Subjects with Baseline and at Least One Post-Baseline Assessment

	Number of Subjects (%)
	CA209032 (N=51)
Baseline ADA Positive	1 (2.0)
ADA Positive[a]	12 (23.5)
Persistent Positive	0
Not PP - Last Sample Positive	5 (9.8)
Other Positive	7 (13.7)
Neutralizing ADA Positive	0
ADA Negative	39 (76.5)

[a] Narratives for these 12 ADA positive subjects summarizing efficacy and safety data are provided in Appendix 7.4A of the CA209032 CSR[12]

Baseline ADA Positive Subject: A subject with Baseline ADA positive sample; ADA Positive Subject: A subject with at least one ADA positive sample relative to baseline at any time after initiation of treatment; Persistent Positive Subject: ADA positive sample at 2 or more consecutive timepoints, where the first and last ADA positive samples at least 16 weeks apart; Not PP - Last Sample Positive Subject: Not persistent but ADA positive sample in the last sampling timepoint; Other Positive Subject: Not persistent but some ADA positive samples with the last sample being negative; Neutralizing ADA Positive Subject: At least one ADA positive sample with neutralizing antibodies detected post baseline; ADA Negative Subject: A subject with no ADA positive sample after the initiation of treatment.

Source: Table 8.15.1-1 of the CA209032 CSR

Twelve subjects (23.5%) were ADA positive following administration of nivolumab. No subject was considered persistent positive or neutralizing ADA positive. The highest titer value observed in ADA positive subjects was 32 (in 2 subjects). Both subjects were negative for ADA at the last sample. All other ADA positive subjects had titer values of 16 or less.

Only 1 subject had an infusion/hypersensitivity reaction, and s/he was ADA positive (other positive). This subject had a Grade 2 hypersensitivity/infusion reaction at the time of the positive ADA sample (cycle 2), but received 7 subsequent doses of nivolumab without additional hypersensitivity/infusion reaction events. Given that this subject continued to receive nivolumab treatment for 7 subsequent doses with no other occurrences of hypersensitivity/infusion reaction, it is unlikely that the cycle 2 occurrence was ADA related. Thus, there were no apparent effects of nivolumab immunogenicity on safety in nivolumab monotherapy treated GC/GEJ subjects in this study.

Among the 12 ADA positive subjects, 2 had PR, 2 had SD, 7 had PD and 1 discontinued due to progression. Thus, the ORR was 16.6% (2/12) in these ADA positive subjects, which is similar to the overall population, suggesting a lack of effect of ADA on efficacy.

All Nivolumab Treated Stomach Cancer or GE Junction Cancer Subjects with at Least 2 Prior Regimens

A summary of nivolumab ADA incidence in all nivolumab monotherapy treated subjects with stomach or GE Junction cancer and at least 2 prior regimens with baseline and at least one post-baseline assessment is presented in Table 16. The incidence of ADA in this subset is similar to all treated GC/GEJ subjects in CA209032.

Table 16: Summary of Anti-Drug Antibody Assessments in Study CA209032 - All Nivolumab Treated Stomach Cancer or GE Junction Cancer Subjects with at Least 2 Prior Regimens

	Number of Subjects (%)
	CA209032 (N=37)
Baseline ADA Positive	1 (2.7)
ADA Positive	9 (24.3)
Persistent Positive	0
Not PP - Last Sample Positive	4 (10.8)
Other Positive	5 (13.5)
Neutralizing ADA Positive	0
ADA Negative	28 (75.7)

Baseline ADA Positive Subject: A subject with Baseline ADA positive sample
ADA Positive Subject: Subject with at least one ADA positive sample relative to baseline at any time after initiation of treatment
Persistent Positive: ADA +ve sample at 2 or more consecutive timepoints, with first and last ADA +ve samples at least 16 weeks apart
Not PP - Last Sample Positive: Not persistent but ADA positive sample in the last sampling timepoint
Other Positive: Not persistent but some ADA positive samples with the last sample being negative
Neutralizing ADA Positive: At least one ADA positive sample with neutralizing antibodies detected post baseline
ADA Negative Subject: A subject with no ADA positive sample after the initiation of treatment
Post-baseline assessments are assessments reported after initiation of treatment
Program Source: /projects/bms219884/stats/ia_bcgc/prog/tables/rt-im-sum.sas

Immunogenicity Summary

A summary of nivolumab immunogenicity incidence in GC/GEJ subjects is presented in Table 17. The overall immunogenicity incidence in GC/GEJ subjects was 13.4% and is similar to that previously reported and within the range of immunogenicity incidences observed across different tumor types (0.6% in cHL subjects to 23.7% in UC subjects). It should be noted that although the ADA incidence rate of nivolumab in GC/GEJ subjects in the CA209032 study was numerically greater than in ONO-4538-12, it is consistent with what was observed with other tumor types.

In total, of the 6 GC/GEJ subjects who had infusion-related or hypersensitivity reactions following administration of nivolumab 3 mg/kg Q2W, 3 were ADA positive (1 in Study CA209032, 2 in ONO-4538-12) and 3 were ADA negative (all 3 in ONO-4538-12). In both ADA positive and ADA negative subsets, 2 of the 3 AEs were considered drug related. Similar to immunogenicity assessments in previous studies, a clear pattern related to ADA formation and safety events could not be established. These data suggest a lack of effect of nivolumab ADA on safety.

Moreover, no effect on efficacy was observed in subjects who were positive for nivolumab ADA. Among the 12 ADA positive subjects in Study CA209032, the ORR was 16.6% (2/12), which is similar to the overall population. Among the 36 ADA positive subjects in Study ONO-4538-12, the ORR was 16.7% (6/36), which is higher than the overall nivolumab treated population. Collectively, these data suggest a lack of effect of ADA on efficacy.

Overall, based on the above data, the incidence of nivolumab ADA following 3 mg/kg Q2W is similar to that observed in other tumor types and did not appear to have an effect on safety or efficacy.

Table 17: Summary of Nivolumab Antibody Assessments Using Method ICDIM 140 Following Nivolumab 3 mg/kg every 2 weeks

	Number of Subjects (%)		
Study Number	CA209032 (GC/GEJ Subjects) (N=51)	ONO-4583-12 (N=307)	GC/GEJ Summary (N=358)
Baseline ADA Positive	1 (2.0)	21 (6.8)	22 (6.1)
ADA Positive	12 (23.5)	36 (11.7)	48 (13.4)
Persistent Positive[b]	0	1 (0.3)	1 (0.3)
Not PP - Last Sample Positive	5 (9.8)	18 (5.9)	23 (6.4)
Other Positive	7 (13.7)	17 (5.5)	24 (6.7)
Neutralizing ADA Positive	0	-	0 (0)
ADA Negative	39 (76.5)	271 (88.3)	310 (86.6)

Source: See Table 4.1.2-1, Table 4.1.3.1-1

2.3.4 PK/PD modelling

No additional information has been provided.

2.3.5 Discussion on clinical pharmacology

Pharmacokinetics

Nivolumab concentration-time data seemed to be well described by the previously-developed linear, two-compartment, zero-order input IV infusion model with first order elimination and time-varying clearance. This model was assessed with variation II/19 (bladder indication) and used in variation II/36 for modification of posology. The final PPK model has been evaluated using pcVPC for GC subjects. When evaluating all concentrations after the previous dose from GC subjects and the trough data from GC subjects, the median, the 5th and 95th percentiles observed profile tracks are apparently well within the simulation results, although a slight under prediction is observed. Overall, the linear two-compartment model with zero-order infusion can be considered to adequately characterize the data. Therefore, the model is apparently appropriate for the evaluation of covariates and generation of exposures (Cmin1, Cmax1, Cavg1, Cminss, Cmaxss and Cavgss) in various comparative PK analysis for subjects with GC. However, an shrinkage higher of 30% for VP (40.6%) and EMAX (48.6%), indicates that analyses of covariates on VP and EMAX should be interpreted with caution. Thus, firm conclusions should not be raised about the effect of type of tumour (GC vs NSCLC 2L+) on Emax.

Regarding the effect of tumour type and race, a confounding effect between them cannot be ruled out since the majority of the GC population are Asian patients (329 out of total 387 patients). As Asian patients have lower CL, a higher exposure would be expected in those patients. However, nivolumab exposures after the first dose were approximately 8% to 14% lower in Asian patients, being these differences with Non-Asian patients smaller after reaching steady state. The effect of race and tumour type (GC) could be underestimated in this PPK since effects of tumour type (GC) and Asian race on CL are opposed, being the effect of tumour type (GC) higher that the effect of race (+33% vs -17.9%). It should also be kept in mind that the median body weight is lower in Asian patients. However, the impact of body weight is expected to be low as the posology for this application is administered by kg of body weight. The

potential confounding effect between tumour type (GC) and race (Asian) was discussed by the applicant. The point estimate for effect of Asian race on CL [point estimate (90% CI)] in the current analysis is 82.1% (75.5, 89.1), where 399 Asian subjects were compared with 833 White and Other race category subjects, who have GC, NSCLC 2L and other solid malignancies, including CRC, melanoma, and RCC. In a previous PPK analysis, using the same model, where 220 Asian subjects were compared to 3070 White and Other race subjects, who had GC, NSCLC, and other similar malignancies, the point estimate was 91.6% (86.8, 97.1). Thus, the effect of Asian race on CL was larger in the current analysis. In the current analyses, which has both Asian and White subjects who have GC, the estimate of effect of GC tumour type on CL is 133% (118, 147), while in the previous PPK analyses, which only had White subjects who have GC, the estimate was 119% (108, 131). The fact that the GC and Asian effects on CL are confounded cannot be fully ruled out. However, as comparison of the current and previous analyses showed that the magnitudes of effects on the point estimates for both GC and Asian race are more profound in the current analyses where number of Asian population included is higher, this issue is not further pursued.

The CL in GC subjects with gastrectomy was lower by 18.1% compared to subjects without gastrectomy. The differences observed in nivolumab exposures were greater (8.51% to 33.2%) at steady state compared to those observed after the first dose (1.4% to 11.2%). According to the applicant justification, this finding could be based on the relative health of those individuals and/or on response to nivolumab treatment. Healthier subjects seem to have slower CL versus those in worse health state and the greater reduction in CL seems to occur in those subjects who are responding to treatment.

Pharmacodynamics

Dose justification

No proper dose selection study has been conducted. Selection of dose is mainly based upon the collective clinical experience of nivolumab monotherapy across multiple tumour types, including melanoma, NSCLC, and RCC. Additionally, in an E-R analysis of the relationship between nivolumab exposure (Cavgss) and OS over the nivolumab 1 mg/kg Q2W to nivolumab 10 mg/kg Q2W dose range, including nivolumab 3 mg/kg Q2W, Cavgss was not a significant predictor of hazard of death in NSCLC, melanoma and RCC, indicating a flat E-R relationship over that dose range. Therefore, nivolumab 3 mg/kg Q2W was selected. Although a 28% lower exposure (Cmax 1) was observed in GC/GEJ subjects relative to NSCLC 2L+ subjects, this would not be considered clinically relevant if efficacy results of clinical trials demonstrated that nivolumab 3 mg/kg Q2W significantly reduced the risk of death in GC/GEJ subjects. In such case it would suggest that this dosing regimen was beneficial to this population regardless of the lower exposures versus NSCLC 2L+ and a similar safety profile was observed in the GC/GEJ population in comparison with other populations. However, since efficacy data of nivolumab 3 mg/kg Q2W in study ONO-4538-12 did not demonstrate a robust effect on efficacy (see efficacy MO), this issue cannot be considered resolved. Additionally, the flat part of the exposure-response curves observed in other indications, such as renal cell carcinoma and melanoma, has not been confirmed in GC/GEJ cancer. While clinical efficacy observed in ONO-4538-12 with these exposures is matter of discussion, this issue cannot be considered resolved, although is not further pursued for the moment.

Immunogenicity

307 out of 330 subjects (93.0%) from Study ONO-4538-12 and in study *CA209032,* 51 out of 59 (86.4%) all subjects with GC/GEJ and 37 out 42 (88.1%) subjects with GC/GEJ cancer and ≥ 2 prior regimens were evaluable for immunogenicity. For subjects to be evaluable, baseline samples prior to, and at least one sample available following initiation of nivolumab treatment need to be collected.

The overall immunogenicity incidence in GC/GEJ subjects was 13.4% which is in line with that previously reported for nivolumab monotherapy in various tumor types (11.4%) and within the range of immunogenicity incidences (0.6% in cHL subjects to 23.7% in UC subjects). However, it should be noted that although the ADA incidence rate of nivolumab in GC/GEJ subjects in both studies is consistent with what was observed with other tumour types, the ADA incidence rate in the CA209032 study was numerically greater (23.5%) than in ONO-4538-12 (11.7%).. As applicant mentioned, these differences between studies could be consequence of high differences in size of the studies (51 patients in CA209032 vs 307 patients in ONO-4538-12), differences in percentages of evaluable subjects in each study (86.4% in CA209032 vs 93.0% in ONO-4538-12), the duration of ADA collection following initiation of treatment (1.84 months, range 0 to 14.3+ months, in CA209032 vs 1.92, range 0 to 19.5 months, in ONO-4538-12), patient populations, and/or differences in drug product. As incidence of ADA positive in ONO-4583-12 seems to be similar to the expected one in overall population treated with nivolumab monotherapy, seemingly higher incidence observed in study CA209032 could be meanly caused by the small sample size of this study.

A clear pattern related to ADA formation and safety events could not be established. Of the 6 GC/GEJ subjects who had infusion-related or hypersensitivity reactions following administration of nivolumab, 3 were ADA positive and 3 were ADA negative.

No effect on efficacy was observed in subjects who were positive for nivolumab ADA. Among the 12 ADA positive subjects in Study CA209032, the ORR was 16.6% (2/12), which is similar to the overall population. Among the 36 ADA positive subjects in Study ONO-4538-12, the ORR was 16.7% (6/36), which is higher than the overall nivolumab treated population.

The incidence of neutralizing ADA positivity in ONO-4583-12 (3.25%) is slightly higher in comparison with the mean incidence observed in the previous studies with nivolumab monotherapy (0.7%, ranged from 0% to 2.8%). However, as the incidence is lower to the mean incidence observed with nivolumab in combination with ipilimumab (4.6%), this incidence of neutralizing ADA positivity is not expected to be clinically relevant.

2.3.6. Conclusions on clinical pharmacology

Clinical pharmacology of nivolumab in patients with GC can be considered well described although since efficacy data of nivolumab 3 mg/kg Q2W in study ONO-4538-12 did not demonstrate a robust effect on efficacy (see efficacy MO), the clinical relevance of 28% lower exposure (Cmax 1) observed in GC/GEJ subjects relative to NSCLC 2L+ subjects cannot be ruled out.

2.4. Clinical efficacy

There are several ongoing studies of nivolumab monotherapy in GC/GEJ cancer. The pivotal Phase 3 study of ONO-4538 (referred to as nivolumab) in advanced or recurrent GC (including GEJ cancer) (ONO-4538-12) and supportive Phase 1/2 study of nivolumab monotherapy or nivolumab combined with ipilimumab in multiple tumour types, including unresectable locally advanced or metastatic GC including GEJ cancer (CA209032 - GC Monotherapy Cohort) are the basis of current application. Both studies enrolled subjects regardless of tumour programmed cell death ligand 1 (PD-L1) expression level.

In addition, several GC/GEJ cancer studies are ongoing in the nivolumab clinical program, including:

- CA209649, a randomised Phase 3 study of nivolumab in combination with ipilimumab or nivolumab in combination with oxaliplatin plus fluoropyrimidine vs oxaliplatin plus fluoropyrimidine as first-line therapy in advanced or metastatic GC/GEJ cancer
- CA209577, a randomised Phase 3 study of adjuvant nivolumab or placebo in subjects with resected esophageal or GEJ cancer

Studies in GC/GEJ cancer being conducted in collaboration with Ono include:

- ONO-4538-37, a randomised Phase 3 study of nivolumab in combination with oxaliplatin vs nivolumab in combination with oxaliplatin plus capacitabine in Asian patients with previously untreated, inoperable, locally advanced, recurrent, or metastatic GC/GEJ cancer
- ONO-4538-38, a randomised Phase 3 study of adjuvant nivolumab in combination with S-1 or adjuvant nivolumab in combination with xelox vs placebo or placebo in combination with xelox in patients with stage III GC/GEJ cancer

The ONO-4528-12 and CA209032 (GC Cohort) studies provide the evidence of efficacy and safety of nivolumab monotherapy in adults with advanced or recurrent GC or GEJ cancer after 2 or more prior systemic therapies refractory to, or intolerant of, standard therapy

2.4.1. Dose response study

Dose response studies were not performed specifically for the indication in GC/GEJ. The dose is the same as the one used in the already approved indications.

2.4.2. Main study

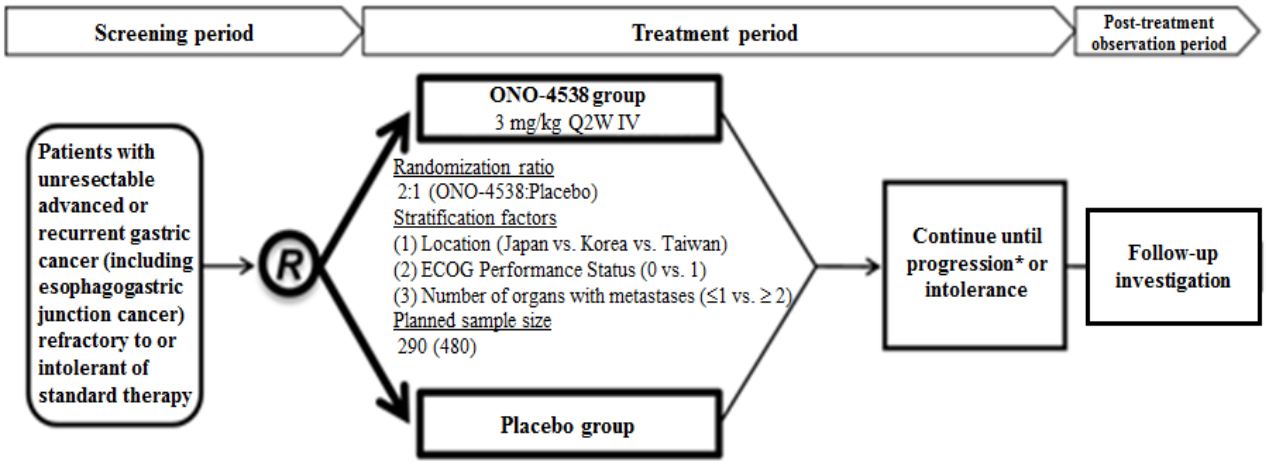
Study ONO-4538-12 is a Phase 3, multicentre, double-blind, randomised, placebo-controlled study in Japanese, Korean, and Taiwanese subjects treated with 2 or more chemotherapy regimens for the treatment of advanced or recurrent GC (including GEJ cancer) histologically confirmed to be adenocarcinoma, were refractory to, or intolerant of, standard therapy, and not planned to newly receive antineoplastic treatments including antibody products.

Subjects were randomised in a 2:1 ratio to the nivolumab group or the placebo group. Randomization was stratified according to location, ECOG PS and number of organs with metastases.

An interim analysis, aiming to determine the need to stop the trial early because of futility and for sample size re-estimation, was performed when approximately 70% (i.e., 183/261) of the required number of events for final OS analysis of this study had occurred.

The entire study period consisted of 3 periods: screening period, treatment period, and post-treatment observation period, and the study design is provided in Figure 12.

Figure 12: Design of Study ONO-4538-12



Abbreviations: ECOG = Eastern Cooperative Oncology Group; IV = intravenous(ly); ONO-4538 = nivolumab; Q2W = every 2 weeks.

*Treatment per protocol could be continued even after documented progression.

Study participants

Subjects in ONO-4538-12 were enrolled with an initial diagnosis of adenocarcinoma, who had previously received 2 or more regimens for the treatment of histologically confirmed advanced or recurrent gastric cancer (including oesophagogastric junction cancer), were refractory to or intolerant of standard therapy, and were not planned to newly receive any antineoplastic treatments including antibody products.

Subjects were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1, a life expectancy of at least 3 months, and age of at least 20 years. Subjects were not required to have measurable disease. Subjects were excluded if they received prior therapy with a therapeutic antibody for the regulation of T-cells.

Treatments

After randomization, the investigational products (nivolumab or placebo) were administered Q2W up to 3 doses per cycle and imaging examination was performed after 6 weeks. These 6 weeks will count as one cycle.

Treatment was continued until progressive disease (PD) (treatment beyond progression was allowed under the pre-specified protocol criteria), as assessed by the investigator according to RECIST 1.1, or onset of severe adverse events (AEs), or other intolerable toxicity would have made it impossible to continue with study treatment per investigator or subinvestigator assessment. Subjects who progressed, but in the opinion of the investigators should receive additional therapy, were allowed to continue treatment.

Objectives

Primary Objective of the Study

To assess the efficacy of ONO-4538 compared to placebo based on overall survival (OS) as the primary endpoint in patients with unresectable advanced or recurrent gastric cancer refractory to or intolerant of standard therapy.

Secondary Objective of the Study

To assess the efficacy and safety of ONO-4538 compared to placebo from multifaceted aspects in patients

with unresectable advanced or recurrent gastric cancer refractory to or intolerant of standard therapy.

The secondary objectives included investigator-assessed PFS, ORR, DOR, disease control rate (DCR) and time to response (TTR) compared to placebo.

Outcomes/endpoints

Table 18: Efficacy Variables in ONO-4538-12

Endpoint	Definition	Assessment
Primary Endpoint		
Overall Survival	Time from randomization until death from any cause	Definition is the same as BMS studies. Same censoring algorithm as used in nivolumab BMS studies.
Key Secondary Endpoints		
PFS	PFS is defined as the time from the date of randomization until the earlier date of PD or death of any cause.	Definition is similar to BMS studies. Limited differences in censoring and collection of tumor assessments after start of subsequent therapy.
ORR	ORR is defined as the percentage of subjects whose BOR is assessed as either CR or PR per RECIST 1.1.	Same definition as nivolumab BMS studies. CR and PR should be confirmed. Since ONO-4538-12 included subjects without measurable disease at baseline, this analysis will be performed on the ITT and RES[a] populations.
DOR	DOR is defined as the time between the date of first assessment of confirmed CR or PR and the earlier date on which either the overall response was assessed as PD for the first time after confirmed response or the patient died of any cause. It is calculated for subjects with confirmed CR or PR during the study.	Definition is similar to BMS studies. Limited differences in censoring and collection of tumor assessments after start of subsequent therapy. Censoring algorithm is the same as PFS.
DCR	DCR is defined as the percentage of all randomized subjects whose BOR is assessed as CR, PR, or SD.	BOR assessed as SD for subjects without an overall response of PD until after Day 43 of Cycle 1 and with SD or a better response at least once.
TTR	TTR is defined as time between the date of randomization and the date of the first assessment of confirmed CR or PR.	Same definition as for nivolumab BMS studies.

Abbreviations: BMS = Bristol-Myers Squibb; BOR = best overall response; CR = complete response; DCR = disease control rate; DOR = duration of response; GCP = Good Clinical Practice; ITT = intention to treat; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; RES = response evaluable set; SD = stable disease; TTR = time to response.

[a] The RES consisted of all subjects which met all of the following items in the ITT population: (1) Subjects were not GCP Noncompliant Subjects, as defined in the statistical analysis plan (see Appendix 16.1.9 of the ONO-4538-12 Final CSR); (2) Subjects had target lesion measurements at baseline.

Additional endpoints include HLA analysis, plasma microRNA expression analysis, PBMC and genetic testing (both optional), tumour markers as needed, and tumour tissue examination (optional).

Sample size

ONO-4538-12 followed an adaptive design for the required number of OS events. Assuming an exponential distribution of OS and a hazard ratio (HR) of 0.65 (which was equivalent to a median OS of 6.154 months in the ONO-4538 group and 4 months in the placebo group) with a one-sided significance level of 2.5%, the original required number of OS events to achieve 90% power was 261. Assuming an enrolment period of 18 months with a follow-up period of 12 months, and taking into account possible drop-outs, the required number of subjects to be randomised was estimated to be 290. The protocol included a pre-specified interim analysis (IA) to determine the need to stop the study early for futility or

to re-estimate the required number of OS events, based on the conditional power (CP) calculated at the IA (limited to a maximum of 436 events). The protocol specified that up to 480 subjects could be randomised to ensure the required number of events.

The Independent Data Monitoring Committee (IDMC) was to perform the unblinded IA when approximately 70% (i.e., 183/261) of the required number of events (deaths) for final OS analysis of the study had occurred. The IDMC decision would be based on the following criteria:

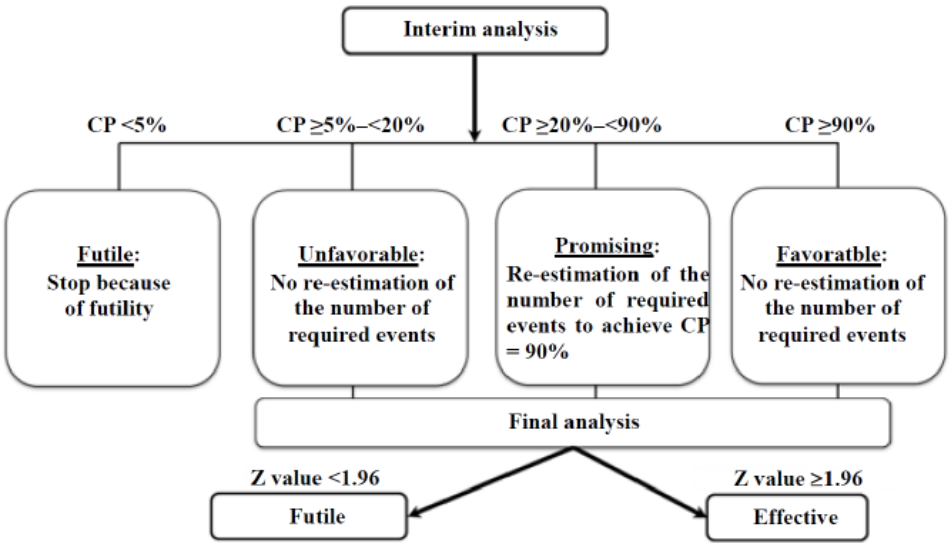
- **Favourable:** If CP ≥ 90%, no re-estimation of the number of required OS events will be performed.
- **Promising:** If CP ≥ 20% – < 90%, re-estimation of the number of required OS events will be performed.
- **Unfavourable:** If CP ≥ 5% – < 20%, no re-estimation of the number of required OS events will be performed.
- **Futile:** If CP < 5%, the study will be stopped because of futility

As pre-specified in the protocol, the number of subjects randomised could be increased up to 480 subjects to ensure the maximum number of events (i.e., 436) be reached. Due to the high enrolment speed, ONO decided not to hold enrolment and to randomize 480 subjects directly before the IDMC IA. However, the final number OS events remained to be adjusted based on the IDMC IA. On 14-Feb-2016, the IDMC met and reviewed the unblinded IA results including 196 OS events. Based on this interim review, the IDMC decided to increase the OS events to 328 based on a calculated CP of 78.3%. After the IDMC review, ONO was informed to continue the study and remained blinded to the IDMC interim reports as well as the actual re-estimated number of final OS events.

The IDMC informed ONO on 13-Aug-2016 that the requisite number of 328 events was reached to conduct the final analysis.

The study actually randomised 493 subjects and the final database lock included 367 OS events.

Figure 13: Flowchart of interim and final analyses



Randomisation

Subjects were randomised in a 2:1 ratio to the ONO-4538 group or the placebo group.

The randomization was stratified according to location (Japan vs. Korea vs. Taiwan), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 vs. 1) and number of organs with metastases (≤1

vs. ≥2).

Blinding (masking)

In this study, allocation to either the ONO-4538 group or the placebo group was double-blinded.

Since only ONO-4538 was supplied to each study centre and no ONO-4538-matching placebo was supplied, the ONO-4538 group and the placebo group could be distinguished at the time of the delivery and dispensing of the investigational product. Thus, each study centre appointed an unblinded pharmacist who managed and dispensed the investigational product according to a written procedure prepared separately to maintain the blinding to others. Also to maintain the blinding, the sponsor appointed unblinded monitors who checked the investigational product management status, delivered the investigational product, and retrieved unused portions of the investigational product according to a written procedure prepared separately.

"Unblinded Interim Analysis" an interim analysis was to be performed when approximately 70% (i.e., 183/261) of the required number of events (deaths) for final OS analysis of this study had occurred, to determine the need to stop the study early because of futility and sample size re-estimation based on the conditional power (CP) in testing the hypothesis of OS. The procedures for unblinding the randomization key codes at the interim analysis were specified in the written procedure for IDMC prepared separately.

The randomization key codes will be unblinded when the required number of OS events determined based on the interim analysis has been reached.

Statistical methods

The primary endpoint (OS) was analysed with a one-sided log-rank test stratified by the 3 stratification factors (based on Interactive Web Response System [IWRS] data) at the 2.5% significance level.

The hazard ratio and its 95% confidence interval (CI) for the ONO-4538 group relative to the placebo group were calculated using the stratified Cox proportional-hazards model with the stratification factors.

The Kaplan-Meier curve was plotted for each treatment group. Using the Kaplan-Meier method, the median OS and its 95% CI were calculated for each treatment group. Also using the Kaplan-Meier method, the survival rate and its 95% CI at Months 3, 6, 9, and 12 were calculated for each treatment group.

Similar methodology was used for the assessment of PFS.

The ORR or DCR and the corresponding exact 95% CIs were calculated by using Clopper-Pearson method for each treatment group. Data were compared between the two treatment groups by using the Cochran-Mantel-Haenszel test.

The Kaplan-Meier curve was plotted for each treatment group for TTR. Summary statistics were calculated for each treatment group for subjects whose BOR was CR or PR. For BOR analysis, the percentage of CR, PR, SD, PD and NE were calculated for each treatment group. For the percentage of CR, PR and SD, exact 95% CI was calculated by using Clopper-Pearson method for each treatment group.

The ITT will be the analysis set for all analyses but for ORR, DOR , DCR, TTR and BOR for which RES will be also evaluated. The maximum percent change from baseline in the sum of diameters of target lesions will be evaluated in the RES analysis set.

Results

The analyses conducted in this study are based on the data collected through the eCRFs and IWRS by data cut-off on 13 Aug 2016.

In this study, subjects were enrolled in 3 countries, at 48 study sites in the ONO-4538 group and 41 study sites in the placebo group.

Participant flow

A total of 601 subjects were enrolled in the study and 493 subjects were randomised: 330 subjects to the nivolumab (all received at least one dose) group and 163 subjects to the placebo group (161 of these subjects received at least one dose).

In the nivolumab and placebo groups, respectively, 87.9% and 98.1% of subjects discontinued study treatment. The most common reason for treatment discontinuation was PD (65.2% in the nivolumab group, 66.5% in the placebo group) followed by apparent worsening of clinical symptoms determined to be due to disease progression that makes it inappropriate to continue with study treatment (16.7%, 23.0% respectively), and The investigator or subinvestigator judges that continuation of study treatment in the subject is inappropriate for other reasons from the viewpoint of efficacy or safety (3.6%, 1.9%, respectively). Table 19 presents a description of the subject populations sets.

Table 19: Subject Disposition - ONO-4538-12

	ONO-4538-12 Primary Study	
Subjects enrolled	601	
Subjects randomized (%)	493 (82.0)	
Non-randomized subjects (%)	108 (18.0)	
Subjects treated	491	
Subjects treated - nivolumab	330	
Subjects treated - placebo	161	
Subjects randomized and not treated	2	
	Nivolumab Monotherapy Treated Subjects N = 330	**Placebo N = 161**
Subjects continuing in the treatment period (%)	40 (12.1)	3 (1.9)
Subjects not continuing in the treatment period (%)	290 (87.9)	158 (98.1)
Reason for not continuing in the treatment period due to disease progression according to the RECIST Guideline Version 1.1 (%)	215 (65.2)	107 (66.5)
Subjects continuing to be followed (%)	93/330 (28.2)	17/163 (10.4)

Source: Refer to Table 10.1-2, Table 11.4-1, Table 14.1.1-3, and Table 14.1.1-4 in the ONO-4538-12 CSR

Table 20: Description of Analysis Populations Sets - ONO-4538-12

ONO-4538-12 - Primary Study			
	Nivolumab	Placebo	Total
Informed Consent Set (INF)	-	-	601
Enrolled Set (ENR)	-	-	601
Intent-to-Treat (ITT)[a]	330	163	493
Response Evaluable Set (RES)[b]	268	131	399
Safety Set (SAF)[c]	330	161	491
Subjects randomized but not treated	0	2	2

[a] Consists of all randomized subjects.

[b] Consists of all randomized subjects with target lesion measurements at baseline (and who were not GCP non-compliant).

[c] Consists of all subjects who received at least 1 dose of study drug.

Recruitment

Conduct of the study

Protocol amendments

There were four minor protocol amendments during the study.

Protocol amendment 1 added a criterion for breastfeeding under subject inclusion criteria (Also, women must agree not to breastfeed from the time of informed consent until 320 days or more after the last dose of the investigational product).

Protocol amendment 2 added Peripheral blood mononuclear cell (PBMC) as an optional test variable.

Protocol amendment 3 clarified the definition of "other medically important events" under definition of serious adverse events (If a spread of any infectious factor mediated by the investigational product is suspected, it must be reported as a medically significant event).

Protocol amendment 4 the duration for contraception and the prohibited period of breastfeeding were reviewed and revised.

Protocol deviations

As of the data cut-off date for this CSR, at least 1 relevant deviation from the protocol was reported in 19.1% of subjects (63 subjects) in the ONO-4538 group and 19.6% of subjects (32 subjects) in the placebo group. The most common relevant deviation from the protocol was "Subjects receiving any concurrent anti-cancer therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, surgery, or radiation therapy) while on study therapy" (19.1% of subjects [63 subjects] in the ONO-4538 group, 19.0% of subjects [31 subjects] in the placebo group).

These numbers differ from those presented the summary of clinical efficacy as symptomatic cancer therapies (i.e., diuretics, ascites drainage, etc.) and therapies started after the last study treatment dose were not considered as relevant protocol deviations in this analysis and therefore protocol deviations were only considered relevant in 1 subject in the placebo arm (0.6%) subject failed to fulfil protocol inclusion criteria number 5, ECOG Performance Status score 0 or 1, which was considered a relevant protocol deviation.

In addition, the blind was broken inadvertently for the two subjects (one in the ONO-4538 group and one

in the placebo group[Japan]) by monitoring personnel or site staff at the study site.

Table 21: Relevant Protocol Deviations

Analysis Set : ITT

		ONO-4538	Placebo
		n (%)	n (%)
	N	330	163
Subjects with at least one deviation		63 (19.1)	32 (19.6)
Eligibility			
Subjects who failed to fulfill inclusion criteria #3		0	0
Subjects who failed to fulfill inclusion criteria #4		0	0
Subjects who failed to fulfill inclusion criteria #5		0	1 (0.6)
On-study			
Subjects receiving any concurrent anti-cancer therapy (ie. chemotherapy,hormonal therapy, immunotherapy, surgery, or radiation therapy) while on study therapy		63 (19.1)	31 (19.0)
Subjects who received wrong randomization number		0	0

Baseline data

In ONO-4538-12, the nivolumab-treated subjects received nivolumab 3 mg/kg IV Q2W. The study was conducted in Japan, Korea and Taiwan, with the majority of subjects from Japan and Korea.

The baseline demographics and disease characteristics were balanced between the nivolumab and placebo groups, and were consistent with what was expected in a population of unresectable advanced or recurrent GC/GEJ cancer (Table 22). Most subjects had GC (82.4% and 82.8% in the nivolumab and placebo groups, respectively).

The median time from the date of initial diagnosis of the primary disease to randomization was 23.4 months (range: 4 - 185 months) in the nivolumab group and 25.0 months (range: 6 – 412 months) in the placebo group. These numbers differ from those presented in the ONO-4538-12 CSR where the date of initial diagnosis was erroneously derived.

Table 22: Demographics and Baseline Characteristics - ONO-4538-12

	ONO-4538-12 Primary Study	
	Nivolumab Monotherapy Subjects (ITT) (N = 330)	Placebo (ITT) (N = 163)
Age (years)		
N	330	163
Mean (SD)	60.7 (11.4)	59.9 (11.9)
Median	62.0	61.0
Min,Max	20, 83	26, 83
Age Categorization (%)		
< 65	189 (57.3)	95 (58.3)
≥ 65	141 (42.7)	68 (41.7)
≥ 75	30 (9.1)	14 (8.6)
≥ 85	-	-
Gender (%)		
Male	229 (69.4)	119 (73.0)
Female	101 (30.6)	44 (27.0)
Race (%)		
White	0	0
Black or African American	0	0
Asian	329 (99.7)	163 (100.0)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	1 (0.3)	0
Other	0	0
Weight (kg)		
Mean (SD)	55.32 (10.24)	54.56 (10.67)
Median	54.90	53.70
Min , Max	31.5 - 91.8	33.0 - 90.8
Performance Status (ECOG [%]) (eCRF)		
0	88. (26.7)	47 (28.8)
1	242 (73.3)	116 (71.2)
Primary tumor location[a]		
Gastric	272 (82.4)	135 (82.8)
GEJ	30 (9.1)	12 (7.4)
Esophagus	0	0
Unknown	28 (8.5)	16 (9.8)
Time from Date of Initial Diagnosis of Primary Disease to Randomization (months) /median (min - max)	23.4 (4, 185)	25.0 (6 ,412)

Histologic Type (Lauren classification) (n, %)		
Intestinal type	120 (36.4)	55 (33.7)
Diffuse type	106 (32.1)	63 (38.7)
Others	17 (5.2)	6 (3.7)
Unknown	87 (26.4)	39 (23.9)
Disease Stage at Primary Diagnosis (Primary Tumor Location) (TNM Classification) (n, %)		
0	0	0
IA	5 (1.5)	1 (0.6)
IB	10 (3.0)	3 (1.8)
IIA	16 (4.8)	8 (4.9)
IIB	20 (6.1)	9 (5.5)
IIIA	23 (7.0)	15 (9.2)
IIIB	33 (10.0)	20 (12.3)
IIIC	37 (11.2)	23 (14.1)
IV	177 (53.6)	81 (49.7)
Unknown/Not Reported	9 (2.7)	3 (1.8)
Recurrent (n, %)		
No	194 (58.8)	91 (55.8)
Yes	136 (41.2)	72 (44.2)
Subjects with at least 1 target lesion (n, %)	268 (81.2)	131 (80.3)
Number of organs with metastases at study entry (eCRF)		
< 2	87 (26.4)	38 (23.3)
≥ 2	243 (73.6)	125 (76.7)
Median	2.0	2.0
Min - Max	0 - 7	1 - 8

Site of metastases at initial diagnosis (%)		
Lymph node	285 (86.4)	138 (84.7)
Liver	78 (23.6)	28 (17.2)
Peritoneum	63 (19.1)	42 (25.8)
Other	36 (10.9)	17 (10.4)
Lung	18 (5.5)	6 (3.7)
Bone	6 (1.8)	5 (3.1)
Adrenal gland	6 (1.8)	4 (2.5)
Pleural Tissue	4 (1.2)	2 (1.2)
Best response to the most recent regimen		
CR or PR	32 (9.7)	14 (8.6)
SD	111 (33.6)	49 (30.1)
PD	157 (47.6)	82 (50.3)
Non-CR/Non-PD	8 (2.4)	1 (0.6)
NE	1 (0.3)	5 (3.1)
Unknown/Not Applicable	21 (6.4)	12 (7.4)

[a] Primary tumor location data are provided in Figure 14.2.6-1 and Table 14.2.3-1 in the ONO-4538-12 CSR. Subjects with lesion sites in both gastric and esophagogastric junction are included gastric category.

Prior therapies

All subjects in ONO-4538-12 were required to have received 2 or more prior regimens for the treatment of advanced or recurrent GC/GEJ cancer.

The most frequent prior agents reported were irinotecan hydrochloride (74.8%), followed by cisplatin (64.8%) and paclitaxel (63.9%) in the ONO-4538 group and irinotecan hydrochloride (75.5%), followed by cisplatin (68.7%) and gimeracil, oteracil potassium, and tegafur (62.0%) in the placebo group (Table 23).

- In the nivolumab group, 20.9%, 41.5%, and 37.6% of subjects received 2, 3, and > 3 prior regimens, respectively. Similarly, in the placebo group, 17.8%, 38.0%, and 44.2% of subjects received 2, 3, and > 3 prior regimens, respectively.
- 157 (47.6%) vs 82 (50.3%) subjects had disease progression as best response to the most recent regimen in the nivolumab and placebo groups, respectively.
- Most subjects received pyrimidine analogues (99.7% vs 100.0%), platinum compounds (94.2% vs 96.3%), and taxanes (86.1% vs 85.9%) in the nivolumab and placebo groups, respectively.
- The majority of subjects had prior surgery for GC (64.5% in the nivolumab group and 68.7% in the placebo group), and had not received prior radiotherapy (87.6% and 84.7%, respectively).

Table 23: Prior Treatment Regimens - ONO-4538-12

	ONO-4538-12 Primary Study	
	Nivolumab Monotherapy Subjects (ITT) (N = 330)	Placebo (ITT) (N = 163)
Prior surgery related to cancer		
Yes	213 (64.5)	112 (68.7)
No	117 (35.5)	51 (31.3)
Prior radiotherapy		
Yes	41 (12.4)	25 (15.3)
No	289 (87.6)	138 (84.7)
Number of prior systemic regimens received[a] (%)		
2	69 (20.9)	29 (17.8)
3	137 (41.5)	62 (38.0)
> 3	124 (37.6)	72 (44.2)
Types of Prior Systemic Therapies[b]		
Platinum compounds	311 (94.2)	157 (96.3)
Carboplatin	2 (0.6)	2 (1.2)
Cisplatin	214 (64.8)	112 (68.7)
Oxaliplatin	157 (47.6)	82 (50.3)
Pyrimidine analogues/Fluoropyrimidine	329 (99.7)	163 (100.0)
Capecitabine	162 (49.1)	68 (41.7)
Fluorouracil	136 (41.2)	66 (40.5)
Gimer/tegfur/otera	175 (53.0)	101 (62.0)
Taxane	284 (86.1)	140 (85.9)
Docetaxel	86 (26.1)	52 (31.9)
Paclitaxel	211 (63.9)	100 (61.3)
Paclitaxel albumin	17 (5.2)	11 (6.7)
VEGF		
Bevacizumab	3 (0.9)	3 (1.8)
Ramucirumab	35 (10.6)	22 (13.5)
HER-2		
Lapatinib	2 (0.6)	0
Trastuzumab	59 (17.9)	22 (13.5)
Trastuzumab emtansine	4 (1.2)	2 (1.2)
Anthracycline		
Epirubicin	5 (1.5)	4 (2.5)
Other		
Irinotecan	247 (74.8)	123 (75.5)
Etoposide	1 (0.3)	2 (1.2)
Gemcitabine	1 (0.3)	0

[a] Includes all prior regimens irrespective of setting (metastatic, adjuvant, neo-adjuvant).

Numbers analysed

ITT consisted of 330 subjects in the ONO-4538 group and 163 subjects in the placebo group. SAF

consisted of 330 subjects in the ONO-4538 group and 161 subjects in the placebo group (Table 24).

Although key codes were broken for 2 subjects due to safety reason, and for other 2 subjects due to inadvertent accident, these 4 subjects were not excluded from the efficacy and safety analyses.

Table 24: Description of Analysis Populations Sets - ONO-4538-12

ONO-4538-12 - Primary Study			
	Nivolumab	**Placebo**	**Total**
Informed Consent Set (INF)	-	-	601
Enrolled Set (ENR)	-	-	601
Intent-to-Treat (ITT)[a]	330	163	493
Response Evaluable Set (RES)[b]	268	131	399
Safety Set (SAF)[c]	330	161	491
Subjects randomized but not treated	0	2	2

[a] Consists of all randomized subjects.

[b] Consists of all randomized subjects with target lesion measurements at baseline (and who were not GCP non-compliant).

[c] Consists of all subjects who received at least 1 dose of study drug.

Outcomes and estimation

The median duration of treatment was 1.92 months (range: 0 - 19.5 months) in the nivolumab group and 1.05 months (range: 0 - 20.5 months) in the placebo group. The median number of doses received was 5.0 doses (range: 1 - 42 doses) in the nivolumab group and 3.0 doses (range: 1 – 45 doses) in the placebo group. The median cumulative dose in the nivolumab group was 14.49 mg/kg (range: 3.0 - 125.2 mg/kg) and the median relative dose intensity was 96.76% (range: 45.6% - 112.6%).

Efficacy Results - ONO-4538-12

Key primary and secondary efficacy results of ONO-4538-12 are presented in Table 25

Table 25: Primary and Secondary Efficacy Results of ONO-4538-12

Efficacy Parameter	ONO-4538-12 Primary Study	
	Nivolumab Monotherapy Subjects (ITT) (N = 330)	Placebo (ITT) (N = 163)
Overall Survival (OS)		
Events, n (%)	226 (68.5)	141 (86.5)
Median (95% CI), months[a]	5.26 (4.60, 6.37)	4.14 (3.42, 4.86)
Min, Max (months)[b]	0.3 - 20.5+	0.2+ - 20.6+
p-value[c]	$p < 0.0001$[d]	
HR (95% CI)[e]	0.63 (0.51, 0.78)	
Rate at 6 months (95% CI), %[a]	46.1 (40.5, 51.4)	34.7 (27.4, 42.1)
Rate at 12 months (95% CI), %[a]	26.2 (20.7, 32.0)	10.9 (6.2, 17.0)
Investigator-assessed Progression-free Survival (PFS)		
Events, n (%)	253 (76.7)	145 (89.0)
Median (95% CI), months[a]	1.61 (1.54, 2.30)	1.45 (1.45, 1.54)
Min, Max (months)[b]	0.0+ - 17.1+	0.0+ - 19.0
p-value[c]	$p < 0.0001$[d]	
HR (95% CI)[e]	0.60 (0.49, 0.75)	
Rate at 6 months (95% CI), %[a]	20.2 (15.7, 25.1)	6.8 (3.3, 11.8)
Investigator-assessed Objective Response Rate (ORR)[f]		
ITT Population		
Responders, n (%)	30 (9.1)	0
95% CI	(6.2, 12.7)	(0.0, 2.2)
RES Population		
Responders, n (%)	30 (11.2)	0
95% CI	(7.7, 15.6)	(0.0, 2.8)
Investigator-assessed Time To Response (TTR) (Months)		
Number of responders	30 (9.1)	0
Mean (SD)	2.67 (1.72)	N.A.(N.A.)
Median (months)	1.61	N.A.
Min, Max	1.4-7.0	N.A.
Investigator-assessed Duration of Response (DOR)[a]		
Median (95% CI), months	9.53 (6.14, 9.82)	N.A. (N.A., N.A.)
DOR of at least 3 months (95% CI), %	96.3 (76.5, 99.5)	N.A.
DOR of at least 6 months (95% CI), %	75.0 (52.2, 88.0)	N.A.
DOR of at least 12 months (95% CI), %	21.7 (3.7, 49.1)	N.A.

a.) This estimation was conducted using the KM method b). Censored value was indicated as "+" c) The calculation of p-value was conducted by using the one-sided stratified log-rank test d) To be compared to 0.025 significance level. e) HR and the corresponding 2-sided 95% CI for the nivolumab group relative to the placebo group was calculated by using the stratified Cox proportional-hazards model adjusted stratification factors f CR+PR, CI based on the Clopper and Pearson method.

Overall Survival - (Primary Endpoint)

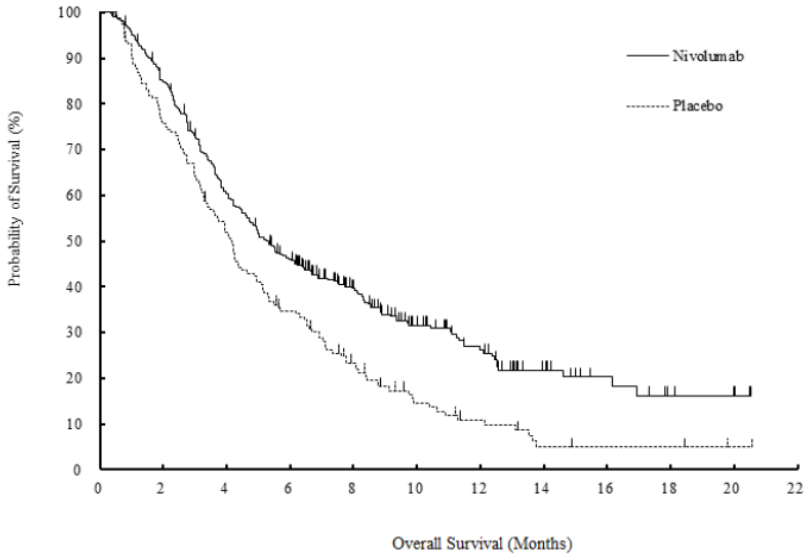
Nivolumab demonstrated superior OS in the all randomised population, with a statistically significant

reduction in the risk of death to placebo (stratified log-rank test, one-sided p < 0.0001). There was continued separation of the curves over time and a consistent improvement across OS parameters was observed. There was a substantial increase in the 6-month OS rate and the increased OS rate also appeared to be maintained at 1 year (minimum follow-up was approximately 6 months).

The Kaplan-Meier estimate of median OS was 5.26 months (95% CI: 4.60 months, 6.37 months) in the nivolumab group and 4.14 months (95% CI: 3.42 months, 4.86 months) in the placebo group (Figure 14). The HR of the nivolumab group relative to the placebo group was 0.63 (95% CI: 0.51, 0.78). The survival rates estimated by the Kaplan-Meier method were higher in the nivolumab group than in the placebo group at Month 6 (46.1% and 34.7%, respectively) (Table 25).

OS events (deaths) were reported in 226 (68.5%) subjects in the nivolumab group and 141 (86.5%) subjects in the placebo group (Table 23). 104 (31.5%) subjects in the nivolumab group and 22 (13.5%) subjects in the placebo group were censored. 93 (28.2%) and 17 (10.4%) of the subjects in the nivolumab and placebo groups, respectively, were still on-study (on-treatment or in follow-up).

Figure 14: Kaplan-Meier Plot of Overall Survival - ONO-4538-12 (ITT)



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22
Nivolumab	330	275	192	141	94	56	38	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

Progression-free survival - (Secondary Endpoint)

Treatment with nivolumab demonstrated a statistically significant reduction in the risk of progression. The data showed a prolongation of investigator-assessed PFS in the nivolumab group as compared with the placebo group. PFS events had occurred in 253 (76.7%) subjects in the nivolumab group and 145 (89.0%) subjects in the placebo group. The HR of the nivolumab group relative to the placebo group was 0.60 (95% CI: 0.49, 0.75).

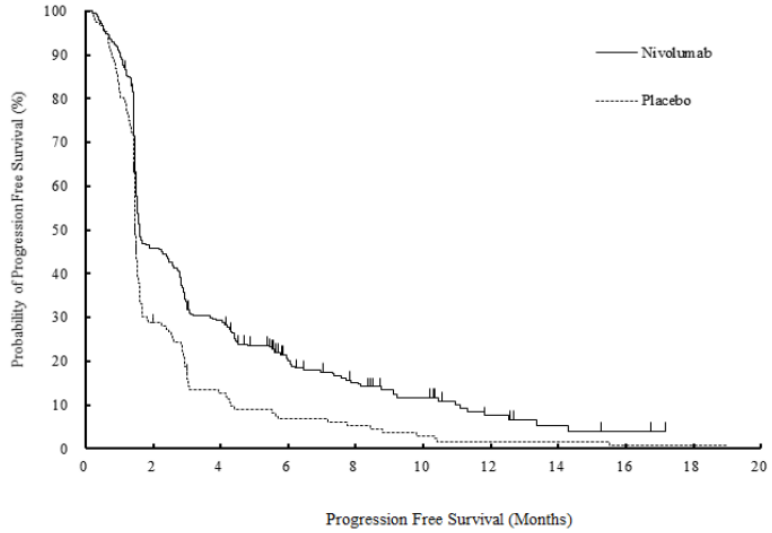
The Kaplan-Meier estimate of median PFS was 1.61 months (95% CI: 1.54 months, 2.30 months) in the nivolumab group and 1.45 months (95% CI: 1.45 months, 1.54 months) in the placebo group (Figure 15). PFS rates estimated by the Kaplan-Meier method in the nivolumab and placebo groups were 20.2% and 6.8% at Month 6, respectively and 7.6% and 1.5% at Month 12, respectively (Table 25).

A total of 77 (23.3%) subjects in the nivolumab group and 18 (11.0%) subjects in the placebo group were

censored. In the nivolumab group, 38 (11.5%) subjects were censored on the date of randomization due to the absence of assessments in the evaluation period, and 39 (11.8%) subjects were censored on the date of last tumour assessment (30/39 subjects were in the study [on the study treatment or in follow-up], 9/39 subjects received subsequent anti-cancer therapy). In the placebo group, 11 (6.7%) subjects were censored on the date of randomization, and 7 (4.3%) subjects were censored on the date of last tumour assessment (5/7 subjects received subsequent anti-cancer therapy, 1/7 subject was at the end of investigating subsequent anti-cancer therapy, and 1/7 subject was on-study [on treatment or in follow-up]).

A pre-specified sensitivity analyses was performed for PFS. In this secondary definition of PFS, tumour assessments, progression, or death, that occurred after anti-cancer therapy (radiotherapy, surgery or systemic therapy) were taken into account. PFS using the secondary definition was similar to that using the primary definition (HR 0.60 (95% CI: 0.54, 0.80). However, per protocol, imaging examinations were not systematically collected after start of subsequent therapy.

Figure 15: Kaplan-Meier Plot of Progression-Free Survival using the Primary Definition of Censoring - ONO-4538-12 (ITT)



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20
Nivolumab	330	131	83	46	31	19	8	4	2	0	0
Placebo	163	41	17	9	7	4	2	2	1	1	0

Objective response rate - (Secondary Endpoint)

In ONO-4538-12, investigator-assessed ORR was a secondary endpoint and there was improved ORR with nivolumab treatment. Results are provided for both the ITT dataset and response evaluable set (RES) (Table 26); there were 30 responders, i.e. all partial responses.

Table 26: Objective Response Rate with the Best Overall Response and Disease Control Rate - ONO-4538-12 (ITT Population)

	Nivolumab	Placebo
	n (%)	n (%)
N	330	163
Best overall response		
CR	0	0
(95% CI)[a]	(0.0, 1.1)	(0.0, 2.2)
PR	30 (9.1)	0
(95% CI) [a]	(6.2, 12.7)	(0.0, 2.2)
SD	78 (23.6)	33 (20.2)
(95% CI) [a]	(19.2, 28.6)	(14.4, 27.2)
PD	124 (37.6)	79 (48.5)
NE	98 (29.7)	51 (31.3)
Subjects with target lesion	36 (10.9)	19 (11.7)
Subjects without target lesion	62 (18.8)	32 (19.6)
Objective response rate		
ORR (CR+PR)	30 (9.1)	0
(95% CI) [a]	(6.2, 12.7)	(0.0, 2.2)
Odds ratio[b]	N.A.	
(95% CI)[b]	(N.A., N.A.)	
Difference[c]	9.05	
(95% CI)[c]	(5.95, 12.15)	
p-value[d]	p<0.0001 *	
Disease control rate		
DCR (CR+PR+SD)	108 (32.7)	33 (20.2)
(95% CI) [a]	(27.7, 38.1)	(14.4, 27.2)
Odds ratio[b]	1.87	
(95% CI) [b]	(1.19, 2.93)	
Difference[c]	11.96	
(95% CI) [c]	(3.94, 19.97)	
p-value[d]	p=0.0058 *	

Best overall response was determined solely by imaging assessment according to the RECIST

a) Exact 95% confidence interval was calculated by using Clopper-Pearson method. b) Odds ratio and the corresponding confidence interval was calculated by using Cochran-Mantel-Haenszel methodology adjusted by stratification factors. c) Difference and the corresponding confidence interval was calculated by using Cochran-Mantel-Haenszel methodology adjusted by stratification factors d) The calculation of p-value was conducted by using Cochran-Mantel-Haenszel test adjusted by stratification factors. *) $p < 0.05$, N.S.: $p \geq 0.05$.

RES consisted of 268 subjects in the ONO-4538 group and 131 subjects in the placebo group (Table 27).

Table 27: Objective Response Rate with the Best Overall Response and Disease Control Rate - ONO-4538-12 (RES Population)

	Nivolumab	Placebo
	n (%)	n (%)
N	268	131
Best overall response		
CR	0	0
(95% CI)[a]	(0.0, 1.4)	(0.0, 2.8)
PR	30 (11.2)	0
(95% CI)[a]	(7.7, 15.6)	(0.0, 2.8)
SD	78 (29.1)	33 (25.2)
(95% CI)[a]	(23.7, 34.9)	(18.0, 33.5)
PD	124 (46.3)	79 (60.3)
NE	36 (13.4)	19 (14.5)
Objective response rate		
ORR (CR+PR)	30 (11.2)	0
(95% CI)[a]	(7.7, 15.6)	(0.0, 2.8)
Odds ratio[b]	N.A.	
(95% CI)[b]	(N.A., N.A.)	
Difference[c]	11.18	
(95% CI)[c]	(7.39, 14.96)	
p-value[d]	p<0.0001 *	
Disease control rate		
DCR (CR+PR+SD)	108 (40.3)	33 (25.2)
(95% CI)[a]	(34.4, 46.4)	(18.0, 33.5)
Odds ratio[b]	1.99	
(95% CI)[b]	(1.24, 3.17)	
Difference[c]	14.85	
(95% CI)[c]	(5.35, 24.35)	
p-value[d]	p=0.0036 *	

Best overall response was determined solely by imaging assessment according to the RECIST Guideline Version 1.1.

a) Exact 95% confidence interval was calculated by using Clopper-Pearson method. b) Odds ratio and the corresponding confidence interval was calculated by using Cochran-Mantel-Haenszel methodology adjusted by stratification factors. c) Difference and the corresponding confidence interval was calculated by using Cochran-Mantel-Haenszel methodology adjusted by stratification factors d) The calculation of p-value was conducted by using Cochran-Mantel-Haenszel test adjusted by stratification factors. *) $p < 0.05$, N.S.: $p \geq 0.05$.

Time to Response and Duration of Response

30 (9.1%) subjects in the nivolumab group were responders (ITT). Responses occurred rapidly and were durable. The median TTR was 1.61 months (range: 1.4 to 7.0 months) in nivolumab-treated subjects with 17 subjects achieving their response within the first 2 months on treatment.

The median DOR was 9.53 months (95% CI: 6.14, 9.82). Of the 30 subjects with a confirmed response, based on Kaplan-Meier estimation, the DOR was estimated to be ≥ 3 months for 96.3% (95% CI: 76.5,

99.5) of subjects, ≥ 6 months for 75.0% (95% CI: 52.2, 88.0) of subjects, and ≥ 12 months for 21.7% (3.7, 49.1) of subjects. No subjects in the placebo group were responders.

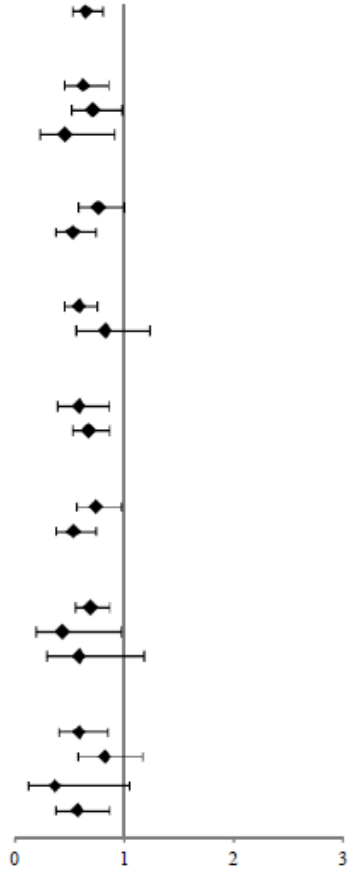
Ancillary analyses

Subgroup Efficacy Analyses of Overall Survival, Progression-free Survival, and Objective Response Rate - ONO-4538-12

For OS, the superior treatment effect of nivolumab over placebo was consistently observed across all subgroups, represented by a HR of < 1 shown in Figure 16, although the 95% CIs for the hazard ratios included 1 in the following subgroups: female, diffuse type, Type III and IV of macroscopic type, less than 2 organs with metastases, positive peritoneal metastasis, positive liver metastasis, no target lesion, and 2 and 3 previous regimens. In some additional subgroups with a few subjects, the 95% CIs were also wide and included. For PFS (Figure 17) and ORR, the results were similar to those for OS.

Figure 16: Forest Plot of Subgroup Analyses for Overall Survival - ONO-4538-12

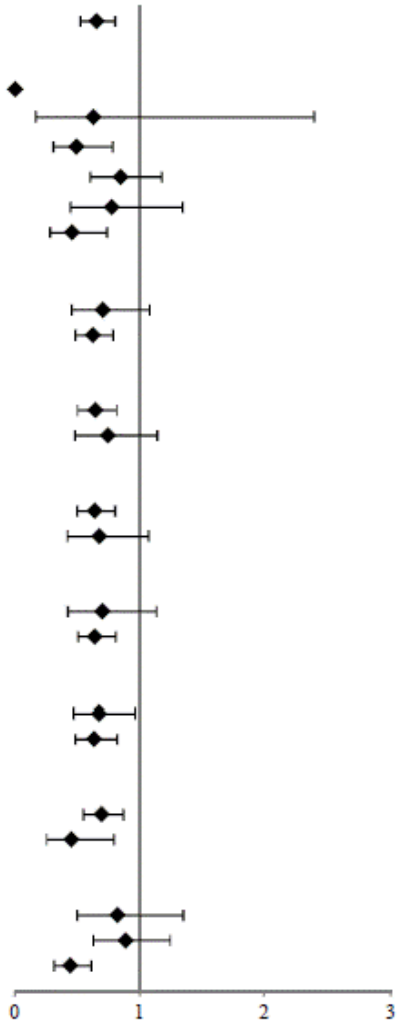
		Nivolumab		Placebo		
	N	N of Events (N of subjects)	median(95% CI)	N of Events (N of subjects)	median(95% CI)	Hazard Ratio (95% CI)
ALL	493	226(330)	5.26 [4.60, 6.37]	141(163)	4.14 [3.42, 4.86]	0.65 [0.53, 0.80]
Location						
Japan	226	107(152)	5.42 [4.60, 7.39]	63(74)	3.58 [2.76, 4.96]	0.63 [0.46, 0.85]
Korea	220	96(146)	5.03 [3.81, 7.20]	63(74)	4.37 [3.75, 6.31]	0.72 [0.52, 0.98]
Taiwan	47	23(32)	5.06 [3.29, 8.48]	15(15)	4.11 [1.84, 4.86]	0.46 [0.23, 0.92]
Age						
<65	284	138(189)	4.83 [3.81, 5.32]	83(95)	4.21 [3.48, 5.32]	0.76 [0.58, 1.00]
>=65	209	88(141)	7.49 [4.76, 8.54]	58(68)	3.71 [2.96, 4.93]	0.53 [0.38, 0.74]
Sex						
Male	348	152(229)	5.68 [4.83, 7.49]	104(119)	3.94 [3.15, 4.50]	0.59 [0.46, 0.75]
Female	145	74(101)	4.21 [3.52, 5.88]	37(44)	4.63 [3.29, 6.54]	0.83 [0.56, 1.23]
ECOG Performance Status score						
0	143	63(95)	7.49 [5.19, 9.76]	43(48)	5.22 [3.58, 7.13]	0.59 [0.40, 0.87]
1	350	163(235)	4.70 [3.84, 5.52]	98(115)	3.75 [3.12, 4.24]	0.68 [0.53, 0.87]
Recurrent						
No	285	145(194)	4.50 [3.75, 5.32]	79(91)	4.14 [3.12, 5.32]	0.74 [0.56, 0.98]
Yes	208	81(136)	7.39 [5.55, 8.84]	62(72)	4.21 [3.29, 5.09]	0.53 [0.38, 0.74]
Lesion sites (TNM classification) [a)]						
Gastric (Fundus, Corpus, Antrum and pylorus)	407	193(272)	5.19 [4.50, 6.14]	115(135)	3.94 [3.22, 4.50]	0.69 [0.55, 0.87]
Esophagogastric junction	42	16(30)	8.84 [3.61, N.A.]	11(12)	4.62 [1.64, 7.62]	0.44 [0.20, 0.97]
Unknown	44	17(28)	4.70 [3.15, 11.99]	15(16)	5.29 [1.18, 5.65]	0.59 [0.29, 1.19]
Histological type (Lauren classification)						
Intestinal type	175	76(120)	6.41 [4.76, 8.90]	48(55)	4.21 [3.02, 5.65]	0.59 [0.41, 0.85]
Diffuse type	169	75(106)	4.63 [3.78, 6.14]	51(63)	3.94 [3.22, 5.13]	0.82 [0.57, 1.17]
Others	23	12(17)	6.05 [3.29, 9.17]	6(6)	3.43 [1.12, 6.54]	0.37 [0.13, 1.04]
Unknown	126	63(87)	5.32 [3.61, 8.34]	36(39)	4.44 [2.40, 5.68]	0.57 [0.38, 0.87]



Analysis Set : ITT

a) Subjects with lesion sites in both gastric and esophagogastric junction included gastric category.

	N	Nivolumab		Placebo		Hazard Ratio (95% CI)
		N of Events (N of subjects)	median(95% CI)	N of Events (N of subjects)	median(95% CI)	
ALL	493	226(330)	5.26 [4.60, 6.37]	141(163)	4.14 [3.42, 4.86]	0.65 [0.53, 0.80]
Macroscopic type (Borrmann's classification)						
Early carcinoma	8	2(7)	N.A. [7.52, N.A.]	1(1)	3.22 [N.A., N.A.]	0.00 [0.00, N.A.]
Advanced carcinoma Type I	17	8(13)	4.21 [2.79, N.A.]	3(4)	3.53 [0.99, N.A.]	0.63 [0.17, 2.39]
Advanced carcinoma Type II	97	38(59)	6.67 [4.99, 11.33]	34(38)	3.75 [2.53, 6.18]	0.49 [0.31, 0.79]
Advanced carcinoma Type III	203	99(141)	4.63 [3.78, 5.95]	54(62)	4.65 [3.94, 7.13]	0.84 [0.61, 1.18]
Advanced carcinoma Type IV	77	37(50)	5.52 [3.52, 8.54]	20(27)	3.58 [2.96, 7.03]	0.78 [0.45, 1.35]
Unknown	91	42(60)	4.99 [3.55, 8.48]	29(31)	3.02 [1.91, 5.29]	0.46 [0.28, 0.74]
Number of organs with metastases						
<2	128	53(84)	8.31 [5.75, 11.07]	34(44)	5.49 [4.11, 8.08]	0.70 [0.46, 1.08]
>=2	365	173(246)	4.60 [3.84, 5.42]	107(119)	3.65 [3.02, 4.24]	0.62 [0.49, 0.79]
Peritoneal metastasis						
No	388	178(267)	5.75 [4.90, 7.52]	105(121)	4.30 [3.75, 5.19]	0.64 [0.50, 0.82]
Yes	105	48(63)	3.65 [2.89, 4.99]	36(42)	3.12 [2.14, 4.21]	0.74 [0.48, 1.15]
Liver metastasis						
No	387	168(252)	5.88 [4.83, 7.20]	115(135)	4.21 [3.35, 5.13]	0.64 [0.50, 0.81]
Yes	106	58(78)	4.07 [3.71, 5.32]	26(28)	3.84 [2.96, 4.50]	0.67 [0.42, 1.07]
Target lesion						
No	94	43(62)	6.14 [4.40, 8.48]	26(32)	4.01 [2.99, 6.90]	0.70 [0.43, 1.14]
Yes	399	183(268)	5.19 [4.27, 6.41]	115(131)	4.17 [3.29, 4.96]	0.64 [0.51, 0.81]
Past treatments for cancer (surgery)						
No	168	87(117)	4.21 [3.55, 5.49]	46(51)	3.20 [2.63, 4.37]	0.67 [0.47, 0.96]
Yes	325	139(213)	6.05 [4.83, 8.05]	95(112)	4.24 [3.75, 5.19]	0.63 [0.49, 0.82]
Past treatments for cancer (radiotherapy)						
No	427	199(289)	5.03 [4.27, 6.37]	118(138)	4.21 [3.48, 5.09]	0.69 [0.55, 0.87]
Yes	66	27(41)	6.14 [4.44, 12.09]	23(25)	3.15 [1.81, 5.29]	0.45 [0.26, 0.80]
Number of Previous regimen						
2	98	47(69)	4.93 [3.58, 7.49]	24(29)	6.47 [3.75, 8.77]	0.82 [0.50, 1.35]
3	199	98(137)	4.50 [3.78, 5.55]	51(62)	4.17 [2.66, 6.90]	0.89 [0.63, 1.25]
>=4	196	81(124)	6.67 [5.19, 8.84]	66(72)	3.65 [2.99, 4.63]	0.44 [0.31, 0.61]

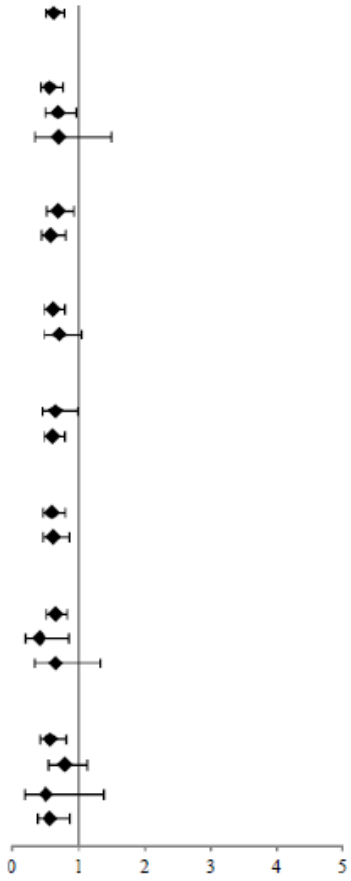


Analysis Set : ITT

Figure

Figure 17: Forest Plot of Subgroup Analyses for Progression-free Survival - ONO-4538-12

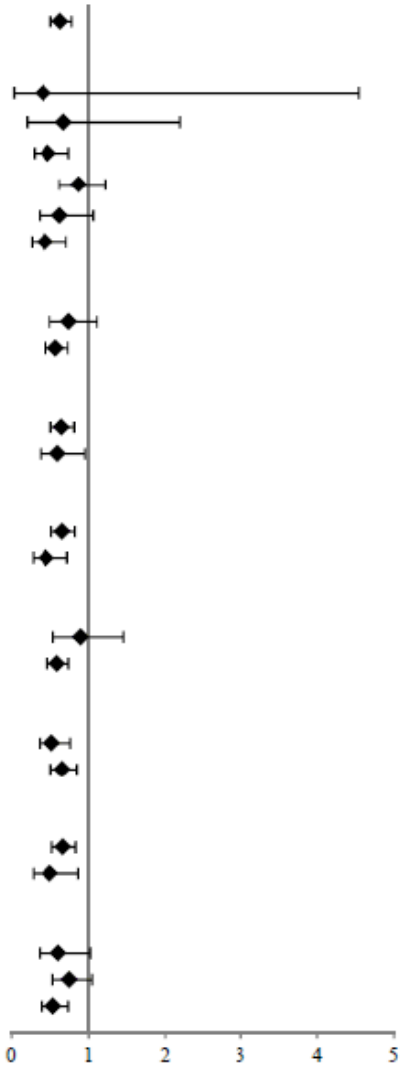
	N	Nivolumab		Placebo		Hazard Ratio (95% CI)
		N of Events (N of subjects)	median(95% CI)	N of Events (N of subjects)	median(95% CI)	
ALL	493	253(330)	1.61 [1.54, 2.30]	145(163)	1.45 [1.45, 1.54]	0.64 [0.52, 0.78]
Location						
Japan	226	124(152)	1.68 [1.58, 2.79]	69(74)	1.48 [1.45, 1.58]	0.57 [0.42, 0.77]
Korea	220	105(146)	1.54 [1.45, 2.30]	65(74)	1.45 [1.41, 1.61]	0.70 [0.51, 0.96]
Taiwan	47	24(32)	1.51 [1.41, 2.96]	11(15)	1.41 [1.28, 3.06]	0.71 [0.34, 1.49]
Age						
<65	284	139(189)	1.48 [1.45, 1.61]	81(95)	1.45 [1.41, 1.51]	0.70 [0.53, 0.92]
>=65	209	114(141)	2.30 [1.61, 2.99]	64(68)	1.51 [1.45, 1.61]	0.59 [0.43, 0.80]
Sex						
Male	348	182(229)	1.61 [1.54, 2.56]	107(119)	1.45 [1.45, 1.54]	0.62 [0.49, 0.79]
Female	145	71(101)	1.61 [1.45, 2.73]	38(44)	1.48 [1.41, 1.61]	0.71 [0.48, 1.06]
ECOG Performance Status score						
0	143	76(95)	2.40 [1.54, 2.92]	42(48)	1.51 [1.45, 1.61]	0.66 [0.45, 0.98]
1	350	177(235)	1.58 [1.48, 2.17]	103(115)	1.45 [1.41, 1.48]	0.62 [0.48, 0.79]
Recurrent						
No	285	152(194)	1.54 [1.48, 2.23]	78(91)	1.45 [1.41, 1.48]	0.60 [0.46, 0.80]
Yes	208	101(136)	1.91 [1.58, 2.92]	67(72)	1.51 [1.45, 2.40]	0.62 [0.46, 0.86]
Lesion sites (TNM classification) [a]						
Gastric (Fundus, Corpus, Antrum and pylorus)	407	209(272)	1.61 [1.54, 2.43]	119(135)	1.48 [1.45, 1.54]	0.66 [0.52, 0.83]
Esophagogastric junction	42	24(30)	1.61 [1.41, 4.80]	12(12)	1.43 [0.89, 2.53]	0.41 [0.20, 0.85]
Unknown	44	20(28)	1.48 [1.41, 4.40]	14(16)	1.48 [1.18, 2.86]	0.66 [0.33, 1.33]
Histological type (Lauren classification)						
Intestinal type	175	98(120)	1.68 [1.54, 2.76]	53(55)	1.45 [1.45, 1.54]	0.58 [0.41, 0.81]
Diffuse type	169	75(106)	1.54 [1.45, 2.83]	51(63)	1.48 [1.45, 2.27]	0.80 [0.55, 1.14]
Others	23	13(17)	1.59 [1.41, 2.83]	6(6)	1.48 [0.30, 2.89]	0.51 [0.19, 1.38]
Unknown	126	67(87)	1.58 [1.45, 2.83]	35(39)	1.45 [1.38, 1.54]	0.57 [0.38, 0.87]



Analysis Set : ITT

[a] Subjects with lesion sites in both gastric and esophagogastric junction included gastric category.

	N	Nivolumab		Placebo		Hazard Ratio (95% CI)
		N of Events (N of subjects)	median(95% CI)	N of Events (N of subjects)	median(95% CI)	
ALL	493	253(330)	1.61 [1.54, 2.30]	145(163)	1.45 [1.45, 1.54]	0.64 [0.52, 0.78]
Macroscopic type (Borrmann's classification)						
Early carcinoma	8	4(7)	6.54 [1.48, 8.77]	1(1)	2.40 [N.A., N.A.]	0.41 [0.04, 4.53]
Advanced carcinoma Type I	17	12(13)	1.58 [1.41, 6.47]	4(4)	1.35 [0.99, 10.41]	0.67 [0.21, 2.21]
Advanced carcinoma Type II	97	44(59)	2.40 [1.48, 2.92]	35(38)	1.45 [1.41, 1.61]	0.47 [0.30, 0.75]
Advanced carcinoma Type III	203	109(141)	1.61 [1.48, 2.23]	55(62)	1.54 [1.45, 1.87]	0.87 [0.63, 1.21]
Advanced carcinoma Type IV	77	36(50)	1.56 [1.45, 2.89]	23(27)	1.45 [1.35, 1.68]	0.62 [0.37, 1.06]
Unknown	91	48(60)	1.61 [1.45, 2.96]	27(31)	1.45 [1.28, 1.58]	0.43 [0.26, 0.71]
Number of organs with metastases						
<2	128	65(84)	2.79 [1.54, 3.12]	42(44)	1.58 [1.45, 2.46]	0.75 [0.50, 1.11]
>=2	365	188(246)	1.61 [1.51, 1.91]	103(119)	1.45 [1.41, 1.48]	0.58 [0.45, 0.74]
Peritoneal metastasis						
No	388	210(267)	1.61 [1.54, 2.43]	113(121)	1.48 [1.45, 1.58]	0.65 [0.52, 0.82]
Yes	105	43(63)	1.53 [1.41, 2.76]	32(42)	1.45 [1.35, 1.54]	0.60 [0.37, 0.95]
Liver metastasis						
No	387	190(252)	1.64 [1.58, 2.76]	118(135)	1.48 [1.45, 1.61]	0.66 [0.52, 0.83]
Yes	106	63(78)	1.54 [1.45, 1.68]	27(28)	1.45 [1.28, 1.48]	0.45 [0.28, 0.72]
Target lesion						
No	94	43(62)	1.61 [1.45, 2.89]	26(32)	1.51 [1.41, 2.92]	0.90 [0.55, 1.47]
Yes	399	210(268)	1.61 [1.54, 2.40]	119(131)	1.45 [1.45, 1.54]	0.59 [0.47, 0.75]
Past treatments for cancer (surgery)						
No	168	94(117)	1.54 [1.45, 2.46]	42(51)	1.45 [1.35, 1.48]	0.53 [0.36, 0.77]
Yes	325	159(213)	1.61 [1.54, 2.73]	103(112)	1.51 [1.45, 1.61]	0.66 [0.51, 0.85]
Past treatments for cancer (radiotherapy)						
No	427	223(289)	1.61 [1.54, 2.23]	122(138)	1.45 [1.45, 1.54]	0.67 [0.53, 0.84]
Yes	66	30(41)	2.51 [1.45, 3.02]	23(25)	1.45 [1.15, 2.53]	0.49 [0.28, 0.87]
Number of Previous regimen						
2	98	47(69)	1.91 [1.45, 2.89]	23(29)	1.46 [1.41, 2.92]	0.61 [0.36, 1.02]
3	199	108(137)	1.54 [1.48, 1.68]	56(62)	1.45 [1.31, 1.61]	0.75 [0.54, 1.04]
>=4	196	98(124)	2.04 [1.54, 2.92]	66(72)	1.45 [1.45, 1.54]	0.54 [0.39, 0.74]



Analysis Set : ITT

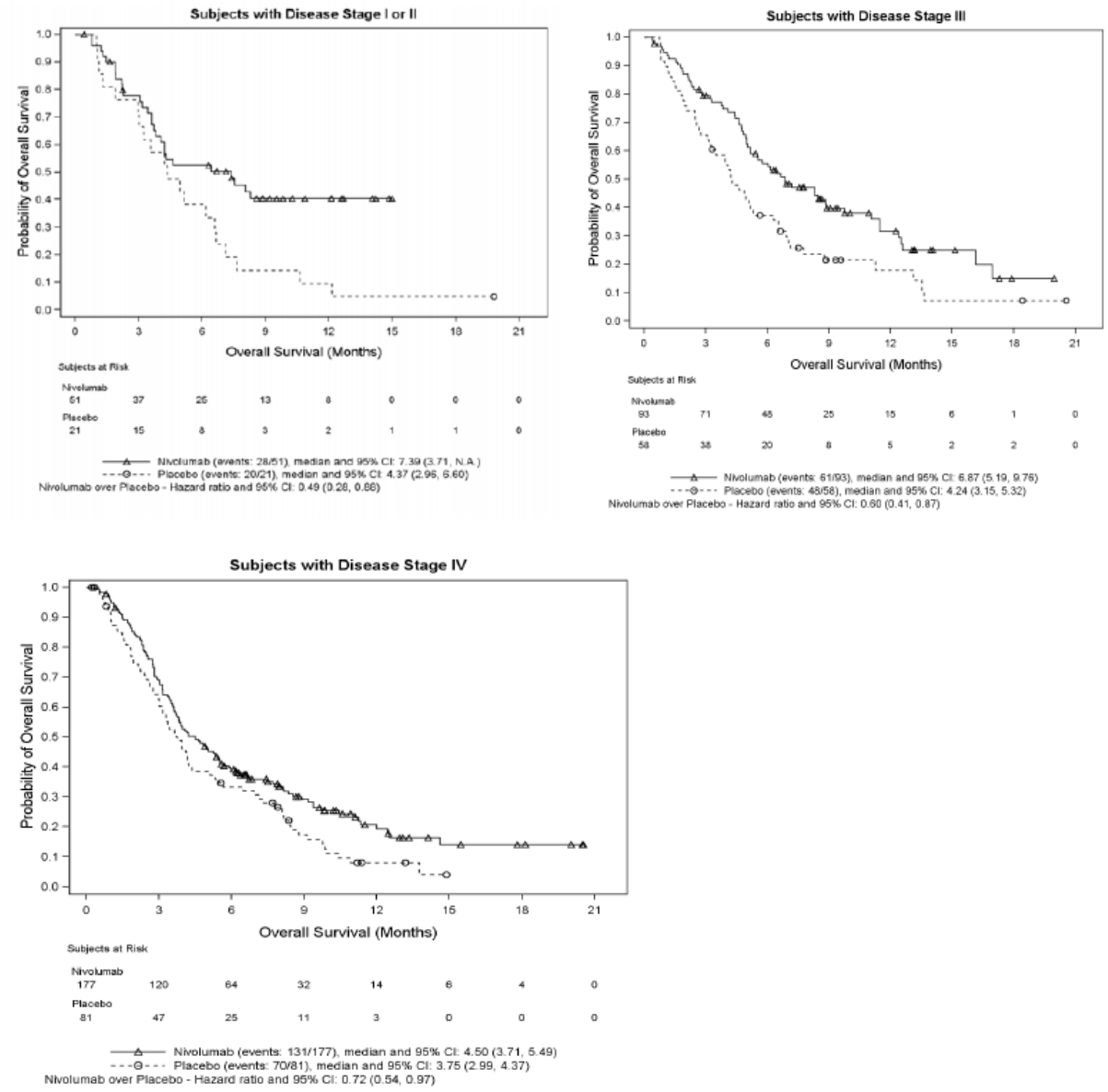
Subgroup analyses from study ONO-4538-12 (for OS, PFS and ORR) by stage at primary diagnosis.
The survival improvement has been seen in nivolumab arm compared with the placebo arm across the subgroup of patients with primary diagnosis stage at I/II, III and IV: the HR was 0.49 (95% CI: 0.28, 0.88), 0.60 (95% CI: 0.41, 0.87) and 0.72 (95% CI: 0.54, 0.97), respectively (Figure 18).

PFS was longer regardless of the primary diagnosis stage at I/II, III and IV in the nivolumab group compared with the placebo group, respectively, depicted in Figure 19.

There was improved ORR with nivolumab treatment across stages I, II, III, and IV, as shown in Table 28, whereas there were no responders in the placebo group. The ORR in the nivolumab group was Stage 1/II 15.6% (95% CI: 6.5, 29.5), Stage III 12.3% (5.5, 22.8), and Stage IV 10.0% (5.7, 16.0).

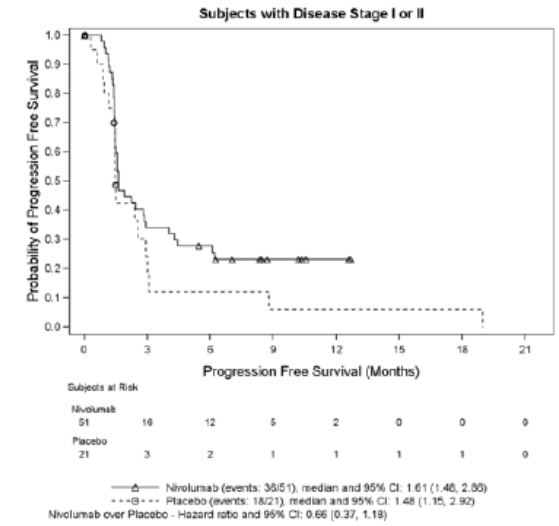
The consistent improvement in OS, PFS and ORR are demonstrated regardless of primary diagnosis stage (I/II, III and IV).

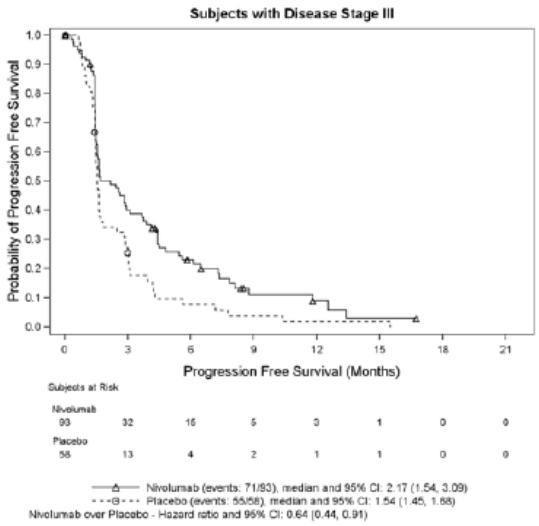
Figure **18**: Kaplan-Meier plot of overall survival, by disease stage at initial diagnosis – all randomized subjects (ITT set) – ONO-4538-12



Symbols represent censored observations
Hazard ratio and two-sided 95% confidence interval for the ONO-4538 group relative to the placebo group from unstratified Cox model.

Figure 19: Kaplan-Meier plot of progression free survival, by disease stage at initial diagnosis – all randomized subjects (ITT set) – ONO-4538-12





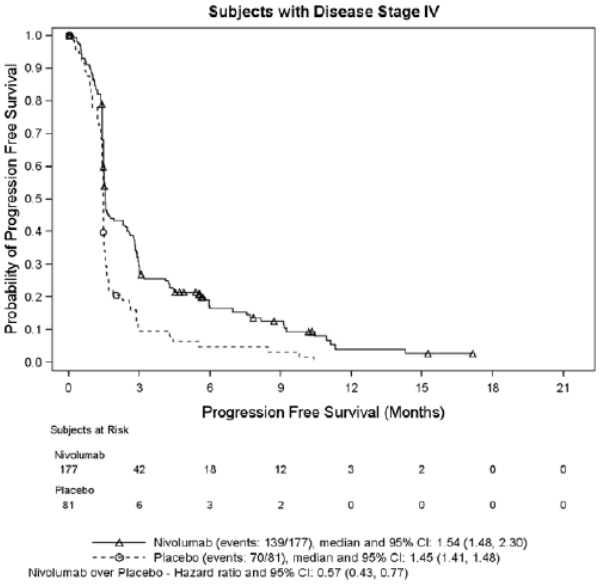


Table **28**: Best overall response by disease stage at initial diagnosis – ONO-4538-12[a]

Analysis Set : RES Analysis item (unit)	N	ONO-4538 n (%) 268	Placebo n (%) 131
Subjects with Disease Stage I or II			
N		45	16
Best overall response			
CR		0 (0.0)	0 (0.0)
PR		7 (15.6)	0 (0.0)
SD		13 (28.9)	7 (43.8)
PD		21 (46.7)	9 (56.3)
NE		4 (8.9)	0 (0.0)
Objective response rate			
ORR [CR+PR]		7 (15.6)	0 (0.0)
[95% CI][b]		[6.5,29.5]	[0.0,20.6]
Subjects with Disease Stage III			
N		65	49
Best overall response			
CR		0 (0.0)	0 (0.0)
PR		8 (12.3)	0 (0.0)
SD		20 (30.8)	15 (30.6)
PD		28 (43.1)	24 (49.0)
NE		9 (13.8)	10 (20.4)
Objective response rate			
ORR [CR+PR]		8 (12.3)	0 (0.0)
[95% CI][b]		[5.5,22.8]	[0.0,7.3]
Subjects with Disease Stage IV			
N		150	65
Best overall response			
CR		0 (0.0)	0 (0.0)
PR		15 (10.0)	0 (0.0)
SD		42 (28.0)	11 (16.9)
PD		73 (48.7)	45 (69.2)
NE		20 (13.3)	9 (13.8)
Objective response rate			
ORR [CR+PR]		15 (10.0)	0 (0.0)
[95% CI][b]		[5.7,16.0]	[0.0,5.5]
Subjects with Disease Stage Unknown			
N		8	1
Best overall response			
CR		0 (0.0)	0 (0.0)
PR		0 (0.0)	0 (0.0)
SD		3 (37.5)	0 (0.0)
PD		2 (25.0)	1 (100.0)
NE		3 (37.5)	0 (0.0)
Objective response rate			
ORR [CR+PR]		0 (0.0)	0 (0.0)
[95% CI][b]		[0.0,36.9]	[0.0,97.5]

[a] Best overall response was determined solely by imaging assessment according to the RECIST Guideline Version 1.1.

[b] Exact 95% confidence interval was calculated by using Clopper-Pearson method.

Source: Table EU.15 in Appendix 4

Baseline PD-L1 Expression (Exploratory Endpoint) - ONO-4538-12

In the ONO-4538-12 study, subjects were enrolled and randomised regardless of PD-L1 expression status. Subjects were not stratified by PD-L1 status at randomization.

The collection of pre-study or baseline tumour tissue samples was optional per the protocol and were collected by biopsy only from subjects who provided separate written consent for the provision of tumour

tissue. 134 (40.6%) nivolumab-treated subjects had a tumour tissue sample collected at baseline and the majority of these subjects (130/134 subjects) had PD-L1 quantifiable at baseline. Samples were tested but not evaluable for PD-L1 expression in 4 subjects in the nivolumab group. 62 (38.0%) subjects in the placebo group had a tumour tissue sample collected at baseline and all placebo-treated subjects had PD-L1 quantifiable at baseline. The PD-L1 positivity rate was numerically lower in the nivolumab group compared to the placebo group (Table 29).

Table 29: PD-L1 Expression at Baseline - ONO-4538-12

	Nivolumab Monotherapy Subjects with Baseline Tumor Tissue Sample (ITT) (N = 134)	Placebo (ITT) with Baseline Tumor Tissue Sample (N = 62)
Subjects With PD-L1 Quantifiable At Baseline (N [%])	130 (97.0)	62 (100.0)
≥ 1%	16 (12.3)	10 (16.1)
< 1%	114 (87.7)	52 (83.9)
≥ 5%	10 (7.7)	7 (11.3)
< 5%	120 (92.3)	55 (88.7)
≥ 10%	6 (4.6)	4 (6.5)
< 10%	124 (95.4)	58 (93.5)
≥ 50%	3 (2.3)	1 (1.6)
< 50%	127 (97.7)	61 (98.4)
Subjects Without PD-L1 Quantifiable At Baseline (N [%])	4 (3.0)	0

PD-L1 Expression and Efficacy

While an identical immunohistochemistry assay was used in both ONO-4538-12 and Study CA209032, comparison of ONO-4538-12 PD-L1 results to Study CA209032 are limited by potential differences in pre-analytical variables associated with tumour sample collection and processing (e.g., age of specimen, fixation conditions, biopsy methodology).

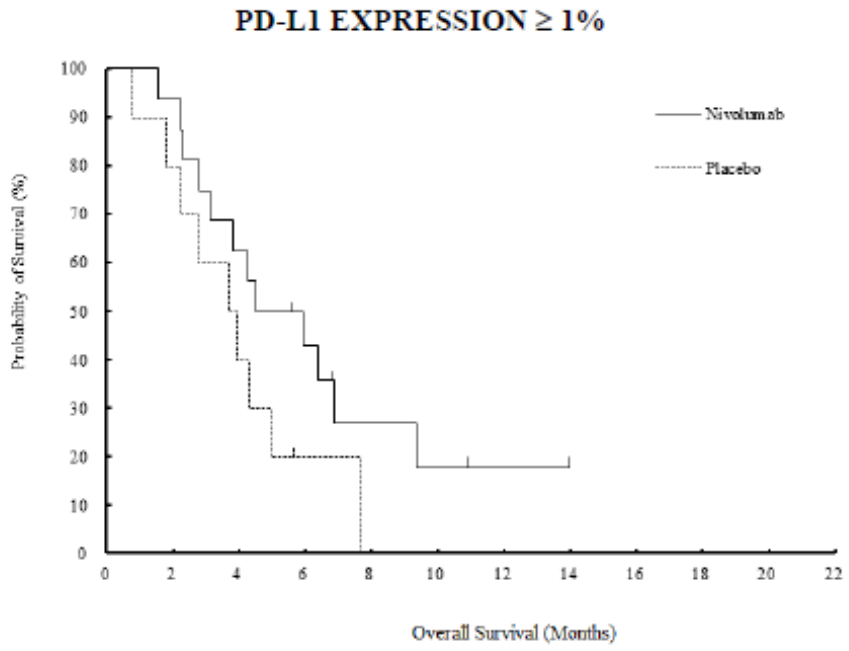
Results of PD-L1 expression status in subjects with ≥ 1%, < 1%, or indeterminate/not evaluable/missing PD-L1 expression and efficacy of ONO-4538-12 (OS, PFS, ORR) are provided in Table 30 and Figure 20 below.

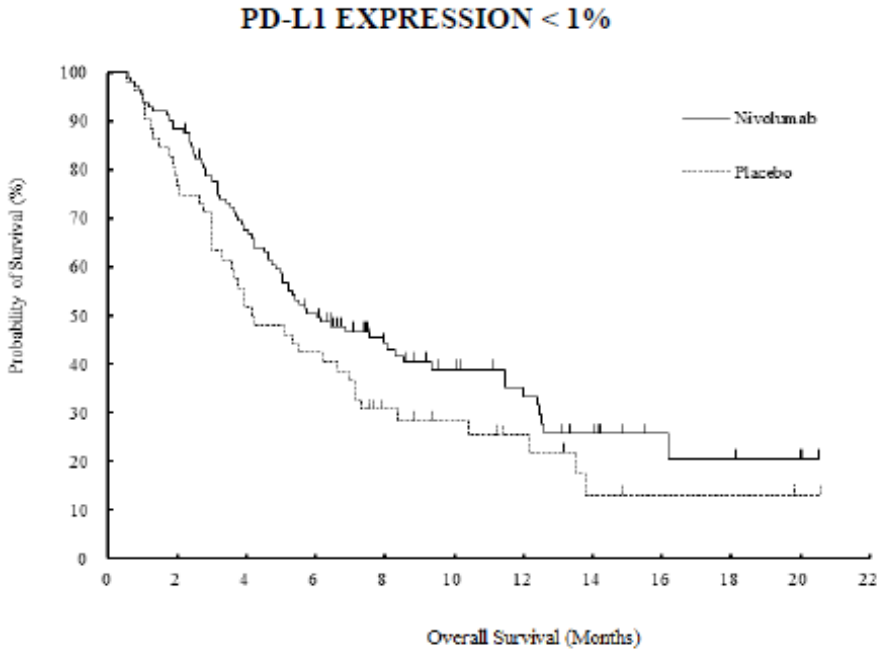
Table 30: PD-L1 Expression and Efficacy - ONO-4538-12

Efficacy by Baseline PD-L1 Expression (1% tumor cell membrane expression)	Nivolumab Monotherapy Subjects (ITT) (N = 330)	Placebo (ITT) (N = 163)
Subjects with ≥ 1% PD-L1 Expression	N = 16	N = 10
Overall Survival		
Events, n (%)	12 (75.0)	9 (90.0)
Median OS (95% CI), months[a]	5.22 (2.79, 9.36)	3.83 (0.79, 4.96)
HR (95% CI)[b]	0.51 (0.21, 1.25)	
Progression-free Survival		
Events, n (%)	12 (75.0)	10 (100.0)
Investigator-assessed median PFS (95% CI), months[a]	2.40 (1.48, 4.50)	1.46 (0.66, 1.81)
HR (95% CI)[b]	0.29 (0.11, 0.72)	
Objective Response Rate[c,d]		
Investigator-assessed ORR (95% CI), n (%)	0/16 (0.0, 20.6)	0/9 (0.0, 33.6)
Subjects with < 1% PD-L1 Expression	N = 114	N = 52
Overall Survival		
Events, n (%)	73 (64.0)	41 (78.8)
Median OS (95% CI), months[a]	6.05 (4.83, 8.54)	4.19 (3.02, 6.93)
HR (95% CI)[b]	0.72 (0.49, 1.05)	
Progression-free Survival		
Events, n (%)	89 (78.1)	48 (92.3)
Investigator-assessed median PFS (95% CI), months[a]	1.64 (1.54, 2.89)	1.48 (1.45, 1.68)
HR (95% CI)[b]	0.70 (0.49, 1.00)	
Objective Response Rate[c,d]		
Investigator-assessed ORR (95% CI), n (%)	14/97 (14.4) (8.1, 23.0)	0/38 (0.0 , 9.3)
Subjects without quantifiable PD-L1 Expression	N = 200	N = 101
Overall Survival		
Events, n (%)	141 (70.5)	91 (90.1)
Median OS (95% CI), months[a]	4.90 (3.91, 6.21)	4.17 (3.15, 4.93)
HR (95% CI)[b]	0.62 (0.48, 0.81)	
Progression-free Survival		
Events, n (%)	152 (76.0)	87 (86.1)
Investigator-assessed median PFS (95% CI), months[a]	1.58 (1.48, 2.17)	1.45 (1.41, 1.54)
HR (95% CI)[b]	0.64 (0.49, 0.83)	
Objective Response Rate[c,d]		
Investigator-assessed ORR (95% CI), n (%)	16/155 (10.3) (6.0, 16.2)	0/84 (0.0, 4.3)

a This estimation was conducted using the Kaplan-Meier method
b HR and the corresponding 2-sided 95% CI for the nivolumab group relative to the placebo group was calculated by using the unstratified Cox proportional-hazards model.
c CR+PR, CI based on the Clopper and Pearson method.
d ONO-4538-12 RES analysis population.

Figure 20: Kaplan-Meier Plot of Overall Survival by PD-L1 Expression (1% Expression Level) - ONO-4538-12 (ITT)





Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22
Nivolumab	16	15	10	6	3	2	1	0	0	0	0	0
Placebo	10	8	4	1	0	0	0	0	0	0	0	0

Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22
ONO-4538	114	100	75	55	35	24	18	11	5	4	2	0
Placebo	52	40	27	22	13	10	7	3	2	2	1	0

Additional exploratory analyses were performed at higher PD-L1 expression cut-off levels (5% and 10%) and results among PD-L1 expression levels 5% and 10% were consistent with 1%, and appeared to favour the nivolumab group.

Efficacy results by MSI status

Of the 493 randomized subjects in ONO-4538-12, most subjects did not have tumor tissue samples available at baseline (196 in nivolumab, 101 in placebo). Among the 196 subjects with tumor tissue sample collected at baseline (nivolumab: 134, placebo: 62) and used for PD-L1 expression evaluation, 136 had tissue available for MSI testing (nivolumab: 91, placebo: 45). 17 of those subjects had MSI reported as unknown (pre-analytical failure and sample QC failure) while 119 had MSI testing results: 83 subjects in the nivolumab group and 36 subjects in the placebo group (Table 31). The median tumor sample age was 50.3 months, (50.2 months for samples in nivolumab and 52.2 months for placebo arms).

In the 83 subjects in the nivolumab arm with MSI testing results, only 1 (1.2%) subject had MSIH status, 82 subjects (98.8%) had MSS status. In the 36 subjects from placebo, 3 subjects (8.3%) had MSI-H and 33 subjects (91.7%) had MSS. There were no subjects reported as MSI-L (Table 32, Table 33). MSS and MSI-low were planned to be grouped under non-MSI-H status for analysis reporting.

Table 31: Microsatellite Instability Result - All Randomized Subjects (ITT Set) - ONO-4538-12

	Number of Subjects (%)		
	Nivolumab N = 330	Placebo N = 163	Total N = 493
MICROSATELLITE INSTABILITY RESULT			
MSI-H	1 (0.3)	3 (1.8)	4 (0.8)
MSS	82 (24.8)	33 (20.2)	115 (23.3)
MSI-L	0	0	0
MSI UNKNOWN (1)	8 (2.4)	9 (5.5)	17 (3.4)
NOT REPORTED (2)	239 (72.4)	118 (72.4)	357 (72.4)
MICROSATELLITE INSTABILITY RESULT ANALYSIS CATEGORIES			
MSI-H	1 (0.3)	3 (1.8)	4 (0.8)
NON MSI-H (3)	82 (24.8)	33 (20.2)	115 (23.3)
MSI UNKNOWN/NOT REPORTED	247 (74.8)	127 (77.9)	374 (75.9)

(1) MSI tested but result unknown
(2) MSI not tested
(3) Includes MSS and MSI-L
Program Source: /projects/bms211280/stats/EBR_032_ONO/prog/tables/rt-km-msist.sas
23JAN2018:06:12:14

Table 32: Microsatellite Instability Result - Randomized Subjects With MSI Status Available - ONO-4538-12

	Number of Subjects (%)		
	Nivolumab N = 83	Placebo N = 36	Total N = 119
MICROSATELLITE INSTABILITY RESULT			
MSI-H	1 (1.2)	3 (8.3)	4 (3.4)
MSS	82 (98.8)	33 (91.7)	115 (96.6)
MSI-L	0	0	0
MICROSATELLITE INSTABILITY RESULT ANALYSIS CATEGORIES			
MSI-H	1 (1.2)	3 (8.3)	4 (3.4)
NON MSI-H (1)	82 (98.8)	33 (91.7)	115 (96.6)

(1) Includes MSS and MSI-L
Program Source: /projects/bms211280/stats/EBR_032_ONO/prog/tables/rt-bm-msist.sas
23JAN2018:06:12:15

Table 33 presents the distribution by MSI status and PD-L1 with 1% cutoff in nivolumab and placebo arms. In the nivolumab arm, the 1 subject with MSI-H is also PD-L1 < 1%. In the placebo arm, among the 3 subjects with MSI-H, two had PD-L1 < 1% and one had PD-L1 ≥ 1%.

Table 33: Microsatellite Instability Result by PD-L1 Status -All randomized Subjects (ITT Set) - ONO-4538-12

Treatment Group: Nivolumab

	Number of Subjects (%)			
	PD-L1 >=1% N = 16	PD-L1 <1% N = 114	PD-L1 NQ (1) N = 200	Total N = 330
MICROSATELLITE INSTABILITY RESULT				
MSI-H	0	1 (0.9)	0	1 (0.3)
MSS	10 (62.5)	71 (62.3)	1 (0.5)	82 (24.8)
MSI-L	0	0	0	0
MSI UNKNOWN (2)	0	7 (6.1)	1 (0.5)	8 (2.4)
NOT REPORTED (3)	6 (37.5)	35 (30.7)	198 (99.0)	239 (72.4)

Treatment Group: Placebo

	Number of Subjects (%)			
	PD-L1 >=1% N = 10	PD-L1 <1% N = 52	PD-L1 NQ (1) N = 101	Total N = 163
MICROSATELLITE INSTABILITY RESULT				
MSI-H	1 (10.0)	2 (3.8)	0	3 (1.8)
MSS	5 (50.0)	28 (53.8)	0	33 (20.2)
MSI-L	0	0	0	0
MSI UNKNOWN (2)	1 (10.0)	8 (15.4)	0	9 (5.5)
NOT REPORTED (3)	3 (30.0)	14 (26.9)	101 (100.0)	118 (72.4)

(1) Subjects without PD-L1 quantifiable at baseline
(2) MSI tested but result unknown
(3) MSI not tested
Program Source: /projects/bms211280/stats/EBR_032_ONO/prog/tables/rt-bm-msipdl1.sas 23JAN2018:06:12:19

Baseline characteristics by MSI status

- The subject in the nivolumab arm with MSI-H was 74 years old, had no target lesion at baseline and ECOG PS was 1.
- For the 3 subjects with MSI-H in placebo arm, 2 were < 65 years old, and 1 ≥ 65 years. All 3 had target lesions at baseline and ECOG PS was 1.
- For the subjects with non-MSI-H status and unknown-MSI status, the baseline characteristics were balanced between the 2 arms.

Efficacy results by MSI status

The efficacy results by MSI status in subjects with MSI-H, non-MSI-H and unknown/not reported MSI status are provided in Table 34.

Table 34: Efficacy by Baseline MSI Status - All Randomized Subjects (ITT) with MSI-H, non-MSI-H, and unknown/not reported MSI status - ONO-4538-12

Efficacy by MSI status at baseline	Nivolumab (ITT) N=330	Placebo (ITT) N=163
Subjects with MSI-H	N=1	N=3
Overall Survival		
Events, n (%)	0/1	3/3 (100.0)
Median OS (95% CI), months[a]	N.A.	3.65 (0.79, 13.54)
HR (95% CI)[b]	N.A.	
Progression Free Survival		
Events, n (%)	1/1 (100.0)	3/3 (100.0)
Median PFS (95% CI), months[a]	13.37 (N.A., N.A.)	1.87 (0.66, 4.21)
HR (95% CI) [b]	N.A.	
Objective Response Rate		
ORR (95% CI), n(%)	0/1 (0.0, 97.5)	0/3 (0.0, 70.8)
Subjects with non-MSI-H	N=82	N=33
Overall Survival		
Events, n (%)	52/82 (63.4)	27/33 (81.8)
Median OS (95% CI), months[a]	6.87 (5.19, 11.47)	3.58 (2.76, 5.49)
HR (95% CI) [b]	0.56 (0.35, 0.90)	
Progression Free Survival		
Events, n (%)	61/82 (74.4)	31/33 (93.9)

Median PFS (95% CI), months[a]	1.91 (1.51, 3.68)		1.46 (1.45, 1.81)
HR (95% CI) [b]		0.56(0.36, 0.87)	
Objective Response Rate			
ORR (95% CI), n(%)	11/82 (13.4%) (6.9, 22.7)		0/33 (0.0, 10.6)
Subjects with MSI unknown/not reported	N=247		N=127
Overall Survival			
Events, n (%)	174/247 (70.4)		111/127 (87.4
Median OS (95% CI), months[a]	4.83 (3.98, 5.52)		4.21 (3.42, 5.13)
HR (95% CI) [b]		0.70 (0.55, 0.89)	
Progression Free Survival			
Events, n (%)	191/247 (77.3)		111/127 (87.4)
Median PFS (95% CI), months[a]	1.61 (1.51, 2.30)		1.45 (1.45, 1.54)
HR (95% CI) [b]		0.68(0.54, 0.86)	
Objective Response Rate			
ORR (95% CI), n(%)	19/247 (7.7%) (4.7, 11.8)		0/127 (0.0, 2.9)

[a] Based on Kaplan-Meier Estimates

[b] Unstratified Cox proportional hazard model. Hazard Ratio is Nivolumab over Placebo.

Source: Table MSI.5 (ORR [ITT Population] by MSI Status) Table MSI.8 (OS by MSI Status); Table MSI.9 (PFS by MSI Status) in Appendix 1.

The 1 subject with MSI-H in the nivolumab arm was not response evaluable since there was no measurable disease at baseline, the PFS was 13.37 months, and the subject was still alive at the time of data cut-off (13-Aug-2016), with a reported OS of 14.1+ months. In the placebo arm, there were no responders among the 3 subjects with MSI-H (similar to the ITT population), the median OS and PFS for the MSI-H subjects was 3.65 months (95% CI: 0.79, 13.54) and 1.87 months (95% CI: 0.66, 4.21), respectively. (K-M curves of OS and PFS are provided in Figure 21, Figure 22).

In the non-MSI-H and unknown MSI subpopulation, the OS favored nivolumab over placebo with HR 0.56 (95% CI: 0.35, 0.9) and 0.70 (95% CI: 0.55, 0.89), respectively. This is consistent with the ITT population of HR 0.63 (95% CI: 0.51, 0.78).

The K-M curves of OS are separated in both subgroups (Figure 21). The PFS analysis also favoured nivolumab over placebo in both non-MSI-H and unknown-MSI subgroups with 0.56 (95% CI: 0.36, 0.87) and 0.68 (95% CI: 0.54, 0.86) (Figure 22), consistent with ITT population of HR 0.60 (95% CI: 0.49, 0.75)

Figure 21: OS by MSI Status - non-MSI-H and unknown MSI subpopulation - All Randomized Subjects (ITT Set) - ONO-4538-12

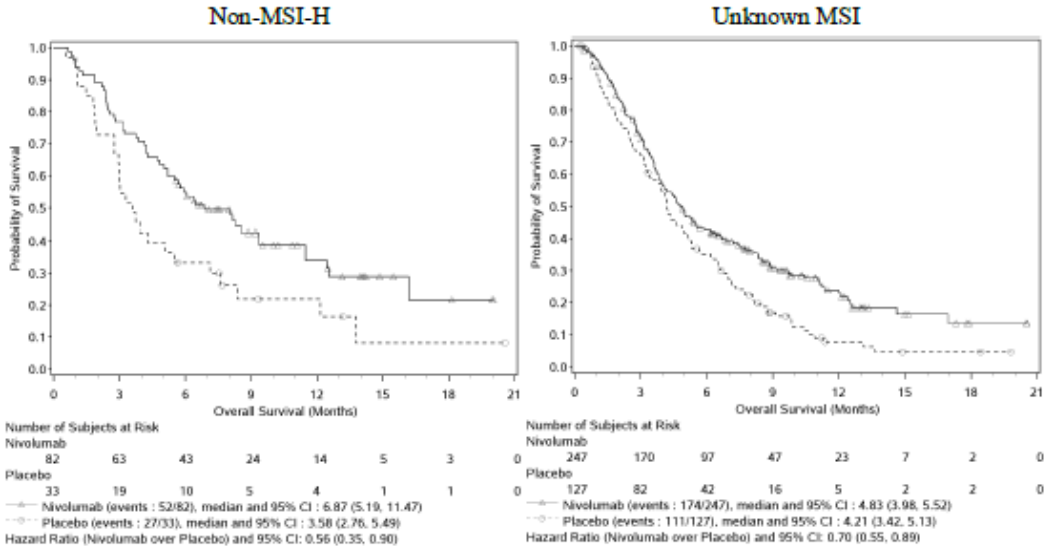
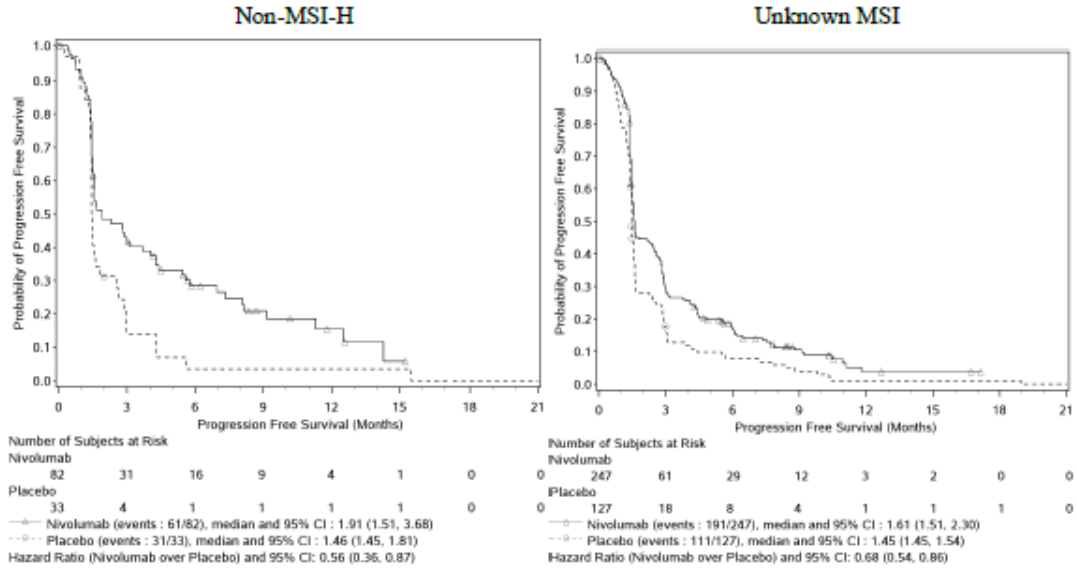


Figure 22: PFS by MSI Status - non-MSI-H and unknown MSI subpopulation - All Randomized Subjects (ITT Set) - ONO-4538-12



In the nivolumab arm, the ORR (ITT population) was 13.4% (95% CI: 6.9, 22.7) and 7.7% (95% CI: 4.7, 11.8) in subjects with non-MSI-H and unknown MSI status respectively. In response evaluable subjects (RES population), ORR was 15.3% (95% CI: 7.9, 25.7) and 9.7% (95% CI: 5.9, 14.7) in subjects with non-MSI-H and unknown MSI status, respectively. There were no responders in the placebo arm.

There was improved efficacy vs placebo as measured by OS, PFS and ORR regardless of MSI status. The small proportion of MSI-H subjects (3.5%) in the MSI evaluable population, 1 (1.2%) subject in the nivolumab group and 3 (8.3%) subjects in the placebo group, is in line with the expected low prevalence of MSI-H in this population. In addition, clinical benefit with nivolumab was observed in the MSS and MSI unknown subgroups, consistent with benefit observed in the overall ITT population. Therefore, there is observed improved clinical efficacy of nivolumab regardless of MSI status.

Efficacy results by combined MSI and PD-L1 status

Due to limited number of subjects with either MSI-H or PD-L1 ≥ 1% expression in both the nivolumab and placebo arms, there was not an expected difference in efficacy the subgroup combining PD-L1 ≥ 1% or MSI-H subjects, and efficacy by these subgroups was not reported. In addition, due to the unavailability of tumor tissue at baseline, the subjects who had PD-L1 'not reported' also had MSI 'not reported.' As such, the discussion is focused on subjects with PD-L1 < 1% by non MSI-H and MSI unknown/not reported.

Among the 166 subjects with PD-L1 < 1%, the majority of subjects, 99 (59.6%), were non-MSI-H and 64 (38.6%) were MSI unknown/not reported. ORR with nivolumab was 18.0% (9.4, 30.0) and 8.3% (1.8, 22.5) in the PD-L1 < 1% and non-MSI-H subgroup, and PD-L1 < 1% and MSI unknown/not reported subgroup, respectively. OS and PFS favored nivolumab over placebo, with observed HR 0.57(95% CI: 0.34, 0.94) and 0.58 (95% CI: 0.36, 0.94) respectively (Figure 23) in subjects with PD-L1 < 1% and non MSI-H.

In the subgroup with PD-L1 < 1% and MSI unknown/not reported, the HR for OS is 1.07 (95% CI 0.58, 1.98) and PFS is 0.97 (95% CI: 0.55, 172) (Figure 24). The median OS in placebo was 6.39 months (95% CI: 2.66, 10.41) in this group, which is higher than in the ITT population, while mOS in nivolumab was 5.03 months (95% CI: 3.91, 7.52) which was similar to ITT population as well as other subpopulations (Table 35).

Figure 23: K-M of OS - All Randomized Subjects (ITT Set) by MSI Status with PD-L1 < 1% - NON-MSI-H and MSI Unknown/Not Reported - ONO- 4538-12

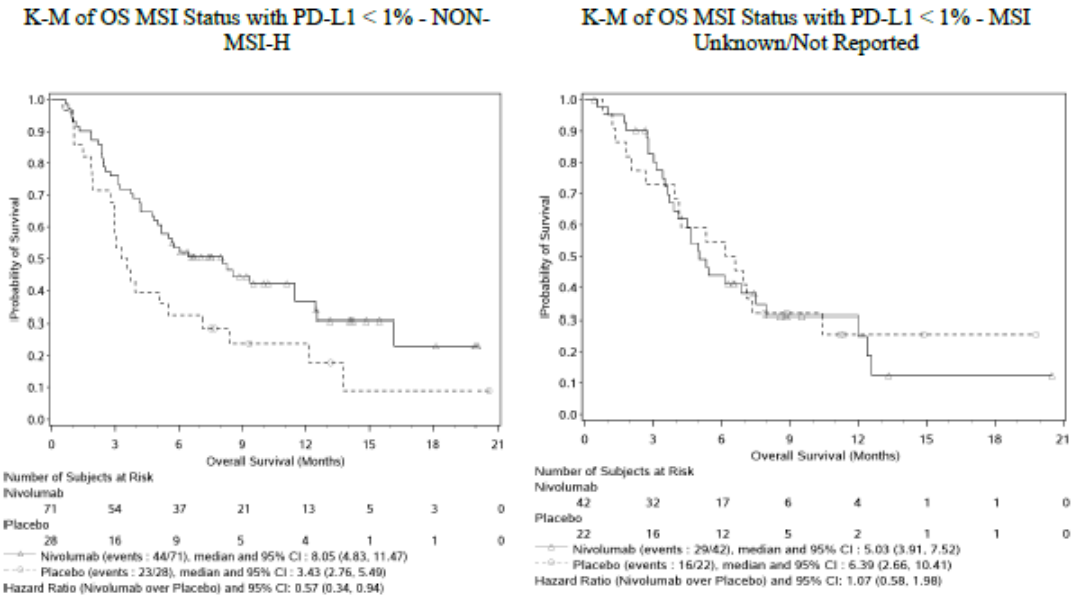


Figure 24: K-M of PFS - All Randomized Subjects (ITT Set) with PD-L1 < 1% and Non MSI-H NON-MSI-H and MSI Unknown/Not Reported - ONO-4538-12

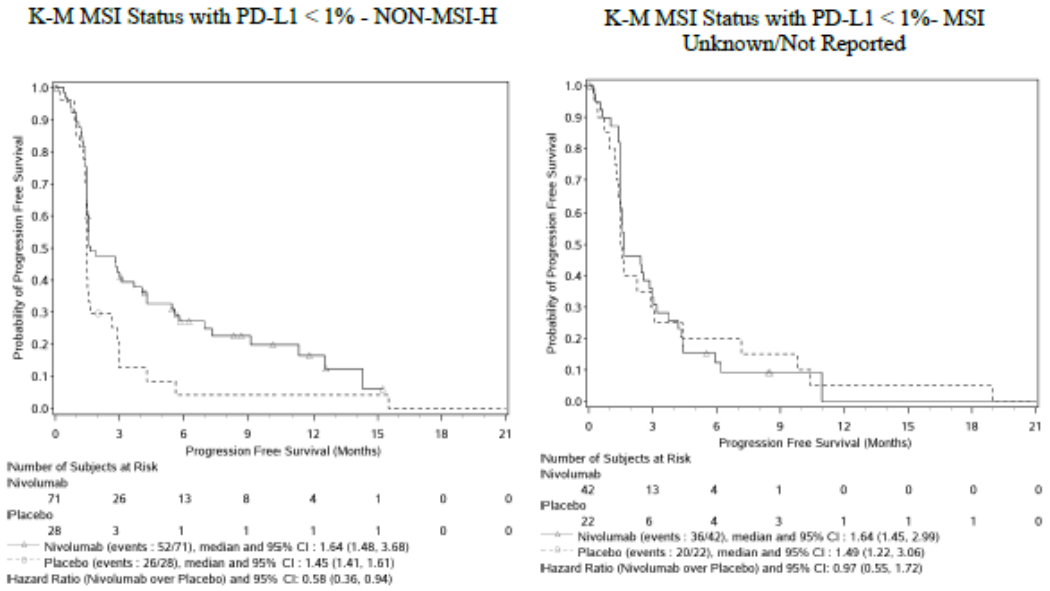


Table 35: Efficacy by subgroups-All randomized Subjects(ITT), subjects with unknown/not reported MSI status, subjects with PD-L1 <1%, and subjects with PD-L1 < 1% and MSI unknown/not reported - ONO- 4538-12

Population	ITT[a]		MSI unknown/not reported subgroup[b]		PD-L1<1%[c] subgroup		PD-L1<1% & MSI unknown/not reported subgroup[d]	
Treatment arm	Nivo N=330	Pbo N=160	Nivo N=247	Pbo N=127	Nivo N= 114	Pbo N=52	Nivo N=42	Pbo N=22
mOS months (95% CI)	5.26 (4.60, 6.37)	4.14 (3.42, 4.86)	4.83 (3.98, 5.52)	4.21 (3.42, 5.13)	6.05 (4.83, 8.54)	4.19 (3.02, 6.93)	5.03 (3.91, 7.52)	6.39 (2.66, 10.41)
HR (95% CI)	0.63 (0.51, 0.78)		0.70 80.55, 0.89)		0.72 (0.49, 1.05)		1.07 (0.58, 1.98)	
mPFS months (95% CI)	1.61 (1.54, 2.30)	1.45 (1.45, 1.54)	1.61 (1.51, 2.30)	1.45 (1.45, 1.54)	1.64 (1.54, 2.89)	1.48 (1.45, 1.68)	1.64 (1.45, 2.99)	1.49 (1.22, 3.06)
HR(95% CI)	0.60 (0.49, 0.75)		0.68 (0.54, 0.86)		0.70 (0.49, 1.00)		0.97 (0.55, 1.72)	

Further examination of baseline demographics and disease characteristics were conducted in the subsets of subjects by MSI and PD-L1 status. In the subset of subjects with PD-L1 < 1% and MSI unknown/not reported, there is some imbalance of baseline characteristics identified between nivolumab and placebo subgroups, such as prior surgery, PD as best response to most recent regimen, and prior line systemic therapy in metastatic setting.

Some of these imbalances in baseline characteristics favor the nivolumab arm and some favor the placebo arm, leaving the results of this small sample size subgroup difficult to interpret.

Subsequent Therapy

155 (47.0%) subjects in the nivolumab group and 72 (44.2%) subjects in the placebo group received subsequent cancer therapy after study treatment. Subsequent therapy included cancer-related symptomatic treatment, such as ascetics tapering, diuretic agents, palliative radiotherapy, and surgery.

An additional analysis of subsequent treatments and/or procedures excluding cancer-related

symptomatic treatment management was also conducted. The proportion of subjects who received subsequent therapy/-ies was similar between the nivolumab and placebo groups, respectively: 31.2% and 31.3%. 84 (25.5%) and 44 (27.0%) of subjects received pharmacotherapy (systemic therapy), 25 (7.6%) and 15 (9.2%) of subjects received radiotherapy, and 5 (1.5%) and 2 (1.2%) of subjects had surgery, in the nivolumab and placebo groups, respectively. The most frequent subsequent pharmacotherapies were fluoropyrimidine, irinotecan, ramucirumab, and taxane.

Summary of main study

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

Table 36. Summary of Efficacy for trial ONO-4538-12

Title: A Phase 3, multicentre, double-blind, randomized study in subjects with advanced or recurrent GC and GEJ cancer			
Study identifier	**ONO-4538-12**		
Design	Phase 3, multicentre, double-blind, placebo-controlled, randomized study		
	Duration of main phase:		From 04-Nov-2014 to 13-Aug-2016 (DCO)
Hypothesis	Superiority over placebo		
Treatments groups	Nivolumab		Nivolumab 3 mg/kg IV infusion Q2W; n=330
	Placebo		Placebo; n=163
Endpoints and definitions	Primary endpoint	OS	Time between the first dosing date and the date of death due to any cause. A subject who had not died was censored at the last known alive date. OS was followed continuously while subjects were on study drug and during the follow-up period.
	Secondary endpoint	PFS	Time from randomization to the earlier date on which either the overall response was assessed as progressive disease (PD) or the subject died of any cause.
	Secondary endpoint	DOR	Time between the date of first confirmed response (CR or PR) to the date of the first documented progression as determined by the investigator (per RECIST v1.1), or death due to any cause, whichever occurs first.
	Secondary endpoint	DCR	Percentage of all randomized subjects whose best overall response (BOR) was assessed as CR, PR, or SD.
	Secondary endpoint	ORR	Percentage of subjects whose best overall response (BOR) is assessed as either confirmed CR or PR per RECIST 1.1.
Database lock	**13-Aug-2016**		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population (Nivolumab n=330; Placebo n=163) RES population (patients with evaluable response at baseline (Nivolumab n=268; Placebo n=131)		
Descriptive statistics and estimate variability	Treatment group	Nivolumab	Placebo
	Number of subjects	330	163
	Primary endpoint OS Median months	**5.26**	**4.14**
	(95% CI)	(4.60, 6.37)	(3.42, 4.86)

	Secondary endpoint PFS Median months	1.61	1.45
	(95% CI)	(1.54, 2.30)	(1.45, 1.54)
	Secondary endpoint ORR n (%) ITT population	30 (9.1)	0
	(95% CI)	(6.2, 12.7)	(0.0, 2.2)
	Secondary endpoint ORR n (%) RES population	30 (11.2)	0
	(95% CI)	(7.7, 15.6)	(0.0, 2.8)
	Secondary endpoint TTR Median months	1.61	N.A.
	Min, Max	1.4-7.0	N.A.
	Secondary endpoint DOR Median months	9.53	N.A.
	(95% CI)	(6.14, 9.82)	(N.A., N.A.)
Effect estimate per comparison	Primary endpoint OS	Comparison groups	Nivolumab vs. Placebo
		HR (stratified)	0.63
		(95% CI)	(0.51, 0.78)
		P-value	p < 0.0001
	Secondary endpoint PFS	Comparison groups	Nivolumab vs. Placebo
		HR (stratified)	0.60
		(95% CI)	(0.49, 0.75)
		P-value	p < 0.0001
Descriptive statistics and estimate variability	Treatment group	Nivolumab	Placebo
Analysis description	**Efficacy per baseline PD-L1 expression**		
Baseline PD-L1 expression ≥1%		n=16	n=10
	OS median (95% CI) months	5.22 (2.79, 9.36)	3.83 (0.79, 4.96)
		HR (95% CI)	0.51 (0.21, 1.25)
	ORR (95% CI)	0 (0/16) (0.0, 20.6)	0 (0/9) (0.0, 33.6)
Baseline PD-L1 expression <1%		N = 114	N = 52
	OS median (95% CI) months	6.05 (4.83, 8.54)	4.19 (3.02, 6.93)
		HR (95% CI)	0.72 (0.49, 1.05)
	ORR (95% CI)	14.4 (14/97) (8.1, 23.0)	0 (0/38) (0.0 , 9.3)
Notes:	All responses were assessed per Investigator. Stratification factors for the primary analysis: location (Japan vs. Korea vs. Taiwan), ECOG PS (0 vs. 1) and number of organs with metastases (≤1 vs. ≥2).		

Supportive study

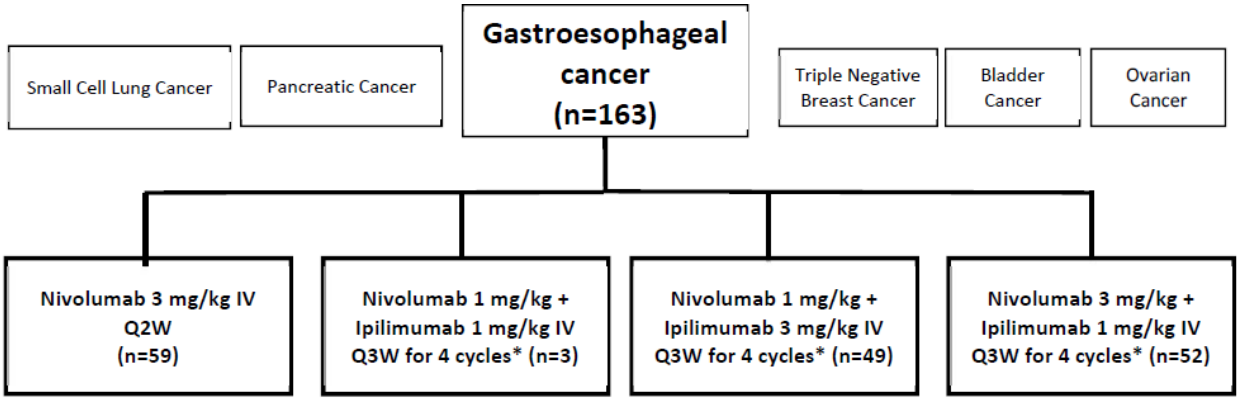
Study CA209032 is an ongoing, multicentre, Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab designed to evaluate the efficacy and safety of nivolumab as monotherapy or in combination with ipilimumab in subjects with 6 different tumour types, including GC (Figure 25).

The study population in the GC cohort included adults (≥ 18 years) with previously treated, advanced or

metastatic GC. Subjects were required to have histologically confirmed GC or GEJ carcinoma, including adenocarcinoma arising from the lower oesophagus, with tumour progression or refractory disease and at least 1 prior chemotherapy regimen, or actively refused chemotherapy, for the treatment of metastatic (stage IV) or locally advanced disease. Subjects with HER-2- positive tumours must have had previous treatment with trastuzumab. Subjects were to have an ECOG PS of 0 or 1.

In Study CA209032, assignment to a treatment arm and evaluation of safety and activity was performed independently for each tumour type. The dose level in the GC monotherapy cohort is nivolumab monotherapy 3 mg/kg IV Q2W.

Figure 25: Protocol Design of Study CA209032 - Gastric Cohort



*Followed by nivolumab 3 mg/kg IV Q2W

This report focuses on data from the GC cohort of patients treated with nivolumab monotherapy (N = 59), more specifically on data from 42 of the 59 subjects with gastric or GEJ cancer with at least 2 prior regimens, most closely reflecting the ONO-4538-12 study population.

The clinical database for the analysis of the GC cohort was locked on **24-Mar-2016** for the primary analysis of ORR, and an interim CSR is available. Subjects treated with nivolumab monotherapy who had confirmed progression were allowed to crossover to 1 of the combination regimens (nivolumab 1 mg/kg + ipilimumab 3 mg/kg or nivolumab 3 mg/kg + ipilimumab 1 mg/kg). Additional information with regards to the combination regimens will be provided in a subsequent CSR.

Efficacy Endpoints

The primary endpoint was to assess the ORR, by BICR and investigator assessments. ORR was defined as the proportion of treated subjects with a confirmed best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST v1.1. Additional efficacy assessments included DOR and PFS according to RECIST v1.1; OS; association between tumour PD-L1 expression and efficacy.

The primary endpoint of ORR was summarized by a binomial response rate and corresponding two-sided 95% exact CI using the Clopper-Pearson method.

Results

In the Gastric cohort a total of 67 subjects were enrolled and 59 (88.1%) were treated with nivolumab monotherapy. As of the 24-Mar-2016 DBL, in the subset of subjects most closely representing the ONO-4538-12 study (n = 42) who had GC or GEJ cancer and received at least 2 prior regimens, 3 (7.1%) subjects continued in the treatment period, 39 (92.9%) had discontinued study treatment, and 30 (71.4%) were continuing to be followed after treatment discontinuation. The most common reason for

treatment discontinuation was disease progression (81.0%) (Table 37).

Of the 42 subjects, 6 crossed over from nivolumab monotherapy to 1 of the 2 combination regimens: 4 crossed over to the nivolumab 3 mg/kg + ipilimumab 1 mg/kg regimen and 2 crossed over to the nivolumab 1 mg/kg + ipilimumab 3 mg/kg regimen. Table 38 presents a description of the subject populations sets.

Table 37: Subject Disposition - Study CA209032

	CA209032 Supportive Study All Nivolumab Monotherapy GC/GEJ Cancer Subset (n = 42)	CA209032 Supportive Study All Nivolumab Monotherapy Treated Subjects (N = 59)
Subjects enrolled[a]	-	67
Subjects treated	42	59
Subjects not treated	-	8
Subjects continuing in the treatment period (%)[b]	3 (7.1)	3 (5.1)
Subjects not continuing in the treatment period (%)[b]	39 (92.9)	56 (94.9)
Reason for not continuing in the treatment period due to disease progression (%)[b]	34 (81.0)	48 (81.4)
Subjects continuing to be followed (%)[b, c, d]	30 (71.4)	40 (67.8)
Subjects not continuing to be followed (%)[b, d]	6 (14.3)	10 (16.9)
Reason for not continuing to be followed due to death (%)	3 (7.1)	6 (10.2)

[a] Subjects with no tumor type reported per CRF are not included. Tumor type was collected per CRF for all assigned and treated subjects, but was not collected for all screen failures.

[b] Percentages based on subjects treated.

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

[d] Subject status at end of treatment: crossover subjects are not counted.

Table 38: Description of Analysis Populations Sets - Study CA209032

	CA209032 Supportive Study All Nivolumab Monotherapy GC/GEJ Cancer Subset (n = 42)	CA209032 Supportive Study All Nivolumab Monotherapy Treated Subjects (N = 59)
Enrolled subjects[a]	-	67
Treated subjects[b]	42	59

[a] Subjects with no tumor type reported per CRF are not included. Tumor type was collected per CRF for all assigned and treated subjects, but was not collected for all screen failures.

[b] All subjects who received at least one dose of study drug.

Demographics and Baseline Characteristics - Study CA209032

Study CA209032 enrolled a patient population of advanced treatment refractory GC, with 59 subjects who received nivolumab 3 mg/kg IV Q2W. The study was conducted in the Western population across 6 countries (Finland, Germany, Italy, Spain, the United Kingdom, and the United States of America).

Most subjects were White (94.9%); no subjects were Asian.

Baseline demographic and disease characteristics and tumour assessments of the GC cohort treated with nivolumab were consistent with the study entry criteria for the 59 subjects in the all-subject population, and the 42 subjects with GC/GEJ cancer previously treated with at least 2 prior regimens (Table 39 and Table 40). In the subset of 42 subjects with GC/GEJ cancer previously treated with at least 2 prior regimens, 26 (61.9%) subjects had GEJ cancer and 16 (38.1%) had GC. In the GC cohort and the subset of 42 subjects with GC or GEJ cancer with at least 2 prior regimens, respectively, the median time from initial diagnosis to study treatment was 1.38 and 1.74 years (16.59 and 20.86 months).

Table 39: Demographics and Baseline Characteristics - Study CA209032

	CA209032 Supportive Study All Nivolumab Monotherapy GC/GEJ Cancer Subset (n = 42)	CA209032 Supportive Study All Nivolumab Monotherapy Treated Subjects (N = 59)
Age (years)		
N	42	59
Mean (SD)	57.0 (11.28)	57.2 (10.99)
Median	58.5	60.0
Min,Max	29, 80	29, 80
Age Categorization (%)		
< 65	32 (76.2)	42 (71.2)
≥ 65	10 (23.8)	17 (28.8)
≥ 75	2 (4.8)	2 (3.4)
≥ 85	0	0
Gender (%)		
Male	31 (73.8)	45 (76.3)
Female	11 (26.2)	14 (23.7)
Race (%)		
White	39 (92.9)	56 (94.9)
Black or African American	3 (7.1)	3 (5.1)
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Other	0	0

Weight (kg)		
Mean (SD)	73.87 (15.243)	75.02 (14.578)
Median	72.15	73.80
Min , Max	42.0, 111.8	42.0, 111.8
Performance Status (ECOG [%])		
0	20 (47.6)	29 (49.2)
1	22 (52.4)	30 (50.8)
Primary tumor location		
Gastric	16 (38.1)	19 (32.2)
GEJ	26 (61.9)	31 (52.5)
Esophagus	0	9 (15.3)
Time From Initial Diagnosis To Study Treatment (years) /median (min - max)	1.74 (0.5 - 5.2)	1.38 (0.4 - 5.2)
Disease Stage at Primary Diagnosis (Primary Tumor Location) (TNM Classification) (n, %)		
0	0	0
I	1 (2.4)	1 (1.7)
II	1 (2.4)	3 (5.1)
III	4 (9.5)	6 (10.2)
IIIA	3 (7.1)	4 (6.8)
IIIB	3 (7.1)	3 (5.1)
IIIC	1 (2.4)	1 (1.7)
IV	28 (66.7)	39 (66.1)
Not Reported	1 (2.4)	2 (3.4)
Subjects with at least 1 target lesion (%)		
BICR assessed	37 (88.1)	53 (89.8)
Investigator-assessed	42 (100.0)	59 (100.0)

Site of lesions (%)[a]		
Lymph node	24 (57.1)	37 (62.7)
Liver	22 (52.4)	32 (54.2)
Lung	12 (28.6)	17 (28.8)
Stomach	10 (23.8)	11 (18.6)
Gastro-esophageal junction	5 (11.9)	8 (13.6)
Peritoneum	5 (11.9)	7 (11.9)
Adrenal gland	4 (9.5)	4 (6.8)
Bone	2 (4.8)	3 (5.1)
Esophagus	2 (4.8)	3 (5.1)
Abdominal wall	2 (4.8)	2 (3.4)
Retroperitoneum	2 (4.8)	2 (3.4)
Pelvis	1 (2.4)	1 (1.7)
Soft tissue	1 (2.4)	1 (1.7)
Other	-	1 (1.7)

[a] Includes both target and non-target lesions. Sites of target lesions data are BICR-assessed. Subjects may have lesions at more than 1 site.

Table 40: Prior Treatment Regimens - Study CA209032

	CA209032 Supportive Study All Nivolumab Monotherapy - GC/GEJ Cancer Subset (n = 42)	CA209032 Supportive Study All Nivolumab Monotherapy Treated Subjects (N = 59)
Prior surgery related to cancer		
Yes	28 (66.7)	37 (62.7)
No	14 (33.3)	22 (37.3)
Prior radiotherapy		
Yes	19 (45.2)	24 (40.7)
No	23 (54.8)	35 (59.3)
Number of prior systemic regimens received[a] (%)		
2	18 (42.9)	20 (33.9)
3	17 (40.5)	22 (37.3)
> 3	7 (16.7)	7 (11.9)
Types of Prior Systemic Therapies		
Platinum compounds	41 (97.6)	57 (96.6)
Carboplatin	12 (28.6)	16 (27.1)
Cisplatin	15 (35.7)	21 (35.6)
Oxaliplatin	33 (78.6)	41 (69.5)
Pyrimidine analogues/Fluoropyrimidine	42 (100.0)	59 (100.0)
Capecitabine	20 (47.6)	28 (47.5)
Fluorouracil	31 (73.8)	42 (71.2)
Gimer/tegfur/otera	1 (2.4)	1 (1.7)
Taxane	30 (71.4)	38 (64.4)
Docetaxel	21 (50.0)	25 (42.4)
Paclitaxel	14 (33.3)	18 (30.5)
EGFR	2 (4.8)	2 (3.4)

Afatinib	1 (2.4)	1 (1.7)
Panitumumab	1 (2.4)	1 (1.7)
VEGF	5 (11.9)	5 (8.5)
Bevacizumab	1 (2.4)	1 (1.7)
Ramucirumab	2 (4.8)	2 (3.4)
Regorafenib	2 (4.8)	2 (3.4)
HER-2	9 (21.4)	14 (23.7)
Lapatinib	-	1 (1.7)
Trastuzumab	9 (21.4)	13 (22.0)
Trastuzumab emtansine	1 (2.4)	1 (1.7)
Anthracycline	15 (35.7)	21 (35.6)
Epirubicin	15 (35.7)	21 (35.6)
Other	31 (73.8)	38 (64.4)
Etoposide	1 (2.4)	1 (1.7)
Gemcitabine	1 (2.4)	1 (1.7)
Investigational antineoplastic	5 (11.9)	7 (11.9)
Investigational drug	1 (2.4)	1 (1.7)
Irinotecan	17 (40.5)	21 (35.6)
Leucovorin	23 (54.8)	27 (45.8)
Trifluridine	-	1 (1.7)

[a] Includes all prior regimens irrespective of setting (metastatic, adjuvant, neo-adjuvant)

Efficacy Results - Study CA209032

The median duration of nivolumab monotherapy in the subset of 42 subjects with GC or GEJ cancer and ≥ 2 prior regimens was 2.33 months with approximately 35% of subjects receiving > 3 months of therapy. The majority (73.8%) of nivolumab treated subjects received ≥ 90% of the planned dose intensity; the median number of nivolumab doses received was 5.0 (range 1 - 31). The median cumulative dose (mg/kg) was 15.00.

Key primary and secondary efficacy results of Study CA209032 are presented in Table 41.

Table 41: Primary and Secondary Efficacy Results of Study CA209032

Efficacy Results	CA209032 Supportive Study All Nivolumab Monotherapy - GC/GEJ Cancer Subset (n = 42)	CA209032 Supportive Study All Nivolumab Monotherapy Treated Subjects (N = 59)
Overall Survival (OS)		
Events, n (%)	27 (64.3)	41 (69.5)
Median (95% CI), months[a]	8.97 (3.35, 14.88)	5.13 (3.35, 12.91)
Rate at 6 months (95% CI), %[a]	57.4 (40.5, 71.1)	50.0 (36.2, 62.3)
Rate at 12 months (95% CI), %[a]	45.1 (28.6, 60.2)	39.4 (26.3, 52.3)
Progression-free Survival (PFS)		
BICR-Assessed PFS		
Events, n (%)	33 (78.6)	49 (83.1)
Median (95% CI), months[a]	1.49 (1.31, 2.76)	1.45 (1.31, 2.56)
Rate at 6 months (95% CI), %[a]	13.9 (5.1, 27.1)	11.9 (4.9, 22.3)
Investigator-Assessed PFS		
Events, n (%)	37 (88.1)	54 (91.5)
Median (95% CI), months[a]	1.38 (1.25, 2.27)	1.36 (1.25, 1.51)
Rate at 6 months (95% CI), %[a]	20.5 (9.6, 34.2)	16.1 (7.9, 26.8)
Objective Response Rate (ORR)[b]		
BICR-Assessed ORR		
Responders, n (%)	3 (7.1)	4 (6.8)
95% CI	(1.5, 19.5)	(1.9, 16.5)
Investigator-Assessed ORR		
Responders, n (%)	7 (16.7)	8 (13.6)
95% CI	(7.0, 31.4)	(6.0, 25.0)

Time To Response (TTR) (Months)		
BICR-Assessed TTR		
Number of responders	3	4
Mean (SD)	1.34 (0.137)	1.52 (0.383)
Median (months)	1.38	1.41
Min, Max	1.2, 1.4	1.2, 2.1
Q1, Q3	1.18, 1.45	1.28, 1.76
Investigator-Assessed TTR		
Number of responders	7	8
Mean (SD)	1.95 (1.013)	2.08 (1.008)
Median (months)	1.51	1.56
Min, Max	1.2, 4.0	1.2, 4.0
Q1, Q3	1.38, 2.56	1.38, 2.78
Duration of Response (DOR)[a]		
BICR-Assessed DOR		
Subjects with ongoing response[c]	1/3 (33.3)	1/4 (25.0)
Median (95% CI), months	N.A. (2.83, N.A.)	14.13 (2.83, 14.13)
Min - Max[d]	2.8, 9.7+	2.8, 14.1
Investigator-Assessed DOR		
Median (95% CI), months	6.97 (2.96, N.A.)	7.13 (2.96, 13.21)
Min - Max	0.0+, 9.7+	0.0+, 13.2

[a] This estimation was conducted using the Kaplan-Meier method.

[b] CR+PR, CI based on the Clopper and Pearson method. Confirmed BOR where response designations before start of subsequent therapy/crossover contribute to the BOR determination.

[c] Ongoing Response includes responders who had neither progressed nor initiated subsequent therapy/crossover at the time of analysis, and excludes responders censored prior to 14 weeks of the clinical data cutoff date.

[d] Symbol + indicates a censored value.

Overall Survival - Study CA209032

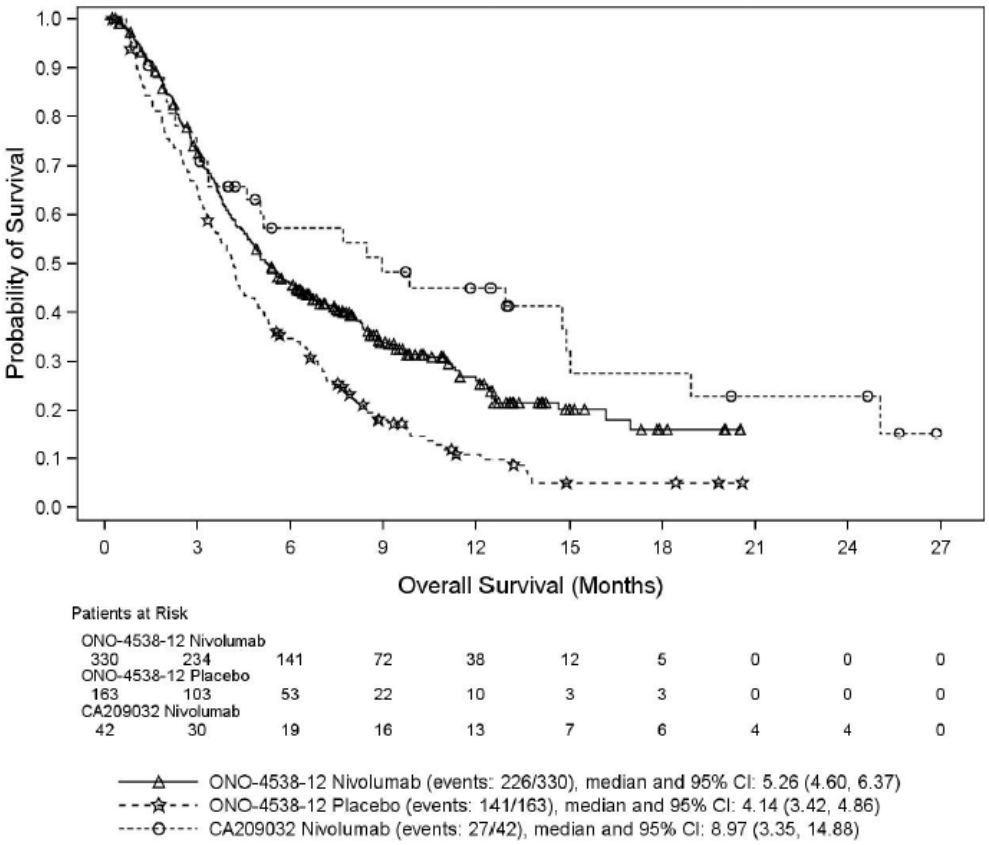
In Study CA209032, OS was a secondary endpoint. For the 42 subjects in Study CA209032 with GC or GEJ cancer and at least 2 prior regimens, corresponding to the ONO-4538-12 subject population, median OS was 8.97 months (3.35, 14.88), aligned with the ONO-4538-12 OS results. OS rates (95% CI) at 3, 6, and 12 months were 73.4% (57.1, 84.3), 57.4% (40.5, 71.1), and 45.1% (28.6, 60.2), respectively (Table 41).

15 (35.7%) of the 42 subjects in the subset were censored. Among those censored, 3 subjects (7.1%) were still on treatment, 6 (14.3%) were in follow-up, and 6 (14.3%) were off-study.

Sensitivity analysis censoring at start of crossover treatment shows that there was no impact on OS from the 6 subjects who crossed over to combination treatment (4 crossed over to the nivolumab 3 mg/kg + ipilimumab 1 mg/kg regimen and 2 crossed over to the nivolumab 1 mg/kg + ipilimumab 3 mg/kg regimen),.

Figure 26, shows the OS K-M curves for the ONO-4538-12 study and the 42 subjects in Study CA209032 with GC or GEJ cancer and at least 2 prior regimens together. The figures demonstrate consistent anti-tumour activity in the 2 studies, in both Asian and non-Asian patient populations.

Figure 26: Kaplan-Meier Plot of Overall Survival - All Randomised Subjects from Study ONO-4538-12 and Study CA209032 (All Nivolumab Monotherapy Treated Subjects with GC or GEJ Cancer and at Least 2 Prior Regimens)

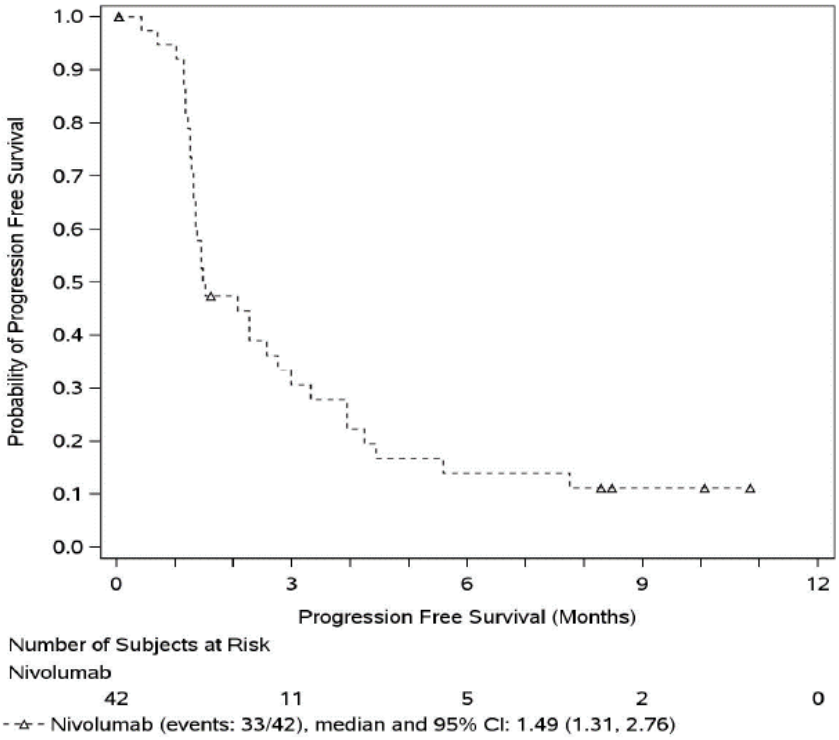


Based on an updated DBL of 07-Nov-2016, OS results remained consistent: median OS was 8.48 months for the 42 subjects with GC or GEJ cancer and at least 2 prior regimens.

Progression-free survival - Study CA209032

In Study CA209032, for the 42 subjects in Study CA209032 with GC or GEJ cancer and at least 2 prior regimens, the BICR-assessed median PFS was 1.49 months (95 % CI: 1.31, 2.76), aligned with ONO-4538-12 (Figure 27). The PFS rates (95% CI) were 30.7% (16.8, 45.6) at 3 months and 13.9% (5.1, 27.1) at 6 months (Table 39). There were 9 (21.4%) subjects censored.

Figure 27: Kaplan-Meier Plot of Progression Free Survival per BICR – All Nivolumab Monotherapy Treated Subjects with GC or GEJ Cancer and at Least 2 Prior Regimens - Study CA209032



Objective Response Rate - Study CA209032

The primary endpoint in Study CA209032 was ORR, and nivolumab monotherapy demonstrated antitumor activity (Table 41). For the 42 subjects in Study CA209032 with GC or GEJ cancer and at least 2 prior regimens, corresponding with the ONO-4538-12 population, the primary endpoint of BICR-assessed ORR using RECIST v1.1 criteria was 3 (7.1%) (95% CI: 1.5, 19.5), and all 3 responders had a BOR of PR (Table 42).

Table 42: Best Overall Response per BICR - Nivolumab Monotherapy Treated Subjects - Study CA209032

	Number of Subjects (%)
	Nivolumab N = 42
BEST OVERALL RESPONSE	
COMPLETE RESPONSE (CR)	0
PARTIAL RESPONSE (PR)	3 (7.1)
STABLE DISEASE (SD)	13 (31.0)
PROGRESSIVE DISEASE (PD)	16 (38.1)
UNABLE TO DETERMINE (UTD)	9 (21.4)
NOT REPORTED	1 (2.4)
OBJECTIVE RESPONSE RATE (1)	3/42 (7.1%)
(95% CI)	(1.5, 19.5)

RECIST 1.1, confirmation of response required.
(1) CR+PR, confidence interval based on the Clopper and Pearson method.
Confirmed best overall response where response designations before start of subsequent therapy/crossover contribute to the BOR determination.

Time to Response and Duration of Response - Study CA209032

In Study CA209032, for the 42 subjects in Study CA209032 with GC or GEJ cancer and at least 2 prior regimens, the BICR-assessed median TTR was 1.38 months. 2 out of the 3 subjects had a DOR of at least 6 months at the time of the CSR interim DBL.

Additional information as of the 07-Nov-2016 DBL has been provided, and TTR/DOR per investigator and per investigator by MSI status for the 42 subjects in Study CA209032 with GC or GEJ cancer and at least 2 prior regimens is available. TTR and DOR were similar regardless of MSI status.

Subgroup Efficacy Analyses of Overall Survival, Progression-free Survival, and Objective Response Rate - Study CA209032

OS efficacy analyses across subgroups for the 42 subjects with GC and GEJ cancer and at least 2 prior regimens, corresponding with the ONO-4538-12 population, is provided in Table below. Due to the small sample size, interpretation is limited (Table 43).

Table 43: Overall Survival by Subsets Summary - All Nivolumab Monotherapy Treated Subjects with GC and GEJ Cancer and at Least 2 Prior Regimens - Study CA209032

	Nivolumab N = 42
AGE CATEGORIZATION	
< 65	
# EVENTS / # SUBJECTS (%)	20/32 (62.5)
MEDIAN OS (MONTHS) (1) (95% CI)	9.86 (4.60, 15.01)
>= 65	
# EVENTS / # SUBJECTS (%)	7/10 (70.0)
MEDIAN OS (MONTHS) (1) (95% CI)	4.24 (1.31, N.A.)
GENDER	
MALE	
# EVENTS / # SUBJECTS (%)	20/31 (64.5)
MEDIAN OS (MONTHS) (1) (95% CI)	8.97 (3.32, 18.92)
FEMALE	
# EVENTS / # SUBJECTS (%)	7/11 (63.6)
MEDIAN OS (MONTHS) (1) (95% CI)	12.91 (2.07, N.A.)
BASELINE ECOG PERFORMANCE STATUS	
0	
# EVENTS / # SUBJECTS (%)	13/20 (65.0)
MEDIAN OS (MONTHS) (1) (95% CI)	14.75 (5.13, 18.92)
1	
# EVENTS / # SUBJECTS (%)	14/22 (63.6)
MEDIAN OS (MONTHS) (1) (95% CI)	3.35 (2.07, N.A.)
PRIMARY TUMOR LOCATION	
GASTRIC	
# EVENTS / # SUBJECTS (%)	10/16 (62.5)
MEDIAN OS (MONTHS) (1) (95% CI)	7.72 (4.60, 12.91)
GASTROESOPHAGEAL JUNCTION	
# EVENTS / # SUBJECTS (%)	17/26 (65.4)
MEDIAN OS (MONTHS) (1) (95% CI)	14.75 (2.76, 18.92)
INITIAL DIAGNOSIS DISEASE STAGE	
I/II/III	
# EVENTS / # SUBJECTS (%)	9/13 (69.2)
MEDIAN OS (MONTHS) (1) (95% CI)	9.86 (3.35, 18.92)
IV	
# EVENTS / # SUBJECTS (%)	17/28 (60.7)
MEDIAN OS (MONTHS) (1) (95% CI)	8.48 (2.07, 14.88)

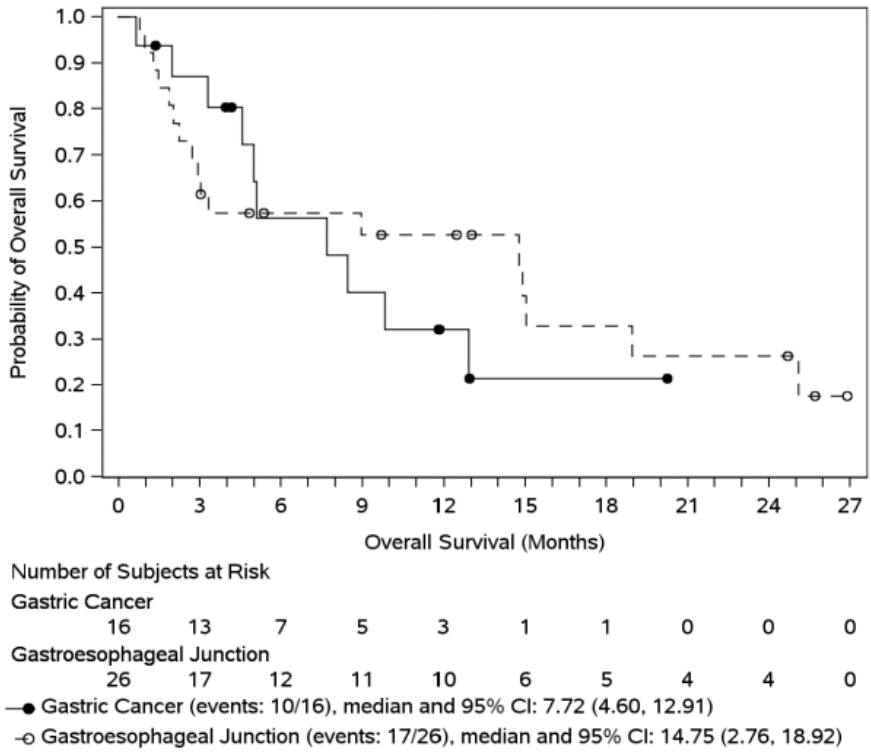
NOT REPORTED	
# EVENTS / # SUBJECTS (%)	1/1 (100.0)
MEDIAN OS (MONTHS) (1) (95% CI)	N.R.
BASELINE LIVER METASTASES (PER INVESTIGATOR)	
YES	
# EVENTS / # SUBJECTS (%)	17/22 (77.3)
MEDIAN OS (MONTHS) (1) (95% CI)	5.13 (2.76, 14.88)
NO	
# EVENTS / # SUBJECTS (%)	10/20 (50.0)
MEDIAN OS (MONTHS) (1) (95% CI)	12.91 (3.32, N.A.)
NUMBER OF SITES WITH LESIONS (PER INVESTIGATOR)	
<2	
# EVENTS / # SUBJECTS (%)	2/8 (25.0)
MEDIAN OS (MONTHS) (1) (95% CI)	N.R.
>=2	
# EVENTS / # SUBJECTS (%)	25/34 (73.5)
MEDIAN OS (MONTHS) (1) (95% CI)	7.72 (3.06, 14.75)
NUMBER OF PRIOR REGIMENS	
2	
# EVENTS / # SUBJECTS (%)	11/18 (61.1)
MEDIAN OS (MONTHS) (1) (95% CI)	12.91 (3.32, 18.92)
3	
# EVENTS / # SUBJECTS (%)	11/17 (64.7)
MEDIAN OS (MONTHS) (1) (95% CI)	8.48 (1.91, 25.03)
>3	
# EVENTS / # SUBJECTS (%)	5/7 (71.4)
MEDIAN OS (MONTHS) (1) (95% CI)	N.R.
PRIOR RADIOTHERAPY	
YES	
# EVENTS / # SUBJECTS (%)	14/19 (73.7)
MEDIAN OS (MONTHS) (1) (95% CI)	7.72 (1.91, 18.92)
NO	
# EVENTS / # SUBJECTS (%)	13/23 (56.5)
MEDIAN OS (MONTHS) (1) (95% CI)	9.86 (3.32, 15.01)
PRIOR SURGERY	
YES	
# EVENTS / # SUBJECTS (%)	16/28 (57.1)
MEDIAN OS (MONTHS) (1) (95% CI)	14.75 (4.60, 18.92)
NO	
# EVENTS / # SUBJECTS (%)	11/14 (78.6)
MEDIAN OS (MONTHS) (1) (95% CI)	4.09 (1.91, 8.97)

(1) Based on Kaplan-Meier estimate
N.A.: Not available N.R.: Not reported when sample size is less than 10 subjects for the subgroup category.
Source Table G.45

Efficacy by Primary Tumour Location

For the 42 subjects in Study CA209032 with GC or GEJ cancer and at least 2 prior regimens, analyses were conducted to assess the efficacy of nivolumab monotherapy by primary tumour location (GC and GEJ cancer). Median OS was shorter for subjects with GC (N = 16) (7.72 months) compared with subjects with GEJ cancer (N = 26) (14.75 months)

Figure 28: Kaplan-Meier Plot of Overall Survival by Primary Tumour Location - All Nivolumab Monotherapy Treated Subjects with GC or GEJ Cancer and at Least 2 Prior Regimens - Study CA209032



Median PFS (BICR-assessed) was similar, 1.35 months and 1.51 months, for subjects with GC and GEJ cancer, respectively. BICR-assessed ORR in the 26 subjects with GEJ cancer was 11.5%, with all 3 responders having a BOR of PR.

Table 44: Best Overall Response per BICR by Primary Tumour Location – All Nivolumab Monotherapy Treated Subjects with GC or GEJ Cancer and at Least 2 Prior Regimens

	Number of Subjects (%)	
	GASTROESOPHAGEAL JUNCTION N = 26	GASTRIC CANCER N = 16
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	0	0
PARTIAL RESPONSE (PR)	3 (11.5)	0
STABLE DISEASE (SD)	7 (26.9)	6 (37.5)
PROGRESSIVE DISEASE (PD)	10 (38.5)	6 (37.5)
UNABLE TO DETERMINE (UTD)	6 (23.1)	3 (18.8)
NOT REPORTED	0	1 (6.3)
OBJECTIVE RESPONSE RATE (1) (95% CI)	3/26 (11.5%) (2.4, 30.2)	0/16 (0.0, 20.6)

RECIST 1.1, confirmation of response required.
(1) CR+PR, confidence interval based on the Clopper and Pearson method.
Confirmed best overall response where response designations before start of subsequent therapy/crossover contribute to the BOR determination.

Efficacy by Number of Prior Cancer Regimens

Subgroup analyses were conducted to assess the impact of number of prior regimens of cancer therapy (2, 3 and > 3 regimens) on the efficacy of all treated nivolumab monotherapy subjects in Study CA209032 with GC and GEJ cancer.

Efficacy was consistent across subgroups suggesting there is no relationship to number of prior lines of cancer therapy. As the number of prior lines increased (range 2 to > 3), there did not appear to be a reduction in efficacy. Median OS and PFS were slightly longer for subjects who had received 2 prior regimens compared with 3 and > 3 prior regimens. ORR was consistent across the ranges (2 to > 3) of prior regimens.

Interpretation is limited due to the small sample size, especially in the subset of subjects who received > 3 prior regimens.

Table 45: Overall Survival, Progression-free Survival, and Objective Response Rate by Number of Prior Cancer Regimens - Study CA209032

	CA209032 Supportive Study All Nivolumab Monotherapy - GC/GEJ Cancer Subset (n = 42)			CA209032 Supportive Study All Nivolumab Monotherapy Treated Subjects (N = 59)		
	Number of Prior Regimens			Number of Prior Regimens		
	2	3	> 3	2	3	> 3
	N = 18	N = 17	N = 7	N=20	N=22	N=7
Overall Survival (OS)						
Events, n (%)	11/18 (61.1)	11/17 (64.7)	5/7 (71.4)	13/20 (65.0)	15/22 (68.2)	5/7 (71.4)
Median (95% CI), (months)	12.91 (3.32, 18.92)	8.48 (1.91, 25.03)	7.72 (0.82, 15.01)	9.86 (3.06, 18.92)	5.03 (1.91, 25.03)	7.72 (0.82, 15.01)
Rate at 6 months (95% CI), %[a]	59.2 (32.7, 78.2)	51.8 (26.2, 72.4)	71.4 (25.8, 92.0)	52.6 (28.4, 72.1)	44.6 (23.5, 63.8)	71.4 (25.8, 92.0)
Rate at 12 months (95% CI), %[a]	52.6 (26.9, 73.1)	37.0 (14.4, 60.0)	47.6 (7.5, 80.8)	46.8 (23.5, 67.1)	33.5 (14.6, 53.7)	47.6 (7.5, 80.8)
Progression-free survival (PFS)						
BICR-Assessed PFS						
Events, n (%)	14/18 (77.8)	13/17 (76.5)	6/7 (85.7)	16/20 (80.0)	18/22 (81.8)	6/7 (85.7)
Median (95% CI), months[a]	2.51 (1.38, 4.44)	1.38 (1.15, 2.56)	1.33 (0.43, 4.24)	2.51 (1.38, 4.44)	1.31 (1.15, 2.27)	1.33 (0.43, 4.24)
Rate at 6 months (95% CI), %[a]	18.8 (4.6, 40.2)	15.0 (2.6, 37.4)	0.0 (N.A., N.A.)	16.7 (4.1, 36.5)	10.9 (1.9, 29.0)	0.0 (N.A., N.A.)
Investigator-Assessed PFS						
Events, n (%)	15/18 (83.3)	15/17 (88.2)	7/7 (100.0)	17/20 (85.0)	20/22 (90.9)	7/7 (100.0)
Median (95% CI), months[a]	1.46 (1.35, 7.20)	1.28 (1.15, 1.61)	1.35 (0.82, 5.49)	1.46 (1.35, 2.92)	1.25 (1.15, 1.61)	1.35 (0.82, 5.49)
Rate at 6 months (95% CI), %[a]	31.3 (11.4, 53.6)	12.5 (2.1, 32.8)	14.3 (0.7, 46.5)	27.8 (10.1, 48.9)	9.5 (1.6, 26.1)	14.3 (0.7, 46.5)
Objective Response Rate (ORR)[b]						
BICR-Assessed ORR						
Responders, n (%)	1/18 (5.6)	1/17 (5.9)	1/7 (14.3)	1/20 (5.0)	1/22 (4.5)	1/7 (14.3)
95% CI	(0.1, 27.3)	(0.1, 28.7)	(0.4, 57.9)	(0.1, 24.9)	(0.1, 22.8)	(0.4, 57.9)
Investigator-Assessed ORR[b]						
Responders, n (%)	3/18 (16.7)	2/17 (11.8)	2/7 (28.6)	3 /20 (15.0)	2/22 (9.1)	2/7 (28.6)
95% CI	(3.6, 41.4)	(1.5, 36.4)	(3.7, 71.0)	(3.2, 37.9)	(1.1, 29.2)	(3.7, 71.0)

[a] Median and rates computed using Kaplan-Meier method.

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

Confirmed best overall response where response designations before start of subsequent therapy/crossover contribute to the BOR determination.
RECIST 1.1, confirmation of response required.

Baseline PD-L1 Expression (Exploratory Endpoint) - Study CA209032

Tumour Tissue Disposition and Frequency of PD-L1 Expression

Baseline PD-L1 expression in Study CA209032 is provided in Table 46 below.

Table 46: PD-L1 Expression and HER-2 Status at Baseline – Study CA209032

	CA209032 Supportive Study All Nivolumab Monotherapy - GC/GEJ Cancer Subset (n = 42)	CA209032 Supportive Study All Nivolumab Monotherapy Treated Subjects (N = 59)
Subjects With PD-L1 Quantifiable At Baseline (N [%])	30 (71.4)	42 (71.2)
≥ 1%	10 (33.3)	16 (38.1)
< 1%	20 (66.7)	26 (61.9)
≥ 5%	4 (13.3)	6 (14.3)
< 5%	26 (86.7)	36 (85.7)
Subjects Without PD-L1 Quantifiable At Baseline (N [%])	12 (28.6)	17 (28.8)
HER-2 Status[a]		
Positive	5 (11.9)	8 (13.6)
Negative	22 (52.4)	31 (52.5)
Unknown	15 (35.7)	20 (33.9)

[a] IHC results were divided into positive and negative to maximize the categorization narrowly. IHC results that did not meet these criteria were assessed as unknown.

PD-L1 Expression and Efficacy

The interpretation of analyses by PD-L1 is limited due to the small number of subjects expressing PD-L1 (n = 10, 33.3% in the 42 subset of subjects in Study CA209032 with GC or GEJ cancer and at least 2 prior regimens). However, the results appear to be consistent with ONO-4538-12 regardless of positive and negative PD-L1 expression.

Table 47: PD-L1 Expression and Efficacy - Study CA209032

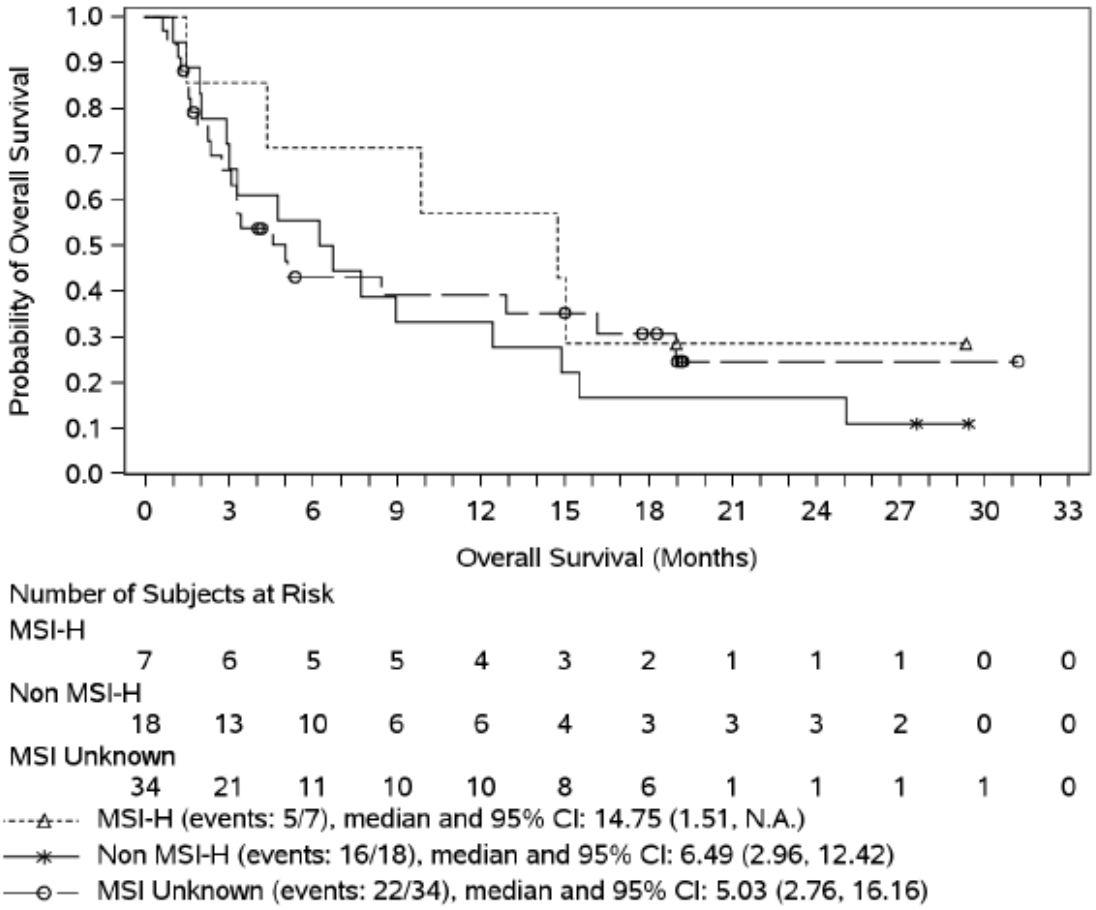
Efficacy by Baseline PD-L1 Expression (1% tumor cell membrane expression)	CA209032 Supportive Study All Nivolumab Monotherapy - GC/GEJ Cancer Subset (n = 42)	CA209032 Supportive Study All Nivolumab Monotherapy Treated Subjects (N = 59)
Subjects with ≥ 1% PD-L1 Expression	N = 10	N=16
Overall Survival		
Events, n (%)	6 (60.0)	12 (75.0)
Median OS (95% CI), months	12.91 (1.02, N.A.)	6.74 (1.91, 12.91)
Progression-free Survival		
Events, n (%)	7 (70.0)	12 (75.0)
BICR-assessed median PFS (95% CI), months	1.35 (1.02, N.A)	1.35 (1.15, 3.35)
Investigator-assessed median PFS (95% CI), months	1.35 (1.02, 8.38)	1.35 (1.15, 1.58)
Rate at 6 months (95% CI) (%)	22.2 (3.4, 51.3)	16.0 (2.7, 39.4)
Objective Response Rate		
BICR-assessed ORR (95% CI), n (%)	2 (20.0) (2.5, 55.6)	2 (12.5) (1.6, 38.3)
Investigator-assessed ORR (95% CI), n (%)	4 (40.0) (12.2, 73.8)	4 (25.0) (7.3, 52.4)
Subjects with < 1% PD-L1 Expression	N = 20	N=26
Overall Survival		
Events, n (%)	14 (70.0)	18 (69.2)
Median OS (95% CI), months	7.72 (3.06, 14.88)	7.72 (4.40, 16.16)
Progression-free Survival		
Events, n (%)	16 (80.0)	22 (84.6)
BICR-assessed median PFS (95% CI), months	2.27 (1.28. 3.94)	2.27 (1.28, 4.40)
Investigator-assessed median PFS (95% CI), months	1.61 (1.22, 2.92)	1.61 (1.31, 2.92)
Rate at 6 months (95% CI) (%)	12.2 (2.0, 32.1)	13.5 (3.4, 30.5)
Objective Response Rate		
BICR-assessed ORR (95% CI), n (%)	0 (0.0, 16.8)	1 (3.8) (0.1, 19.6)
Investigator-assessed ORR (95% CI), n (%)	2 (10.0) (1.2, 31.7)	3 (11.5) (2.4, 30.2)
Subjects without quantifiable PD-L1 Expression	N = 12	N=17
Overall Survival		
Events, n (%)	7 (58.3)	11 (64.7)
Median OS (95% CI), months	8.48 (1.31, N.A.)	3.45 (1.54, 25.03)
Progression-free Survival		
Events, n (%)	10 (83.3)	15 (88.2)
BICR-assessed median PFS (95% CI), months	1.45 (1.25, 2.76)	1.36 (1.18, 2.20)
Investigator-assessed median PFS (95% CI), months	1.31 (0.66, 1.51)	1.28 (1.15, 1.45)
Rate at 6 months (95% CI) (%)	9.1 (0.5, 33.3)	6.3 (0.4, 24.7)
Objective Response Rate		
BICR-assessed ORR (95% CI), n (%)	1 (8.3) (0.2, 38.5)	1 (5.9) (0.1, 28.7)
Investigator-assessed ORR (95% CI), n (%)	1 (8.3) (0.2, 38.5)	1 (5.9) (0.1, 28.7)

Efficacy by MSI Status (Exploratory Endpoint) - Study CA209032

In Study CA209032, analyses assessing the impact of baseline MSI status on efficacy were performed in the n = 59 cohort. A PCR test was utilized for retrospective central testing for cases in which clinical specimens were available. For all the GC cohort (n=59) 7 subjects had MSI-H status, 18 subjects had non-MSI-H status, and for 34 subjects the MSI status was unknown. For the efficacy analyses, MSI-S and MSI-L subjects were presented pooled (as non MSI-H status) since there is only 1 MSI-L subject.

Median OS values, as of the 07-Nov-2016 DBL, across MSI subgroups were: 14.75 months (95% CI: 1.51, N.A.), 6.49 months (95% CI: 2.96, 12.42), and 5.03 months (95% CI: 2.76, 16.16) in the MSI-H, non MSI-H, and MSI unknown subgroups, respectively.

Figure 29: Kaplan-Meier Plot of Overall Survival by MSI Status – Nivolumab Monotherapy Treated Subjects from the GC Cohort



In the 42 patients who received ≥ 2 prior systemic regimens in Study CA209032, for subjects with MSI-H (n = 5), non MSI-H (n = 14), and unknown MSI status (n = 23), respectively, the median OS was 15.01 months (95% CI: 9.86, N.A.), 6.98 months (95% CI: 2.00, 15.51), and 5.13 months (95% CI: 2.76, 18.92).

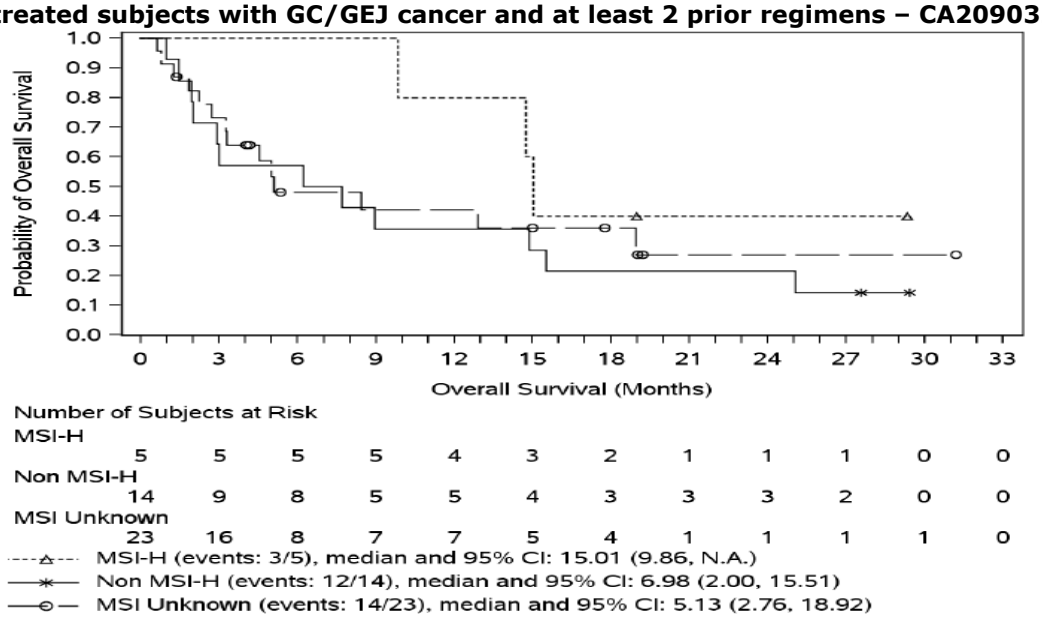
The PFS K-M by MSI status in the subjects who received ≥ 2 prior systemic regimens in Study CA209032 is provided in Figure 13. The PFS was 4.24 months (95% CI: 1.28, N.A.) in MSI-H group, 1.45 months (95% CI: 1.18, 2.56) in non-MSI-H group, and 1.87 months (95% CI: 1.25, 3.32) in the MSI unknown group.

For MSI-H subjects (n = 5), ORR per investigator was 40.0% (95% CI: 5.3, 85.3), and there was 1 CR, 1 PR and 2 SD (Table 48). The ORR for subjects with non MSI-H (n=14) and MSI unknown (n = 23) was 14.3% (95% CI: 1.8, 42.8) and 8.7% (95% CI: 1.1, 28.0), respectively.

There were 2 responders in each MSI status subgroup. The DOR in the MSI-H group was 6.8 - 13.2 months, 3.0 - 26.5+ months in the non-MSI-H group, and 6.1 - 7.1 months in the MSI unknown group (Table 49).

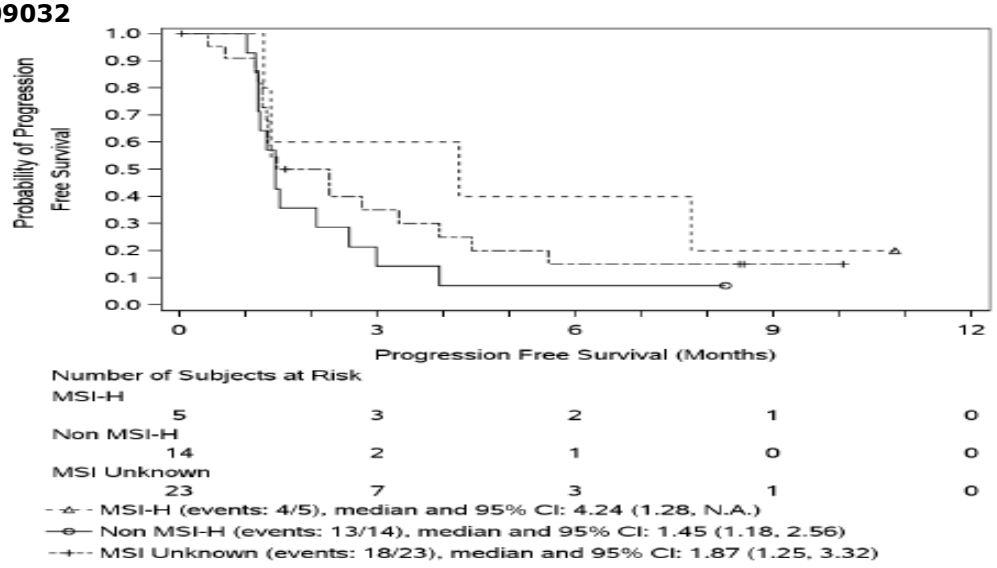
Overall, subjects with MSI-H status seemed to have a longer OS and PFS, and higher ORR, compared with the subjects with non-MSI-H or MSI- unknown. Although a benefit was observed across all MSI-H, non-MSI-H and MSI unknown subgroups, no conclusions can be made due to the small sample size. Of note, the efficacy by MSI status results in CA209032 are consistent with those observed in ONO-4538-12 (see BMS Response 2d). Benefits were observed independent of MSI status, and given the small number of MSI-H subjects between both studies, the study results are unlikely driven by the subjects with MSI-H status. The role of MSI-H as predictive biomarker is unclear.

Figure 30: Kaplan-Meier plot of Overall Survival by MSI status – Nivolumab monotherapy treated subjects with GC/GEJ cancer and at least 2 prior regimens – CA209032



Symbols represent censored observations
Database lock date: November 7, 2016
Program Source: /projects/bms219884/stats/ia_nov16/prog/figures
Program Name: rg-ef-dor_93.sas 22FEB20I7:11:17:59

Figure 31: Kaplan-Meier plot of Progression Free Survival per BICR, by MSI status – All Nivolumab monotherapy treated subjects with GC/GEJ cancer and at least 2 prior regimens – CA209032



Symbols represent censored observations
Database lock date: November 7, 2016; BICR data were not updated for this lock.
Program Source: /projects/bms219884/stats/ia_nov16/prog/figures
Program Name: rg-ef-pfsbicrggemsi.sas 19DEC2017:08:08:18

Table 48: Best Overall Response per investigator, by MSI status –Nivolumab monotherapy treated subjects with GC/GEJ cancer and at least 2 prior regimens – CA209032

	Number of Subjects (%)		
	MSI-H N = 5	Non MSI-H N = 14	MSI Unknown N = 23
BEST OVERALL RESPONSE (A):			
COMPLETE RESPONSE (CR)	1 (20.0)	0	0
PARTIAL RESPONSE (PR)	1 (20.0)	2 (14.3)	2 (8.7)
STABLE DISEASE (SD)	2 (40.0)	1 (7.1)	5 (21.7)
PROGRESSIVE DISEASE (PD)	1 (20.0)	9 (64.3)	13 (56.5)
UNABLE TO DETERMINE (UTD)	0	2 (14.3)	3 (13.0)
NEVER TREATED	0	0	0
WRONG CANCER DIAGNOSIS	0	0	0
DEATH PRIOR TO DISEASE ASSESSMENT	0	0	3 (13.0)
EARLY DISCONTINUATION DUE TO TOXICITY	0	0	0
OTHER	0	2 (14.3)	0
OBJECTIVE RESPONSE RATE (1)	2/5 (40.0%)	2/14 (14.3%)	2/23 (8.7%)
(95% CI)	(5.3, 85.3)	(1.8, 42.8)	(1.1, 28.0)

(a) Using RECIST 1.1 criteria.
(1) CR+PR, confidence interval based on the Clopper and Pearson method
Database lock date: November 7, 2016
Program Source: /projects/bms219884/stats/ia_nov16/prog/tables/rt-ef-bor-nov16.sas 22FEB2017:05:05:50

Table 49: Time to response and duration of response per investigator, by MSI status – Nivolumab monotherapy treated responders with GC/GEJ cancer and at least 2 prior regimens – CA209032

	MSI-H N = 2	Non MSI-H N = 2	MSI Unknown N = 2
TIME TO RESPONSE (MONTHS)			
NUMBER OF RESPONDERS	2	2	2
MEAN	1.40	1.97	2.69
MEDIAN	1.40	1.97	2.69
MIN, MAX	1.2, 1.6	1.4, 2.6	1.4, 4.0
Q1, Q3	1.18, 1.61	1.38, 2.56	1.38, 4.01
STANDARD DEVIATION	0.302	0.836	1.859
DURATION OF RESPONSE (MONTHS)			
MIN, MAX (A)	6.8, 13.2	3.0, 26.5+	6.1, 7.1
MEDIAN (95% CI) (B)	10.00 (6.80, 13.21)	N.A. (2.96, N.A.)	6.60 (6.08, 7.13)
N EVENT/N RESP (%)	2/2 (100.0)	1/2 (50.0)	2/2 (100.0)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)			
3 MONTHS	2 (100.0)	1 (50.0)	2 (100.0)
6 MONTHS	2 (100.0)	1 (50.0)	2 (100.0)
12 MONTHS	1 (50.0)	1 (50.0)	0
18 MONTHS	0	1 (50.0)	0
24 MONTHS	0	1 (50.0)	0
NUMBER OF SUBJECTS ACHIEVED PR OR CR (%) (C)			
WITHIN THE FIRST 9 WEEKS	2 (40.0)	1 (7.1)	1 (4.3)
WITHIN THE FIRST 4 MONTHS	2 (40.0)	2 (14.3)	1 (4.3)
WITHIN THE FIRST 6 MONTHS	2 (40.0)	2 (14.3)	2 (8.7)
WITHIN THE FIRST 8 MONTHS	2 (40.0)	2 (14.3)	2 (8.7)
WITHIN THE FIRST 12 MONTHS	2 (40.0)	2 (14.3)	2 (8.7)
WITHIN THE FIRST 18 MONTHS	2 (40.0)	2 (14.3)	2 (8.7)

(a) Symbol + indicates a censored value.
(b) Median computed using Kaplan-Meier method.
(c) Denominator based on Nivolumab Monotherapy Treated Subjects with Gastric Cancer
Database lock date: November 7, 2016
Program Source: /projects/bms219884/stats/ia_nov16/prog/tables/rt-ef-ttr-dor-nov16.sas 21FEB2017:10:38:08

Subsequent Therapy

19 (45.2%) of the 42 subjects with GC or GEJ cancer with at least 2 prior regimens received subsequent therapy: 14 (33.3%) received systemic therapy (chemotherapy), 7 (16.7%) received subsequent radiotherapy, and 3 (7.1%) had surgery.

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

Applicability of ONO-4538-12 and CA209032 Results to the Non-Asian Population

The pivotal study, ONO-4538-12, was conducted in Asian countries, while the supportive study CA209032 was conducted in US and Europe. Therefore, the study population in the ONO-4538-12 study should be compared with the population in CA209032.

Given the properties of nivolumab, it is not expected that exposures in safety or efficacy profiles would be

different across ethnic groups. As demonstrated in the PPK analysis across different tumor types, race did not have a clinically relevant effect on CL, and exposures were similar between Asian and Non-Asian subjects. Thus, in the Non-Asian and Asian GC/GEJ cancer population, it is expected that there will be similar PK profiles.

Baseline disease characteristics of subjects were generally similar between the subject population in ONO-4538-12 and in the 42 subjects with GC/GEJ cancer and ⩾2 prior regimens from CA209032. However, differences noted between the populations included primary tumour location or regional practices of screening and treatment (e.g. disease stage at diagnosis and number of prior therapies).

Geographic differences in survival outcomes have been well documented in randomized controlled trials with chemotherapy and targeted therapies for 1L and 2L treatments of advanced GC. Longer OS has generally been observed in patients from Asia, specifically Japan, relative to Non-Asian patients, likely impacted by several factors:

- Asian patients have greater use of subsequent treatment compared with Non-Asian patients even in the absence of approved therapies. Up to 70% of Japanese patient and 66% of Asian patients received chemotherapy following failure of 1L therapy compared with 21% of Pan-American patients and 31% of European patients. Similarly, up to 69% of Asian patients received chemotherapy following failure of 2L therapy compared with 38% of non-Asian patients. As a result, there appears to be a higher threshold for demonstrating survival benefit in the Asian population against standard of care.
- In the RAINBOW trial, a Phase 3, randomized, placebo-controlled trial in advanced gastric or GEJ cancer, evaluating a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist, ramucirumab + paclitaxel as 2L treatment, no survival benefit was demonstrated in Asian patients although the longer median OS was longer compared with the overall population (11.4 vs 8.6 months) due to high frequencies of subsequent therapy.
- Asian patients treated in the earlier setting differ on some disease characteristics:
  - Trials conducted in Asia often include patients with better baseline prognostic factors than those trials conducted outside of Asia, with Asians presenting with better ECOG PS, less number of metastatic sites, and longer time to progression in 1L treatment, which might contribute to longer survival.
  - REGATE, a registry established to examine how baseline characteristics and treatment patterns vary between regions, reported[1] a meta-analysis and meta-regression on 25 trials (8 Asian, 13 Western, 4 international) exploring systemic chemotherapy as 1L treatment for advanced or metastatic GC or gastroesophageal cancer.
    - The rate of GC surgery was highest in the Asia-Pacific region at 73.9% compared with 63.4% in Europe, 50.8% in Latin America, and 49.8% in North Africa.**Error! Bookmark not defined.**
    - Per the meta-regression analysis, the increased percentage of non-Asian patients with GEJ cancer was associated with poor PFS rate; however, the analysis did not identify geographic region as an independent predictor of 1-year OS or 6-month PFS rates.1 Of note, in other analyses[2,3] , PFS and OS were very similar between GC and GEJ cancer. Thus, treatment effects in GC and GEJ cancers should be interpreted with caution.

2.4.3. Discussion on clinical efficacy

The new claimed indication for OPDIVO is for the treatment of adult patients with advanced or recurrent gastric or GEJ cancer after two or more prior systemic therapies. The evidence presented in support of the present application for the claimed indication comes from results of a phase III clinical trial (ONO-4538-12) conducted exclusively in an Asian population with supportive evidence from a nivolumab monotherapy cohort from a phase 1/2 Study CA209032 conducted in a non-Asian population.

In both trials nivolumab 3 mg/kg was administered as a 60-minute intravenous (IV) infusion every 2 weeks (Q2W) until either RECIST 1.1 progression, unacceptable toxicity, or other protocol-defined reasons.

Currently there is no approved therapy for patients progressing beyond 2nd line treatment in Europe. Nevertheless, although there are no approved therapies beyond 2nd line, various treatment options are used sequentially in clinical practice for the small proportion of GC patients that is eligible for third-line treatment.

For the time being, the main drawback of nivolumab clinical development in GC/GEJ is the lack of comparative data in a non-Asian population. This submission is based mainly on results from a comparative study in an Asian population, while race is a relevant prognostic factor in GC based on historical series and, importantly, response to treatment of different drugs has been shown to be strongly influenced by race (discussed below in section on extrapolation of results).

Design and conduct of clinical studies

ONO-4538-12 is a phase 3 multicentre, double-blind, randomised study of nivolumab monotherapy in Asian patients with unresectable advanced or recurrent gastric cancer (including oesophagogastric junction cancer) with histological confirmation of adenocarcinoma after at least 2 prior systemic therapies for advanced/recurrent disease, refractory to or intolerant of standard therapies and not planned to receive any additional anticancer therapy.

Only patients with ECOG 0-1 and life expectancy of at least 3 months were recruited. Subjects with active brain metastases; active, known, or suspected autoimmune disease; or a condition requiring systemic treatment with either corticosteroids or other immunosuppressants within 14 days of study drug administration were excluded from the trial.

601 subjects were enrolled and 493 randomised 2:1 to either the nivolumab or placebo arm (330 nivolumab; 163 placebo). Randomisation was stratified according to location (Japan vs. Korea vs. Taiwan), ECOG-PS (0 vs. 1) and number of organs with metastases (≤1 vs.≥2).

The supportive study conducted in a non-Asian population, study **CA209032,** is a multicentre, Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab designed to evaluate the efficacy and safety of nivolumab as monotherapy or in combination with ipilimumab in subjects with 6 different tumour types, including GC. The study population in the GC cohort included previously treated patients with advanced or metastatic GC. Subjects were required to have histologically confirmed GC or GEJ carcinoma, including adenocarcinoma arising from the lower oesophagus, with tumour progression or refractory disease and at least 1 prior chemotherapy regimen, or actively refused chemotherapy, for the treatment of metastatic (stage IV) or locally advanced disease. Subjects with HER-2-positive tumours must have had previous treatment with trastuzumab.

In study **CA209032,** a total of 59 patients who had GC or GEJ cancer were treated with nivolumab monotherapy 3 mg/kg, of them 42 had received at least 2 prior regimens and are therefore the subset of subjects most similar to patients in the ONO-4538-12 study. However, not only regimens administered in

the advanced/metastatic setting were considered but also numbers of prior regimens were summed up for both the neoadjuvant, adjuvant, and metastatic setting. Only 32 patients had received ≥2 prior systemic regimens in the metastatic setting and are therefore considered similar to the target population for the present indication.

Background expression of PD-L1 has been shown to be upregulated in some patients with gastric cancer. Patients in these nivolumab trials were recruited regardless expression of PD-L1; nevertheless there is data of other anti-PD-1 compounds that have shown efficacy primarily in the PD-L1-high population and less in the PD-L1-low population. Furthermore, the currently presented data on PD-L1 expression in relation to response are not adequate, because the scoring of PD-L1 expression was based only on expression of PD-L1 on tumour cells, while it is considered that scoring of PD-L1 expression on tumour-associated/infiltrating immune cells in addition to tumour cells would provide additional valuable information. This especially since there is little PD-L1 expressed on the cancer cells of upper gastrointestinal tumours, but rather expression occurs predominantly on infiltrating myeloid cells at the invasive margin (Kelly. Am Soc Clin Oncol Educ Book. 2017).

Study endpoints

In the ONO-4538-12 study the primary objective was to evaluate the efficacy of nivolumab compared to placebo based on overall survival (OS) as the primary endpoint. Secondary endpoints included investigator-assessed (RECIST 1.1-defined progression) PFS, ORR, DOR, disease control rate (DCR) and time to response (TTR) compared to placebo. OS is considered the most relevant endpoint in this setting due to the dismal prognosis of the patients (survival is around 4 months).

A total of 48 sites in 3 countries enrolled subjects (226 patients in Japan , 220 patients in in Korea and 47 patients in Taiwan). Data are presented based on the database lock of 13-Aug-2016.

The primary endpoint evaluated in the gastric cohort of study CA209032 was ORR, by BICR and investigator assessments. Secondary endpoints included OS, PFS, DOR and TTR. This trial was conducted in Western population across 6 countries (Finland, Germany, Italy, Spain, the United Kingdom, and the United States of America). Data are presented based on the database lock date of 24-Mar-2016.

Trial population

The ITT of the **ONO-4538-12** trial comprises data from 493 patients (330 nivolumab arm and 163 placebo arm). From the all ITT population, 399 patients (268 nivolumab; 131 placebo) were response-evaluable by investigator assessment as they had measurable lesions at baseline.

At the DBL most patients had discontinued treatment period (mainly because of disease progression) and 28.2% of patients in the nivolumab arm and 10.4% in the placebo arm were under follow-up.

Protocol deviations were reported in 19.1% of subjects (63 subjects) in the nivolumab group and 19.6% of subjects (32 subjects) in the placebo group. For most of them, protocol deviation was due to administration of any concurrent anti-cancer therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, surgery, or radiation therapy) while on study therapy. The applicant clarified that, however, that this is not a true protocol deviation because this was for symptomatic treatment of cancer, thus these concurrent therapies are not considered to have had an impact on study outcomes

Among nivolumab-treated subjects, the median age was 62 years (range: 20 to 83), with 42.7% of patients ≥65 years and 9.1% ≥75 years. Median age in placebo arm was 61 years (range: 26 to 83)), with 41.7% of patients ≥65 years and 8.6% ≥75 years. The majority were male (69.4% and 73% in nivolumab and placebo arms) and all were Asian. Primary tumour location was gastric for the majority of patients (82.4 % and 82.8% for nivolumab and placebo respectively) or GEJ (9.1% and 7.4%

respectively), tumours of unknown treatment location were present in 8.5% and 9.8% of patients respectively. Baseline ECOG PS was 1 (73.3% nivolumab; 71.2% placebo) or 0 (26.7% nivolumab; 28.8% placebo).

Most European patients with advanced or metastatic gastric cancer after 1st line systemic treatment demonstrate a performance score >1 and those relatively fit might not reflect the real-life frail population of pre-treated gastric carcinoma patients. This difference has been be properly reflected in SmPC. On the other hand, the inclusion of GEJ cancer is agreed based on the fact that the clinical approach in GEJ is practically the same as that used in GC.

Median time from initial diagnosis was 23.4 (range: 4-185) and 25.0 (6-412) months for nivolumab and placebo arms respectively according to data submitted in the summary of clinical efficacy. Shorter median times from diagnoses were wrongly shown in the CSR due to a mistake in the programming derivation used for the CSR analysis. The dates of recurrence instead of dates of primary disease diagnosis were erroneously used for calculation but this was corrected in the summary of clinical efficacy. Histologic subtypes according to Lauren classification were distributed between treatment arms as follows, intestinal type in 36.4% and 33.7% in nivolumab and placebo arms respectively, and diffuse type 32.1% and 38.7% in nivolumab and placebo arms respectively. Thus, a slightly greater proportion of patients in the placebo arm had diffuse type which is a known factor of poor prognosis. Different sensitivity analyses were performed in order to assess the impact of such imbalance in diffuse histological type between study arms. Overall, sensitivity analyses results are considered robust and supportive for main outcomes pointing out that the imbalance observed in the percentage of patients with diffuse subtype do not significantly impact results which is reassuring. The Disease stage at initial diagnosis was Stage IV for 53.6% in the nivolumab arm and 49.7% in placebo arm and Stage III for 11.2 and 14.1% nivolumab and placebo arms. 41.2% and 44.2% of patients had recurrent disease. The majority of patients (73.6% and 76.7%) had 2 or more sites of metastasis at study entry with lymph node, liver and peritoneum, as the main sites of metastases.

In the nivolumab group, 20.9%, 41.5%, and 37.6% of subjects received 2, 3, and > 3 prior regimens, respectively. In the placebo group, 17.8%, 38.0%, and 44.2% of subjects received 2, 3, and > 3 prior regimens, respectively. According to these data, most patients received study therapies as a 4th or greater line however, these data included all prior regimens irrespective of the setting (metastatic, adjuvant, neo-adjuvant). The adjuvant and neo-adjuvant settings cannot be considered as true single lines of therapy, unless the relapse occurs within 6 months after the last administration of the platinum-fluoropyrimidine in that setting. The applicant was asked to clarify this issue (for both the main and the supportive study), because the nature of the studied population with regard to number of prior regimens in the metastatic setting was unclear.

Whereas according to initial baseline data all study population from trial ONO-4538-012 had received at least 2 prior therapies, if agents administered in the (neo)adjuvant setting were excluded there were 97.0% of patients in the nivolumab arm 95.7% in the placebo arm that comply with the definition of ≥2 lines in the metastatic setting (i.e. 10 patients in the nivolumab arm and 7 patients in the placebo arm had just received 1 prior therapy in the metastatic setting) . In the nivolumab group, 32.4%, 38.5%, and 26.1% of subjects received 2, 3, and > 3 prior regimens in the metastatic setting, respectively. In the placebo arm percentages were 28.2%, 39.3% and 28.2% respectively.

The majority of subjects had prior surgery for GC (64.5% in the nivolumab group and 68.7% in the placebo group), and had not received prior radiotherapy (87.6% and 84.7%, respectively). Most patients had received prior platinum compounds (94.2% and 96.3% for nivo and placebo), pyrimidine analogues (99.7% and 100% for nivo and placebo), taxanes (86.1% and 85.9% for nivo and placebo) and irinotecan (74.8% and 75.5% for nivo and placebo).

There is no standard treatment for patients with advanced gastric or GEJ adenocarcinoma who have progressed after two prior lines of chemotherapy for advanced disease. Most patients had received 5-FU-based combination with a platinum compound as 1st-line treatment, followed by either taxane- or irinotecan-based 2nd-line treatment. For 3rd line, no SoC treatment can be recommended, but in case of irinotecan-based 2nd-line treatment, taxanes can be given as 3rd line, and, vice versa, in case of taxane-based 2nd-line treatment, irinotecan can be considered as 3rd line in patients who are fit enough and who have benefited from earlier treatments. Supposedly, 20.9% of patients in nivolumab arm and 17.8% in placebo arm received nivolumab as 3rd-line therapy which could have deferred other available treatments.

Less than half of subjects (40.6% nivolumab, 38.0% placebo) had PD-L1 tested at baseline and of these, all but 4 subjects in the placebo arm had quantifiable tumour PD-L1 expression at baseline. Of the 130 subjects with quantifiable tumour PD-L1 expression at baseline in the nivolumab arm, 16 (12.3%) subjects had > 1% baseline PD-L1 expression and 114 (87.7%) had < 1% baseline PD-L1 expression. These numbers were 10 (16.1%) and 52 (83.9%) in the placebo arm.

Study population from the subset of 42 patients from **Study CA209032** who had received at least 2 prior regimens had a median age of 59 years (29 to 80) with 23.8% of patients ⩾65 years and 4.8% ⩾75 years. The majority were male (73.8%) and White (92.9%). Primary tumour location was GEJ for the majority of patients (61.9%) and GC in 38.1% of trial population. Baseline ECOG PS was 1 in 52.4% of population. Time from initial diagnosis was 1.74 years (0.5-5.2).

No information about histological type (Lauren classification) was collected in this trial. Despite this it is agreed that the histological subtypes do not have any impact on treatment decisions, but nonetheless it is of prognostic value and such data could help in interpretability of extrapolation of results from the pivotal trial to the target European population.42.9% of subjects had received 2 prior regiments, 40.5% of subjects received 3 prior regimens and 16.7% of subjects received > 3 prior regimens. Of note, it appears that in study CA209032, of the 42 patients that had received at least 2 prior systemic regimens, only 32 patients had received at least 2 prior systemic regimens in the metastatic setting. The applicant clarified that 7 patients had only received one line in the metastatic setting. If patients that did not comply with the definition of having received at least 2 prior systemic regimens in the metastatic setting were excluded, 34.4% of patients received nivolumab as 3rd line therapy, 43.8% as 4th line therapy and 21.9% as 5th or greater line.

All subjects received pyrimidine analogues, most subjects received platinum compounds (97.6%), and taxanes (71.4%).

The majority of subjects (62.7% and 66.7%) had prior surgery for GC and had not received prior radiotherapy (59.3% and 54.8%). Half of population has previously received irinotecan (40.5%).

Generally speaking, patients included trial CA209032 had predominant GEJ disease, a shorter time from diagnosis and better PS. This population also was significantly less pre-treated than the patient population in the main study.

Statistical assessment

ONO-4538-12 trial followed an adaptive design. An initial sample size of 290 pts was estimated and a pre-specified interim analysis was to be performed at 70% of targeted events (183/261 events) with the possibility of stopping the trial for futility or re-estimating targeted events. Prior to performance of IA, based on the targeted number of events the sample size was increased up to 436. The unblinded IA was performed on 14-Feb-2016 and based on conditional power led to a sample size increase (from 290 to at least 393 patients, and from 261 to 328 events). The interim decision to include at least 36% more

patients, could in principle have influenced the investigator's recruitment, treatment and/or assessment behavior. However, the applicant clarified that recruitment had been completed at the time of IA, thus the IDMC recommendation only concerned a recalculation of the number of events rather than a change in sample size calculation. Enrollment is therefore not considered to have been influenced by the IA. Overall, statistical analyses methods used by the Applicant to assess trial endpoints are those commonly used and deemed acceptable.

Efficacy data and additional analyses

- Results of trial **ONO-4538-12** show a relatively modest benefit in terms of overall survival and even more questionable in terms of the secondary endpoints PFS and ORR.

  Mature OS data (event rate 68.5% nivo; 86.5% placebo) showed a statistically significant improvement in favour of the nivolumab arm (HR: 0.63; 95%CI 0.51, 0.78). The K-M curves are clearly separated throughout the course of the trial however differences in median survival time remain around 1 month (5.26 (95%CI 4.60, 6.37) for nivo arm and 4.14 (95%CI 3.42, 4.86) for placebo arm). Although it is likely that median time is not the best estimator of effect, in view of the difference in plateaus of the curves. OS rates favoured nivolumab in a consistent manner with differences that remained around 10-15% (OS rate at 6-months 46.1% vs. 34.7%; OS rate at 12-months 26.2% vs. 10.9%; OS rate at 18-months 16.2% vs. 5%).

  Subsequent therapies were received by 155 (47.0%) subjects in the nivolumab group and 72 (44.2%) subjects in the placebo group. The most frequent subsequent pharmacotherapies were fluoropyrimidine, irinotecan, ramucirumab, and taxane. Although there are no approved therapies beyond second-line of treatment, it is likely that patients could still benefit from re-challenge with chemotherapy or from further therapies (of note ramucirumab had been previously administered to 10.6% of patients in nivo arm and 13.5% of patients in placebo arm). Therefore, there is the potential for an influence of next-line therapies on the OS results.

  An additional analysis was conducted excluding cancer-related symptomatic treatment management (such as ascites tapping, diuretic agents), to reflect the impact of subsequent therapies. In this analysis, the proportion of subjects who received subsequent therapy/ies was similar between the nivolumab and placebo groups, respectively: 31.2% and 31.3%. A sensitivity analysis censoring at start of subsequent therapy was performed, and a survival benefit was observed in the nivolumab arm compared to placebo (HR: 0.55 (95%CI: 0.42, 0.71)), consistent with the results of the primary analysis (HR: 0.63 (95%CI: 0.51, 0.78)). The use of subsequent therapies is therefore not considered to have had a major impact on study results. Regarding secondary endpoints, based on investigator assessment a rather modest clinical benefit is shown. PFS data (76.7% events in nivolumab arm and 89.0% events in placebo arm) showed a HR of 0.60 (95%CI 0.49, 0.75) and a difference in median PFS time of 0.16 months (1.61 months vs. 1.45 months). Again, medians might not be the best marker of benefit as K-M curves show an initial similar sharp decline followed by a split of curves after the first 50% of population experienced PFS events. Once curves separate rate differences remain in the range of 7-13%. This profile of PFS curve has been previously shown in other nivolumab developments, with rapid decline in the PFS curves and a benefit in the last portion of the curve indicative of disproportional HRs among the studied population.

  ORR per investigator assessment in the ITT population, showed an ORR of 9.1% (95% CI 6.2, 12.7) in the nivolumab arm (all of them PR) compared to 0% in the nivolumab arm. SD was achieved by 23.6% of patients in the nivolumab arm and 2.2% in the placebo arm. Responses were durable, median DoR was 9.53 months.

  ORR was slightly higher in nivolumab arm for the response-evaluable subgroup of patients (measurable disease at baseline) being 11.2% in nivolumab arm and 0% in placebo.

Median duration of treatment was strikingly short within this ONO trial, 1.92 months (range: 0 - 19.5 months) in the nivolumab group and 1.05 months (range: 0 - 20.5 months) in the placebo group. Although this is consistent with a rapidly progressing tumour such as gastric cancer, this points out that patients returning to first tumour assessment had unequivocal disease progression (even treatment beyond progression was permitted at investigator´s criteria). In addition a time to tumour response of 1.61 months (range: 1.4 to 7.0 months) further calls into question whether immunotherapy could have time enough to exert its clinical effect. This question is particularly relevant in view of the fact that an Asian population was studied, which is known to have better prognosis than non-Asian patients. Whether non-Asian patients will benefit to the same extent from treatment with nivolumab is still an uncertainty that has not been fully clarified by the company.

Subgroup analysis stress relevant results in certain subgroups of population, i.e. data appears to be driven by the subgroup of patients who received at least 4 prior regimens and in this regard it is not clear what the proportion of treatment lines can be considered outside the (neo)adjuvant setting. This may be important as in clinical practice patients that had received 2 prior treatment lines could still be benefited from chemotherapy regimens. The applicant detected significant interactions between nivolumab treatment and the number of lines of prior treatment, as well as between nivolumab treatment and age and sex (refer to forest plot, and Kang et al. 2017, Lancet, Published Online October 6, 2017). Patients who had received 2 or 3 prior therapies appeared to have a considerably less relevant OS benefit. These findings point towards an issue with internal consistency of efficacy results. According to histological subtype, patients with diffuse type (factor of worse prognosis) appear to be less benefited from nivolumab therapy and this would be also consistent with the lesser benefit observed for younger and female population, as in this two populations the frequency of the diffuse type is higher. If considering that a modest treatment effect is observed for the overall population, it cannot be assumed that a clinically relevant effect is still maintained in those subgroups of populations were treatment differences are less evident.

Additionally, the Applicant was requested to provide subgroup analyses from study ONO-4538-12 (for OS, PFS and ORR) by stage at primary diagnosis. Although most patients in both study arms presented with metastatic disease and this is thus the most numerous subgroup (53.6% of patients in nivolumab arm and 49.7% of patients in placebo arm), OS data according to disease stage tend to show better outcomes for earlier disease stages compared to the metastatic setting. Although decreasing outcomes are observed when disease stage increases, a response rate of 10.0% is still observed for patients with stage IV. Analyses are presented by PD-L1 expression, which is based on tumour cell expression. Up-regulation at myeloid level is known to be a relevant factor in GC cancer (Kelly. Am Soc Clin Oncol Educ Book. 2017). Importantly, patients in this gastric cancer/GEJ indication were recruited irrespective of PD-L1 expression at baseline and the collection of pre-study or baseline tumour tissue samples was optional in the protocol.

Less than half of population had PD-L1 tested at baseline. The sample size of patients with PD-L1 ≥1 is limited to 16 patients in the nivolumab arm (12.3%) and 10 patients in the placebo arm (16.1%). 114 and 52 patients had PD-L1 expression < 1 respectively. Although results in terms of OS appear to point out in right direction, i.e. a possible better result in patients with PD-L1 ≥1 (HR 0.51; 95% CI: 0.21, 1.25) compared to PD-L1 <1 patients (HR 0.72; 95% CI: 0.49, 1.00) the extremely limited simple size of the PD-L1≥1 subgroup prevents drawing any reliable conclusion about the role that PD-L1 expression may have on gastric cancer. There are indications that PD-L1 status affects response to treatment with PD-L1 inhibitors such as nivolumab. The currently presented data on PD-L1 expression in relation to response are not adequate, because the scoring of PD-L1 expression was based only on expression of PD-L1 on tumour cells, while the scoring of PD-L1 expression on tumour-associated/infiltrating immune cells would provide valuable information. This especially since there is little PD-L1 expressed on the cancer cells of

upper gastrointestinal tumours, but rather expression occurs predominantly on infiltrating myeloid cells at the invasive margin (Kelly. Am Soc Clin Oncol Educ Book. 2017). An important uncertainty is related to expected benefit in subgroups of patients according to molecular subtype of gastric cancer. Gastric cancer is a heterogeneous disease at the molecular level, and there is accumulating evidence that there are broadly four molecular subtypes of gastric cancer: Epstein–Barr virus-positive tumours, microsatellite instable tumours, genomically stable tumours, and tumours with chromosomal instability (The Cancer Genome Atlas Research Network Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202–209). In relation to the treatment effect of nivolumab as well as other PD-1 inhibitors, there is evidence that in particular microsatellite instable tumours are likely to respond to treatment. The applicant did not present data on MSI status in relation to response to treatment for patients in the main study, although the MSI data from the supportive study CA209032 suggested that indeed patients with MSI tumours might be more likely to experience clinical benefit (although patient numbers were small). Only a small proportion of patients in the main study responded to treatment with a durable response (11%). Of interest, the size of this proportion of patients responding to treatment with a durable response is comparable with the expected proportion of patients with MSI-high status likely to respond to treatment. Therefore, and because there is accumulating evidence that MSI status is a key predictive biomarker for response to PD-1 inhibitors such as nivolumab, it is considered that obtaining data on MSI status in relation to response to nivolumab in gastric cancer is key for further assessment of the benefit/risk of nivolumab in gastric cancer. While data according to MSI has not been provided for the ONO trial, tumour tissue was collected per protocol.

Only 83 patients from nivo arm and 36 patients from placebo arm had evaluable results for MSI, whereas 17 patients had unknown results for MSI test. Only 1 subject in the nivolumab arm (1.2%) and 3 in the placebo arm (8.3%) had MSI-H status and the remaining subjects had MSS. The single patient that had MSI-H in nivo arm had also PD-L1 positive status and 2 out of 3 patients in the placebo arm showed both MSI-H and PD-L1 positive status. The extremely limited sample size of patients with MSI-H status (that may be due to the low percentage of patients evaluable) precludes from drawing any reliable conclusion in this regard.

Results for the subset of GC ≥ 2nd line (n=42) from trial **CA209032** showed and ORR of 7.1% (95%CI 1.5, 19.5) as assessed by BIRC with median DOR not reached and a median TTR of 1.38 months.

PFS data (BIRC; 78.6% of events) show a median PFS time of 1.49 months (95% CI 1.31, 2.76) and a median OS of 8.97 (95% CI 3.35, 14.88) months was observed. OS rates at 6 months and 12 months were 57.4% and 45.1 % respectively.

Results in the subset of 32 patients that had received at least 2 prior regimens in the metastatic setting (excluding prior therapies in the (neo)adjuvant settings) showed consistent results to that of the overall (n=42) population. The median OS for these 32 subjects was 8.48 months (95% CI: 3.06, 15.01). The survival rate at 3 months was 71.3% (95% CI: 52.1, 83.9), 6 months 56.2 % (95% CI: 36.4, 72.0), and 12 months 43.3% (95% CI: 24.3, 60.9%).

The median PFS in these 32 subjects was 1.45 months (95% CI: 1.25, 2.56). The PFS rate at 3 and 6 months was 23.4% (95% CI: 9.7, 40.5%), 11.7% (95% CI: 3.0, 26.9).

In CA209032 subgroup of 32 subjects, the ORR per BICR was 6.3% (95% CI: 0.8, 20.8%), 2 subjects achieved PR, and DOR for these 2 subjects was 2.8 and 6.9+ months.

Regarding subgroups, data seems to be driven by the subgroup of patients with GEJ cancer for which an ORR of 11.5% was observed vs. 0% in patients with GC.

Most subjects (71.4%) had quantifiable PD-L1 at baseline, of them 33.3% (n=10) has PD-L1≥1 and

66.7% (n=20) had PD-L1≤1. ORR was 20% in PD-L1≥1 patients vs. 0% in PD-L1≤1. Median OS were 12.91 months vs. 7.72 months.

Exploratory analyses have been conducted according to MSI status for the whole GC cohort (n=59) of trial CA209032. 7 subjects had MSI-H status, 18 subjects had non-MSI-H status, and for 34 subjects the MSI status was unknown. Median OS values were: 14.75 months (95% CI: 1.51, N.A.), 6.49 months (95% CI: 2.96, 12.42), and 5.03 months (95% CI: 2.76, 16.16) in the MSI-H, non MSI-H, and MSI unknown subgroups, respectively. Though merely exploratory this could be suggesting a potential better benefit in MSI-H patients. Having said that, the applicant was asked to submit data for the subset of subset of GC ≥ 2nd line (n=42) from GC cohort of trial CA209032. 5/42 patients had MSI-H, 14/42 patients had non MSI-H and 23 had MSI unknown status. Despite that the limited sample size is of concern, better outcomes seem to be observed for patients with MSI-H. Further data would be needed to confirm such findings.

It is considered that the interpretability of the supportive study is limited by the small number of patients, and the fact that the studied phase I population is likely not representative of the to-be-treated EU population. Moreover, the external validity of the efficacy results could be questioned, as the fact that there were only 2 were responders in the n = 32 cohort seems in conflict with the long median OS of 8.48 months when compared to the median OS of 5.26 months for the nivolumab arm of ONO-4538-12. Also, of the 16 GC patients in the n = 42 cohort none responded to therapy and only 6 (37.5%) had SD as BOR. Nevertheless, median OS in this group was 7.72 months which is much longer than can be expected for patients with GC or GEJ cancer that have failed two prior lines of systemic treatment and are (considered to be) non-responders to 3rd-line treatment.

Extrapolation of results between Asian and non-Asian patients

A key uncertainty is the fact that no comparative data are available for the non-Asian population. The single comparative study was performed exclusively in Asian patients, mainly from Korea and Japan. The current benefit/risk assessment therefore almost completely relies on extrapolation of the efficacy and safety results from this trial, performed in Asian patients, to the non-Asian patient population. This is problematic, because gastric/gastroesophageal adenocarcinoma differs in a number of relevant aspects between non-Asian and Asian patients.

It is well known that prognosis of Asian patients with gastric cancer is better than prognosis of non-Asian patients. This is thought to be related to different factors, including differences in disease biology, differences in treatment patterns, and differences in methods for screening/diagnosis. For example, in Europe approximately 50% of the patients have advanced disease at the time of diagnosis, while this is ~20% in Asian patients (likely due to national screening programmes for gastric cancer in Asia).

Furthermore, due to better prognosis, Asian patients are treated with more lines of therapy for advanced disease than patients in the West. For example, in Japan almost all patients with metastatic gastric cancer receive second-line therapy, and more than half of patients receive three lines of therapy. In Europe, on the other hand, only half of the patient population is offered second-line treatment on progression after first-line therapy, and only a small proportion of the patients receive third-line therapy. This difference is also reflected by the fact that the non-Asian patients in study CA209032 were less pre-treated compared with the Asian patients in study ONO-4538-12.

Furthermore, there are differences in the initial tumour localisation between regions, as GEJ cancer is much more common in non-Asian patients compared with Asian patients. This is also reflected in the differences between the pivotal and the supportive study.

The observed differences in outcome between non-Asian and Asian patients are likely to be related to

differences in molecular disease biology, as shown in different studies. Importantly, the differences between Asian and non-Asian patients are not without consequences for drug development. In fact, there is a history of drugs tested in phase III which showed large differences in treatment effect between Asian and non-Asian patients (described below). This illustrates that although gastric cancer is a global disease, there are strong indications that response to treatment is not uniform. The previously observed regional/ethnic differences in drug response are highly relevant in the current extension of indication for nivolumab, since they bring into question to which extent the benefits observed for nivolumab in the comparative study in Asian patients can be extrapolated to the non-Asian patient population.

The MAH states that no meaningful differences in clinical activity were observed between Asians and non-Asians with advanced or metastatic GC/GEJ cancer treated with another anti-PD-1 agent, pembrolizumab. However, recently published data contradicts this statement (Fuchs et al. JAMA Oncol. 2018). In a cohort of patients with previously treated (≥2 prior therapies) advanced GC/GEJ where both Asian and non-Asian patients were enrolled, overall median OS was 5.6 months, but more importantly, median OS for the 200 patients of white race was 4.6 months versus 8.4 months for the 41 patients of Asian race. This information suggests the previously observed regional/ethnic differences in drug response in gastric cancer patients are also relevant for immunotherapy (i.e. that the prognosis of Asian patients with gastric cancer is better than prognosis of non-Asian patients and/or that response to treatment is not uniform). As stated in the first round, this brings into question to which extent the benefits observed for nivolumab in the comparative study in Asian patients can be extrapolated to the non-Asian patient population.

The presented real-world data not only evidence some differences in clinical practice across regions but mainly reinforce the idea that patients receiving 4L treatment are very scarce (in the real world).

Taking into account previous experience in gastric cancer, it seems premature and risky to assume the lack of differences between Asian and non-Asian population. Teysuno, a combination of tegafur, gimeracil and oteracil approved as treatment of advanced gastric cancer when given in combination with cisplatin, failed to demonstrate survival superiority for the treatment of patients with advanced gastric cancer in a trial conducted in non-Asian population and the study was switched to a non-inferiority trial. In two prior studies, carried out in a Japanese population (JCOG 9912 and SPIRITS), Teysuno demonstrated superiority vs. the comparator, however this was not the same in non-Asian population. Furthermore, a phase III trial with bevacizumab as first-line treatment of advanced gastric or gastro-oesophageal adenocarcinoma in combination with chemotherapy conducted in Asia, Europe and North and South America, showed that efficacy was strongly heterogeneous across regions, e.g., the HR for OS was 0.97 in Asia, versus 0.63 and 0.85 in America and Europe, respectively). Conversely, in the LOGiC trial, benefit from lapatinib was observed in Asians (HR for OS 0.68) but not in non-Asians (HR for OS 1.04). These examples illustrate that although gastric cancer is a global disease, there are strong indications that response to treatment is not uniform. This brings into question to which extent the results for the current pivotal study in an Asian population can be extrapolated to patients of non-Asian race.

All in all, taking into account that gastric or gastro-oesophageal adenocarcinoma is a heterogeneous disease across regions, and that it appears likely that shorter life expectancy can be expected for the to-be-treated non-Asian population, further discussion is warranted whether results from the ONO-4538-012 can support extrapolation to non-Asian population.

A difference in median survival of 1.12 months (HR: 0.63; 95%CI 0.51, 0.78) and differences around 10-15% in long-term OS rates were observed. The clinical relevance of effect appears even less impressive in terms of PFS (0.16 month-difference in median PFS and HR 0.60 (IC 95% 0.49-0.75) and

ORR (9%)). This benefit of doubtful clinical relevance could only be seen within the context of a last-line therapy where no other treatment options are available and further discussion in this regard is awaited.

It seems unlikely that the modest observed effect can still be considered of relevance in a worst-case scenario as some relevant subgroups such as patients with diffuse histology (younger patients, women) showed lower efficacy in the pivotal trial.

Last but not least, it was not possible to identify a population that could more likely benefit from nivolumab therapy based on immune features. No firm conclusions can be drawn regarding the efficacy of nivolumab according to PD-L1 expression. In this regard, similar molecules have focused its clinical development on a pure PD-L1+ population and exploratory data from nivolumab development appears to suggest the potential better outcomes in PD-L1≥1 patients. In addition, data according to MSI could potentially be key in identifying a population more likely to benefit from nivolumab therapy, however no firm conclusions can be drawn based on the little available data on MSI status or MSI status combined with PD-L1 obtained in the nivolumab clinical trials.

Apart from the differences in disease highlighted above, there are several other potential differences that appear not to be relevant for nivolumab treatment, such as potential PK differences (indicated by the applicant), as metabolism of MoAb are less likely to be sensitive to extrinsic or intrinsic ethnic factors.

2.4.4. Conclusions on the clinical efficacy

Data in support of the present application mainly comes from Asian patients. Based on historical series as well as previous drug development experience in GC indication, it appears likely that shorter life expectancy can be expected for non-Asian population - as a result of e.g. differences in disease biology, patients' characteristics, and variability in treatment practice - and in this regard the limited benefit of results from the ONO-4538-012 can hardly support extrapolation to the non-Asian population.

Contrary to this assumption better outcomes in terms of OS were observed in the supportive study CA209032 in a GC cohort of non-Asian population included within this submission, however the fact that this was a small-sized and potentially selected population (i.e. patient that generally have better prognosis than patients not eligible for a phase I trials) hampers drawing conclusions regarding the benefit of nivolumab in non-Asian patients. Moreover, the external validity of the efficacy results of study CA209032 could be questioned.

It seems unlikely that the modest observed effect (from an absolute point of view, although better from a relative perspective) can still be considered of relevance in a worst-case scenario as some relevant subgroups such as patients who had received less than 4 lines of therapy and patients with diffuse histology (younger patients, women) showed lower efficacy in the pivotal trial.

Last but not least, based on available data it was not possible to identify a population that could more likely benefit from nivolumab therapy based on immune features. No firm conclusions can be drawn regarding the efficacy of nivolumab according to PD-L1 expression. In this regard, similar molecules have focused its clinical development on a pure PD-L1+ population and exploratory data from nivolumab development appears to suggest the potential better outcomes in PD-L1≥1 patients. In addition, no conclusive data according to MSI status, which are considered key to determine B/R, has been provided for the pivotal study, strongly hampering assessment of which types of gastric cancer patients do and do not respond to therapy with nivolumab.

2.5. Clinical safety

Introduction

Safety data from studies ONO-4538-12 (CA209316)1 and CA209032, which support the use of nivolumab (BMS-936558) monotherapy at the recommended dose and schedule of 3 mg/kg administered as an intravenous (IV) infusion every 2 weeks (Q2W) for the treatment of adults with advanced or recurrent gastric cancer (GC) or gastroesophageal junction (GEJ) cancer after 2 or more prior systemic therapies are provided.

Safety data across ONO-4538-12 and CA209032, respectively, was not pooled due to different study designs (randomised control vs single arm), different primary endpoints (overall survival vs objective response rate), and different subject populations (evaluable disease vs measurable disease and different prior treatment [≥ 2 vs ≥ 1 prior treatment]), as well as the differences in AE collection and follow-up (28 days past last dose vs 100 days past last dose). No formal statistical inter-study comparison was performed.

Table 50: Summary of Safety Results in ONO-4538-12 and CA209039 (All Nivolumab Monotherapy Subjects with GC/GEJ Cancer and at Least 2 Prior Regimens)

	ONO-4538-12 (A)						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
DEATHS									
NUMBER OF SUBJECTS WHO DIED (%)	226 (68.5)			140 (87.0)			25 (59.5)		
WITHIN 28 DAYS OF LAST DOSE (B)	25 (7.6)			32 (19.9)			NA		
WITHIN 30 DAYS OF LAST DOSE	NA			NA			6 (14.3)		
WITHIN 100 DAYS OF LAST DOSE	NA			NA			18 (42.9)		
STUDY DRUG TOXICITY	NA (C)			NA (C)			0		
	Any Grade	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
ALL AES	300 (90.9)	137 (41.5)	16 (4.8)	135 (83.9)	63 (39.1)	18 (11.2)	41 (97.6)	19 (45.2)	5 (11.9)
MOST FREQUENTLY REPORTED AES (≥ 20% OF SUBJECTS IN ANY GROUP)									
ABDOMINAL PAIN	70 (21.2)	14 (4.2)	0	39 (24.2)	6 (3.7)	0	14 (33.3)	2 (4.8)	0
DECREASED APPETITE	65 (19.7)	9 (2.7)	0	44 (27.3)	8 (5.0)	0	13 (31.0)	3 (7.1)	0
NAUSEA	65 (19.7)	1 (0.3)	0	23 (14.3)	2 (1.2)	0	16 (38.1)	0	0
DIARRHOEA	58 (17.6)	4 (1.2)	0	15 (9.3)	1 (0.6)	0	12 (28.6)	3 (7.1)	0
PRURITUS	53 (16.1)	0	0	15 (9.3)	0	0	11 (26.2)	0	0
ANAEMIA	43 (13.0)	38 (11.5)	0	23 (14.3)	19 (11.8)	0	13 (31.0)	4 (9.5)	0
CONSTIPATION	47 (14.2)	1 (0.3)	0	10 (6.2)	0	0	14 (33.3)	0	0
VOMITING	45 (13.6)	4 (1.2)	0	18 (11.2)	3 (1.9)	0	15 (35.7)	1 (2.4)	0
PYREXIA	34 (10.3)	3 (0.9)	0	19 (11.8)	1 (0.6)	0	12 (28.6)	0	0
FATIGUE	32 (9.7)	3 (0.9)	0	28 (17.4)	5 (3.1)	0	25 (59.5)	3 (7.1)	0
ARTHRALGIA	6 (1.8)	0	0	1 (0.6)	0	0	9 (21.4)	0	0
DRUG-RELATED AES	141 (42.7)	34 (10.3)	4 (1.2)	43 (26.7)	7 (4.3)	2 (1.2)	27 (64.3)	6 (14.3)	0
MOST FREQUENTLY REPORTED DRUG-RELATED AES (≥ 10% OF SUBJECTS IN ANY GROUP)									
PRURITUS	30 (9.1)	0	0	9 (5.6)	0	0	9 (21.4)	0	0
DIARRHOEA	23 (7.0)	2 (0.6)	0	3 (1.9)	0	0	6 (14.3)	1 (2.4)	0
FATIGUE	18 (5.5)	2 (0.6)	0	9 (5.6)	2 (1.2)	0	14 (33.3)	0	0
DECREASED APPETITE	16 (4.8)	4 (1.2)	0	7 (4.3)	1 (0.6)	0	5 (11.9)	0	0
NAUSEA	14 (4.2)	0	0	4 (2.5)	0	0	5 (11.9)	0	0
PYREXIA	8 (2.4)	1 (0.3)	0	3 (1.9)	0	0	5 (11.9)	0	0
ARTHRITIS	3 (0.9)	0	0	0	0	0	5 (11.9)	0	0
ALL SAES	131 (39.7)	91 (27.6)	16 (4.8)	75 (46.6)	47 (29.2)	18 (11.2)	24 (57.1)	14 (33.3)	5 (11.9)
DRUG-RELATED SAES	33 (10.0)	21 (6.4)	4 (1.2)	8 (5.0)	4 (2.5)	2 (1.2)	3 (7.1)	1 (2.4)	0

	ONO-4538-12 (A)						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ALL AES LEADING TO DC	23 (7.0)	13 (3.9)	6 (1.8)	12 (7.5)	9 (5.6)	3 (1.9)	3 (7.1)	2 (4.8)	0
DRUG-RELATED AES LEADING TO DC	9 (2.7)	4 (1.2)	3 (0.9)	4 (2.5)	3 (1.9)	1 (0.6)	1 (2.4)	0	0
DRUG-RELATED SELECT ADVERSE EVENTS, BY CATEGORY									
ENDOCRINE	16 (4.8)	4 (1.2)	0	1 (0.6)	0	0	4 (9.5)	1 (2.4)	0
GASTROINTESTINAL	23 (7.0)	3 (0.9)	0	4 (2.5)	0	1 (0.6)	7 (16.7)	1 (2.4)	0
HEPATIC	18 (5.5)	5 (1.5)	0	5 (3.1)	1 (0.6)	0	2 (4.8)	2 (4.8)	0
PULMONARY	7 (2.1)	2 (0.6)	0	0	0	0	2 (4.8)	0	0
RENAL	1 (0.3)	0	0	0	0	0	0	0	0
SKIN	51 (15.5)	0	0	13 (8.1)	0	0	10 (23.8)	0	0
HYPERSENSITIVITY/ INFUSION REACTIONS	3 (0.9)	0	0	0	0	0	1 (2.4)	0	0

DC = discontinuation; NA = not available.
MedDRA Version: 20.0, CTC Version 4.0 (all AEs in ONO-4538-12 and CA209032, except endocrine select AEs in CA209032)
Analysis generated from integrated database.

ONO-4538-12:
For ONO-4538-12, includes events reported between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of the post-treatment observation period.
CA209032: MedDRA Version 18.1, CTC Version 4.0 (endocrine select AEs)
For CA209032, includes events reported between first dose and 30 days after last dose of study therapy. Crossover subjects in CA209032 are truncated at the first dose date of crossover period.
(A) SAF set consists of all subjects given at least one dose of the investigational product.
(B) Deaths occurring in ONO-4538-12 between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of subsequent anti-cancer therapy after the end of treatment period were tabulated.

Source: Refer to Table G.85-SCS (AEs), Table G.86-SCS (drug-related AEs), Table G.87-SCS (AEs leading to discontinuation), Table G.88-SCS (drug-related AEs leading to discontinuation), Table G.89-SCS (SAEs), Table G.90-SCS (drug-related SAEs), and Table G.92-SCS (sdrug-related select AEs) of SCS, Module 2.7.4; refer to Appendix G.147-EUSCS (select AEs, ONO-4538-12), Appendix G.149-EUSCS (endocrine select AEs, ONO-4538-12) in Appendix 2 of SCS, Module 2.7.4; refer to Appendix G.153-EUSCS (deaths, CA209032), Appendix G.160-SCS (drug-related select AEs, CA209032), and Appendix G.162-SCS (drug-related endocrine select AEs, CA209032) in Appendix 3 of SCS, Module 2.7.4; refer to Table 14.3.1.1-27 (deaths, ONO-4538-12) in ONO-4538-12 Final CSR

Patient exposure

As of the ONO-4538-12 clinical database cut-off on 13-Aug-2016 and CA209032 database lock (DBL) dated 24-Mar-2016, the majority of nivolumab monotherapy-treated subjects in the ONO-4538-12 (79.7%) and CA209032 studies (79.7%, GC Cohort; 73.8% of subjects with GC/GEJ cancer and ≥ 2 prior regimens) received ≥ 90% of the planned dose intensity.

ONO-4538-12

Nivolumab was administered at 3 mg/kg monotherapy as an IV infusion Q2W. The median duration of treatment was 1.92 months (range: 0 to 19.5 months) in the nivolumab group and 1.05 months (range: 0 to 20.5 months) in the placebo group. The median cumulative dose was 14.49 mg/kg (range: 3.0 to 125.2 mg/kg) and the median relative dose intensity was 96.76% (range: 45.6% to 112.6%) in the nivolumab group.

2.1% subjects in the nivolumab group and no subjects in the placebo group experienced at least 1 infusion interruption. Reasons for infusion interruptions included AE (6 subjects) and "other" reason (5 subjects) in the nivolumab group. No subjects in the nivolumab group or the placebo group experienced an infusion rate reduction. 50.9% of subjects in the nivolumab group and 40.4% of subjects in the placebo group experienced a dose delay. Most subjects with dose delay experienced only 1 delay (30.3% and 31.1% in the nivolumab group or the placebo group, respectively).

CA209032

Nivolumab was administered at 3 mg/kg monotherapy as an IV infusion Q2W. The median duration of nivolumab monotherapy was 2.33 months. The majority (73.8%) of nivolumab treated subjects received ≥ 90% of the planned dose intensity.

The median number of nivolumab doses received and median cumulative dose were median 5.0 doses [range: 1 - 31]; median cumulative dose, 15.00 mg/kg).

No infusion interruptions occurred in treated subjects. Most subjects received all doses of study medication without an infusion rate reduction or dose delay.

Adverse events

Common Adverse events

ONO-4538-12

A total of 330 subjects received nivolumab monotherapy, and 161 subjects received placebo. Overall, a similar frequency of AEs between groups was observed (Table 41).

In the nivolumab group, the most common (incidence ≥ 10%) AEs reported were abdominal pain (21.2%), nausea (19.7%), decreased appetite (19.7%), diarrhoea (17.6%), pruritus (16.1%), constipation (14.2%), vomiting (13.6%), anaemia (13.0%), pyrexia (10.3%), and AST increased (10.0%).

In the placebo group, the most common (incidence ≥ 10%) AEs reported were decreased appetite (27.3%), abdominal pain (24.2%), fatigue (17.4%), nausea and anaemia (each 14.3%), pyrexia (11.8%), and vomiting (11.2%).

In each group, the most common (incidence ≥ 5%) worst Grade 3-4 AE reported was anaemia (nivolumab monotherapy: 11.5%, placebo: 11.8%). The majority of Grade 5 AEs were due to disease progression.

AEs of any grade with a higher incidence in the nivolumab group than in the placebo group (difference ≥ 5%) were nausea (19.7% vs 14.3%), diarrhoea (17.6% vs 9.3%), pruritus (16.1% vs 9.3%), constipation (14.2% vs 6.2%), rash (9.4% vs 3.7%), and blood alkaline phosphatase (ALP) increased (7.6% vs 1.9%). AEs with a lower incidence in the nivolumab group than in the placebo group (difference ≥ 5%) were decreased appetite (19.7% vs 27.3%) and fatigue (9.7% vs 17.4%).

Study CA209032 (GC Cohort)

In the subset of 42 subjects with GC/GEJ cancer and ≥ 2 prior regimens, the frequencies of any grade (97.6%) and worst Grade 3-4 AEs (45.2%) were comparable with ONO-4538-12 (90.9% and 41.5%, respectively).

The most frequently reported AEs (incidence ≥ 20%) were fatigue (59.5%), nausea (38.1%), vomiting (35.7%), abdominal pain and constipation (both 33.3% of subjects), decreased appetite and anaemia (both 31.0% of subjects), diarrhoea and pyrexia (28.6%), pruritus (26.2%), and arthralgia (21.4%). The most common types of AEs in CA209032 were similar to those in ONO-4538-12, though at generally higher frequencies.

Grade 3-4 AEs (worst grade, regardless of causality) were reported in 45.2% of subjects. The most frequently reported worst Grade 3-4 AEs (incidence ≥ 5%) were ascites and anaemia (both 9.5% of subjects), and fatigue, decreased appetite, increased aspartate aminotransferase (AST) and diarrhoea (7.1% for each).

All Grade 5 AEs were due to malignant neoplasm progression.

Table 51: Summary of Any Adverse Events by Worst CTC Grade with 5% Cutoff - ONO-4538-12 and CA209032 (All Nivolumab Monotherapy Treated Subjects with GC or GEJ Cancer and at Least 2 Prior Regimens)

	ONO-4538-12						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
INVESTIGATIONS	100 (30.3)	38 (11.5)	0	34 (21.1)	11 (6.8)	0	12 (28.6)	4 (9.5	0
ASPARTATE AMINOTRANSFERASE INCREASED	33 (10.0)	12 (3.6)	0	11 (6.8)	4 (2.5)	0	4 (9.5)	3 (7.1	0
BLOOD ALKALINE PHOSPHATASE INCREASED	25 (7.6)	12 (3.6)	0	3 (1.9)	3 (1.9)	0	4 (9.5)	0	0
ALANINE AMINOTRANSFERASE INCREASED	22 (6.7)	8 (2.4)	0	9 (5.6)	3 (1.9)	0	4 (9.5)	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	18 (5.5)	8 (2.4)	0	3 (1.9)	2 (1.2)	0	1 (2.4)	0	0
WEIGHT DECREASED	18 (5.5)	1 (0.3)	0	8 (5.0)	0	0	5 (11.9)	0	0
BLOOD BILIRUBIN INCREASED	17 (5.2)	14 (4.2)	0	4 (2.5)	4 (2.5)	0	2 (4.8)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	96 (29.1)	0	0	24 (14.9)	0	0	15 (35.7)	0	0
PRURITUS	53 (16.1)	0	0	15 (9.3)	0	0	11 (26.2)	0	0
RASH	31 (9.4)	0	0	6 (3.7)	0	0	4 (9.5)	0	0
HYPERHIDROSIS	0	0	0	0	0	0	3 (7.1)	0	0
INFECTIONS AND INFESTATIONS	72 (21.8)	19 (5.8)	1 (0.3)	39 (24.2)	13 (8.1)	4 (2.5)	11 (26.2)	7 (16.7)	0
PNEUMONIA	12 (3.6)	5 (1.5)	1 (0.3)	8 (5.0)	5 (3.1)	1 (0.6)	4 (9.5)	2 (4.8)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	63 (19.1)	7 (2.1)	2 (0.6)	27 (16.8)	5 (3.1)	1 (0.6)	21 (50.0)	5 (11.9)	0
DYSPNOEA	22 (6.7)	2 (0.6)	1 (0.3)	7 (4.3)	0	0	7 (16.7)	2 (4.8)	0
COUGH	14 (4.2)	0	0	4 (2.5)	0	0	4 (9.5)	0	0
PLEURAL EFFUSION	6 (1.8)	2 (0.6)	0	8 (5.0)	1 (0.6)	0	3 (7.1)	0	0
PNEUMONITIS	4 (1.2)	1 (0.3)	0	0	0	0	3 (7.1)	0	0
PULMONARY EMBOLISM	1 (0.3)	1 (0.3)	0	1 (0.6)	0	1 (0.6)	4 (9.5)	2 (4.8)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	62 (18.8)	6 (1.8)	0	21 (13.0)	2 (1.2)	0	18 (42.9)	0	0
BACK PAIN	18 (5.5)	3 (0.9)	0	7 (4.3)	2 (1.2)	0	8 (19.0)	0	0
MUSCULOSKELETAL PAIN	10 (3.0)	0	0	3 (1.9)	0	0	3 (7.1)	0	0
MYALGIA	10 (3.0)	0	0	2 (1.2)	0	0	7 (16.7)	0	0
ARTHRALGIA	6 (1.8)	0	0	1 (0.6)	0	0	9 (21.4)	0	0
FLANK PAIN	5 (1.5)	0	0	5 (3.1)	0	0	3 (7.1)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	46 (13.9)	39 (11.8)	0	27 (16.8)	20 (12.4)	2 (1.2)	13 (31.0)	4 (9.5)	0
ANAEMIA	43 (13.0)	38 (11.5)	0	23 (14.3)	19 (11.8)	0	13 (31.0)	4 (9.5)	0
NERVOUS SYSTEM DISORDERS	46 (13.9)	3 (0.9)	0	18 (11.2)	3 (1.9)	0	19 (45.2)	2 (4.8)	0
DIZZINESS	10 (3.0)	1 (0.3)	0	8 (5.0)	2 (1.2)	0	2 (4.8)	0	0
HEADACHE	8 (2.4)	0	0	3 (1.9)	0	0	5 (11.9)	0	0
PSYCHIATRIC DISORDERS	28 (8.5)	3 (0.9)	1 (0.3)	15 (9.3)	0	0	8 (19.0)	0	0
INSOMNIA	21 (6.4)	1 (0.3)	0	14 (8.7)	0	0	5 (11.9)	0	0
DEPRESSION	4 (1.2)	0	0	1 (0.6)	0	0	3 (7.1)	0	0
ENDOCRINE DISORDERS	17 (5.2)	1 (0.3)	0	1 (0.6)	0	0	5 (11.9)	1 (2.4)	0
HYPOTHYROIDISM	14 (4.2)	0	0	1 (0.6)	0	0	3 (7.1)	1 (2.4)	0
HYPERTHYROIDISM	2 (0.6)	0	0	0	0	0	4 (9.5)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	17 (5.2)	9 (2.7)	4 (1.2)	11 (6.8)	7 (4.3)	2 (1.2)	10 (23.8)	2 (4.8)	5 (11.9)
MALIGNANT NEOPLASM PROGRESSION	7 (2.1)	3 (0.9)	3 (0.9)	4 (2.5)	3 (1.9)	1 (0.6)	7 (16.7)	2 (4.8)	5 (11.9)
TUMOUR PAIN	3 (0.9)	1 (0.3)	0	1 (0.6)	0	0	3 (7.1)	0	0
UNASSIGNED	5 (1.5)	1 (0.3)	0	8 (5.0)	3 (1.9)	0	0	0	0
UNASSIGNED	5 (1.5)	1 (0.3)	0	8 (5.0)	3 (1.9)	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
For CA209032, includes events reported between first dose and 30 days after last dose of study therapy.
For ONO-4538-12, includes events reported between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Table G.85-SCS

Drug-related AEs

ONO-4538-12

Drug-related AEs were reported in 42.7% of subjects in the nivolumab group and 26.7% of subjects in the placebo group (Table 42).

- Common drug-related AEs (incidence ≥ 5%) reported in the nivolumab group were pruritus (9.1%), diarrhoea (7.0%), rash (5.8%), and fatigue (5.5%).
- Common drug-related AEs (incidence ≥ 5%) reported in the placebo group were fatigue and pruritus (each 5.6%).

Drug-related AEs with a higher incidence in the nivolumab group than in the placebo group (difference ≥5%) included diarrhoea (7.0% vs 1.9%). There were no drug-related AEs with a lower incidence in the nivolumab group than in the placebo group (difference ≥5%).

Drug-related worst Grade 3-4 AEs were reported in 10.3% and 4.3% of subjects in the nivolumab monotherapy and placebo groups, respectively. The most frequently reported worst Grade 3-4 AEs in the nivolumab group was decreased appetite (4 subjects, 1.2%) and in the placebo group was fatigue (2 subjects, 1.2%).

Study CA209032 (GC Cohort)

In the subset of 42 subjects with GC/GEJ cancer and ≥2 prior regimens, any-grade drug-related AEs were reported in 64.3% of subjects (Table 42).

- The most frequently reported drug-related AEs (frequency ≥5%) were fatigue (33.3%), pruritus (21.4%), diarrhea (14.3%), pyrexia, decreased appetite, nausea, and arthralgia (each 11.9%), rash and vomiting (each 9.5%), and constipation, hyperthyroidism, and myalgia (each 7.1%).

Worst Grade 3-4 drug-related AEs were reported in 14.3% of subjects. The most frequently reported worst Grade 3-4 drug-related AE was increased AST (4.8%).

Table 52: Summary of Drug-related Adverse Events by Worst CTC Grade with 5% Cutoff - ONO-4538-12 and CA209032 (All Nivolumab Monotherapy Treated Subjects with GC or GEJ Cancer and at Least 2 Prior Regimens)

	ONO-4538-12						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	141 (42.7)	34 (10.3)	4 (1.2)	43 (26.7)	7 (4.3)	2 (1.2)	27 (64.3)	6 (14.3)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	55 (16.7)	0	0	13 (8.1)	0	0	11 (26.2)	0	0
PRURITUS	30 (9.1)	0	0	9 (5.6)	0	0	9 (21.4)	0	0
RASH	19 (5.8)	0	0	5 (3.1)	0	0	4 (9.5)	0	0
GASTROINTESTINAL DISORDERS	46 (13.9)	6 (1.8)	0	13 (8.1)	1 (0.6)	1 (0.6)	14 (33.3)	2 (4.8)	0
DIARRHOEA	23 (7.0)	2 (0.6)	0	3 (1.9)	0	0	6 (14.3)	1 (2.4)	0
NAUSEA	14 (4.2)	0	0	4 (2.5)	0	0	5 (11.9)	0	0
VOMITING	6 (1.8)	1 (0.3)	0	0	0	0	4 (9.5)	1 (2.4)	0
CONSTIPATION	1 (0.3)	0	0	1 (0.6)	0	0	3 (7.1)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	44 (13.3)	4 (1.2)	1 (0.3)	17 (10.6)	2 (1.2)	1 (0.6)	18 (42.9)	0	0
FATIGUE	18 (5.5)	2 (0.6)	0	9 (5.6)	2 (1.2)	0	14 (33.3)	0	0
PYREXIA	8 (2.4)	1 (0.3)	0	3 (1.9)	0	0	5 (11.9)	0	0
METABOLISM AND NUTRITION DISORDERS	29 (8.8)	13 (3.9)	0	8 (5.0)	2 (1.2)	0	8 (19.0)	2 (4.8)	0
DECREASED APPETITE	16 (4.8)	4 (1.2)	0	7 (4.3)	1 (0.6)	0	5 (11.9)	0	0
ENDOCRINE DISORDERS	13 (3.9)	1 (0.3)	0	1 (0.6)	0	0	5 (11.9)	1 (2.4)	0
HYPERTHYROIDISM	2 (0.6)	0	0	0	0	0	3 (7.1)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	13 (3.9)	2 (0.6)	0	1 (0.6)	0	0	6 (14.3)	0	0
MYALGIA	6 (1.8)	0	0	1 (0.6)	0	0	3 (7.1)	0	0
ARTHRALGIA	3 (0.9)	0	0	0	0	0	5 (11.9)	0	0

MedDRA Version: 20.0, CTC Version 4.0
For CA209032, includes events reported between first dose and 30 days after last dose of study therapy.
For ONO-4538-12, includes events reported between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Table G.86-SCS

The time to resolution of drug-related AEs was analyzed in both ONO-4538-12 and CA209032 studies. In these exploratory analyses, time to resolution was defined as the longest time from onset to complete resolution or improvement to the grade at baseline among AEs with the same PT experienced by the subjects. Contiguous events with the same PT term were collapsed and considered as a single event. Events that did not resolve were censored at the last known date alive of the subject. Note that grade of baseline events were not systematically collected for ONO-4538-12.

ONO-4538-12

The median duration of drug-related AEs were generally less than 3 months (range of durations, nivolumab group: 0.1 to 88.6+ weeks; placebo group: 0.1 to 78.1+ weeks).

PTs of clinical interest in the nivolumab group include diarrhoea (20/23 subjects resolved in a median of 6.57 weeks; range: 0.1 to 34.7+ weeks), AST increased (9/11 subjects resolved in a median of 4.14 weeks; range: 0.7 to 14.4+ weeks), and rash (8/19 subjects resolved in a median of 30.86 weeks; range: 0.9+ to 58.1 weeks). The maximum time to resolution among events that resolved was reported for an event of alanine aminotransferase (ALT) increased that resolved in 42.9 weeks.

CA209032 (GC Cohort)

The median duration of drug-related AEs were generally less than 3 months (range of durations, nivolumab group: 0.1 to 107.4+ weeks) in subjects with GC/GEJ cancer and ≥ 2 prior regimens.

PTs of clinical interest include diarrhoea (5/6 subjects resolved in a median of 2.57 weeks; range: 0.3 to 11.0+ weeks), AST increased (2/2 subjects resolved in a median of 8.57 weeks; range: 4.1 to 13.0 weeks), rash (4/4 subjects resolved in a median of 19.36 weeks; range: 4.9 to 22.9 weeks), and

autoimmune hepatitis (1/1 subject resolved in 14.14 weeks). The maximum time to resolution among events that resolved was reported for an event of pruritus that resolved in 35.7 weeks.

Select Adverse Events

Select AEs analyses presented in this section for ONO-4538-12 were based on BMS coding of AEs with MedDRA 20.0.

In both ONO-4538-12 and CA209032, across select AE categories, the majority of events were manageable, with resolution occurring when IMMs (mostly systemic corticosteroids) were administered. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

The majority of reported select AEs were Grade 1 to 2, with some higher grade Grade 3 events in ONO-4538-12 and CA209032. There were no Grade 4 or Grade 5 drug-related select AEs reported in either study for subjects in the nivolumab group. Most endocrine and all hypersensitivity/infusion reaction select AEs were considered drug-related by the investigator. A lower proportion of select AEs were reported as drug-related in the GI, hepatic, renal, and skin categories. There were no pulmonary select AEs considered drug-related by the investigator in ONO-4538-12, and no renal select AEs considered drug-related by the investigator in subjects with GC/GEJ cancer and ≥ 2 prior regimens in CA209032. The most frequently reported any-grade drug-related select AE categories in ONO-4538-12 were skin (15.5%) and GI (7.0%), and in subjects with GC/GEJ cancer and ≥ 2 prior regimens in CA209032, skin (23.8%) and GI (16.7%); see Table 48.

Endocrine Events

The endocrine select AEs category included the following subcategories: adrenal disorders, diabetes, pituitary disorders, and thyroid disorders.

ONO-4538-12

Endocrine select AEs were reported in 6.4% of subjects in the nivolumab group and 1.2% of subjects in the placebo group. Grade 3-4 endocrine select AEs were reported in 1.2% and 0% of subjects, respectively. The most commonly reported endocrine AEs reported in the nivolumab group was hypothyroidism (4.2%) followed by type 1 diabetes mellitus (0.9%). The most commonly reported endocrine AEs in the placebo group were diabetes mellitus and hypothyroidism (each 0.6%).

Drug-related endocrine AEs were reported in 4.8% of subjects in the nivolumab group and 0.6% of subjects in the placebo group (Table 53). The most commonly reported drug-related endocrine AE in each group was hypothyroidism (3.0% and 0.6%, respectively).

In the nivolumab group, there were no endocrine AEs classified into the subcategory of adrenal disorder. In the placebo group, there were no endocrine AEs classified into the subcategory of adrenal disorder or pituitary disorder.

Two subjects in the nivolumab group with Grade 3 diabetes events (Type 1 diabetes mellitus and diabetic ketoacidosis) were reported. No drug-related endocrine select AEs led to permanent discontinuation of nivolumab.

In the nivolumab group, the median time to onset of drug-related endocrine AEs was 9.14 weeks (Table 54). One subject was treated with IMM for a duration of 9.14 weeks. Overall, 3 of the 16 subjects with drug-related endocrine select AEs resolved; the median time to resolution was not reached (range 2.0+ to 31.4+ weeks).

Table 53: Summary of Drug-related Endocrine Select Adverse Events Reported up to 28 days after Last Dose -Treated Subjects in ONO-4538-12

Subcategory (%) Preferred Term (%)	Nivolumab 3mg/kg N = 330			Placebo N = 161		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	16 (4.8)	4 (1.2)	0	1 (0.6)	0	0
THYROID DISORDER	13 (3.9)	0	0	1 (0.6)	0	0
HYPOTHYROIDISM	10 (3.0)	0	0	1 (0.6)	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED	2 (0.6)	0	0	0	0	0
HYPERTHYROIDISM	2 (0.6)	0	0	0	0	0
AUTOIMMUNE THYROIDITIS	1 (0.3)	0	0	0	0	0
DIABETES	3 (0.9)	3 (0.9)	0	0	0	0
TYPE 1 DIABETES MELLITUS	3 (0.9)	2 (0.6)	0	0	0	0
DIABETIC KETOACIDOSIS	2 (0.6)	2 (0.6)	0	0	0	0
PITUITARY DISORDER	1 (0.3)	1 (0.3)	0	0	0	0
HYPOPITUITARISM	1 (0.3)	1 (0.3)	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Appendix G.149-EUSCS in Appendix 2

Table 54: Onset, Treatment, and Resolution of Drug-Related Endocrine Select Adverse Events Reported up to 28 Days after Last Dose - Treated Subjects in ONO-4538-12

Category: ENDOCRINE ADVERSE EVENT	Nivolumab 3mg/kg		Placebo	
	Any Grade N = 16	Grade 3-5 N = 4	Any Grade N = 1	Grade 3-5 N = 0
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	9.14 (2.4 - 39.1)	22.79 (14.1 - 28.1)	2.14 (2.1 - 2.1)	N.A. (N.A. - N.A.)
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%)	1 (6.3)	1 (25.0)	0	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	9.14 (9.1 - 9.1)	9.14 (9.1 - 9.1)		
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	0	0	0	0
NUMBER OF SUBJECTS WHO RESOLVED (%)	3 (18.8)	0	1 (100.0)	0
TIME TO RESOLUTION (WEEKS)				
MEDIAN(A) (95% CI)	N.A. (12.14 - N.A.)	N.A. (N.A. - N.A.)	0.71 (N.A. - N.A.)	
RANGE(B) (MIN - MAX)	2.0+ - 31.4+	10.1+ - 20.6+	0.7 - 0.7	

MedDRA Version: 20.0
CTC Version 4.0
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
(A) From Kaplan-Meier estimation.
(B) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Source: Appendix G.159-EUSCS in Appendix 2 (time to onset), Appendix G.126-ono12 in Appendix 2 (immune-modulating medication), and Appendix G.161-EUSCS in Appendix 2 (time to resolution)

CA209032 (GC Cohort)

In subjects with GC/GEJ cancer and ≥ 2 prior regimens, endocrine select AEs were reported in 11.9% of subjects, all from the thyroid disorder subcategory.

A total of 9.5% of subjects had endocrine select AEs that were considered to be drug related by the investigator (Table 55). The most commonly reported drug-related event was hyperthyroidism (7.1%). The majority of drug-related endocrine events were Grade 1-2. One Grade 3 event (hypothyroidism) was reported. No events led to permanent discontinuation of nivolumab.

The median time to onset of drug-related endocrine AEs was 8.29 weeks (Table 56). One subject was treated with high-dose corticosteroids for a duration of 3.00 weeks; the subject did not have resolution of the event at the time of DBL. Overall, 3 of the 4 subjects with drug related endocrine select AEs resolved, with a median time to resolution of 5.43 weeks.

In the 59 subjects in the GC cohort of CA209032, 5 (8.5%) subjects had endocrine select AEs that were

considered to be drug-related by the investigator, and the most commonly reported drug related event was hyperthyroidism (4 subjects, 6.8%).

Table 55: Summary of Drug-related Endocrine Select Adverse Events Reported up to 30 days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

Sub Category (%) Preferred Term (%)	Nivolumab N = 42		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	4 (9.5)	1 (2.4)	0
THYROID DISORDER	4 (9.5)	1 (2.4)	0
HYPERTHYROIDISM	3 (7.1)	0	0
HYPOTHYROIDISM	2 (4.8)	1 (2.4)	0

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix G.162-EUSCS in Appendix 3

Table 56: Onset, Treatment, and Resolution of Drug-Related Endocrine Select Adverse Events Reported up to 30 Days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

Category: Endocrine Adverse Event	Nivolumab Any Grade N = 4	Nivolumab Grade 3-5 N = 1
TIME TO ONSET (WEEKS)		
MEDIAN	8.29	20.29
MIN - MAX	2.1 - 19.4	20.3 - 20.3
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%)	1 (25.0)	0
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	1 (25.0)	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)		
MEDIAN (MIN-MAX)	3.00 (3.0 - 3.0)	
DURATION OF CORTICOSTEROID AT A DOSE >= 40 MG OR EQUIVALENT (WEEKS)		
MEDIAN (MIN-MAX)	3.00 (3.0 - 3.0)	
NUMBER OF SUBJECTS WHO RESOLVED (%)	3 (75.0)	0
NUMBER OF SUBJECTS WHO RESOLVED (%) (C)	0/1	0/1
TIME TO RESOLUTION (WEEKS)		
MEDIAN (A)	5.43	N.A.
(95%CI)	(2.14, N.A.)	(N.A., N.A.)
RANGE (B) (MIN - MAX)	2.1 - 53.7+	45.1+ - 45.1+
TIME TO RESOLUTION (WEEKS) (C)		
MEDIAN (A)	N.A.	N.A.
(95%CI)	(N.A., N.A.)	(N.A., N.A.)
RANGE (B) (MIN - MAX)	53.7+ - 53.7+	45.1+ - 45.1+

MedDRA Version: 18.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
(A) From Kaplan-Meier estimation.
(B) Symbol + indicates a censored value.
(C) Restricted to subjects who received immune modulating medication during longest select AE.
Subjects who experienced select adverse event 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.
Source: Appendix G.165-EUSCS (time to onset), Appendix G.168-EUSCS (time to resolution), Appendix G.170-EUSCS (duration immune-modulating medication) in Appendix 3

Gastrointestinal Events

ONO-4538-12

GI select AEs were reported in 17.6% of subjects in the nivolumab group and 9.9% of subjects in the placebo group. Grade 3-4 GI select AEs were reported in 1.5% and 0.6% of subjects, respectively. The most commonly reported GI AE in the nivolumab group was diarrhoea (17.6%), followed by colitis (0.6%). The most commonly reported GI AE in the placebo group was diarrhoea (9.3%), followed by gastrointestinal perforation (0.6%).

Drug-related GI select AEs were reported in 7.0% and 2.5% of subjects in the nivolumab monotherapy and placebo groups, respectively (Table 57). The most commonly reported drug-related GI AE in each group was diarrhoea (7.0% and 1.9%, respectively). No drug-related GI select AE lead to discontinuation of study treatment in the nivolumab group.

In subjects in the nivolumab group, the median time to onset of the drug-related GI event was 2.29 weeks (Table 58). 3 subjects were treated with IMM for a median duration of 13.86 weeks, with 2 treated with high-dose corticosteroids. Overall, 18 of the 23 subjects with drug-related GI select AEs resolved, with a median time to resolution of 9.14 weeks.

Table 57: Summary of Drug-related GI Select Adverse Events Reported up to 28 days after Last Dose – Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg N = 330			Placebo N = 161		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	23 (7.0)	3 (0.9)	0	4 (2.5)	0	1 (0.6)
DIARRHOEA	23 (7.0)	2 (0.6)	0	3 (1.9)	0	0
GASTROINTESTINAL PERFORATION	0	0	0	1 (0.6)	0	1 (0.6)
COLITIS	2 (0.6)	1 (0.3)	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Appendix G.147-EUSCS in Appendix 2

Table 58: Onset, Treatment, and Resolution of Drug-Related GI Select Adverse Events Reported up to 28 Days after Last Dose - Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg		Placebo	
Category: GASTROINTESTINAL ADVERSE EVENT	Any Grade N = 23	Grade 3-5 N = 3	Any Grade N = 4	Grade 3-5 N = 1
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	2.29 (0.3 - 18.9)	4.14 (1.1 - 13.4)	4.00 (0.6 - 9.3)	3.43 (3.4 - 3.4)
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%)	3 (13.0)	1 (33.3)	0	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	13.86 (10.7 - 14.1)	13.86 (13.9 - 13.9)		
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	2 (8.7)	1 (33.3)	0	0
NUMBER OF SUBJECTS WHO RESOLVED (%)	18 (78.3)	2 (66.7)	3 (75.0)	0
TIME TO RESOLUTION (WEEKS)				
MEDIAN (A) (95% CI)	9.14 (4.00 - 16.14)	3.43 (2.00 - N.A.)	1.29 (1.00 - 3.14)	N.A. (N.A. - N.A.)
RANGE (B) (MIN - MAX)	0.1 - 34.7+	2.0 - 14.0+	0.1+ - 3.1	0.1+ - 0.1+

MedDRA Version: 20.0
CTC Version 4.0
Denominator is based on the number of subject who experienced the event.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
(A) From Kaplan-Meier estimation.
(B) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Source: Appendix G.159-EUSCS in Appendix 2 (time to onset), Appendix G.125-ono12 in Appendix 2 (duration of IMM), and Appendix G.161-EUSCS (time to resolution) in Appendix 2

CA209032 (GC Cohort)

In subjects with GC/GEJ cancer previously treated with ≥ 2 prior regimens, GI select AEs were reported in 28.6% of subjects. A total of 16.7% of subjects had GI select AEs that were considered to be drug-related by the investigator (Table 59). Most drug-related events were Grade 1-2 diarrhoea, with 1 subject with an event of Grade 2 colitis and 1 subject with a Grade 3 event of diarrhoea. The Grade 2 drug-related event of colitis led to permanent discontinuation of nivolumab.

The median time to onset of drug-related GI AEs was 4.14 weeks (Table 60). 1 subject was treated with high-dose corticosteroids for a duration of 0.57 weeks; this event did not resolve at the time of DBL. Overall, 5 of the 7 subjects with drug-related GI select AEs resolved, with a median time to resolution of 4.00 weeks.

In the 59 subjects in the GC cohort of CA209032, 10 (16.9%) subjects had GI select AEs that were considered to be drug-related by the investigator, and the most commonly reported drug-related event was diarrhea (9 subjects, 15.3%).

Table 59: Summary of Drug-related GI Select Adverse Events Reported up to 30 days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

Sub Category (%) Preferred Term (%)	Nivolumab N = 42		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	7 (16.7)	1 (2.4)	0
DIARRHOEA	6 (14.3)	1 (2.4)	0
COLITIS	1 (2.4)	0	0

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix G.160-EUSCS in Appendix 3

Table 60: Onset, Treatment, and Resolution of Drug-Related GI Select Adverse Events Reported up to 30 Days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

	Nivolumab	
	Any Grade	Grade 3-5
Category: Gastrointestinal Adverse Event	N = 7	N = 1
TIME TO ONSET (WEEKS)		
MEDIAN	4.14	8.43
MIN - MAX	0.3 - 22.1	8.4 - 8.4
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%) (A)	1 (14.3)	0
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%) (A)	1 (14.3)	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)		
MEDIAN (MIN-MAX)	1.71 (1.7 - 1.7)	
DURATION OF CORTICOSTEROID AT A DOSE >= 40 MG OR EQUIVALENT (WEEKS)		
MEDIAN (MIN-MAX)	0.57 (0.6 - 0.6)	
NUMBER OF SUBJECTS WHO RESOLVED (%)	5 (71.4)	0
NUMBER OF SUBJECTS WHO RESOLVED (%) (B)	0/1	0/0
TIME TO RESOLUTION (WEEKS)		
MEDIAN (C)	4.00	N.A.
(95%CI)	(0.29, N.A.)	(N.A., N.A.)
RANGE (D) (MIN - MAX)	0.3 - 42.1+	6.1+ - 6.1+
TIME TO RESOLUTION (WEEKS) (B)		
MEDIAN (C)	N.A.	
(95%CI)	(N.A., N.A.)	
RANGE (D) (MIN - MAX)	42.1+ - 42.1+	

MedDRA Version: 18.1, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
(A) Denominator is based on the number of subject who experienced the event.
(B) Restricted to subjects who received immune modulating medication during longest select AE.
(C) From Kaplan-Meier estimation.
(D) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Crossover subjects are truncated at the first dose date of crossover period.

Source: Appendix G.165-EUSCS (time to onset), Appendix G.167-EUSCS (time to resolution), Appendix G.170-EUSCS (duration immune-modulating medication), and Appendix G.168-EUSCS (time to resolution with immune-modulating medication) in Appendix 3

Hepatic Events

ONO-4538-12

Hepatic select AEs were reported in 18.8% of subjects in the nivolumab group and 12.4% of subjects in the placebo group. Grade 3-4 hepatic select AEs were reported in 10.0% and 6.8% of subjects, respectively. The most commonly reported hepatic AE in the nivolumab group was AST increased (10.0%), followed by blood ALP increased (7.6%). The most commonly reported hepatic AE in the placebo group was AST increased (6.8%), followed by ALT increased (5.6%).

Drug-related hepatic select AEs were reported in 5.5% of subjects in the nivolumab group and 3.1% of subjects in the placebo group (Table 61). The most commonly reported drug-related hepatic AEs in the nivolumab group was AST increased (3.3%). Hepatic select AEs leading to discontinuation of study treatment were reported in 1.2% of subjects in the nivolumab group (drugrelated hepatitis acute in 1 subject [0.3%]).

In subjects in the nivolumab group, the median time to onset of the drug-related hepatic event was 3.57 weeks (Table 62). 2 subjects were treated with IMM for a median duration of 2.14 weeks, with 1 treated with high-dose corticosteroids. Overall, 12 of the 18 subjects with drug-related hepatic select AEs resolved, with a median time to resolution of 6.43 weeks.

Table 61: Summary of Drug-related Hepatic Select Adverse Events Reported up to 28 days after Last Dose -Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg N = 330			Placebo N = 161		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	18 (5.5)	5 (1.5)	0	5 (3.1)	1 (0.6)	0
ASPARTATE AMINOTRANSFERASE INCREASED	11 (3.3)	2 (0.6)	0	3 (1.9)	0	0
ACUTE HEPATIC FAILURE	0	0	0	1 (0.6)	1 (0.6)	0
ALANINE AMINOTRANSFERASE INCREASED	7 (2.1)	1 (0.3)	0	1 (0.6)	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	3 (0.9)	0	0	1 (0.6)	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED	6 (1.8)	1 (0.3)	0	0	0	0
BLOOD BILIRUBIN INCREASED	2 (0.6)	1 (0.3)	0	0	0	0
HEPATIC ENZYME INCREASED	1 (0.3)	1 (0.3)	0	0	0	0
HEPATITIS ACUTE	1 (0.3)	1 (0.3)	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Appendix G.147-EUSCS in Appendix 2

Table 62: Onset, Treatment, and Resolution of Drug-Related Hepatic Select Adverse Events Reported up to 28 Days after Last Dose - Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg		Placebo	
Category: Hepatic Adverse Event	Any Grade N = 18	Grade 3-5 N = 5	Any Grade N = 5	Grade 3-5 N = 1
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	3.57 (0.9 - 19.1)	3.14 (2.4 - 7.0)	4.00 (2.7 - 14.9)	3.86 (3.9 - 3.9)
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%)	2 (11.1)	2 (40.0)	0	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	2.14 (1.0 - 3.3)	2.14 (1.0 - 3.3)		
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	1 (5.6)	1 (20.0)	0	0
NUMBER OF SUBJECTS WHO RESOLVED (%)	12 (66.7)	3 (60.0)	2 (40.0)	0
TIME TO RESOLUTION (WEEKS)				
MEDIAN (A) (95% CI)	6.43 (2.29 - 45.14)	1.71 (0.71 - N.A.)	10.43 (2.86 - 10.43)	N.A. (N.A. - N.A.)
RANGE (B) (MIN - MAX)	0.7 - 65.0+	0.7 - 7.4+	0.6+ - 10.4	0.6+ - 0.6+

MedDRA Version: 20.0
CTC Version 4.0
Denominator is based on the number of subject who experienced the event.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
(A) From Kaplan-Meier estimation.
(B) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Source: Appendix G.159-EUSCS in Appendix 2 (time to onset), Appendix G.125-ono12 in Appendix 2 (duration of IMM), and Appendix G.161-EUSCS in Appendix 2 (time to resolution)

CA209032 (GC Cohort)

In subjects with GC/GEJ cancer previously treated with ≥ 2 prior regimens, the frequency of hepatic select AEs was consistent with ONO-4538-12 (14.3%). A total of 4.8% of subjects had hepatic AEs that were considered to be drug-related by the investigator (Table 63). No subjects had drug-related events that led to permanent discontinuation of nivolumab.

The median time to onset of drug-related hepatic events was 14.43 weeks (Table 64). Two subjects were treated with IMM, of which 1 subject was treated with high-dose corticosteroids. The duration of high-dose corticosteroids was 22.14 weeks. Overall, both subjects had drug-related hepatic select AEs that resolved, with a median time to resolution of 13.57 weeks.

In the 59 subjects in the GC cohort of CA209032, 8 (13.6%) subjects had hepatic select AEs that were considered to be drug-related by the investigator, and the most commonly reported drug related event was AST increased (7 subjects, 11.9%). Other drug-related hepatic select AEs reported in the GC cohort not reported in the 42-subject subset included blood ALP increased (2 subjects, 3.4%), and gamma-glutamyltransferase increased and transaminases increased (1 subject each, 1.7%).

Table 63: Summary of Drug-related Hepatic Select Adverse Events Reported up to 30 days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

Sub Category (%) Preferred Term (%)	Nivolumab N = 42		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	2 (4.8)	2 (4.8)	0
ALANINE AMINOTRANSFERASE INCREASED	2 (4.8)	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	2 (4.8)	2 (4.8)	0
AUTOIMMUNE HEPATITIS	1 (2.4)	1 (2.4)	0

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix G.160-EUSCS in Appendix 3

Table 64: Onset, Treatment, and Resolution of Drug-Related Hepatic Select Adverse Events Reported up to 30 Days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at least 2 Prior Regimens) Subjects

	Nivolumab	
Category: Hepatic Adverse Event	Any Grade N = 2	Grade 3-5 N = 2
TIME TO ONSET (WEEKS)		
MEDIAN	14.43	46.00
MIN - MAX	2.7 - 26.1	26.1 - 65.9
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%) (A)	2 (100.0)	2 (100.0)
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%) (A)	1 (50.0)	1 (50.0)
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)		
MEDIAN (MIN-MAX)	30.21 (22.1 - 38.3)	30.21 (22.1 - 38.3)
DURATION OF CORTICOSTEROID AT A DOSE >= 40 MG OR EQUIVALENT (WEEKS)		
MEDIAN (MIN-MAX)	22.14 (22.1 - 22.1)	22.14 (22.1 - 22.1)
NUMBER OF SUBJECTS WHO RESOLVED (%)	2 (100.0)	2 (100.0)
NUMBER OF SUBJECTS WHO RESOLVED (%) (B)	2 (100.0)	2 (100.0)
TIME TO RESOLUTION (WEEKS)		
MEDIAN (C)	13.57	13.57
(95%CI)	(13.00, 14.14)	(13.00, 14.14)
RANGE (D) (MIN - MAX)	13.0 - 14.1	13.0 - 14.1
TIME TO RESOLUTION (WEEKS) (B)		
MEDIAN (C)	13.57	13.57
(95%CI)	(13.00, 14.14)	(13.00, 14.14)
RANGE (D) (MIN - MAX)	13.0 - 14.1	13.0 - 14.1

MedDRA Version: 18.1, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
(A) Denominator is based on the number of subject who experienced the event.
(B) Restricted to subjects who received immune modulating medication during longest select AE.
(C) From Kaplan-Meier estimation.
(D) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Crossover subjects are truncated at the first dose date of crossover period.

Source: Appendix G.165-EUSCS (time to onset), Appendix G.167-EUSCS (time to resolution), Appendix G.170-EUSCS (duration immune-modulating medication), and Appendix G.168-EUSCS (time to resolution with immune-modulating medication) in Appendix 3

Pulmonary Events

ONO-4538-12

Pulmonary select AEs were reported in 3.0% of subjects in the nivolumab group and no subjects in the placebo group. Grade 3-4 pulmonary AEs were reported in 0.6% of subjects in the nivolumab group. The most commonly reported pulmonary AE in the nivolumab group was interstitial lung disease (1.8%), followed by pneumonitis (1.2%).

Drug-related pulmonary AEs were reported in 2.1% of subjects in the nivolumab group (Table 65). The most common drug-related pulmonary AE in the nivolumab group was interstitial lung disease (1.8%). Drug-related pulmonary select AEs leading to discontinuation of study treatment were reported in 1.2% of subjects in the nivolumab group (interstitial lung disease in 3 subjects [0.9%] and pneumonitis in 1 subject [0.3%]).

In subjects in the nivolumab group, the median time to onset of the drug-related pulmonary events was 6.14 weeks (Table 66). 4 subjects were treated with IMM, with 3 treated with high-dose corticosteroids,

for a median duration of 15.07 weeks. Overall, 2 of the 7 subjects with drug-related pulmonary select AEs resolved; the median time to resolution was not reached (range: 1.1+ to 43.7+ weeks).

Table 65: Summary of Drug-related Pulmonary Select Adverse Events Reported up to 28 days after Last Dose -Nivolumab Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg N = 330			Placebo N = 161		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	7 (2.1)	2 (0.6)	0	0	0	0
INTERSTITIAL LUNG DISEASE	6 (1.8)	1 (0.3)	0	0	0	0
PNEUMONITIS	1 (0.3)	1 (0.3)	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Appendix G.147-EUSCS in Appendix 2

Table 66: Onset, Treatment, and Resolution of Drug-Related Pulmonary Select Adverse Events Reported up to 28 Days after Last Dose - Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg		Placebo	
Category: Pulmonary Adverse Event	Any Grade N = 7	Grade 3-5 N = 2	Any Grade N = 0	Grade 3-5 N = 0
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	6.14 (6.1 - 66.1)	12.64 (6.1 - 19.1)	N.A. (N.A. - N.A.)	N.A. (N.A. - N.A.)
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%)	4 (57.1)	2 (100.0)	0	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	15.07 (4.9 - 41.6)	15.07 (7.3 - 22.9)		
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	3 (42.9)	2 (100.0)	0	0
NUMBER OF SUBJECTS WHO RESOLVED (%)	2 (28.6)	0	0	0
TIME TO RESOLUTION (WEEKS)				
MEDIAN (A) (95% CI)	N.A. (3.14 - N.A.)	N.A. (N.A. - N.A.)		
RANGE (B) (MIN - MAX)	1.1+ - 43.7+	7.7+ - 22.9+		

MedDRA Version: 20.0
CTC Version 4.0
Denominator is based on the number of subject who experienced the event.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
(A) From Kaplan-Meier estimation.
(B) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Source: Appendix G.159-EUSCS in Appendix 2 (time to onset), Appendix G.125-ono12 in Appendix 2 (duration of IMM), and Appendix G.161-EUSCS in Appendix 2 (time to resolution)

CA209032 (GC Cohort)

In subjects with GC/GEJ cancer and ≥ 2 prior regimens, pulmonary select AEs were reported in 7.1% of subjects. A total of 2 subjects (4.8%) had pulmonary AEs (all pneumonitis) considered to be drug-related by the investigator, all Grade 1-2 events (Table 67). There were no subjects with drug-related pulmonary AEs that led to permanent discontinuation of nivolumab.

The median time to onset of the drug-related pulmonary event was 15.00 weeks (Table 68). One subject was treated with high-dose corticosteroids for a duration of 8.86, and had resolution of the event with a median time to resolution of 3.14 weeks. Overall, both subjects with drug-related pulmonary select AEs had resolution of their events, with a median time to resolution of 2.57 weeks.

In the 59 subjects in the GC cohort of CA209032, 3 (5.1%) subjects had pulmonary select AEs that were considered to be drug-related by the investigator (pneumonitis).

Table 67: Summary of Drug-related Pulmonary Select Adverse Events Reported up to 30 days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

Sub Category (%) Preferred Term (%)	Nivolumab N = 42		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	2 (4.8)	0	0
PNEUMONITIS	2 (4.8)	0	0

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix G.160-EUSCS in Appendix 3

Table 68: Onset, Treatment, and Resolution of Drug-Related Pulmonary Select Adverse Events Reported up to 30 Days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

Category: Pulmonary Adverse Event	Nivolumab Any Grade N = 2	Nivolumab Grade 3-5 N = 0
TIME TO ONSET (WEEKS)		
MEDIAN	15.00	N.A.
MIN - MAX	11.9 - 18.1	N.A. - N.A.
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%) (A)	1 (50.0)	0
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%) (A)	1 (50.0)	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)		
MEDIAN (MIN-MAX)	8.86 (8.9 - 8.9)	
DURATION OF CORTICOSTEROID AT A DOSE >= 40 MG OR EQUIVALENT (WEEKS)		
MEDIAN (MIN-MAX)	8.86 (8.9 - 8.9)	
NUMBER OF SUBJECTS WHO RESOLVED (%)	2/2 (100.0)	0
NUMBER OF SUBJECTS WHO RESOLVED (%) (B)	1/1 (100.0)	0
TIME TO RESOLUTION (WEEKS)		
MEDIAN (C)	2.57	
(95%CI)	(2.00, 3.14)	
RANGE (D) (MIN - MAX)	2.0 - 3.1	
TIME TO RESOLUTION (WEEKS) (B)		
MEDIAN (C)	3.14	
(95%CI)	(N.A., N.A.)	
RANGE (D) (MIN - MAX)	3.1 - 3.1	

MedDRA Version: 18.1, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
(A) Denominator is based on the number of subject who experienced the event.
(B) Restricted to subjects who received immune modulating medication during longest select AE.
(C) From Kaplan-Meier estimation.
(D) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Crossover subjects are truncated at the first dose date of crossover period.

Source: Appendix G.165-EUSCS (time to onset), Appendix G.167-EUSCS (time to resolution), Appendix G.170-EUSCS (duration immune-modulating medication), and Appendix G.168-EUSCS (time to resolution with immune-modulating medication) in Appendix 3

Renal Events

ONO-4538-12

Renal select AEs were reported in 3.6% of subjects in the nivolumab group and 1.9% of subjects in the placebo group. Grade 3-4 renal AEs were reported in 0.6% of subjects in each group.

The only drug-related renal AE in the nivolumab group was blood creatinine increased (1 subject, 0.3%). No drug-related renal select AEs leading to treatment discontinuation in the nivolumab group were reported.

In subjects in the nivolumab group, the time to onset of the drug-related renal event was 2.14 weeks. No subjects were treated with IMM. The subject with drug-related renal select AE did not have resolution of their events.

CA209032 (GC Cohort)

In subjects with GC/GEJ cancer and ≥ 2 prior regimens, renal select AEs were reported in 1 (2.4%) subject. There were no renal select AEs that were considered to be drug-related by the investigator.

No additional subjects were reported with renal select AEs in the 59 subjects in the GC cohort of CA209032.

Skin Events

ONO-4538-12

Skin select AEs were reported in 26.1% of subjects in the nivolumab group and 13.0% of subjects in the placebo group. No Grade 3-4 skin AEs were reported in either group. The most commonly reported skin select AE in the nivolumab group was pruritus (16.1%), followed by rash (9.4%). The most common skin AE in the placebo group was pruritus (9.3%), followed by rash (3.7%).

Drug-related skin select AEs were reported in 15.5% of subjects in the nivolumab group and 8.1% of subjects in the placebo group (Table 69). The most commonly reported drug-related skin AE in the nivolumab group was pruritus (9.1%), followed by rash (5.8%). The most common skin AE in the placebo group was pruritus (5.6%), followed by rash (3.1%). No skin select AEs leading to treatment discontinuation in the nivolumab group were reported.

In subjects in the nivolumab group, the median time to onset of the drug-related skin events was 4.14 weeks (Table 70). 25 subjects were treated with IMM (none received high-dose corticosteroids), for a median duration of 5.14 weeks. Overall, 27 of the 51 subjects with drug-related pulmonary select AEs resolved with a median time to resolution of 18.86 weeks.

Table 69: Summary of Drug-related Skin Select Adverse Events Reported up to 28 days after Last Dose – Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg N = 330			Placebo N = 161		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	51 (15.5)	0	0	13 (8.1)	0	0
PRURITUS	30 (9.1)	0	0	9 (5.6)	0	0
RASH	19 (5.8)	0	0	5 (3.1)	0	0
DERMATITIS	0	0	0	1 (0.6)	0	0
RASH MACULO-PAPULAR	4 (1.2)	0	0	1 (0.6)	0	0
DRUG ERUPTION	1 (0.3)	0	0	0	0	0
ECZEMA	1 (0.3)	0	0	0	0	0
ERYTHEMA MULTIFORME	1 (0.3)	0	0	0	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1 (0.3)	0	0	0	0	0
URTICARIA	3 (0.9)	0	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Appendix G.147-EUSCS in Appendix 2

Table 70: Onset, Treatment, and Resolution of Drug-Related Skin Select Adverse Events Reported up to 28 Days after Last Dose - Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg		Placebo	
Category: Skin Adverse Event	Any Grade N = 51	Grade 3-5 N = 0	Any Grade N = 13	Grade 3-5 N = 0
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	4.14 (0.1 - 52.1)	N.A. (N.A. - N.A.)	2.29 (0.3 - 17.7)	N.A. (N.A. - N.A.)
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%)	25 (49.0)	0	5 (38.5)	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	5.14 (0.1 - 58.1)		10.14 (1.9 - 37.6)	
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	0	0	0	0
NUMBER OF SUBJECTS WHO RESOLVED (%)	27 (52.9)	0	3 (23.1)	0
TIME TO RESOLUTION (WEEKS)				
MEDIAN (A) (95% CI)	18.86 (10.14 - 58.14)		N.A. (17.57 - N.A.)	
RANGE (B) (MIN - MAX)	0.1 - 58.1		2.6+ - 78.1+	

MedDRA Version: 20.0
CTC Version 4.0
Denominator is based on the number of subject who experienced the event.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
(A) From Kaplan-Meier estimation.
(B) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Source: Appendix G.159-EUSCS in Appendix 2 (time to onset), Appendix G.125-ono12 in Appendix 2 (duration of IMM), and Appendix G.161-EUSCS in Appendix 2 (time to resolution)

CA209032 (GC Cohort) In subjects with GC/GEJ cancer and ≥ 2 prior regimens, skin select AEs were reported in 31.0% of subjects. A total of 23.8% of subjects had skin AEs that were considered to be drug-related by the investigator (Table 71). The majority of the events were pruritus. All of the drug-related events were Grade 1-2, and none led to permanent discontinuation of nivolumab.

The median time to onset of the drug-related skin event was 2.93 weeks (Table 72). 3 subjects were treated with IMM (none with high-dose corticosteroids) for a median duration of 31.00 weeks, and all 3 subjects had resolution of the event, with a median time to resolution of 22.86 weeks. Overall, 10 subjects with skin select AEs had resolution of their events with a median time to resolution of 10.29 weeks.

In the 59 subjects in the GC cohort of CA209032, 11 (18.6%) subjects had skin select AEs that were considered to be drug-related by the investigator, and the most commonly reported drug-related event was pruritus (10 subjects, 16.9%).

Table 71: Summary of Drug-related Skin Select Adverse Events Reported up to 30 days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

Sub Category (%) Preferred Term (%)	Nivolumab N = 42		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	10 (23.8)	0	0
PRURITUS	9 (21.4)	0	0
RASH	4 (9.5)	0	0
RASH MACULO-PAPULAR	1 (2.4)	0	0
RASH PRURITIC	1 (2.4)	0	0

MedDRA Version: 18.1
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix G.160-EUSCS in Appendix 3

Table 72: Onset, Treatment, and Resolution of Drug-Related Skin Select Adverse Events Reported up to 30 Days after Last Dose - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

Category: Skin Adverse Event	Nivolumab Any Grade N = 10	Nivolumab Grade 3-5 N = 0
TIME TO ONSET (WEEKS)		
MEDIAN	2.93	N.A.
MIN - MAX	0.3 - 41.9	N.A. - N.A.
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%) (A)	3 (30.0)	0
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%) (A)	0	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)		
MEDIAN (MIN-MAX)	31.00 (5.3 - 68.3)	
SUBJECTS WHO UNDERWENT CORTICOSTEROID TAPER (%)	0	0
NUMBER OF SUBJECTS WHO RESOLVED (%)	10 (100.0)	0
NUMBER OF SUBJECTS WHO RESOLVED (%) (B)	3 (100.0)	0
TIME TO RESOLUTION (WEEKS)		
MEDIAN (C)	10.29	
(95%CI)	(0.14, 22.86)	
RANGE (D) (MIN - MAX)	0.1 - 37.6	
TIME TO RESOLUTION (WEEKS) (B)		
MEDIAN (C)	22.86	
(95%CI)	(3.14, 37.57)	
RANGE (D) (MIN - MAX)	3.1 - 37.6	

MedDRA Version: 18.1, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
(A) Denominator is based on the number of subject who experienced the event.
(B) Restricted to subjects who received immune modulating medication during longest select AE.
(C) From Kaplan-Meier estimation.
(D) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Crossover subjects are truncated at the first dose date of crossover period.

Source: Appendix G.165-EUSCS (time to onset), Appendix G.167-EUSCS (time to resolution), Appendix G.170-EUSCS (duration immune-modulating medication), and Appendix G.168-EUSCS (time to resolution with immune-modulating medication) in Appendix 3

Hypersensitivity/Infusion Reactions

ONO-4538-12

Hypersensitivity/infusion reactions were reported in 1.5% of subjects in the nivolumab group and no subjects in the placebo group. 3 subjects (0.9%) had hypersensitivity/infusion reactions that were

considered related to study drug (Table 73). No drug-related Grade 3-4 hypersensitivity/infusion reactions were reported.

Drug-related hypersensitivity/infusion reactions in the nivolumab group were infusion related reaction (2 subjects, 0.6%) and hypersensitivity (1 subject, 0.3%). No hypersensitivity/infusion reactions leading to treatment discontinuation in the nivolumab group were reported.

In subjects in the nivolumab group, the time to onset of the drug-related hypersensitivity/infusion reactions was 6.14 weeks (Table 74). 1 subject was treated with IMM for a duration of 0.14 weeks. Overall, all 3 subjects with drug-related hypersensitivity/infusion reaction resolved with a time to resolution of 0.14 weeks.

Table 73: Summary of Drug-related Hypersensitivity/Infusion Reaction Select Adverse Events Reported up to 28 days after Last Dose - Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg N = 330			Placebo N = 161		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (0.9)	0	0	0	0	0
HYPERSENSITIVITY	1 (0.3)	0	0	0	0	0
INFUSION RELATED REACTION	2 (0.6)	0	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Appendix G.147-EUSCS in Appendix 2

Table 74: Onset, Treatment, and Resolution of Drug-Related Hypersensitivity/Infusion Reaction Select Adverse Events Reported up to 28 Days After Last Dose - Treated Subjects in ONO-4538-12

	Nivolumab 3mg/kg		Placebo	
Category: Hypersensitivity/Infusion Reaction	Any Grade N = 3	Grade 3-5 N = 0	Any Grade N = 0	Grade 3-5 N = 0
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	6.14 (0.3 - 6.7)	N.A. (N.A. - N.A.)	N.A. (N.A. - N.A.)	N.A. (N.A. - N.A.)
SUBJECTS WHO RECEIVED IMMUNE MODULATING MEDICATION (%)	1 (33.3)	0	0	0
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	0.14 (0.1 - 0.1)			
SUBJECTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	0	0	0	0
NUMBER OF SUBJECTS WHO RESOLVED (%)	3 (100.0)	0	0	0
TIME TO RESOLUTION (WEEKS)				
MEDIAN(A) (95% CI)	0.14 (0.14 - 0.71)			
RANGE(B) (MIN - MAX)	0.1 - 0.7			

MedDRA Version: 20.0
CTC Version 4.0
Denominator is based on the number of subject who experienced the event.
Includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
(A) From Kaplan-Meier estimation.
(B) Symbol + indicates a censored value.
Subjects who experienced select adverse event 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.
Source: Appendix G.159-EUSCS in Appendix 2 (time to onset), Appendix G.125-ono12 in Appendix 2 (duration of IMM), and Appendix G.161-EUSCS in Appendix 2 (time to resolution)

CA209032 (GC Cohort)

In subjects with GC/GEJ cancer and ≥ 2 prior regimens, a hypersensitivity/infusion reaction was reported in 1 (2.4%) subject. The 1 hypersensitivity/infusion reaction select AE (Grade 2) was considered to be drug-related by the investigator, and did not lead to permanent discontinuation of nivolumab.

The time to onset of the drug-related hypersensitivity/infusion reaction event was 2.14 weeks. The subject was not treated with IMM, and the subject had resolution of the event with a median time to resolution of 0.14 weeks.

In the 59 subjects in the GC cohort of CA209032, 1 (1.7%) subject had hypersensitivity/infusion reaction select AEs that were considered to be drug-related by the investigator.

Other Events of Special Interest (OESIs)

OESIs for the nivolumab program were analysed to support the product information. OESIs are events that do not fulfil all criteria to qualify as select AEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management, but do not benefit from pooling of multiple AE terms for full characterization and are therefore presented as unique events rather than using select AE methodology. OESI included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, pancreatitis, myocarditis, myositis, rhabdomyolysis, and uveitis.

ONO-4538-12

In ONO-4538-12, no OESIs were reported, from the start date of the first administration of the study treatment and the earlier date on which either 28 days after the end of the treatment period or the start date of the post-treatment observation period, in the nivolumab group. One (0.6%) subject in the placebo group reported with Grade 2 pancreatitis.

CA209032 (GC Cohort)

In CA209032, no OESIs were reported between first dose and 100 days after last dose of study therapy (extended follow-up) in the nivolumab group.

Serious adverse events

All Causality

ONO-4538-12

SAEs of any grade were reported in 39.7% of subjects in the nivolumab group and 46.6% of subjects in the placebo group (Table 65). Worst Grade 3 to 4 SAEs were reported in 27.6% and 29.2% of subjects, respectively.

- Common SAEs (incidence ≥ 2%) reported in the nivolumab group were disease progression (4.8%), asthenia (2.7%), malignant neoplasm progression (2.1%), and ileus (2.1%). The most common worst Grade 3-4 SAE was disease progression (2.4%).
- Common SAEs (incidence ≥ 2%) reported in the placebo group were disease progression (6.2%), pneumonia (3.7%), abdominal pain (3.7%), malignant neoplasm progression (2.1%), and pleural effusion (3.1%), and ileus (2.5%). The most common worst Grade 3-4 SAEs were pneumonia (3.1%), and ileus, abdominal pain, and disease progression (2.5% each).

Study CA209032 (GC Cohort)

In the subset of 42 subjects with GC/GEJ cancer and ≥ 2 prior regimens, SAEs were reported in 57.1% of subjects (Table 75). The most frequently reported SAEs (incidence ≥ 5%) were malignant neoplasm progression (16.7%) and dyspnoea (7.1%). The most frequently reported Grade 3-4 SAEs were malignant neoplasm progression, pulmonary embolism, and hip fracture (all 4.8%). The frequency of SAEs (52.5%) in the GC cohort was similar to that in subjects with GC/GEJ cancer and ≥ 2 prior regimens.

Table 75: Summary of Serious Adverse Events by Worst CTC Grade in ≥ 2 Subjects - ONO-4538-12 and CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

	ONO-4538-12						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	131 (39.7)	91 (27.6)	16 (4.8)	75 (46.6)	47 (29.2)	18 (11.2)	24 (57.1)	14 (33.3)	5 (11.9)
GASTROINTESTINAL DISORDERS	35 (10.6)	28 (8.5)	0	23 (14.3)	18 (11.2)	2 (1.2)	9 (21.4)	6 (14.3)	0
ILEUS	7 (2.1)	6 (1.8)	0	4 (2.5)	4 (2.5)	0	0	0	0
ABDOMINAL PAIN	6 (1.8)	3 (0.9)	0	6 (3.7)	4 (2.5)	0	2 (4.8)	1 (2.4)	0
VOMITING	3 (0.9)	2 (0.6)	0	1 (0.6)	1 (0.6)	0	1 (2.4)	1 (2.4)	0
ABDOMINAL DISTENSION	2 (0.6)	2 (0.6)	0	0	0	0	0	0	0
COLITIS	2 (0.6)	1 (0.3)	0	0	0	0	1 (2.4)	1 (2.4)	0
GASTROINTESTINAL HAEMORRHAGE	2 (0.6)	1 (0.3)	0	1 (0.6)	1 (0.6)	0	0	0	0
INTESTINAL OBSTRUCTION	2 (0.6)	2 (0.6)	0	1 (0.6)	1 (0.6)	0	1 (2.4)	1 (2.4)	0
RECTAL OBSTRUCTION	2 (0.6)	2 (0.6)	0	1 (0.6)	1 (0.6)	0	0	0	0
UPPER GASTROINTESTINAL HAEMORRHAGE	2 (0.6)	2 (0.6)	0	2 (1.2)	2 (1.2)	0	0	0	0
ASCITES	1 (0.3)	1 (0.3)	0	2 (1.2)	2 (1.2)	0	2 (4.8)	1 (2.4)	0
GASTROINTESTINAL OBSTRUCTION	1 (0.3)	1 (0.3)	0	2 (1.2)	1 (0.6)	1 (0.6)	0	0	0
DIARRHOEA	0	0	0	2 (1.2)	1 (0.6)	0	1 (2.4)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	33 (10.0)	18 (5.5)	6 (1.8)	15 (9.3)	8 (5.0)	6 (3.7)	2 (4.8)	1 (2.4)	0
DISEASE PROGRESSION	16 (4.8)	8 (2.4)	5 (1.5)	10 (6.2)	4 (2.5)	5 (3.1)	0	0	0
ASTHENIA	9 (2.7)	6 (1.8)	0	1 (0.6)	1 (0.6)	0	0	0	0
PYREXIA	3 (0.9)	1 (0.3)	0	0	0	0	1 (2.4)	0	0
FATIGUE	2 (0.6)	2 (0.6)	0	3 (1.9)	3 (1.9)	0	0	0	0
INFECTIONS AND INFESTATIONS	18 (5.5)	14 (4.2)	1 (0.3)	15 (9.3)	9 (5.6)	4 (2.5)	5 (11.9)	5 (11.9)	0
PNEUMONIA	6 (1.8)	5 (1.5)	1 (0.3)	6 (3.7)	5 (3.1)	1 (0.6)	1 (2.4)	1 (2.4)	0
URINARY TRACT INFECTION	2 (0.6)	1 (0.3)	0	1 (0.6)	1 (0.6)	0	1 (2.4)	1 (2.4)	0
SEPSIS	1 (0.3)	1 (0.3)	0	3 (1.9)	0	3 (1.9)	0	0	0
BACTERAEMIA	0	0	0	2 (1.2)	2 (1.2)	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	15 (4.5)	9 (2.7)	4 (1.2)	9 (5.6)	7 (4.3)	2 (1.2)	7 (16.7)	2 (4.8)	5 (11.9)
MALIGNANT NEOPLASM PROGRESSION	7 (2.1)	3 (0.9)	3 (0.9)	4 (2.5)	3 (1.9)	1 (0.6)	7 (16.7)	2 (4.8)	5 (11.9)
TUMOUR HAEMORRHAGE	2 (0.6)	2 (0.6)	0	1 (0.6)	1 (0.6)	0	0	0	0
TUMOUR PAIN	2 (0.6)	1 (0.3)	0	0	0	0	0	0	0
HEPATOBILIARY DISORDERS	13 (3.9)	9 (2.7)	1 (0.3)	6 (3.7)	5 (3.1)	1 (0.6)	2 (4.8)	1 (2.4)	0
CHOLANGITIS	6 (1.8)	4 (1.2)	0	0	0	0	0	0	0
JAUNDICE CHOLESTATIC	3 (0.9)	3 (0.9)	0	1 (0.6)	1 (0.6)	0	0	0	0
BILE DUCT OBSTRUCTION	0	0	0	2 (1.2)	2 (1.2)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	12 (3.6)	11 (3.3)	0	9 (5.6)	7 (4.3)	0	2 (4.8)	2 (4.8)	0
DECREASED APPETITE	4 (1.2)	3 (0.9)	0	3 (1.9)	2 (1.2)	0	0	0	0
DEHYDRATION	2 (0.6)	2 (0.6)	0	0	0	0	1 (2.4)	1 (2.4)	0
DIABETIC KETOACIDOSIS	2 (0.6)	2 (0.6)	0	0	0	0	0	0	0
HYPOGLYCAEMIA	1 (0.3)	1 (0.3)	0	2 (1.2)	2 (1.2)	0	0	0	0
HYPOPHAGIA	0	0	0	2 (1.2)	1 (0.6)	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12 (3.6)	5 (1.5)	2 (0.6)	9 (5.6)	5 (3.1)	1 (0.6)	8 (19.0)	4 (9.5)	0
DYSPNOEA	3 (0.9)	1 (0.3)	1 (0.3)	0	0	0	3 (7.1)	1 (2.4)	0
INTERSTITIAL LUNG DISEASE	3 (0.9)	1 (0.3)	0	0	0	0	0	0	0
PNEUMOTHORAX	2 (0.6)	0	0	2 (1.2)	2 (1.2)	0	0	0	0
PLEURAL EFFUSION	1 (0.3)	1 (0.3)	0	5 (3.1)	1 (0.6)	0	2 (4.8)	0	0
PNEUMONIA ASPIRATION	0	0	0	2 (1.2)	2 (1.2)	0	0	0	0
PULMONARY EMBOLISM	0	0	0	1 (0.6)	0	1 (0.6)	2 (4.8)	2 (4.8)	0
INVESTIGATIONS	7 (2.1)	7 (2.1)	0	1 (0.6)	1 (0.6)	0	1 (2.4)	1 (2.4)	0
BLOOD BILIRUBIN INCREASED	4 (1.2)	4 (1.2)	0	0	0	0	0	0	0

	ONO-4538-12						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
ASPARTATE AMINOTRANSFERASE INCREASED	2 (0.6)	2 (0.6)	0	1 (0.6)	1 (0.6)	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	6 (1.8)	4 (1.2)	0	0	0	0	0	0	0
BACK PAIN	3 (0.9)	2 (0.6)	0	0	0	0	0	0	0
RENAL AND URINARY DISORDERS	6 (1.8)	5 (1.5)	0	5 (3.1)	3 (1.9)	1 (0.6)	1 (2.4)	1 (2.4)	0
HYDRONEPHROSIS	2 (0.6)	1 (0.3)	0	2 (1.2)	2 (1.2)	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (0.9)	3 (0.9)	0	4 (2.5)	2 (1.2)	2 (1.2)	2 (4.8)	1 (2.4)	0
ANAEMIA	3 (0.9)	3 (0.9)	0	2 (1.2)	2 (1.2)	0	2 (4.8)	1 (2.4)	0
DISSEMINATED INTRAVASCULAR COAGULATION	0	0	0	2 (1.2)	0	2 (1.2)	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.3)	1 (0.3)	0	2 (1.2)	1 (0.6)	0	2 (4.8)	2 (4.8)	0
HIP FRACTURE	0	0	0	0	0	0	2 (4.8)	2 (4.8)	0
UNASSIGNED	0	0	0	3 (1.9)	2 (1.2)	0	0	0	0
UNASSIGNED	0	0	0	3 (1.9)	2 (1.2)	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
For CA209032, includes events reported between first dose and 30 days after last dose of study therapy.
For ONO-4538-12, includes events reported between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Table G.89-SCS

Drug-related SAEs

ONO-4538-12

Drug-related SAEs were reported in 10.0% of nivolumab monotherapy-treated subjects and 5.0% of placebo-treated subjects, respectively (Table 66). Drug-related SAEs (reported in 2 or more subjects) were interstitial lung disease (0.9%), and colitis, pyrexia, pneumonia, urinary tract infection, and diabetic ketoacidosis (each 0.6%). No drug-related SAEs were reported in 2 or more subjects in the placebo group.

Drug-related worst Grade 3-4 SAEs were reported in 6.4% and 2.5% of subjects in the nivolumab monotherapy and placebo groups, respectively:

- Drug-related worst Grade 3-4 SAEs in the nivolumab group were diabetic ketoacidosis (0.6%), and hypopituitarism, dry eye, colitis, dry mouth, upper gastrointestinal haemorrhage, vomiting, fatigue, pyrexia, hepatitis acute, pneumonia, rash pustular, urinary tract infection, splenic infection, AST increased, blood bilirubin increased, hepatic enzyme increased, decreased appetite, type 1 diabetes mellitus, Sjogren's syndrome, dyspnoea, interstitial lung disease, pneumonitis, and pneumomediastinum (each 1 subject, 0.3%).
- Drug-related worst Grade 3-4 SAEs in the placebo group were upper gastrointestinal haemorrhage, fatigue, acute hepatic failure, hepatic function abnormal, pneumonia, and pneumonia aspiration (each 1 subject, 0.6%).

Drug-related Grade 5 SAEs were reported in 1.2% of subjects in the nivolumab group and 1.2% of subjects in the placebo group. Drug-related Grade 5 SAEs reported in the nivolumab group were cardiac arrest, death, pneumonia, and dyspnoea exertional (1 subject, 0.3% each). Drug-related Grade 5 SAEs reported in the placebo group were gastrointestinal perforation and sudden death (1 subject, 0.6% each).

Study CA209032 (GC Cohort)

In subjects with GC/GEJ cancer and ≥ 2 prior regimens, drug-related SAEs were reported in 7.1% of subjects (Table 76). Worst Grade 3-4 drug-related SAEs were reported in 1 subject (2.4%); no Grade 3-4 drug-related SAEs reported in more than 1 subject.

Table 76: Summary of Drug-related Serious Adverse Events by Worst CTC Grade with 2% Cutoff - ONO-4538-12 and CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

	ONO-4538-12						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	33 (10.0)	21 (6.4)	4 (1.2)	8 (5.0)	4 (2.5)	2 (1.2)	3 (7.1)	1 (2.4)	0
GASTROINTESTINAL DISORDERS	6 (1.8)	4 (1.2)	0	3 (1.9)	1 (0.6)	1 (0.6)	2 (4.8)	1 (2.4)	0
VOMITING	1 (0.3)	1 (0.3)	0	0	0	0	1 (2.4)	1 (2.4)	0
DIARRHOEA	0	0	0	1 (0.6)	0	0	1 (2.4)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (1.5)	2 (0.6)	1 (0.3)	2 (1.2)	1 (0.6)	1 (0.6)	1 (2.4)	0	0
PYREXIA	2 (0.6)	1 (0.3)	0	0	0	0	1 (2.4)	0	0

MedDRA Version: 20.0
CTC Version 4.0
For CA209032, includes events reported between first dose and 30 days after last dose of study therapy.
For ONO-4538-12, includes events reported between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Table G.90-SCS

Deaths/other significant events

ONO-4538-12

As of the CSR data cut-off date (13-Aug-2016), deaths from any cause during the study were reported in 226 subjects (68.5%) in the nivolumab group and 140 subjects (87.0%) in the placebo group (Table 77).

Table 77: Death Summary - ONO-4538-12

	n (%)	
	Nivolumab	Placebo
N	330	161
Number of subjects who died (%)[a]	226 (68.5)	140 (87.0)
Primary reason for death (%)		
Initial Disease	210 (63.6)	135 (83.9)
Other Cancer	0	0
Other	16 (4.8)	5 (3.1)
Number of subjects who died within 28 days of last dose (%)[b]	25 (7.6)	32 (19.9)
Primary reason for death (%)		
Initial Disease	19 (5.8)	30 (18.6)
Other Cancer	0	0
Other	6 (1.8)	2 (1.2)

[a] Deaths until data cutoff (13-Aug-2016).

[b] Deaths occurring between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of subsequent anti-cancer therapy after the end of treatment period were tabulated.

Disease progression was the most common reason for death in each group (210 subjects [63.6%] and 135 subjects [83.9%], respectively).

Deaths occurring during the treatment period or within 28 days after the last dose of investigational product (or by the start date of post-study treatment, if used) were reported in 25 subjects (7.6%) in the nivolumab group and 32 subjects (19.9%) in the placebo group. Among them, reasons for death were the initial disease 5.8% (19 subjects) in the nivolumab group and 18.6% (30 subjects) in the placebo group. A total of 6 (1.8%) subjects in the nivolumab group and 2 (1.2%) subjects in the placebo group had a reason for death given as "other," as detailed below:

- Nivolumab group: cardiac arrest; PD, pneumonia; cause of death unclear; suicide; progressive exertional dyspnoea; sudden death
- Placebo group: unknown; sepsis

AEs of any cause leading to death, occurring between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of subsequent anti-cancer therapy after the end of treatment period, that were reported in the nivolumab group were malignant neoplasm progression (19 subjects, 5.8%), dyspnoea (2 subjects, 0.6%), and cardiac arrest, asthenia, death, cholangitis, hepatic failure, hepatitis acute, bronchopulmonary aspergillosis, pneumonia, muscular weakness, metastases to lung, tumour haemorrhage, completed suicide, dyspnoea exertional, and pleural effusion (each 1 subject, 0.3%).

Of these AEs leading to death, those considered drug related by the investigator were reported for 5 (1.5%) and 2 (1.2%) subjects in the nivolumab monotherapy and placebo groups, respectively. AEs leading to death reported as drug related in the nivolumab group were cardiac arrest in a subject with confirmed PD and mediastinal emphysema, death of indeterminate cause in a subject with PD, hepatitis acute in a subject with history of chronic liver parenchymal disease and PD, pneumonia in a subject with PD, and dyspnoea exertional in a subject with suspect of PD

AEs of any cause leading to death reported in the placebo group were malignant neoplasm progression (10 subjects, 6.2%), sepsis (3 subjects, 1.9%), disseminated intravascular coagulation and gastrointestinal obstruction (each 2 subjects, 1.2%), and gastrointestinal perforation, sudden death, hepatic failure, pneumonia, metastases to liver, metastases to central nervous system, renal failure, renal impairment, and pulmonary embolism (each 1 subject, 0.6%). Of these, drug-related AEs in the placebo group were gastrointestinal perforation and sudden death (each 1 subject, 0.6%).

Study CA209032 (GC Cohort)

As of the interim CSR DBL, 25 (59.5%) subjects in the 42-subject subset with GC/GEJ and ≥ 2 prior regimens had died (Table 78). Among subjects who died, disease progression was the most common cause of death (59.5%), including the deaths occurring within 30 days (14.3%) and 100 days (42.9%) of last dose. There were no deaths attributed to study drug toxicity.

Table 78: Death Summary - CA209032 (All Nivolumab Monotherapy Treated with GC or GEJ Cancer and at Least 2 Prior Regimens) Subjects

	Nivolumab N = 42
NUMBER OF SUBJECTS WHO DIED (%)	25 (59.5)
PRIMARY REASON FOR DEATH (%)	
DISEASE PROGRESSION	25 (59.5)
STUDY DRUG TOXICITY	0
UNKNOWN	0
OTHER	0
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	6 (14.3)
PRIMARY REASON FOR DEATH (%)	
DISEASE PROGRESSION	6 (14.3)
STUDY DRUG TOXICITY	0
UNKNOWN	0
OTHER	0
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	18 (42.9)
PRIMARY REASON FOR DEATH (%)	
DISEASE PROGRESSION	18 (42.9)
STUDY DRUG TOXICITY	0
UNKNOWN	0
OTHER	0

Crossover subjects are truncated at the first dose date of crossover period.
Program Source: /projects/bms219884/stats/ia bogc/prog/tables/rt-dtgge.sas 21JUN2017:03:25:44

Immunogenicity

ONO-4538-12 and CA209032 (GC Cohort with GC/GEJ and ≥ 2 prior regimens)

Of the 307 subjects from Study ONO-4538-12 treated with nivolumab 3 mg/kg Q2W and evaluable for immunogenicity, 36 (11.7%) were ADA positive. Of the 36 subjects, 1 was persistent positive for ADA, 18 had positive samples at the last sampling timepoint, and 17 were considered other positive.

Of the 37 subjects with GC/GEJ and ≥ 2 prior regimens from Study CA209032 treated with nivolumab 3 mg/kg Q2W and evaluable for immunogenicity, 9 subjects (24.3%) were ADA positive. Of the 9 subjects, none were persistent positive or neutralizing positive, 4 had positive samples at the last sampling timepoint, and 5 were considered other positive.

Overall, the immunogenicity incidence in subjects with GC/GEJ and ≥ 2 prior regimens was 13.1% and is similar to that previously reported and within the range of immunogenicity incidences observed across different tumour types (see Clinical Pharmacology).

In total, of the 6 GC subjects who had infusion-related or hypersensitivity reactions following administration of nivolumab 3 mg/kg Q2W, 3 were ADA positive (1 in Study CA209032, 2 in ONO-4538-12) and 3 were ADA negative (all 3 in ONO-4538-12). In both ADA positive and ADA negative subsets, 2 of the 3 AEs were considered drug related. Thus, a clear pattern related to ADA formation and safety events cannot be established. These data suggest a lack of effect of nivolumab ADA on safety.

Laboratory findings

Hematology

Hematology was assessed through laboratory evaluation of haemoglobin, platelet count, leukocytes, lymphocytes, and absolute neutrophils.

ONO-4538-12

The majority of abnormal hematology values were Grade 1 or 2 in both treatment groups. The majority of subjects in the nivolumab group did not have on-study worsening of hematology values. There were no

clear differences in the frequencies of worsened hematology parameters between the treatment groups. In the nivolumab group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ Grade 3 for haemoglobin decreased in 18 subjects, lymphocyte count decreased in 13 subjects, and platelet count decreased in 5 subjects. In the placebo group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ Grade 3 for lymphocyte count decreased in 13 subjects, haemoglobin decreased in 12 subjects, platelet count decreased in 6 subjects, white blood cell decreased in 2 subjects, and neutrophil count decreased in 1 subject.

CA209032 (GC Cohort)

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

The only Grade 3-4 hematologic abnormalities reported in ≥ 5% of treated GC/GEJ cancer subjects and ≥ 2 prior regimens with on-treatment laboratory results were decreased haemoglobin (11.9% Grade 3 only) and decreased absolute lymphocytes (21.4% Grade 3; 2.4% Grade 4).

For the 59 subjects in the GC cohort, the only Grade 3- 4 hematologic abnormalities reported in ≥ 5% of treated subjects with on-treatment laboratory results were decreased haemoglobin (10.2% Grade 3 only) and decreased absolute lymphocytes (18.6% Grade 3; 1.7% Grade 4).

Serum Chemistry

Liver Function Tests

ONO-4538-12

The majority of abnormal liver function test (LFT) values were Grade 1 or 2 in both treatment groups, and the majority of subjects in the nivolumab group did not have on-study worsening of LFT values. There were no clear differences in the frequencies of worsened hepatic function parameters between the treatment groups. In the nivolumab group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ Grade 3 for AST increased in 31 subjects, blood bilirubin increased in 27 subjects, ALP increased in 26 subjects, and ALT increased in 18 subjects. In the placebo group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ Grade 3 for blood bilirubin increased in 17 subjects, AST increased in 15 subjects, ALP increased in 14 subjects, and ALT increased in 7 subjects.

The ALT or AST level was > 3 x upper limit of normal (ULN) and the bilirubin level (measured within 30 days before or after ALT or AST measurement) was > 2 x ULN in 7.6% of subjects (25 subjects) in the nivolumab group and 8.1% of subjects (13 subjects) in the placebo group (Table 79).

Table 79: Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests, SI Units - Treated Subjects in ONO-4538-12

	n (%)	
	Nivolumab Group (N = 330)	Placebo Group (N = 161)
ALT or AST > 3× ULN	57 (17.3)	31 (19.3)
ALT or AST > 5× ULN	37 (11.2)	18 (11.2)
ALT or AST > 10× ULN	14 (4.2)	7 (4.3)
ALT or AST > 20× ULN	4 (1.2)	3 (1.9)
Total bilirubin > 2× ULN	34 (10.3)	21 (13.0)
ALT or AST > 3× ULN as well as total bilirubin collected 1day before and after > 2× ULN	23 (7.0)	13 (8.1)
ALT or AST > 3× ULN as well as total bilirubin collected 30 days before and after > 2× ULN	25 (7.6)	13 (8.1)
ALT or AST > 3× ULN as well as total bilirubin collected 1 day before and after ≥ 2× ULN, ALP < 2× ULN	2 (0.6)	0

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = Upper Limit of Normal.

Laboratory tests occurring between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of subsequent anti-cancer therapy after the end of treatment period were tabulated.

Safety analysis set.

Source: Refer to Table 14.3.1.2.3-1 in the ONO-4538-12 Final CSR

CA209032 (GC Cohort)

In treated GC/GEJ cancer subjects and ≥ 2 prior regimens, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2. 1 subject had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 1 day, and within 30 days, of last dose of study therapy (Table 80).

Table 80: Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests, SI Units - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

	Nivolumab N = 42
	N = 41
ALT OR AST > 3XULN	6 (14.6)
ALT OR AST > 5XULN	4 (9.8)
ALT OR AST > 10XULN	1 (2.4)
ALT OR AST > 20XULN	0
	N = 41
TOTAL BILIRUBIN > 2XULN	1 (2.4)
	N = 41
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	1 (2.4)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	1 (2.4)

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
Crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix G.174-EUSCS in Appendix 3

Kidney Function Tests

ONO-4538-12

CTCAE grade of creatinine increased was worsened by at least 2 grades from baseline to ≥ Grade 3 in 6 subjects of the nivolumab group and 5 subjects of the placebo group.

CA209032 (GC Cohort)

Among subjects with GC/GEJ cancer and ≥ 2 prior regimens, with at least 1 on-treatment measurement, 87.8% had normal creatinine values during the treatment reporting period, similar to subjects in the nivolumab monotherapy GC cohort (87.9%).

Reported abnormalities in creatinine (increases) were all Grade 1 or 2. No Grade 3 or 4 abnormalities were reported.

Thyroid Function Tests

ONO-4538-12

The majority of subjects in both treatment groups had normal thyroid-stimulating hormone (TSH) values throughout the treatment reporting period (Table 81). Percentages of subjects with a baseline TSH ≤ ULN and a post-baseline TSH increase to > ULN were 13.6% in the nivolumab group and 3.7% in the placebo group.

Elevated (> ULN) TSH on study was observed in 21.2% of subjects. The frequency of subjects with at least 1 on-study elevated TSH and 1 free T3 or T4 < LLN was 17.3%.

Low TSH levels were reported in 10.9% and 1.2% of subjects in the nivolumab monotherapy and placebo groups, respectively. A total of 9.4% of subjects had on-study low TSH with ≥ lower limit of normal (LLN) at baseline.

Percentages of subjects who experienced a TSH decrease to < LLN accompanied by an increase at least once in free T3 or free T4 to > ULN were 5.2% in the nivolumab group and 0.6% in the placebo group.

Table 81: Summary of On-Treatment Laboratory Abnormalities in Specific Thyroid Tests, SI Units - Treated Subjects in ONO-4538-12

	n (%)	
	Nivolumab Group (N = 330)	Placebo Group (N = 161)
TSH > ULN	70 (21.2)	18 (11.2)
TSH > ULN as well as TSH ≤ ULN at the baseline	45 (13.6)	6 (3.7)
TSH > ULN as well as either free T3 or free T4 < LLN	57 (17.3)	11 (6.8)
TSH > ULN as well as both free T3 and free T4 ≥ LLN	12 (3.6)	6 (3.7)
TSH > ULN as well as either free T3 or free T4 is missing value	0	0
TSH < LLN	36 (10.9)	2 (1.2)
TSH < LLN as well as TSH ≥ LLN at the baseline	31 (9.4)	1 (0.6)
TSH < LLN as well as either free T3 or free T4 > ULN	17 (5.2)	1 (0.6)
TSH < LLN as well as both free T3 and free T4 ≤ ULN	19 (5.8)	1 (0.6)
TSH < LLN as well as either free T3 or free T4 is missing value	0	0

Abbreviations: LLN = lower limit of normal; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.
Hormone tests occurring between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of subsequent anti-cancer therapy after the end of treatment period were tabulated.
Safety analysis set.
Source: Refer to Table 14.3.1.3.1-1 in the ONO-4538-12 Final CSR

CA209032 (GC Cohort)

The majority of subjects with GC/GEJ cancer and ≥ 2 prior regimens had normal TSH levels at baseline and throughout the treatment period (Table 82). The proportion of subjects with TSH increases (> ULN) or decreases (< LLN) from baseline were 26.8% and 22.0%, respectively, similar to subjects in the nivolumab monotherapy GC cohort (24.1% and 20.7%, respectively).

Table 82: Summary of On-Treatment Laboratory Abnormalities in Specific Thyroid Tests, SI Units - CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

	Nivolumab N = 41
TSH > ULN	11 (26.8)
TSH > ULN	
WITH TSH <= ULN AT BASELINE	6 (14.6)
TSH > ULN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	7 (17.1)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	4 (9.8)
WITH FT3/FT4 TEST MISSING (A) (B)	0
TSH < LLN	9 (22.0)
TSH < LLN	
WITH TSH >= LLN AT BASELINE	9 (22.0)
TSH < LLN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	4 (9.8)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	4 (9.8)
WITH FT3/FT4 TEST MISSING (A) (B)	1 (2.4)

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.
Crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix G.175-EUSCS in Appendix 3

Electrolytes

ONO-4538-12

There were no clear differences in the frequencies of worsened electrolyte levels between the treatment groups. In the ONO-4538 group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ Grade 3 for sodium decreased in 31 subjects, potassium decreased in 9 subjects, potassium increased in 7 subjects, calcium decreased in 1 subject, and sodium increased in 1 subject. In the placebo group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ Grade 3 for sodium decreased in 21 subjects, potassium increased in 5 subjects, potassium decreased in 3 subjects, calcium increased in 2 subjects, and calcium decreased in 1 subject.

CA209032 (GC Cohort)

Most subjects with GC/GEJ cancer and ≥ 2 prior regimens had normal electrolyte levels during the treatment reporting period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. The only Grade 3-4 abnormalities in electrolytes reported in ≥ 5% of treated subjects with on-treatment laboratory results were hyponatremia (9.8% Grade 3 and 2.4% Grade 4), similar to subjects in the nivolumab monotherapy GC cohort (10.3% Grade 3 and 1.7% Grade 4).

Vital Signs

Vital signs and oxygen saturation by pulse oximetry were monitored and recorded at the site per institutional standard of care during screening and treatment visits. In ONO-4538-12, 12-lead electrocardiograms were also collected. These assessments were intended to be used as safety monitoring by the treating physician.

12-lead electrocardiogram: QTcF after the start of study treatment was 500 ms or below in all subjects.

Safety in special populations

Intrinsic and Extrinsic Factors

ONO-4538-12

The overall incidences of AEs in subgroups were generally similar to that in all the treated subject population, suggesting no effects of the examined demographic and other baseline factors on their incidences.

CA209032 (GC Cohort)

In the nivolumab monotherapy GC cohort, the frequencies of all-causality and drug-related AEs in the nivolumab group for subgroups of gender, race, age, and region were similar to the AE frequencies in the overall treated population. Small numerical differences in frequencies of AEs were observed in nivolumab-treated subjects in the following subgroups:

- Any-grade and Grade 3-4 drug-related AEs for male (73.3% and 13.3%) vs female (57.1% and 28.6%).
- Any grade and Grade 3-4 AEs for < 65 years age (100% and 40.5%) vs ≥ 65 years age (94.1% and 52.9%). Any grade and Grade 3-4 drug-related AEs for < 65 years age (64.3% and 14.3%) vs ≥ 65 years age (82.4% and 23.5%).
- A greater frequency of all causality Grade 3-4 AEs were reported in Rest of the World (55.6%) vs US (34.4%).

These differences are of limited interpretability due to low sample sizes and event rates, and do not alter the overall safety profile of nivolumab in these subgroups.

Special Population - Age Groups

Safety by Age in ONO-4538-12 and CA209032 (GC Cohort) Studies

In the ONO-4538-12 and CA209032 (subjects with GC/GEJ cancer and ≥ 2 prior regimens) studies, the frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group in pooled nivolumab monotherapy treated subjects (ONO-4538-12: N = 330; CA209032: [subjects with GC/GEJ cancer and ≥ 2 prior regimens], N = 42) are presented in Table 83. Interpretation is limited by small number of subjects in the 75 to 84 years of age subgroup (n = 32) and there were no subjects ≥ 85 years of age.

Table 83: Summary of Safety Results by Age Group - All Pooled Nivolumab Monotherapy Treated Subjects in ONO-4538-12 and CA209032 (All Nivolumab Monotherapy Subjects with GC/GEJ Cancer and at Least 2 Prior Regimens)

	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 221	65-74 N = 119	75-84 N = 32	>= 85 N = 0	Total N = 372
TOTAL SUBJECTS WITH AN EVENT	206 (93.2)	106 (89.1)	29 (90.6)	0	341 (91.7)
SERIOUS AE - TOTAL	100 (45.2)	42 (35.3)	13 (40.6)	0	155 (41.7)
FATAL (DEATH)	27 (12.2)	11 (9.2)	2 (6.3)	0	40 (10.8)
HOSPITALIZATION/PROLONGATION	94 (42.5)	38 (31.9)	12 (37.5)	0	144 (38.7)
LIFE THREATENING	3 (1.4)	3 (2.5)	0	0	6 (1.6)
CANCER	0	0	0	0	0
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	2 (0.9)	1 (0.8)	1 (3.1)	0	4 (1.1)
AE LEADING TO DISCONTINUATION	10 (4.5)	13 (10.9)	3 (9.4)	0	26 (7.0)
PSYCHIATRIC DISORDERS	26 (11.8)	6 (5.0)	4 (12.5)	0	36 (9.7)
NERVOUS SYSTEM DISORDERS	45 (20.4)	16 (13.4)	4 (12.5)	0	65 (17.5)
ACCIDENT AND INJURIES	5 (2.3)	4 (3.4)	2 (6.3)	0	11 (3.0)
CARDIAC DISORDERS	4 (1.8)	1 (0.8)	0	0	5 (1.3)
VASCULAR DISORDERS	16 (7.2)	9 (7.6)	2 (6.3)	0	27 (7.3)
CEREBROVASCULAR DISORDERS	5 (2.3)	0	0	0	5 (1.3)
INFECTIONS AND INFESTATIONS	52 (23.5)	21 (17.6)	10 (31.3)	0	83 (22.3)
ANTICHOLINERGIC SYNDROME	55 (24.9)	21 (17.6)	6 (18.8)	0	82 (22.0)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	13 (5.9)	7 (5.9)	2 (6.3)	0	22 (5.9)

CTC Version 4.0; MedDRA Version: 20.0. Analysis generated from integrated database.

For ONO-4538-12 includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period. For CA209032, includes events reported between first dose and 30 days after last dose of study therapy.
Program Source: /projects/bms211280/stats/Gastric_EU_SCS/prog/tables/rt-ae-eusumage.sas 29JUN2017:11:53:13

Safety by Age across Integrated Monotherapy Studies, Including ONO-4538-12 and CA209032 (GC Cohort)

Nivolumab monotherapy integrated across indications (GC, NSCLC, SCCHN, melanoma, RCC, cHL, and urothelial cancer) is presented below. Frequencies of SAEs, AEs leading to dropout, and postural hypotension increased slightly with increasing age. Interpretation of the frequencies in the ≥ 85 years age group is limited due to the small number of subjects.

Table 84: Summary of On-treatment AEs by Age Group - All Treated Subjects - Nivolumab Monotherapy Data Integrated Across Indications, Including ONO-4538-12 and CA209032 (All Nivolumab Monotherapy Subjects with GC/GEJ Cancer and at Least 2 Prior Regimens)

	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 1852	65-74 N = 820	75-84 N = 253	>= 85 N = 25	Total N = 2950
TOTAL SUBJECTS WITH AN EVENT	1807 (97.6)	793 (96.7)	244 (96.4)	25 (100.0)	2869 (97.3)
SERIOUS AE - TOTAL	807 (43.6)	395 (48.2)	127 (50.2)	14 (56.0)	1343 (45.5)
FATAL (DEATH)	203 (11.0)	100 (12.2)	30 (11.9)	3 (12.0)	336 (11.4)
HOSPITALIZATION/PROLONGATION	715 (38.6)	348 (42.4)	115 (45.5)	11 (44.0)	1189 (40.3)
LIFE THREATENING	32 (1.7)	15 (1.8)	2 (0.8)	0	49 (1.7)
CANCER	25 (1.3)	19 (2.3)	10 (4.0)	2 (8.0)	56 (1.9)
DISABILITY/INCAPACITY	1 (<0.1)	1 (0.1)	0	0	2 (<0.1)
IMPORTANT MEDICAL EVENT	68 (3.7)	32 (3.9)	9 (3.6)	1 (4.0)	110 (3.7)
AE LEADING TO DISCONTINUATION	237 (12.8)	141 (17.2)	56 (22.1)	5 (20.0)	439 (14.9)
PSYCHIATRIC DISORDERS	334 (18.0)	119 (14.5)	41 (16.2)	7 (28.0)	501 (17.0)
NERVOUS SYSTEM DISORDERS	624 (33.7)	247 (30.1)	81 (32.0)	14 (56.0)	966 (32.7)
ACCIDENT AND INJURIES	132 (7.1)	68 (8.3)	28 (11.1)	3 (12.0)	231 (7.8)
CARDIAC DISORDERS	154 (8.3)	68 (8.3)	19 (7.5)	5 (20.0)	246 (8.3)
VASCULAR DISORDERS	273 (14.7)	141 (17.2)	41 (16.2)	10 (40.0)	465 (15.8)
CEREBROVASCULAR DISORDERS	27 (1.5)	25 (3.0)	8 (3.2)	1 (4.0)	61 (2.1)
INFECTIONS AND INFESTATIONS	745 (40.2)	332 (40.5)	98 (38.7)	14 (56.0)	1189 (40.3)
ANTICHOLINERGIC SYNDROME	642 (34.7)	254 (31.0)	80 (31.6)	11 (44.0)	987 (33.5)
QUALITY OF LIFE DECREASED	1 (<0.1)	0	0	0	1 (<0.1)
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	192 (10.4)	90 (11.0)	33 (13.0)	4 (16.0)	319 (10.8)

CTC Version 4.0; MedDRA Version: 20.0
Includes events reported between first dose and 30 days after last dose of study therapy, except for ONO-4538-12.
For ONO-4538-12 includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, CA209141, CA209275, ONO-4538-12 and CA209032 (UC and GC/GEJ 3L+ subjects).
Program Source: /projects/bms211280/stats/Gastric_EU_SCS/prog/tables/rt-ae-eusumage.sas 29JUN2017:11:52:17

Use in Pregnancy and Lactation

ONO-4538-12

Although 1 female subject had a positive pregnancy test result in the follow-up period, the investigator confirmed that the subject was not pregnant. Therefore, pregnancy was not reported in this study.

CA209032 (GC Cohort)

No positive pregnancy tests were reported.

Overdose

No new information.

Drug Abuse

No new information.

Withdrawal and Rebound

No cases of withdrawal symptoms related to nivolumab were reported during human clinical trials.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Nivolumab has minor influence on the ability to drive and use machines. Fatigue is a common side effect which may also impair the ability to drive and use machines (see Common Adverse Events). Patients should be advised not to drive or use machines if they feel tired.

Safety related to drug-drug interactions and other interactions

No new information

Discontinuation due to adverse events

All AEs Leading to Discontinuation (All Causality)

ONO-4538-12

AEs leading to discontinuation of study treatment were reported in 7.0% of subjects in the nivolumab group and 7.5% of subjects in the placebo group (Table 85). Worst Grade 3-4 AEs leading to treatment discontinuation were reported in 3.9% and 5.6% of subjects, respectively.

The common AEs leading to discontinuation of study treatment reported in the nivolumab monotherapy and placebo groups, excluding disease progression, included interstitial lung disease (0.9%, 3 subjects), blood bilirubin increased (0.9%, 3 subjects), and muscular weakness (0.6%, 2 subjects).

Study CA209032 (GC Cohort)

In subjects with GC/GEJ cancer and ≥ 2 prior regimens, AEs leading to discontinuation of study drug were reported in 7.1% of subjects (Table 2.4-1). Worst Grade 3-4 AEs leading to discontinuation were reported in 2 subjects (4.8%) (colitis and pneumonia, in 1 subject each).

Table 85: Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) - ONO-4538-12 and CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

	ONO-4538-12						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	23 (7.0)	13 (3.9)	6 (1.8)	12 (7.5)	9 (5.6)	3 (1.9)	3 (7.1)	2 (4.8)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (2.1)	3 (0.9)	3 (0.9)	1 (0.6)	0	1 (0.6)	0	0	0
DISEASE PROGRESSION	6 (1.8)	3 (0.9)	2 (0.6)	1 (0.6)	0	1 (0.6)	0	0	0
DEATH	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (1.5)	2 (0.6)	1 (0.3)	1 (0.6)	1 (0.6)	0	0	0	0
INTERSTITIAL LUNG DISEASE	3 (0.9)	1 (0.3)	0	0	0	0	0	0	0
DYSPNOEA EXERTIONAL	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
PNEUMONITIS	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
PNEUMONIA ASPIRATION	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
INVESTIGATIONS	3 (0.9)	3 (0.9)	0	0	0	0	0	0	0
BLOOD BILIRUBIN INCREASED	3 (0.9)	3 (0.9)	0	0	0	0	0	0	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	0	0	0	0	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	0	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	2 (0.6)	1 (0.3)	0	3 (1.9)	2 (1.2)	1 (0.6)	1 (2.4)	1 (2.4)	0
ABDOMINAL PAIN	1 (0.3)	0	0	0	0	0	0	0	0
CONSTIPATION	1 (0.3)	0	0	0	0	0	0	0	0
NAUSEA	1 (0.3)	0	0	0	0	0	0	0	0
SMALL INTESTINAL OBSTRUCTION	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
VOMITING	1 (0.3)	0	0	0	0	0	0	0	0
ASCITES	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
COLITIS	0	0	0	0	0	0	1 (2.4)	1 (2.4)	0
GASTROINTESTINAL PERFORATION UPPER	0	0	0	1 (0.6)	0	1 (0.6)	0	0	0
GASTROINTESTINAL HAEMORRHAGE	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.6)	1 (0.3)	0	0	0	0	0	0	0
MUSCULAR WEAKNESS	2 (0.6)	1 (0.3)	0	0	0	0	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (0.6)	1 (0.3)	1 (0.3)	4 (2.5)	4 (2.5)	0	0	0	0
MALIGNANT NEOPLASM PROGRESSION	2 (0.6)	1 (0.3)	1 (0.3)	2 (1.2)	2 (1.2)	0	0	0	0
METASTASES TO CENTRAL NERVOUS SYSTEM	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
TUMOUR PSEUDOPROGRESSION	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
CARDIAC DISORDERS	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
CARDIAC ARREST	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
HEPATOBILIARY DISORDERS	1 (0.3)	1 (0.3)	0	1 (0.6)	1 (0.6)	0	0	0	0
HEPATITIS ACUTE	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
HEPATIC FUNCTION ABNORMAL	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0

	ONO-4538-12						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
INFECTIONS AND INFESTATIONS	1 (0.3)	1 (0.3)	0	1 (0.6)	1 (0.6)	0	1 (2.4)	1 (2.4)	0
BILIARY TRACT INFECTION	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
PNEUMONIA	0	0	0	1 (0.6)	1 (0.6)	0	1 (2.4)	1 (2.4)	0
RENAL AND URINARY DISORDERS	1 (0.3)	0	0	0	0	0	0	0	0
URINARY INCONTINENCE	1 (0.3)	0	0	0	0	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	1 (0.6)	0	1 (0.6)	0	0	0
DISSEMINATED INTRAVASCULAR COAGULATION	0	0	0	1 (0.6)	0	1 (0.6)	0	0	0
METABOLISM AND NUTRITION DISORDERS	0	0	0	2 (1.2)	2 (1.2)	0	0	0	0
HYPERCALCAEMIA	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
HYPOGLYCAEMIA	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
NERVOUS SYSTEM DISORDERS	0	0	0	0	0	0	1 (2.4)	0	0
CEREBRAL HAEMORRHAGE	0	0	0	0	0	0	1 (2.4)	0	0
CEREBRAL ISCHAEMIA	0	0	0	0	0	0	1 (2.4)	0	0

MedDRA Version: 20.0
CTC Version 4.0
For CA209032, includes events reported between first dose and 30 days after last dose of study therapy.
For ONO-4538-12, includes events reported between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Table G.87-SCS

Drug-related AEs Leading to Discontinuation

ONO-4538-12

The frequency of drug-related AEs leading to discontinuation was similar between nivolumab and placebo-treated subjects. Drug-related AEs leading to discontinuation of study treatment were reported in 2.7% of subjects in the nivolumab group and 2.5% of subjects in the placebo group. The most frequently reported drug-related AE leading to discontinuation was interstitial lung disease (0.9%, 3 subjects in the nivolumab group). Drug-related worst Grade 3-4 AEs leading to discontinuation of study treatment were reported in 1.2% and 1.9% of subjects, respectively (Table 86).

Study CA209032 (GC Cohort)

In subjects with GC/GEJ cancer and ≥ 2 prior regimens, a Grade 1-2 drug related AE of colitis was reported in 1 subject (2.4%) which led to discontinuation.

Table 86: Summary of Drug-Related Adverse Events Leading to Discontinuation by Worst CTC Grade - (Any Grade, Grade 3-4, Grade 5) - ONO-4538-12 and CA209032 (All Nivolumab Monotherapy with GC/GEJ Cancer and at Least 2 Prior Regimens) Subjects

	ONO-4538-12						CA209032 Gastric Monotherapy		
	Nivolumab 3mg/kg N = 330			Placebo N = 161			Nivo 3mg/kg GC/GEJ Cancer Subset N = 42		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	9 (2.7)	4 (1.2)	3 (0.9)	4 (2.5)	3 (1.9)	1 (0.6)	1 (2.4)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (1.5)	2 (0.6)	1 (0.3)	1 (0.6)	1 (0.6)	0	0	0	0
INTERSTITIAL LUNG DISEASE	3 (0.9)	1 (0.3)	0	0	0	0	0	0	0
DYSPNOEA EXERTIONAL	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
PNEUMONITIS	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
PNEUMONIA ASPIRATION	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
CARDIAC DISORDERS	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
CARDIAC ARREST	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
DEATH	1 (0.3)	0	1 (0.3)	0	0	0	0	0	0
HEPATOBILIARY DISORDERS	1 (0.3)	1 (0.3)	0	1 (0.6)	1 (0.6)	0	0	0	0
HEPATITIS ACUTE	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
HEPATIC FUNCTION ABNORMAL	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
MUSCULAR WEAKNESS	1 (0.3)	1 (0.3)	0	0	0	0	0	0	0
GASTROINTESTINAL DISORDERS	0	0	0	2 (1.2)	1 (0.6)	1 (0.6)	1 (2.4)	0	0
COLITIS	0	0	0	0	0	0	1 (2.4)	0	0
GASTROINTESTINAL PERFORATION UPPER	0	0	0	1 (0.6)	0	1 (0.6)	0	0	0
GASTROINTESTINAL HAEMORRHAGE	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
INFECTIONS AND INFESTATIONS	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
PNEUMONIA	0	0	0	1 (0.6)	1 (0.6)	0	0	0	0
INVESTIGATIONS	0	0	0	0	0	0	0	0	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	0	0	0	0	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	0	0	0	0	0	0	0

MedDRA Version: 20.0
CTC Version 4.0
For CA209032, includes events reported between first dose and 30 days after last dose of study therapy.
For ONO-4538-12, includes events reported between the start date of the first administration of the product and the earlier date on which either 28 days after the end of the treatment period or the start date of the post-treatment observation period.
Analysis generated from integrated database.
Source: Table G.88-SCS

Adverse Events Leading to Dose Delay

ONO-4538-12

AEs leading to dose delay were reported in 19.1% of subjects in the nivolumab group and 16.8% of subjects in the placebo group. The most frequently reported AE leading to dose delay in the nivolumab group was pneumonia and AST increased (7 subjects, 2.1% [each PT]). Drug-related AEs leading to dose delay were reported in 7.6% and 1.2% of subjects in the nivolumab monotherapy and placebo groups, respectively.

Study CA209032 (GC Cohort)

In subjects with GC/GEJ cancer and ≥ 2 prior regimens, the overall frequency of AEs (regardless of causality) leading to a dose delay was 31.0%. The most frequently reported AEs were pyrexia, anaemia, AST increased, and ALT increased (each 2 subjects, 4.8%).

Post marketing experience

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved across multiple countries, including the US and the EU, and for other indications (eg, metastatic NSCLC, advanced RCC, cHL, SCCHN, and urothelial carcinoma). Based on routine pharmacovigilance activities conducted by BMS Global Pharmacovigilance and Epidemiology, review of post marketing safety data confirms the clinical trial safety data for nivolumab. The established positive benefit-risk profile of nivolumab in the post marketing setting remains consistent. Post marketing data for nivolumab are subject to continued active pharmacovigilance monitoring and evaluation, and are reported as per applicable post-marketing safety reporting requirements, as well as periodically to global health authorities.

2.5.1. Discussion on clinical safety

For the purpose this variation, the safety dataset consist of safety data from studies ONO-4538-12 and CA209032 (GC cohort ≥2 prior lines), which support the use of nivolumab monotherapy at the recommended dose and schedule of 3 mg/kg administered as an intravenous (IV) infusion every 2 weeks (Q2W) for the treatment of adults with advanced or recurrent gastric cancer (GC) or gastroesophageal junction (GEJ) cancer after 2 or more prior systemic therapies.

Data from trial ONO-4538-12 and the GC≥2 prior lines has been presented separately which is agreed given the differences between studies and populations.

At the date of the clinical database lock for trial ONO-4538-12 (13-Aug-2016), the majority of patients had discontinued study treatment (87.9% in nivo arm and 98.1% in placebo arm) mainly because of disease progression. The median duration of treatment was 1.92 months (range: 0 - 19.5 months) in the nivolumab group and 1.05 months (range: 0 - 20.5 months) in the placebo group.

Discontinuation due to AEs was similar between nivolumab and placebo arms (7.0% and 7.5% respectively; 2.7% and 2.5% respectively were drug related). The most frequently reported drug-related AE leading to discontinuation was interstitial lung disease (0.9%, 3 subjects in the nivolumab group). AEs leading to dose delay were reported in 19.1% and 16.8% of nivolumab and placebo groups respectively.

The median duration of nivolumab monotherapy in CA209032 was similar to that of the phase III trial, 2.33 months. As of the 24-Mar- 2016 DBL, 3 subjects (7.1%) subjects continued in the treatment period and 30 subjects (71.4%) continued to be followed after treatment discontinuation.

7.1% of patients discontinued due to AEs. Worst Grade 3-4 AEs leading to discontinuation were reported in 2 subjects (4.8%) (colitis and pneumonia, in 1 subject each). A Grade 1-2 drug related AE of colitis was reported in 1 subject (2.4%) which led to discontinuation. Dose delays due to AEs were reported less frequently than in the phase III trial (31% of patients). The most frequently reported AEs leading to dose delay were pyrexia, anaemia, AST increased, and ALT increased (each 2 subjects, 4.8%).

Overall profile of Adverse events

The overall incidence of AEs (90.9% in nivo arm and 41.5% in placebo arm) (97.6% GC ≥2 prior lines from CA209032), drug-related AEs (42.7% in nivo arm and 26.7% in placebo arm) (64.3% GC ≥2 prior lines from CA209032), G3/4 AEs (41.5% in nivo arm and 39.1% in placebo arm) (45.2% GC ≥2 prior lines from CA209032), drug-related 20.2%), drug-related G3/4 AEs (10.3% in nivo arm and 4.3% in placebo arm) (14.3% GC ≥2 prior lines from CA209032) during treatment with nivolumab in this GC/GEJ population was high.

SAEs were also high (overall 39.7% in nivo arm and 46.6% in placebo arm) (57.1% GC ≥2 prior lines from CA209032), drug-related 20.2%), Drug-related SAEs (10.0% in nivo arm and 5.0% in placebo arm)

(7.1% GC ≥2 prior lines from CA209032). Drug-related AEs leading to death were reported in 5 subjects from ONO-4538-12, most of them with confirmed or suspected progression disease and no deaths were directly attributed to study drug toxicity in trial CA209032.

Although the underlying condition may be contributing to the overall toxicity, which is not unexpected bearing the mind the overall heavily pretreated population with a rapid evolving metastatic disease, only in few cases led to treatment discontinuation in both trials (7.0% overall AEs in nivo arm and 7.5 in placebo arm from ONO-4538-12, 2.7% and 2.5% drug-related AEs respectively) (7.1% GC ≥2 prior lines from CA209032; 2.4% drug-related AEs). Having said that, median duration on study treatment is particularly short, not reaching 2 months in any of the trials.

Drug-related Adverse Events

In ONO-4538-12 the most frequently reported drug-related AE leading to discontinuation interstitial lung disease (0.9% in nivolumab group). 19.1% and 16.8% of patients in nivolumab an placebo arms respectively had dose delays.

In GC ≥2 prior lines from CA209032 grade 1-2 drug-relates colitis was reported in 1 subject (2.4%) which led to discontinuation.

In trial ONO-4538-12, the most common treatment-related AEs for the nivolumab-treated patients were: pruritus (9.1%), diarrhoea (7.0%), fatigue (5.5%), decreased appetite (4.8%), nausea (4.2%), pyrexia (2.4%), arthritis (0.9%). Most of them were mild-moderate in severity.

Although the distribution of most common treatment related AEs were similar in CA209032 GC cohort (n=42) these were consistently more frequently reported: pruritus (21.4%), diarrhoea (14.3%), fatigue (33.3%), decreased appetite (11.9%), nausea (11.9%), pyrexia (11.9%), arthritis (11.9%). Again, most of them were mild-moderate in severity with only 1 patient who experienced a grade 3-4 AE of diarrhoea.

Thus, the safety profile was comparable between the two studies, but the most common types of (both any Grade as well as Grade 3-4) (DR)AEs were generally reported at higher frequencies in study CA209032.

In general, the overall safety profile of nivolumab monotherapy in patients with GC/GEJ seems to be consistent with the profile known from previous indications.

Selected AEs

As with other authorized indications, selected AEs were more frequently reported in the skin (15.5%) followed by GI (7.0%) and hepatic (5.5%) SOCs in ONO-4538-12 trial. Most of them were of mild-moderate intensity. In general, the observed profile of selected AEs is largely similar to that observed in other indications.

Similarly in CA209032 GC≥2 prior lines AEs were more frequently reported in the skin (23.8%) followed by GI (16.7%) and endocrine (9.5%).

The most commonly reported drug related GI AEs were diarrhoea an colitis in both trials.

Drug.-related hepatitis was notified in 1 patient from ONO-4538-12 trial.

There were 6 patients who reported interstitial lung disease (1.8%) and 1 patient who reported pneumonitis in ONO trial. 2 patients reported pneumonitis in CA209032 GC≥2 prior lines.

Skin events more frequently reported were pruritus and rash, all of them grade 1-2 in both trials.

Select AEs were generally manageable with few discontinuations due to drug-related AEs (interstitial lung

disease [3 subjects], hepatitis acute [1 subject], and pneumonitis [1 subject] in ONO-4538-12;).

SAEs and deaths

In **ONO-4538-12**, drug-related SAEs were reported in 10.0% of nivolumab monotherapy-treated subjects and 5.0% of placebo-treated subjects in ONO-4538-12, respectively. Drug-related SAEs (reported in 2 or more subjects) were interstitial lung disease (0.9%), and colitis, pyrexia, pneumonia, urinary tract infection, and diabetic ketoacidosis (each 0.6%). No drug-related SAEs were reported in 2 or more subjects in the placebo group.

Drug-related worst Grade 3-4 SAEs in the nivolumab group were diabetic ketoacidosis (0.6%), and hypopituitarism, dry eye, colitis, dry mouth, upper gastrointestinal haemorrhage, vomiting, fatigue, pyrexia, hepatitis acute, pneumonia, rash pustular, urinary tract infection, splenic infection, AST increased, blood bilirubin increased, hepatic enzyme increased, decreased appetite, type 1 diabetes mellitus, Sjogren's syndrome, dyspnoea, interstitial lung disease, pneumonitis, and pneumomediastinum (each 1 subject, 0.3%).

Drug-related Grade 5 SAEs reported in the nivolumab group were cardiac arrest, death, pneumonia, and dyspnoea exertional (1 subject, 0.3% each). Drug-related Grade 5 SAEs reported in the placebo group were gastrointestinal perforation and sudden death (1 subject, 0.6% each).

In Study CA209032 (GC Cohort) drug-related SAEs were reported in 7.1% of subjects. Worst Grade 3-4 drug-related SAEs were reported in 1 subject (2.4%; vomiting); no Grade 3-4 drug-related SAEs were reported in more than 1 subject.

Drug-related AEs leading to death were reported in 5 subjects, most of them with confirmed or suspected progression disease. These included cardiac arrest in a subject with mediastinal emphysema, death of indeterminate cause in a subject, hepatitis acute in a subject with history of chronic liver parenchymal disease, pneumonia in a subject and dyspnoea exertional in a subject. All of them showed PD but he last subject who has only suspect of PD.

No deaths related to study drug toxicity were reported in study CA209032 (GC cohort).

Immunogenicity

The immunogenicity incidence in subjects with GC/GEJ and $\geqslant$ 2 prior regimens was similar to that observed in other tumour types and did not appear to have an effect on safety.

2.5.1. Conclusions on clinical safety

In conclusion, the safety profile of nivolumab monotherapy in the studied patients with GC/GEJ advanced or recurrent GC or GEJ cancer after 2 or more prior systemic therapies seems to be consistent with the profile known from previous indications. No new safety events with nivolumab monotherapy treatment were identified in studies ONO-4538-12 and CA209032.

Overall, the safety profile was comparable between the two studies. However, the most common types of (both any Grade as well as Grade 3-4) (DR)AEs generally occurred at numerically higher frequencies in study CA209032.

2.5.2. PSUR cycle

NA

2.5.3. Direct Healthcare Professional Communication

NA

2.6. Risk management plan

The risk management plan version 11.0 with the following content was assessed by the PRAC Rapporteur:

Safety concerns

Table 87: Summary of the Safety Concerns

Summary of safety concerns	
Important Identified Risks	Immune-related pneumonitis
	Immune-related colitis
	Immune-related hepatitis
	Immune-related nephritis and renal dysfunction
	Immune-related endocrinopathies
	Immune-related skin ARs
	Other immune-related ARs
	Severe infusion reactions
Important Potential Risks	Embryofetal toxicity
	Immunogenicity
	Cardiac arrhythmias (previously treated melanoma indication, only)
	Complications of allogeneic HSCT following nivolumab therapy

Summary of safety concerns	
Missing Information	Pediatric patients <18 years of age
	Elderly patients with: - cHL≥ 65 years of age - SCCHN ≥ 75 years of age
	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab
	Use in patients who have undergone influenza vaccination
	Patients with brain metastases: • Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases • NSCLC – active brain metastases • RCC – any history of or concurrent brain metastases

CHMP Rapporteur's Conclusions on clinical safety

In conclusion, the safety profile of nivolumab monotherapy in the studied patients with GC/GEJ advanced or recurrent GC or GEJ cancer after 2 or more prior systemic therapies seems to be consistent with the profile known from previous indications. No new safety events with nivolumab monotherapy treatment were identified in studies ONO-4538-12 and CA209032.

Overall, the safety profile was comparable between the two studies. However, the most common types of (both any Grade as well as Grade 3-4) (DR)AEs generally occurred at numerically higher frequencies in study CA209032.

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan (changes in bold underlined).

Table 88: On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Activity/ Study title (type of activity, study title, category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started**	**Date for submission of interim or final reports (planned or actual)**
CA209835: A registry study in patients who underwent post-nivolumab allogeneic HSCT Category 3	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	Planned	Final CSR submission: 4Q2022
CA209234:	To assess use pattern,	Postmarketing use safety	Started	Final CSR

Activity/ Study title (type of activity, study title, category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started	Date for submission of interim or final reports (planned or actual)
Pattern of Use, Safety, and Effectiveness of Nivolumab in Routine Oncology Practice. Category 3	effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, and 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		submission: 4Q2024

Editorial Comment: "Rash" was already replaced by "(Immune related) Skin ARs". The wording should be consistent in all parts of the RMP.

There are no imposed mandatory additional PV activities (Category 1).
There are no mandatory additional PV activities (Category 2).
Two studies (CA209835; CA209234) are considered Category 3 (i.e. additional PV studies/activities not imposed or mandatory).
The ongoing studies in melanoma (CA209172) and in NSCLC (CA209171), both are considered Category 4 (i.e. stated additional PV activities); final CSR 4Q2017 applies for both. The same category holds true for study CA20999J (Title: Evaluation of Risk of Muscle Damage in Cancer Patients on Checkpoint Inhibitor Therapies after Receiving Influenza Vaccination: A Nested Case-Control Study Using Claims Data) with the estimated due date 4Q2018 for the final CSR.

The proposed post-authorisation PhV development plan remains sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Table 89: Proposal from applicant for risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
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	The SmPC warns the risks of immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies, immune-related skin ARs, and other immune-related adverse reactions in Section 4.4 (Special warnings and precautions for use), and provides specific guidance on their monitoring and management, including treatment delay or discontinuation and intervention with corticosteroids in Sections 4.2, 4.4 and 4.8, as appropriate. Further ADRs are included in Section 4.8. In addition, the package leaflet also includes specific warnings and descriptions of the most important safety information in the language suitable for patients.	To further raise awareness of HCPs on important risks and their appropriate management, additional risk minimization activity includes a Communication Plan. The Plan comprising 2 tools to be distributed to potential prescribers at launch by BMS: • Adverse Reaction Management Guide • Patient Alert Card
Severe infusion reactions	The SmPC warns the risk of severe infusion reactions in Section 4.4 and ADR in Section 4.8.	None
Important Potential Risks		
Embryofetal Toxicity	SmPC includes Embryofetal Toxicity in Section 4.6 Fertility, pregnancy and lactation, Section 5.3 Preclinical safety data The package leaflet also includes specific description on the safety information in the language suitable for patients.	None
Immunogenicity	SmPC Section 4.8 Immunogenicity	None
Cardiac arrhythmias (previously treated melanoma indication, only)	SmPC Section 4.8 Undesirable effects	None
Complications of allogeneic HSCT following nivolumab therapy	SmPC Section 4.4 recommends case by case considerations, and close monitoring of patients undergoing allogeneic HSCT for hyperacute GVHD, Grade 3-4 acute GVHD, steroid requiring febrile syndrome, hepatic veno-occlusive disease, and other transplant related	Adverse Reaction Management Guide

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	complications. Related information is found in SmPC Section 4.8 Undesirable effects.	
Missing Information		
Pediatric patients	SmPC Section 4.2 Posology and method of administration, subsection on Pediatric population	None
Elderly patients with: - cHL≥ 65 years of age - SCCHN ≥ 75 years of age	SmPC Section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties	None
Severe hepatic and/or renal impairment	SmPC Section 4.2 Posology and method of administration: Patients with hepatic or renal impairment; SmPC Section 5.2 Pharmacokinetic properties: Hepatic or renal impairment	None
Patients with autoimmune disease	SmPC Section 4.4 provides warning and cautionary information for patients with a history of autoimmune disease	None
Patients already receiving systemic immunosuppressants before starting nivolumab	SmPC Sections 4.4 Special populations and 4.5 Systemic Immunosuppressants	None
Use in patients who have undergone influenza vaccination	Safety monitoring and signal detection	None
Patients with brain metastases: • Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases • NSCLC – active brain metastases • RCC – any history of or concurrent brain metastases	SmPC Section 4.4 provides warning and cautionary information for patients with active brain metastases or leptomeningeal metastases	None

The proposed risk minimisation measures remain sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

We considered that the submitted variation type II submitted to extend the current approved therapeutic indication for OPDIVO to include "treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer after two or more prior systemic therapies" does not involve a relevant impact on the PIL. Therefore, the company´s justification to not undertake further consultation with target patient groups is considered acceptable.

2.7.2. Quick Response (QR) code

NA

2.8. Significance of paediatric studies

NA

3. Benefit-Risk Balance

The new claimed indication for OPDIVO® is for the treatment of adults with advanced or recurrent gastric or GEJ cancer after two or more prior systemic therapies. The recommended dose and schedule of nivolumab monotherapy for the GC/GEJ indication is 3 mg/kg administered as IV infusion over 60 minutes Q2W, which is consistent with existing approved dose and schedule of nivolumab monotherapy in adults.

3.1. Therapeutic Context

3.1.1. Disease or condition

GC is the third most common cause of cancer death worldwide. GEJ cancer anatomically straddles the distal oesophagus and proximal stomach. Due to its location and given that, like GC, the majority of GEJ tumours are adenocarcinomas, GEJ tumours are frequently grouped together with GC in the advanced setting and treated the same way.

3.1.2. Available therapies and unmet medical need

Globally, palliative therapy (systemic therapy, clinical trial, or best supportive care [BSC]) is recommended for patients with unresectable, recurrent, or metastatic GC or GEJ cancer. The choice of 2 or 3 drug-cytotoxic regimens as first-line therapy is made in the context of the performance status (PS), comorbid conditions, and toxicity profile.

Platinum compounds (oxaliplatin and cisplatin) in combination with fluoropyrimidines (5-fluorouracil, capecitabine, and tegafur/gimeracil/oteracil potassium [S-1]), and the addition of trastuzumab for HER2-positive tumours, are generally considered as first-line SOC treatment options in metastatic GC and GEJ cancer across geographic regions. Most patients will ultimately progress, and the overall prognosis remains poor with median survival between 7 and 10 months. The selection of a second-line therapy for these patients is highly dependent on prior therapy and PS and for many patients in the EU, BSC is an acceptable option. For those medically fit to receive 2L therapy, treatment options include single-agent taxane (paclitaxel, docetaxel), irinotecan, or ramucirumab, or ramucirumab in combination with paclitaxel. Although there are no recommended therapies in the third-line and beyond across regions, in clinical practice treatment options may be used sequentially in second and third line (e.g. ramucirumab, paclitaxel, and irinotecan can be used sequentially in second and third line).

3.1.3. Main clinical studies

The evidence presented in support of the present application comes from a phase III clinical trial (ONO-4538-12) conducted in an exclusively Asian population, and there is supportive evidence from a nivolumab monotherapy cohort in a phase 1/2 Study CA209032 conducted in a non-Asian population.

- **ONO-4538-12** is a phase 3 multicentre, double-blind, randomised study of nivolumab monotherapy in Asian patients with unresectable advanced or recurrent gastric cancer (including esophagogastric junction cancer) with histological confirmation of adenocarcinoma after at least 2 prior systemic therapies, refractory to or intolerant of standard therapies and not planned to

receive any additional anticancer therapy. In total 493 patients were randomised 2:1 to either nivolumab or placebo.

- Supportive evidence comes from a subset of 42 patients of the GC cohort of trial **CA209032** who had received at least 2 prior regimens and are thus comparable to the population from ONO-4538-12. CA209032, is a multicentre, Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab designed to evaluate the efficacy and safety of nivolumab as monotherapy or in combination with ipilimumab in subjects with 6 different tumour types, including GC.

3.2. Favourable effects

OS results from trial **ONO-4538-12** (event rate 68.5% nivolumab; 86.5% placebo) showed a statistically significant improvement in favour of the nivolumab arm (HR: 0.63; 95%CI 0.51, 0.78). Although differences in median survival time remain around 1 month (5.26 (95%CI 4.60, 6.37) for nivolumab arm and 4.14 (95%CI 3.42, 4.86) for placebo arm), K-M curves are clearly separated thought the course of the trial. OS rates at different time points numerically favoured nivolumab arm: OS rate at 6-months 46.1% vs. 34.7%; OS rate at 12-months 26.2% vs. 10.9%; OS rate at 18-months 16.2% vs. 5%.

An updated analysis with 6 months of additional follow-up has been submitted according to data cut-off of 25-Feb-2017 (previous DCO 13-Aug-2016). More mature OS data, with event rates of 78.8% and 91.4% for nivolumab and placebo arms, respectively, still show a statistically significant improvement in favour of nivolumab arm (HR: 0.63; 95%CI 0.51, 0.78) that is consistent with data from the previous DCO. Median OS remained unchanged, i.e. 5.26 months (95%CI 4.60, 6.37) for nivolumab arm and 4.14 months (95%CI 3.42, 4.86) for placebo arm. Further, 12-months OS rates were 27.3% and 11.6% for nivolumab and placebo arms.

PFS data (76.7% events in nivolumab arm and 89.0% events in placebo arm) showed a HR of 0.60 (95%CI 0.49, 0.75) and a difference in median PFS time of 0.16 months (1.61 months vs. 1.45 months).

ORR per investigator assessment in the ITT population, showed an ORR of 9.1% (95% CI 6.2, 12.7) in the nivolumab arm (all of them PR) compared to 0% in the placebo arm. SD was achieved by 23.6% of patients in the nivolumab arm and 2.2% in the placebo arm. Responses were durable, median DoR was 9.53 months.

A post-hoc analysis considering only the 476 patients who had received at least 2 prior regimens in the metastatic setting showed similar results.

Results for the subset of GC ≥ 2nd line (n=42) from trial **CA209032** showed an ORR of 7.1% (95%CI 1.5, 19.5) as assessed by BIRC with median DOR not reached and a median TTR of 1.38 months.

PFS data (78.6% of events) show a median PFS time of 1.49 months (95% CI 1.31, 2.76) and a median OS of 8.97 months (95% CI 3.35, 14.88) was observed. OS rates at 6 months and 12 months were 57.4% and 45.1 % respectively.

Again, a post-hoc analysis considering only the 32 patients who had received at least 2 prior regimens in the metastatic setting showed similar results.

Uncertainty in the knowledge about the beneficial effects

A key uncertainty is the fact that gastric cancer in Asia is in many aspects a different disease than gastric cancer in the EU, and that no comparative data are available for the non-Asian population. The single comparative study was performed exclusively in Asian patients, mainly from Korea and Japan. The current benefit/risk assessment therefore almost completely relies on extrapolation of the efficacy and safety results from this trial, performed in Asian patients, to the non-Asianpatient

population. This is problematic, because gastric/gastroesophageal adenocarcinoma differs in a number of relevant aspects between non-Asian and Asian patients.

It is well known that prognosis of Asian patients with gastric cancer is better than prognosis of non-Asian patients. This is thought to be related to different factors, including differences in disease biology, differences in treatment patterns, and differences in methods for screening/diagnosis (as described in detail in discussion on clinical efficacy). Importantly, the differences between Asian and non-Asian patients are not without consequences for drug development. In fact, there is a history of drugs tested in phase III which showed large differences in treatment effect between Asian and non-Asian patients (outlined in discussion on clinical efficacy). This illustrates that although gastric cancer is a global disease, there are strong indications that response to treatment is not uniform. The previously observed regional/ethnic differences in drug response are highly relevant in the current extension of indication for nivolumab, since they bring into question to which extent the benefits observed for nivolumab in the comparative study in Asian patients can be extrapolated to the non-Asian patient population.

A second uncertainty about the presented results is related to the consistency of treatment effects in subgroups of patients. This is particularly relevant, in view of the fact that in study ONO-4538-12 the treatment effect on OS appears to be driven by patients who previously received 4 or more lines of systemic therapy – thus when nivolumab is given as 5th line treatment or beyond. Furthermore, the applicant detected significant interactions between nivolumab treatment and the number of lines of prior treatment, as well as between nivolumab treatment and age and sex (refer to forest plot, and Kang et al. 2017, Lancet, Published Online October 6, 2017). Patients who had received 2 or 3 prior therapies appeared to have a considerably less relevant OS benefit. The same holds true for patients with diffuse type tumours. These findings point towards an issue with internal consistency of efficacy results. Especially as this is a submission with only one pivotal study, this is considered an issue (CPMP/EWP/2330/99).

A third uncertainty is related to how representative the studied patient population is for the non-Asian patients. As the studied patient population comprised patients able to undergo many lines of treatment, whereas non-Asian patients rarely undergo three or more lines of treatment for metastatic disease. Importantly, in the pivotal study the clinical relevance of the effect of nivolumab on OS could be challenged in the patient population with 2-3 prior lines of therapy and the overall effect of nivolumab appears to be driven by patients who receive nivolumab as 5th line of therapy or beyond, while 5th line therapy in the metastatic setting is rarely or almost never given in the EU.

A fourth uncertainty is related to expected benefit in subgroups of patients according to biomarker status. Gastric cancer is a heterogeneous disease on the molecular level, and there is accumulating evidence that there are broadly four molecular subtypes of gastric cancer: Epstein–Barr virus-positive tumours, microsatellite instable tumours, genomically stable tumours, and tumours with chromosomal instability (The Cancer Genome Atlas Research Network Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513:202–209.). In relation to the treatment effect of nivolumab as well as other PD-1 inhibitors, there is evidence that in particular microsatellite instable tumours are likely to respond to treatment. Although the MSI data from the supportive study CA209032 show that indeed patients with MSI tumours might be more likely to experience clinical benefit (although sample sizes were small), data from the pivotal trial does not allow to confirm or reject these findings, as for patients in the pivotal study only very limited data is available on MSI status in relation to response to treatment.
Only a small proportion of patients in the pivotal study responded to treatment with a durable response (9.1%). Interestingly, the size of this proportion of patients responding to treatment with a durable response is comparable to the expected proportion of patients with MSI-high status likely to respond to treatment however this could not be confirmed as there was only a low percentage of patients evaluable

for MSI. Because there is accumulating evidence that MSI status is a key predictive biomarker for response to PD-1 inhibitors such as nivolumab, the absence of good quality data in this regard is considered problematic for further assessment of the benefit/risk of nivolumab in gastric cancer. Also, there are indications that PD-L1 status affects response to treatment with PD-L1 inhibitors such as nivolumab. The currently presented data on PD-L1 expression in relation to response are not adequate, because the scoring of PD-L1 expression was based only on expression of PD-L1 on tumour cells, while the scoring of PD-L1 expression on tumour-associated/infiltrating immune cells would provide valuable information. Especially since there is little PD-L1 expressed on the cancer cells of upper gastrointestinal tumours, but rather expression occurs predominantly on infiltrating myeloid cells at the invasive margin (Kelly. Am Soc Clin Oncol Educ Book. 2017). In response to the first RSI, the MAH provided some data on PD-L1 expression on immune cells in relation to response on nivolumab, but too limited data/inconclusive data to resolve this matter.

The supportive study CA209032 is intended to support the efficacy of nivolumab in non-Asian patients. As based on the literature a shorter life expectancy can be expected for the non-Asian patient population, it is unsure whether immunotherapy could have time enough to exert its clinical effect on a rapidly progressing tumour such as gastric cancer. However, contrary to initial assumptions, results from the nivolumab CA209032 trial in a non-Asian population, show an OS that is clearly superior to both treatment arms from trial ONO-4538-12. The fact that this trial is non-comparative and included a less pre-treated population makes it difficult to extrapolate results to the intended EU target patient population. It is considered that the data from the supportive study are severely limited by the small number of patients, and the fact that the studied phase I population is likely not representative of the to-be-treated EU population. Moreover, the external validity of the efficacy results observed in the phase 1/2 non-comparative study CA209032 could be questioned. E.g. of the only 32 patients in study CA209032 confirmed to have received ≥2 prior lines of therapy in the metastatic setting, only 2 were responders, which seems in conflict with the long median OS of 8.48 months of these patients when compared to the median OS of 5.26 months for the nivolumab arm of ONO-4538-12. In addition, of the 16 GC patients in the n = 42 cohort of study CA209032, none responded to therapy and only 6 (37.5%) had SD as BOR. Nevertheless, median OS in this group was 7.72 months which is much longer than can be expected for patients with GC or GEJ cancer that have failed two prior lines of systemic treatment and are non-responders to 3rd-line treatment.

Risks

Unfavourable effects

The safety profile for the intended indication has been characterised in the entire population from trial ONO-4538-12 and a subset of 42 patients from the CG cohort of trial CA209032 who had received at least two prior regimens. In general, the overall safety profile of nivolumab monotherapy in patients with GC/GEJ seems to be consistent with the profile known from previous indications.

In ONO-4538-12, the most common treatment-related AEs for the nivolumab-treated patients were: pruritus, diarrhoea, fatigue, decreased appetite, nausea, pyrexia and arthritis. Most of them were mild-moderate in severity.

Although the distribution of most common treatment-related AEs were similar in CA209032 GC cohort (n=42) these were consistently more frequently reported. Again, most of them were mild-moderate in severity.

Immune-mediated select AEs were more frequently reported in the skin (15.5%) followed by GI (7.0%) and hepatic (5.5%) SOCs. Most of them were of mild-moderate intensity.

SAEs (all causalities) were reported 39.7% of patients in the nivolumab group and 46.6% of subjects in the placebo group of trial ONO-4538-12, with 27.6% and 29.2% of patients reporting grade 3-4 SAEs respectively, and 4.8% and 11.2% were grade 5 SAEs respectively.

Drug-related Grade 5 SAEs reported in the nivolumab group were cardiac arrest, death, pneumonia, and dyspnoea exertional (1 subject, 0.3% each). Drug-related Grade 5 SAEs reported in the placebo group were gastrointestinal perforation and sudden death (1 subject, 0.6% each).

In Study CA209032 (GC Cohort) drug-related SAEs were reported in 7.1% of subjects. Worst Grade 3-4 drug-related SAEs were reported in 1 subject (2.4%); no Grade 3-4 drug-related SAEs were reported in more than 1 subject.

Drug-related AEs leading to death were reported in 5 subjects, most of them with confirmed or suspected progression disease. These included cardiac arrest in a subject with mediastinal emphysema, death of indeterminate cause in a subject, hepatitis acute in a subject with history of chronic liver parenchymal disease, pneumonia in a subject and dyspnoea exertional in a subject. All of them showed PD but the last subject who has only suspect of PD.
No deaths related to study drug toxicity were reported in study CA209032 (GC cohort).

Uncertainty in the knowledge about the unfavourable effects

The differences observed in the safety profile (numerically greater rates of both any Grade as well as Grade 3-4 common drug-related AEs) between study ONO-4538-12 and the subset of 42 patients from the CG cohort of trial CA209032 could be pointing out potential differences between Asian and non-Asian patients from a safety point of view.

Effects Table

Table 90. Effects Table for Nivolumab GC/GEJ indication (ONO-4538-12 data cut-off: 13-Aug-2016; CA209032 data cut-off: 24-Mar-2016)

Effect	Short Description	Unit	Nivolumab	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
OS	Overall survival	Median (mo)	5.26	4.14	HR (95%CI): 0.63 (0.51, 0.78) Data comes from Asian population	**ONO-4538-12 CSR**
PFS-investigator	Progression-free survival in months assessed by investigator	Median (mo)	1.61	1.45	HR (95%CI): 0.60 (0.49, 0.75) Data comes from Asian population	
ORR-investigator	Overall response rate assessed by investigator	%	9.1	0	Data comes from Asian population	
DOR-investigator	Duration of response rate assessed by investigator	Median (mo)	9.53	NA	Data comes from Asian population	
OS	Overall survival	Median (mo)	8.97	Single arm cohort	Non-comparative data from a subset of patients from a multicohort trial	**CA209032 CSR**
PFS- BICR	Progression-free survival in months	Median (mo)	1.49	Single arm cohort	Non-comparative data from a subset of patients from a multicohort trial	
ORR- BICR	Overall response rate	%	7.1	Single arm cohort	Non-comparative data from a subset of patients from a	

Effect	Short Description	Unit	Nivolumab	Placebo	Uncertainties/ Strength of evidence	References
	assessed by investigator				multicohort trial	
DOR- BICR	Duration of response rate assessed by investigator	Median (mo)	NA	Single arm cohort	Non-comparative data from a subset of patients from a multicohort trial	
Unfavourable Effects						
Pruritus	Drug-related AEs	%	AE 9.1% G3/4 0%	AE 5.6% G3/4 0%		**ONO-4538-12 CSR**
Diarrhoea	Drug-related AEs	%	AE 7.0% G3/4 0%	AE 1.9% G3/4 0%		
Fatigue	Drug-related AEs	%	AE 5.5% G3/4 0.6%	AE 5.6% G3/4 1.2%		
decreased appetite	Drug-related AEs	%	AE 4.8% G3/4 1.2%	AE 4.3% G3/4 0.6%		
Nausea	Drug-related AEs	%	AE 4.2% G3/4 0%	AE 2.5% G3/4 0%		
Tolerability	All-causality AEs		AE 90.9% SAE 39.7% AE leading to DC 7.0%	AE 83.9% SAE 46.6% AE leading to DC 7.5%		
Pruritus	Drug-related AEs	%	AE 21.4% G3/4 0%			**CA209032 CSR**
Diarrhoea	Drug-related AEs	%	AE 14.3% G3/4 2.4%			
Fatigue	Drug-related AEs	%	AE 33.3% G3/4 0%			
decreased appetite	Drug-related AEs	%	AE 11.9% G3/4 1.2%			
Nausea	Drug-related AEs	%	AE 11.9% G3/4 0%			
Tolerability			AE 97.6% SAE 57.1% AE leading to discontinuations 7.1%			

4. Benefit-risk balance

Importance of favourable and unfavourable effects

Nivolumab conferred a statistically significant OS benefit compared to placebo in a third- or later-line setting in metastatic gastric/gastroesophageal adenocarcinoma. While median survival was only ~1 month longer with nivolumab than with placebo, the late separation of the Kaplan-Meier OS curve, leading to an approximately 15% difference in 1-year survival, could be considered a clinically relevant treatment effect within the context of a clear late-line GC/GEJ population where no other effective treatments are available. Importantly, however, there are major uncertainties in the knowledge about the beneficial effects in the target population of EU patients (as outlined above and in the discussion on clinical efficacy).

Firstly, it is considered insufficiently substantiated that the efficacy results from the trial performed in Asian patients can be extrapolated to a non-Asian patient population. While PK has been demonstrated to be sufficiently comparable between Asian and non-Asian patients, the disease itself (gastric/gastroesophageal adenocarcinoma) differs in a number of relevant aspects between non-Asian

and Asian patients – including differences in disease biology, patients' characteristics, and variability in treatment practices – which makes it is highly uncertain that non-Asian patients will derive a similar benefit from treatment with nivolumab (a benefit which is already relatively small and appears to be driven by a small subset of the patients (see below)). No comparative data are available in non-Asian populations, and the small group of non-Asian patients treated with nivolumab in the supportive study is not considered representative for the target population, thereby not relieving the uncertainties on the benefits in the target population.

Secondly, there is questionable consistency of treatment effects among important subgroups of patients. The overall treatment effect appears to be driven by the subgroup of patients who received nivolumab as 5th-line or beyond therapy, a subgroup of questionable representativeness for the to-be-treated European patient population, which rarely undergoes three or more lines of treatment for metastatic disease. Importantly, Furthermore, in the patient population with 2-3 prior lines the clinical relevance of the effect of nivolumab on OS could be challenged. Due to these uncertainties, the actual benefits in the non-Asian patient population can currently not be adequately assessed, and it is unlikely that the effects observed in Asian patients can be extrapolated to non-Asian patients.

No new safety signals related to nivolumab treatment were detected in the pivotal study in Asian patients. The supportive study in non-Asian patients showed numerically higher frequencies of (drug-related) adverse events compared to the pivotal comparative study. This could be pointing out potential differences between Asian an non-Asian patients from a safety point of view, i.e. another uncertainty.

Due to these uncertainties related to the content of the current dossier, the B/R in the non-Asian patient population cannot be satisfactorily determined.

Moreover, the reported efficacy in the pivotal study is on the lower bound of what could be accepted as clinically meaningful, and because the differences between the Asian and non-Asian patient populations are expected to be large, there is a strong rationale (considering short mPFS and low ORR) for the assumption that for a large proportion of the non-Asian patient population the benefit could be even less than observed in the main study. As the toxicity of treatment with nivolumab is non-negligible, the benefit-risk balance could turn out negative for non-Asian patients. Unfortunately, both too limited as well as inconclusive information on potential biomarkers such as MSI status and PD-L1 expression (both on tumour cells as well as on tumour-associated/infiltrating immune cells) has been provided. As a consequence, it is not possible to select a patient population who could more likely benefit from nivolumab therapy and thereby prevent other patients from receiving a treatment from which they will not gain a clinically relevant benefit, but can possibly suffer non-negligible toxicity.

Benefit-risk balance

The benefit-risk balance for nivolumab in the treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer after two or more prior systemic therapies cannot currently be established.

Discussion on the Benefit-Risk Balance

The gain in OS although disputable from an absolute perspective, could be deemed as clinically meaningful when considering alternative treatment options. Due to the lack of clear SoC and the limited benefit associated to chemotherapy along with the worse toxicity, nivolumab might be a real alternative to patients in last line of GC. However, this discussion of the benefit of nivolumab in this setting, must be contextualized in the clinical practice. The better prognosis of Asian patients, widely accepted in scientific community and recently documented with other clinical development in GC (Teysuno, bevacizumab, lapatinib) pose important uncertainties related to the actual survival benefit in non-Asian patients. In this

scenario of doubtful importance of clinical results, it is of utmost importance to value the real survival gain in non-Asian patients. Unfortunately, the latter does not seem possible from the data submitted. These uncertainties could be even more worrisome in some subgroups of patients, where the gain in survival has not been shown in the pivotal study. Last but not least, it is not possible to identify a population where to maximize the benefit in non-Asian patients, decreasing the risks linked to the above-mentioned uncertainties.

5. Recommendations

The application for: Extension of Indication to include treatment of adult patients with advanced or recurrent gastric or gastroesophageal junction (GEJ) cancer after two or more prior systemic therapies, based on data from study ONO-4538-12. As a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. The RMP version version 11.0 has also been submitted.

☒ is not approvable since major objection and other concerns have been identified, which preclude a recommendation at the present time.

☐ could be approvable since other concerns <has><have> been identified, which preclude a recommendation at the present time.

The details of these <major objections>< other concerns> are provided in Annex <> (RSI 1) and should be addressed in writing <and in an oral Explanation>.

☐ is approvable <since other concerns <major objections> <has><have> all been resolved>.

Annex 1: CHMP 2nd Request for Supplementary Information

Quality aspects

Other concerns

1. The applicant is requested to provide information (CoAs, batch release and stability data) on all batches administered to patient in the clinical studies (ONO-4538-12 and CA209032) and to add this information in the submitted assessment. In addition, it should be confirmed that these batches have been manufactured according to the same drug product manufacturing process. The applicant should note that available stability data from Ono batches should be submitted as part of the comparability assessment

Clinical efficacy aspects

Major Objections

2. In the pivotal study ONO-4538-12 in Asian patients with metastatic gastric/gastroesophageal junction adenocarcinoma, nivolumab conferred a limited but statistically significant OS benefit compared to placebo in the third- or later-line setting. However, the clinical relevance of the observed effect of nivolumab in trial ONO-4538 is considered too limited to outweigh the risks of a possible less impressive result in non-Asian patients with gastric cancer, which is known to differ in some respects from the Asian population. In the absence of robust data supporting extrapolation of results, major uncertainties regarding efficacy remain and the benefit/risk balance of nivolumab in non-Asian population cannot be established. Further contributing to the uncertainty, is the heterogeneity of treatment effects in important subgroups, specifically the fact that the overall effect of nivolumab appears to be driven by patients who received nivolumab as 5L+ therapy. In addition, very limited data are available on MSI status and PD-L1 expression. The applicant is invited to present stronger arguments to substantiate that nivolumab treatment in the non-Asian population will result in clinically relevant efficacy, and thereby patient benefit.

Other concerns

3. Main efficacy data (OS, PFS and ORR) should be submitted for the true target population of patients who had received $\geqslant$2 lines in the metastatic setting in ONO-4538-012 trial.
4. The applicant is asked to elaborate on how further biomarker studies, including other markers than the ones discussed, will be performed in the gastric cancer indication if approval would be obtained.

[1] Hsu C, Shen Y-C, Cheng C-C, et al. Geographic difference in safety and efficacy of systemic chemotherapy for advanced gastric or gastroesophageal carcinoma: A meta-analysis and meta-regression. Gastric Cancer. 2012;15:265-80.
[2] Lordick F, Kang Y-K, Chung H-C, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14:490-9.
[3] Muro K, Chung HC, Shankaran V, et al. Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): A multicentre, open-label, phase 1b trial. Lancet Oncol. 2016;17:717-26.