15 October 2020
EMA/CHMP/584553/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0080

Note

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

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List of abbreviations

1L	first-line
2L	second-line
5-FU	5-flurouracil
ADA	anti-drug antibody
ADH	alcohol dehydrogenase
AE	adverse event
ALDH	aldehyde dehydrogenase
BICR	Blinded Independent Central Review
BLA	Biologics Licensing Application
BMS	Bristol-Myers Squibb
BOR	best overall response
BSC	best supportive care
CE	capillary electrophoresis
cHL	classic Hodgkin lymphoma
CI	confidence interval
CL	clearance
CO	clinical overview
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBL	database lock
DCR	disease control rate
DFS	disease free survival
dMMR	deficient mismatch repair (gene)
DoR	duration of response
ECL	electrochemiluminscence
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic Common Technical Document
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
E-R	exposure-response
EQ-5D-3L	EuroQol 5-dimension 3-level version
ESMO	European Society of Medical Oncology
EU	European Union
FDA	Food and Drug Administration

f/u	follow-up
GCP	good clinical practice
GEJ	gastro esophageal junction
HCC	hepatocellular carcinoma
HR	hazard ratio
IB	Investigator's Brochure
IARC	International Agency for Research on Cancer
ICF	informed consent form
ICH	International Council for Harmonization
ICIEF	Imaged capillary isoelectric focusing
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IEF	Isoelectric focusing
ILD	interstitial lung disease
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IND	Investigational New Drug
ITT	intention to treat
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive Web Response System
JPN	Japan
KM	Kaplan Meier
LDH	lactate dehydrogenase
LPFT	last patient's first treatment
LS	least square
LSMD	least square mean difference
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MMRM	mixed model repeated measures
mOS	median overall survival
MSI-H	microsatellite instability high
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OESI	Other Event of Special Interest
ONO	ONO Pharmaceutical Co. Ltd
ORR	objective response rate
OS	overall survival
OAC	oesophageal adenocarcinoma

OC	oesophageal cancer
OSCC	oesophageal squamous cell carcinoma
PAGE	Polyacrylamide gel electrophoresis
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PK	pharmacokinetic
popPK	population pharmacokinetic
PR	partial response
PS	performance status
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RES	response evaluable set
RSE	relative standard error
RWD	Real-World Data
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
SCCHN	squamous cell cancer of the head and neck
SCE	Summary of Clinical Efficacy
SCLC	small cell lung cancer
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	stable disease or standard deviation
SDS	Sodium dodecyl sulfate
SEER	Surveillance, Epidemiology, and End Results
SOC	standard of care
TCGA	The Cancer Genome Atlas
ToC	table of contents
TTP	time to progression
TTR	time to response
UC	urothelial carcinoma
UI	utility index
UK	United Kingdom
UMC	Uppsala Monitoring Centre
US	United States

USPI	United States Prescribing Information
VAS	visual analog scale
Vc	central compartment volume of distribution
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 15 January 2020 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.2 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0026/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0026/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP for this indication.

1.2. Steps taken for the assessment of the product

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

Rapporteur: n/a Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	15 January 2020
Start of procedure:	1 February 2020
CHMP Co-Rapporteur's preliminary assessment report circulated on:	27 March 2020
PRAC Rapporteur's preliminary assessment report circulated on:	2 April 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	17 April 2020
CHMP Co-Rapporteur's updated assessment report circulated on:	23 April 2020
Request for supplementary information and extension of timetable adopted by the CHMP on:	30 April 2020
MAH's responses submitted to the CHMP on:	19 May 2020
CHMP Co-Rapporteur's preliminary assessment report on the MAH's responses circulated on:	25 June 2020
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 June 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	9 July 2020
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	23 July 2020
MAH's responses submitted to the CHMP on:	14 September 2020
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 September 2020
CHMP Co-Rapporteur's preliminary assessment report on the MAH's responses circulated on:	30 September 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	1 October 2020
SAG Oncology Working Party to address questions raised by the CHMP	7 October 2020
An Oral explanation took place on:	14 October 2020
CHMP opinion adopted on:	15 October 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This application concerns an extension of indication to include treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based combination chemotherapy. Of note, the word "*combination*" was added in response to the first RSI. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. Consequently, the requested variation proposes amendments to the Summary of Product Characteristics (SmPC) and Package Leaflet (PL), and to the Risk Management Plan (RMP).

Disease or condition

Oesophageal cancer (OC) is the 7th most common cancer worldwide and the 6th most common cause of death from cancer in 2018, with an estimated 572,034 new cases (3.2% of all cancers) and 508,585 cancer deaths (5.3% of all cancer deaths) (GLOBOCAN 2018 [accessed on 24-Jan-2020]). Although OC is a rare disease in Europe, accounting for ~1.4% of all new cancers (20th most common cancer type) (Ferlay et al. 2018; Orphanet [accessed on 26-Jun-2019]), it remains a major global health threat. According to the GLOBOCAN 2018 estimates, the age-standardized rate of OC per 100,000 among males and females were 5.6 and 1.2, respectively (Bray at al. 2018).

OC consists of two major histological types: OSCC and oesophageal adenocarcinoma (OAC). OSCC accounts for 88% of OCs worldwide and is more common in the regions with the highest incidence rates for OC, while OAC is more common in the regions with the lowest OC incidence rates. High-risk areas for OSCC include South America and the "Asian Esophageal Cancer Belt," which extends from eastern Turkey, through Iraq, Iran, and the southern part of the former Soviet Union (Kazakhstan, Turkmenistan, Uzbekistan, and Tajikistan) to Mongolia and Western/Northern China (Zhang et al. 2015). OSCC is the predominant histological type (~65%) in most European countries (Arnold et al. 2015). Nevertheless, the incidence of OSCC is in decline in Europe. In Western European countries, the age-standardized incidence rate per 100,000 men ranged from 1.57 to 5.34 in 2005 and by 2030 this is expected to drop to a range of 0.72 to 4.14 depending on the country. In Central and Eastern European countries, the age-standardized incidence rate per 100,000 men ranged from 3.19 to 6.14 and is expected to drop to a range of 2.17 to 4.14. The age-standardized incidence rate per 100,000 women in Western European countries ranged from 0.32 to 1.40 in 2005 and expected to drop to a range of 0.26 to 1.25 by 2030, depending on the country. In Central and Eastern European countries the incidence rate per 100,000 women ranged from 0.29 to 0.48 in 2005 and is expected to be within the range of 0.26 to 1.48 by 2030. In the UK and Netherlands, the rates of OSCC in men have already been surpassed by those of OAC. In certain other European countries such as France, Italy, or Spain, this shift is expected to occur within the next few years (Arnold et al. 2017).

State the claimed therapeutic indication

The proposed new indication for OPDIVO in this procedure is:

Oesophageal Squamous Cell Carcinoma (OSCC)

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

The proposed posology for the new OSCC indication is 240 mg intravenous (IV) over 30 minutes every two weeks (Q2W). This is the same dose regimen as is currently approved for all other nivolumab monotherapy indications (OPDIVO SmPC).

Management

Current systemic treatment of oesophageal squamous cell carcinoma

Patients with advanced (metastatic or disseminated) and recurrent OSCC are treated with palliative intent with chemotherapy to extend survival, and with localized treatments, such as radiotherapy (including external radiation or brachytherapy), or endoscopic therapies, such as stents, for the symptomatic treatment of obstruction and dysphagia (Lordick et al. 2016). Generally, chemotherapy is offered to selected patients with good performance status (PS). However, as the prognosis of OSCC is considered to

be poor (i.e. poorer than for OAC) and the value of palliative chemotherapy is not clear for OSCC (i.e. less proven than for OAC), best supportive care (BSC) could also be considered, especially for unfit patients.

Platinum-based doublet chemotherapy such as the combination of platinum and fluoropyrimidine is a widely accepted **first-line (1L)** treatment option, though with modest outcomes (Lordick et al. 2016; Kitagawa et al. 2019; 2019 NCCN Guidelines). There are no approved therapies in Europe for patients progressing beyond 1L therapy and treatment decisions in **second line (2L)** are made in the absence of evidence from randomised controlled trials. However, the administration of single-agent chemotherapy is an established 2L option. For example, taxane (docetaxel or paclitaxel) monotherapy is recommended by various clinical guidelines (Lordick et al. 2016; Kitagawa et al. 2019; 2019 NCCN Guidelines) and represents a commonly used chemotherapy option in the 2L setting worldwide (Jaffe et al. 2019a; Jaffe et al. 2019b). Survival prolongation with these agents has not been confirmed in comparative OSCC studies, though. Results of two small, non-comparative phase 2 studies in Asian patients suggested median OS of 8.1-10.4 months with docetaxel and paclitaxel (Muro et al. 2004; Kato et al. 2011).

The modest benefits with chemotherapy in the 2L setting are associated with significant toxicities. The use of taxanes is often complicated by haematological, gastrointestinal, and neurological side effects leading to frequent treatment interruptions, delays, and dose reductions. Docetaxel is linked to severe (Grade 3 and 4) haematological toxicity including leukopenia (73%), neutropenia (88%), febrile neutropenia (18%), and anaemia (12%) as well as non-haematological toxicity including Grade 3 anorexia (18%), fatigue (12%), and diarrhoea (6%). Likewise, commonly reported Grade 3 or 4 adverse events (AEs) with paclitaxel are neutropenia (52.8%), leukopenia (45.3%), anorexia (9.4%), fatigue (9.4%), constipation (7.5%), pneumonia (7.5%), and sensory neuropathy (5.7%). Sensory neuropathy of any grade can be observed in 81.1% of patients treated with paclitaxel and often can be bothersome and debilitating (Muro et al. 2004; Kato et al. 2011).

Unmet medical need

In the 2L setting, palliative chemotherapy for advanced OSCC offers modest outcomes, and cytotoxic therapy for subjects who have progressed on or after standard chemotherapy with platinum and fluoropyrimidine combinations are associated with haematological, gastrointestinal, and neurological toxicities and offer poor long-term survival. This highlights a clear unmet need for new treatment options in 2L OSCC.

2.1.2. About the product

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

In the EU nivolumab as monotherapy has been approved for the treatment of melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin's lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), and urothelial carcinoma (Opdivo SmPC). The combination of nivolumab with ipilimumab (Yervoy; a mAb that blocks T-cell inhibitory signals induced by the cytotoxic T-lymphocyte antigen-4 pathway) has been approved for the treatment of melanoma and RCC.

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

Scientific advice

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

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. Animal models of efficacy suggest a broad applicability of nivolumab against PD-1 positive tumours independent of tissue type.

2.2.1. Ecotoxicity/environmental risk assessment

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

2.2.2. Conclusion on the non-clinical aspects

Animal models of efficacy suggest a broad applicability of nivolumab against PD-1 positive tumours independent of tissue type. The new/extended indication does not lead to a significant increase in environmental exposure further to the use of nivolumab. Nivolumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.
The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

The clinical development program for the assessment of nivolumab as a monotherapy or in combination with ipilimumab in patients with advanced OSCC includes the following clinical studies: ONO-4538-07, CA209577, CA209648 and ONO-4538-24 (CA209473) (see Table 1).

Table 1 Clinical studies of nivolumab in advanced oesophageal squamous cell carcinoma

Study/Phase/Status	Study design	Study population	Endpoints	Test drugs and dose	Number of patients	Timing of endpoint analyses
Nivolumab Monotherapy						
ONO-4538-24 (CA209473)/ **Phase 3 / Complete** *** Pivotal study ***	Global, randomized (1:1), open-label, docetaxel- or paclitaxel-controlled study	Patients with histologically confirmed advanced OSCC refractory to or intolerant of combination therapy with fluoropyrimidine- and platinum-based drugs.	Primary: OS Secondary: Investigator-assessed PFS, ORR, DoR, TTR, DCR, maximum percent change from baseline in the sum of diameters of target lesions	Nivo arm: nivo monotherapy 240 mg IV Q2W Control arm: docetaxel 75 mg/m^2 IV Q3W or paclitaxel 100 mg/m^2 IV weekly for 6 weeks followed by a 2-week washout period	419 patients randomized	clinical cut-off date for final assessment: 12-Nov-2018
ONO-4538-07 (non-IND)/ **Phase 2 / Complete** *** Supportive study ***	Multicentre, open-label, uncontrolled study	Japanese patients with OC refractory or intolerant to fluoropyrimidine-, platinum-based, and taxane-based chemotherapy	Primary: ORR (central imaging assessment) Secondary: ORR, ir-ORR, DCR, ir-DCR, OS, PFS, ir-PFS, TTP, DoR, TTR, BOR, ir-BOR, percent change from baseline in the sum of tumour diameters, maximum percent change from baseline, response of primary esophageal lesion	Nivo (ONO-4538) 3 mg/kg Q2W	65 patients enrolled	data cut-off for final assessment: 17-Nov-2016

Table 1 Clinical studies of nivolumab in advanced oesophageal squamous cell carcinoma

Study/Phase/Status	Study design	Study population	Endpoints	Test drugs and dose	Number of patients	Timing of endpoint analyses
CA209577/ **Phase 3 / Ongoing**	Global, randomized (2:1), double-blind, placebo controlled two-arm study	Patients with resected OC, or GEJ cancer who have received chemoradiotherapy followed by surgery	Primary: DFS Secondary: OS and OS rates at 1, 2, and 3 years	Nivo monotherapy 240 mg or placebo Q2W for 16 weeks followed by nivo 480 mg Q4W or placebo	793 patients randomized	DFS Interim analysis/ OS: 3Q 2020 DFS final analysis /OS: 2Q 2021 OS final analysis: 4Q 2022
Nivolumab in Combination with Ipilimumab						
CA209648/ **Phase 3/ Ongoing**	Global, randomized (1:1:1), open-label study	Patients with advanced, recurrent or metastatic OSCC, who did not receive prior systemic therapy for advanced OSCC	Primary: OS and PFS (by BICR) in patients with PD-L1 expressing tumours Secondary: OS and PFS (by BICR) in all randomized patients, and ORR (by BICR) in PD-L1 expressing tumours and all randomized patients	Arm A: nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W Arm B: nivo 240 mg as Q2W, fluorouracil 800 mg/m²/day IV on days1 to 5 days, and cisplatin 80 mg/m² on day 1 of 4-week cycle Arm C: fluorouracil 800	871 patients randomized out of planned 939	PFS final analysis/OS interim: June 2020 OS final analysis: Aug 2021

Table 1 Clinical studies of nivolumab in advanced oesophageal squamous cell carcinoma

Study/Phase/Status	Study design	Study population	Endpoints	Test drugs and dose	Number of patients	Timing of endpoint analyses
				mg/m²/day IV Day 1 through Day 5 and cisplatin 80 mg/m²/day on day 1 of 4-week cycle		

Abbreviations: BICR: blinded independent central review; BOR: best overall response; DCR: disease control rate; DFS: disease free survival; DoR: duration of response; OC: oesophageal cancer; OSCC: oesophageal squamous cell cancer; GEJ: gastroesophageal junction; ipi: ipilimumab; ir: immune-related; IV: intravenous; nivo: nivolumab; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; QxW: every x weeks; TTP: time to progression; TTR: time to response

2.3.2. Pharmacokinetics

The clinical pharmacology of nivolumab has been described in previously submitted clinical pharmacology packages and included single- and multiple-dose pharmacokinetic parameters, drug-drug interaction potential, pharmacodynamics, QT prolongation potential, and dose selection for Phase 2/3 studies.

The clinical pharmacology data evaluated the nivolumab serum concentration-time profiles when administered as monotherapy (240 mg Q2W) in subjects with unresectable advanced, recurrent or metastatic OSCC from study ONO-4538-24 (CA209473) by popPK analysis. For this submission, updates to the nivolumab popPK analyses were performed, and pharmacokinetics of nivolumab in subjects with oesophageal cancer were compared with other tumour types. This analysis also included a comparison of nivolumab exposures in subjects with OSCC across different ethnic groups to support the extrapolation of exposures across populations.

Population pharmacokinetics

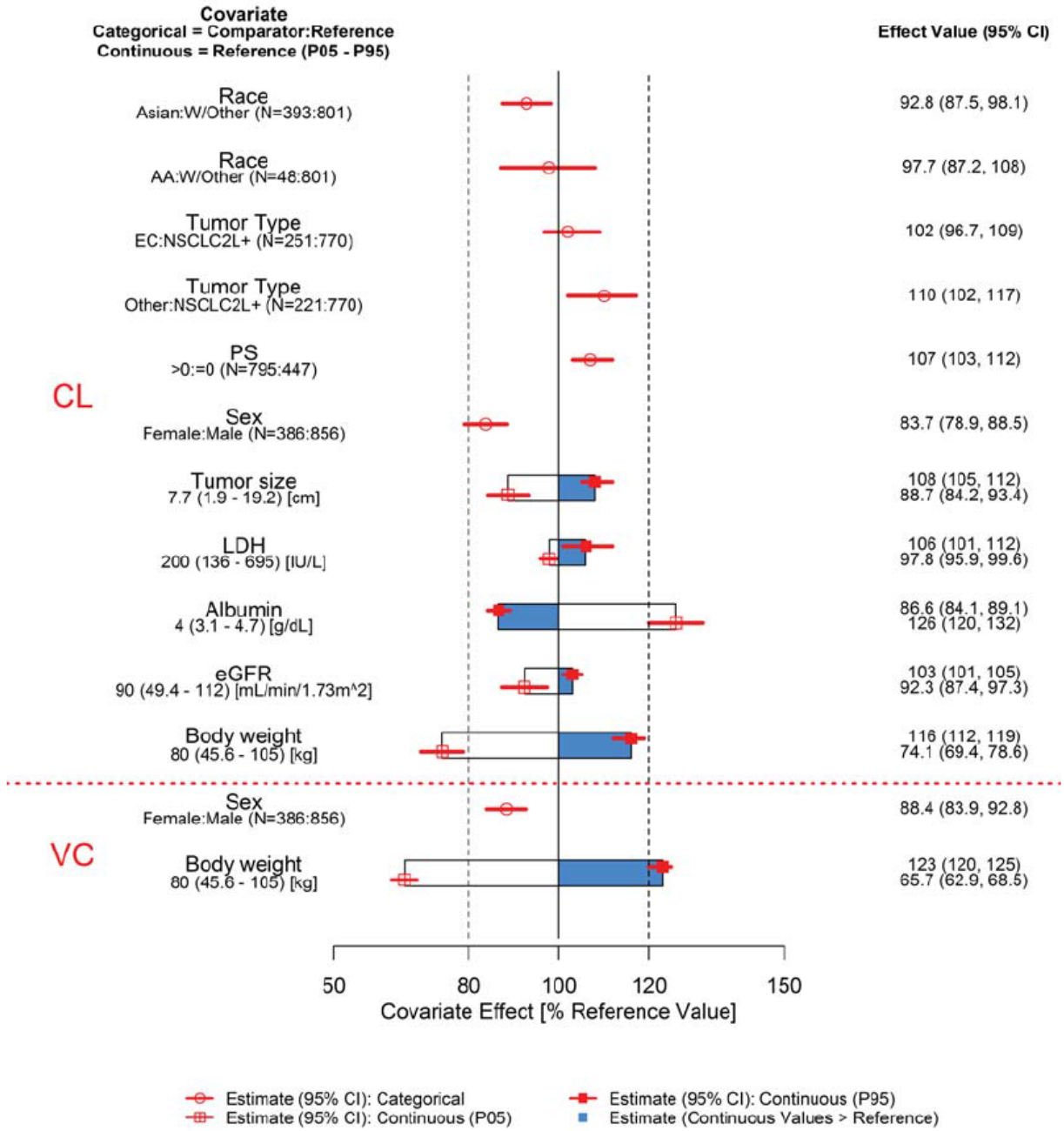
The purpose of the popPK analyses was to characterize the pharmacokinetics of nivolumab in subjects with OSCC, and to determine the effect of key covariates (in particular, tumour type and race) on nivolumab pharmacokinetics and exposure.

The nivolumab popPK analysis dataset included a total of 7,775 nivolumab concentration values from 1,242 subjects in 10 studies in subjects with solid tumours, including OSCC, receiving nivolumab monotherapy. The data included in the analyses were from Phase 1 studies with frequent blood sampling (ONO-4538-01, CA209001, and CA209003), clinical studies in subjects with NSCLC (ONO-4538-05,

ONO-4538-06, CA209017, CA209057, and CA209063), and clinical studies in subjects with OSCC (ONO-4538-07 and ONO-4538-24/CA209473).

Model development consisted of re-estimating parameters of the previously developed final model (Procedure EMEA/H/C/003985/II/0019). The model was a 2-compartment, zero-order infusion model with time-varying total CL described using a sigmoidal Emax function. The full model was developed from the base model by including the following covariates for CL body weight, estimated glomerular filtration rate (eGFR), performance status, sex, race, tumour type (categorized into OSCC, NSCLC 2L+ and Others, with NSCLC 2L+ being the reference), albumin, lactate dehydrogenase, and tumour size, and covariates for the volume of distribution of the VC were body weight and sex. **Figure 1** shows that the magnitudes of the effects on the parameters (CL and VC) were less than 20% for all the covariates except body weight and albumin. The effects of tumour type and race on the parameters were limited (i.e., <20%) in the full model, indicating that these covariates do not have a marked effect on the pharmacokinetics of nivolumab.

Figure 1 Covariate effects on nivolumab pharmacokinetic model parameters



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

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

Note 3: Reference subject is male, white/other race, body weight=80 kg, performance status=0, eGFR=90 mL/min/1.73 m^2, tumor size=7.7 cm, LDH=200 U/L, albumin=4 g/dL with NSCLC 2L+ as 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.

Using the developed full model, nivolumab exposures were predicted following nivolumab 240 mg Q2W in subjects with OSCC and NSCLC. Table 2 shows that exposures were higher (Cavgss was ~23% higher) in subjects with OSCC than those with NSCLC.

Table 2 Summary statistics of individual measures of nivolumab exposure for oesophageal cancer subjects and NSCLC 2L+ subjects (240 mg Q2W)

	Esophageal Cancer		NSCLC 2L+		% Difference in Geometric Mean (Esophageal cancer vs NSCLC)
Summary Exposure	Geometric Mean (% CV) [ug/mL]	Median (5^{th}-95^{th} percentile) [ug/mL]	Geometric Mean (% CV) [ug/mL]	Median (5^{th}-95^{th} percentile) [ug/mL]	
Cavgd14	34.9 (17.8)	34.8 (26.0 - 47.0)	30.6 (25.1)	30.1 (21.1 - 45.1)	14.3
Cmax1	80.1 (20.6)	79.2 (57.9 - 116)	69.4 (63.2)	68.7 (45.5 - 107)	15.4
Cmind14	23.2 (22.3)	23.4 (15.6 - 32.8)	19.5 (31.2)	19.2 (12.1 - 32.2)	19.0
Cavgss	118 (32.2)	119 (65.8 - 194)	95.9 (58.1)	94.3 (53.3 - 172)	23.1
Cmaxss	176 (27.2)	174 (113 - 271)	146 (53.2)	142 (89.5 - 254)	20.3
Cminss	93.8 (37.2)	94.8 (46.4 - 166)	73.9 (70.5)	73.3 (36.3 - 144)	27.0

Esophageal cancer: N=251, NSCLC 2L+: N=770
%Difference in Geometric Mean: [(Geometric Mean in Esophageal cancer – Geometric Mean in NSCLC 2L+)/ Geometric Mean in NSCLC 2L+]*100

2.3.3. Pharmacodynamics

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.

The recommended dose for nivolumab in OSCC is 240 mg every 2 weeks which is the approved dose for nivolumab monotherapy across all tumour types.

An assessment of the exposure-response for efficacy and safety was conducted to characterize the relationship between nivolumab exposure (Cavg1) and response (safety and efficacy) and to inform the benefit-risk evaluation of the nivolumab monotherapy in subjects with OSCC from study ONO-4538-24/CA209473. Additionally, the immunogenicity of nivolumab was assessed in ONO-4538-24 (CA209473) in OSCC.

Exposure-response analyses

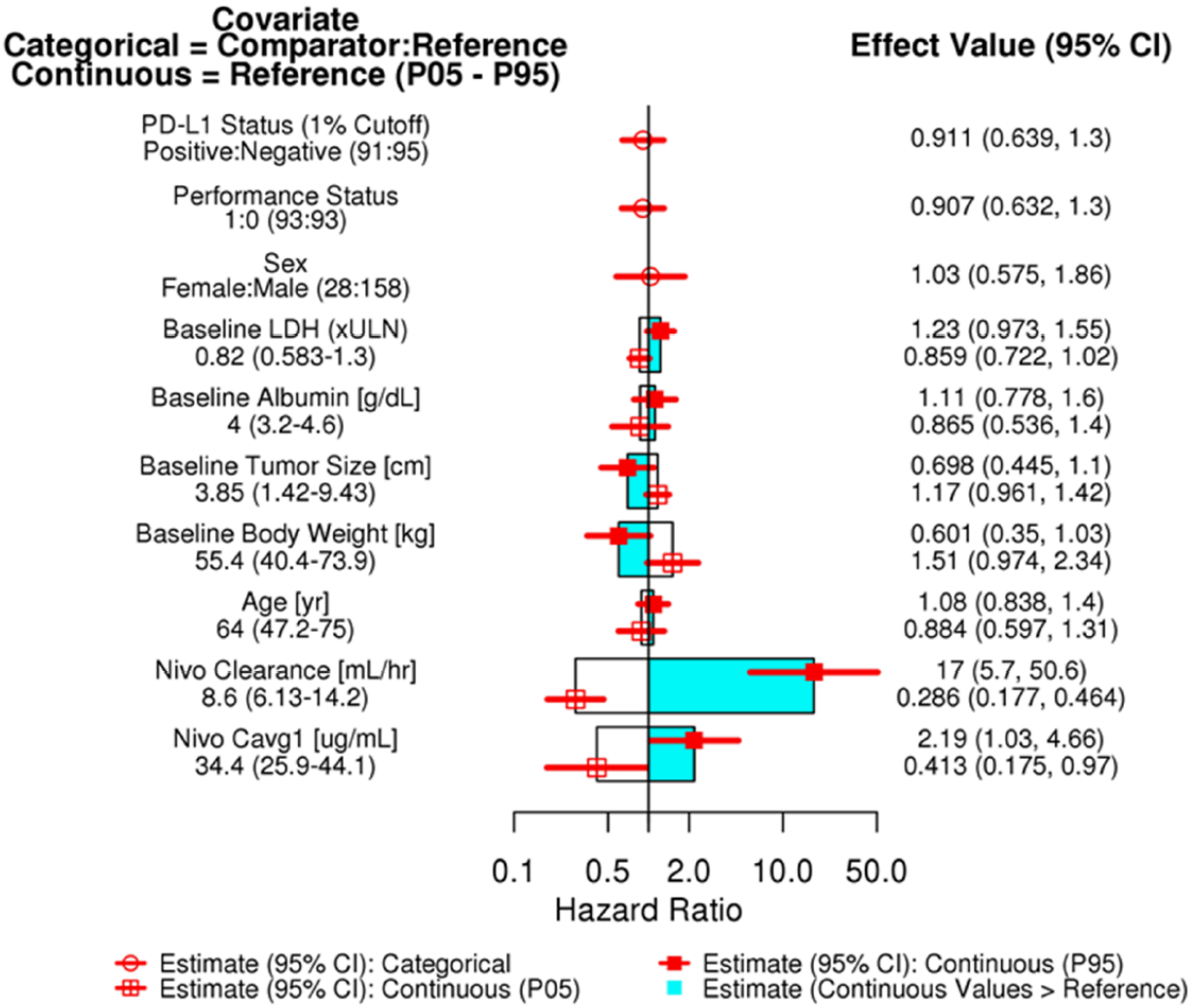
The purpose of the exposure-response analysis was to assess the relationship between nivolumab exposure (the popPK model-predicted time-averaged concentration over the first dosing interval [Cavg1]) and efficacy (OS) or safety (Grade 2+ select AEs). Use of an early measure of exposure is most appropriate for characterization of exposure-response relationship, as it avoids the potential confounding effects of time-varying clearance on evaluating of a potential relationship between exposure and response.

The exposure-response relationship was derived from 186 OSCC subjects treated with nivolumab in ONO-4538-24 (CA209473), who had nivolumab exposure data available. The relationship between the nivolumab exposure and OS was characterized by a Cox Proportional-Hazards (CPH) model. The following baseline covariates were assessed in the full model: baseline nivolumab clearance, age, baseline body weight, baseline tumour size, baseline albumin, baseline LDH, sex, performance status, and PD-L1 status (cut off at 1%).

The full exposure-response model (**Figure 2**) showed that nivolumab Cavg1 and baseline CL were both significant predictors of OS (95% CI of HR did not include 1). The risk of death was lower in subjects with lower Cavg1, and in subjects with lower baseline nivolumab CL over the range of exposure achieved by nivolumab 240 mg Q2W dosing regimen. This unexpected exposure-response relationship is likely attributed to confounding effect of CL as the parameter estimates of nivolumab Cavg1 and baseline CL were highly correlated (R = 0.84), indicating that the effect of Cavg1 and CL on OS is not independent.

Age, baseline body weight, baseline tumour size, baseline albumin, baseline LDH, sex, performance status, and PD-L1 status were not significant covariates of OS in the full model.

Figure 2 Estimated effects of exposure-response efficacy (OS) in OSCC (study ONO-4538-24 (CA209473)



Source: Refer to Figure 5.1.1.1-1 in the ER report.[9]

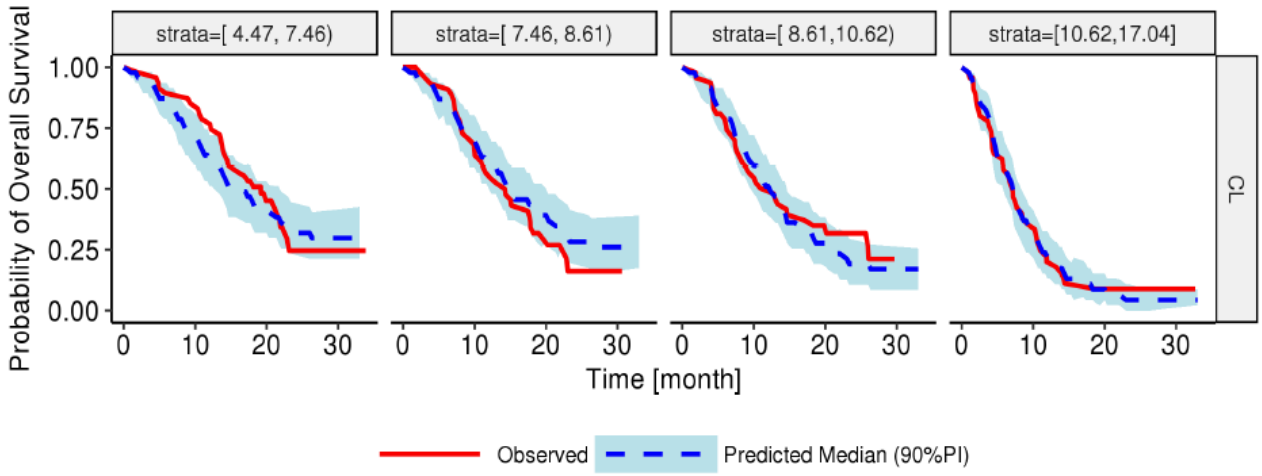
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).

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

Note 3: Hazard Ratio plotted on a log scale

The model performance was evaluated by comparing the cumulative probability of OS predicted by the full model with that determined by Kaplan-Meier analyses. Exposure-response efficacy (OS) by CL quartiles is presented in **Figure 3**. The K-M curves were in good agreement with the CPH model predictions, indicating an adequate model performance.

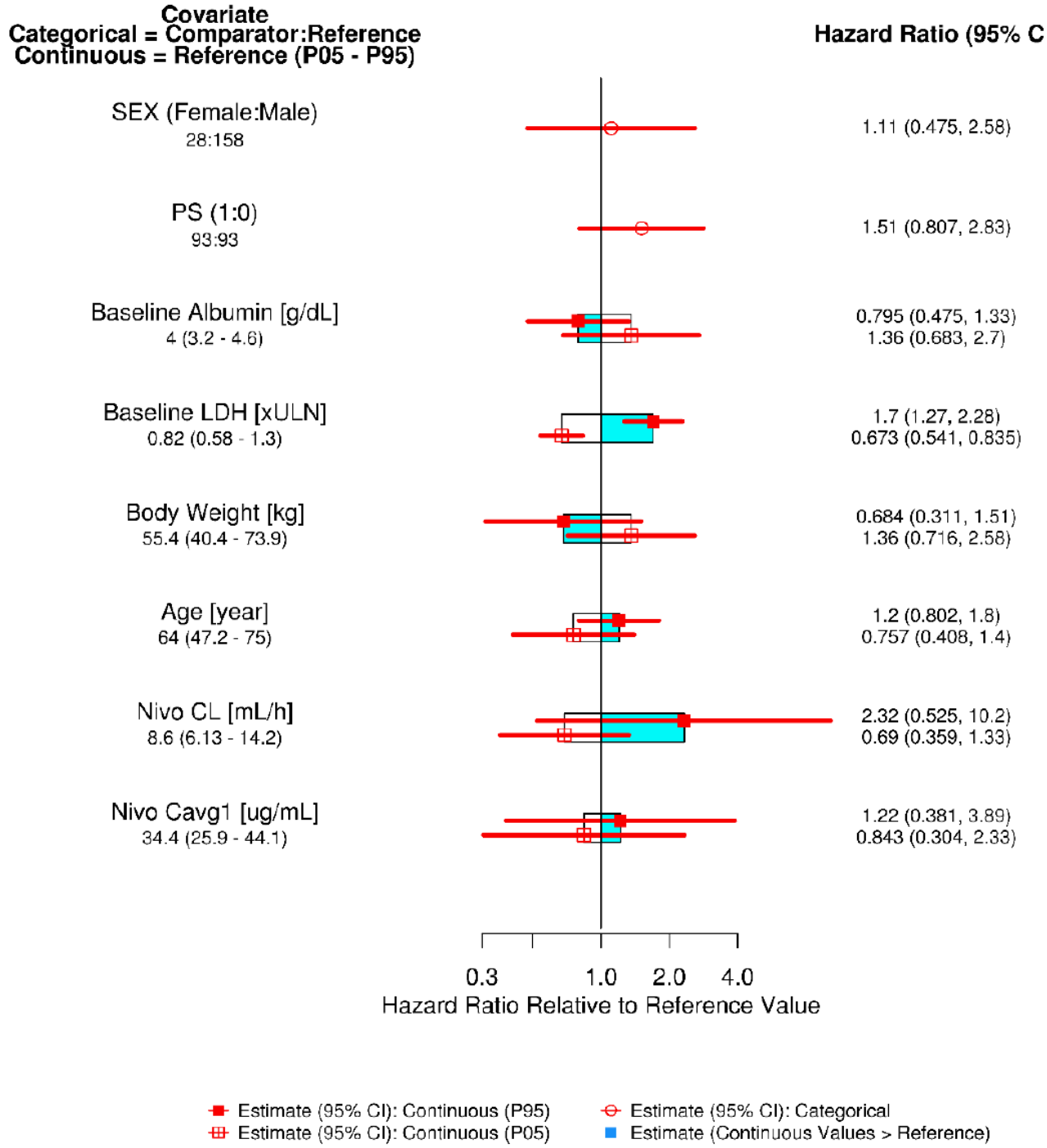
Figure 3 Model evaluation of exposure-response efficacy (OS) by baseline nivolumab clearance quartiles OSCC (study ONO-4538-24 (CA209473)



Analysis-Directory: /global/pkms/data/CA/209/473/prd/er-os/final/
Program Source: Analysis-Directory/R/scripts/er-efficacy-ec.Rmd
Source: Analysis-Directory/R/scripts/er-efficacy-ec.docx

For exposure-response safety, the relationship between nivolumab exposure (Cavg1) and time to Gr. 2+ immune-mediated adverse event (IMAE) was described by a Cox Proportional-hazard (CPH) model. The following baseline covariates were assessed in the full model: baseline nivolumab clearance, age, baseline body weight, baseline albumin, baseline LDH, sex, and performance status). The estimated magnitude of effect of nivolumab exposure Cavg1 on the risk of Grade 2+ select AEs was negligible (HR 95% CI of 0.905 to 1.15) and not statistically significant (**Figure 4**). Thus, higher nivolumab exposures are unlikely to be associated with higher risk of Grade 2+ select AEs. Even though Cavg1 and CL are correlated, when CL was removed from the full model, the HR of Cavg1 was still not statistically significant (95% CI of effect include 1). The risk of Grade 2+ select AEs was higher in subjects with higher baseline LDH (HR 95% CI of 1.699 to 6.032). Higher LDH may indicate more severe disease, and corresponds to have a higher risk of safety events. The other covariates did not have significant effects on the risk of Grade 2+ select AEs.

Figure 4 Estimated effects of exposure-response safety (Gr. 2+ IMAE) in OSCC (study ONO-4538-24 (CA209473)



Summary of immunogenicity of nivolumab

Of the 184 patients from study ONO-4538-24 (CA209473) treated with nivolumab 240 mg Q2W and evaluable for immunogenicity, 9 (4.9%) were ADA positive and 3 (1.6%) were ADA baseline-positive. Of the 9 anti-nivolumab antibody-positive patients (defined as having at least 1 ADA positive sample after first treatment administration), 1 was persistent positive for ADA, 3 had positive samples at the last

sampling timepoint, and 5 were considered other positive. None of the ADA positive subjects were neutralizing nivolumab ADA positive.

Among the 9 ADA positive patients, 1 patient had a BOR of PR, 3 patients had BOR of SD, and 3 patients had a BOR of PD. None of the patients who were ADA positive had a hypersensitivity/infusion reaction category event after nivolumab treatment.

2.3.4. PK/PD modelling

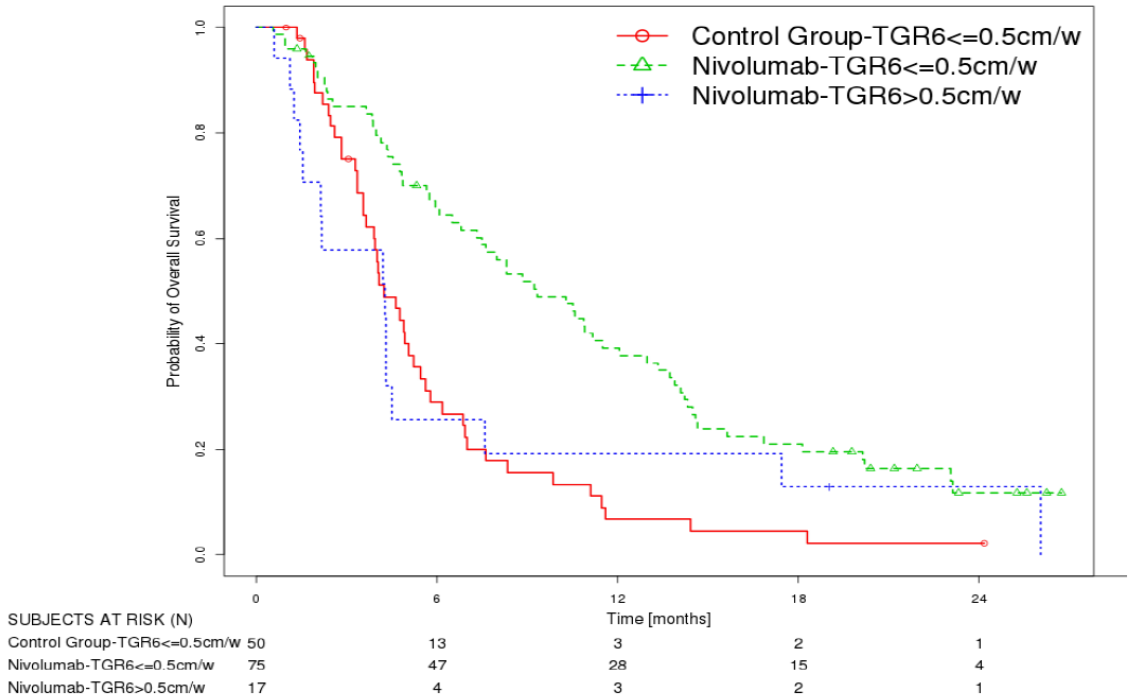
Tumour growth dynamics

Tumour growth dynamics - Clinical modelling

The purpose of the tumour growth dynamics (TGD) analyses was to describe the tumour burden profiles of patients with advanced OSCC, and to characterize the effect of nivolumab vs. chemotherapy control (docetaxel or paclitaxel) on tumour growth rate (TGR) utilizing TGD modelling. This retrospective (post hoc) analysis was conducted to gain a better understanding of the effect of treatment on tumour response, and the relationship of tumour response to OS. The focus of the analysis was on patients with a BOR of PD, as there was a higher proportion of patients with BOR of PD in the nivolumab group compared to the control group, and also because of the early crossing of the OS and PFS curves, despite nivolumab demonstrating statistically significant superior OS and longer DoR. The sum of longest diameter of target lesions (SLD) was used to define tumour burden in this analysis. The time course of the individual TGR was calculated based on estimated TGD parameters of tumour shrinkage and tumour growth of individual patients. Patients without measurable disease at baseline and patients who did not have at least one post-treatment tumour burden data, were excluded from the analysis. This comprised 25.5% of the ITT patient population, similarly distributed amongst the nivolumab and control arms (i.e. 51 and 56 patients, respectively).

In the TGD model data from a total of 312 patients ([210-51 =] 159 nivolumab and [209-56 =] 153 control) from the pivotal study ONO-4538-24 (CA209473) could be included, which comprises 74.5% of the ITT patient population. Based on model evaluation criteria such as diagnostic plots and visual predictive checks, the TGD model provided an adequate description of the tumour burden data over time for OSCC patients in both the nivolumab and control arms. In patients with CR+PR or SD, the predicted tumour growth rate in the nivolumab arm was lower than that in the control arm. In patients with BOR of PD, the tumour growth rate was higher in the nivolumab arm compared with the control arm. However, further assessment of OS in these patients with BOR of PD indicated that the risk of death is not worse in patients with BOR of PD treated with nivolumab who had higher tumour growth rate at Week 6 than the patients with BOR of PD in the control arm (Figure 5).

Figure 5 Kaplan-Meier of overall survival by TGR at week 6 (cut-off at 0.5 cm/week) and treatment in subjects who had PD



Analysis -Directory: /global/pkms/data/CA/209/473/prd/er-tgd/final/
Program Source: Analysis-Directory/R/scripts/main-nmplots-473.r
Source: Analysis-Directory/nm/b00-stein-212c1/plots/os-km-arm-prw6-pd.png
Note: TGR6: tumor growth rate at week 6; subjects who had NE were not included in the Kaplan-Meier analysis
Note: PD: progressive disease

2.3.5. Discussion on clinical pharmacology

Nivolumab pharmacokinetic characteristics, with a decrease in clearance with time over the course of treatment, are comparable in subjects with oesophageal cancer to what was seen for other tumour types. However, the average clearance was slightly lower in subjects with oesophageal cancer, which is likely due to the relative low body weight of the subjects with OSCC, median body weight, 55.2 kg vs 69 kg in the total popPK population. The effects of race - Asian on the pharmacokinetic parameters were limited (i.e., < 10%), which is in agreement with previous analyses.

In the exposure-OS analysis, both nivolumab Cavg1 and baseline CL were included in the full model despite the high degree of correlation (R = 0.846) as examination of the exposure-OS relationship of nivolumab at a single dose level may lead to incorrect conclusions due to the confounding effect of nivolumab clearance (see exposure response RCC EMEA/H/C/003985/II/0008). Baseline CL has been identified as a significant predictor of overall survival in subjects treated with nivolumab and other anti-PD-1 antibody across tumour types (e.g., specifically, Mel, NSCLC and RCC). High baseline antibody clearance might be associated with subject's poor disease status due to cancer cachexia. In line with these data, subjects with the highest antibody clearance had a shorter OS (**Figure 3**). In study ONO-4538-24, there was an early crossing of the KM OS curves at approximately 5 months (

Figure 8), only afterwards favouring nivolumab and it should be discussed if subjects at risk for an early death were subjects with high nivolumab clearance. A retrospective exploratory analysis demonstrated that 50% of the patients in nivolumab arm who had early death (<5 months) had a high nivolumab clearance (Q4) vs 20-25% of the patients in nivolumab arm with death ≥5 months. This is in agreement with nivolumab baseline clearance as predictive factor for OS, but there is a great overlap in nivolumab clearance between the groups. Hence, baseline clearance cannot be used as a biomarker to select patients at risk of early death.

The risk of death in subjects with OSCC administered nivolumab 240 mg Q2W was not higher in subjects with lower nivolumab exposure. Nivolumab exposure is approximately 25-30% lower in subjects with higher body weight (>90 kg) following flat dosing 240 mg Q2W compared to subjects with a low body weight (<65kg). Nevertheless, subjects with OSCC with a higher body weight tended to have a lower risk of death than subjects with a low body weight. Similar trends that patients with higher body weight had a lower risk of death, have been observed for nivolumab across other tumour types dosed with 3 mg/kg. This is what can be expected for a flat exposure-response over the exposure range achieved by nivolumab 240 mg Q2W dosing regimen.

In the exposure- Gr2+IMAE analysis, nivolumab Cavg1 did not have statistically significant effect on the risk of Gr. 2+ IMAE within the exposure range obtained with 240 mg Q2W. The only significant predictor of hazard factor was baseline LDH, where higher LDH corresponds to higher risk of Gr. 2+ IMAE.

Current immunogenicity results are in line with previous results observed in treatments for nivolumab in monotherapy low persistent positive rates. The nivolumab ADA incidence of 4.9% in patients with 2L OSCC is similar to previously observed in other tumour types. In study ONO-4538-24 (CA209473) the incidence of ADA did not appear to have an effect on efficacy or safety of nivolumab.

2.3.6. Conclusions on clinical pharmacology

Pharmacology data in patients with oesophageal cancer are overall in line with previous observed data in patients with other tumour types. No relevant differences have been observed.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study

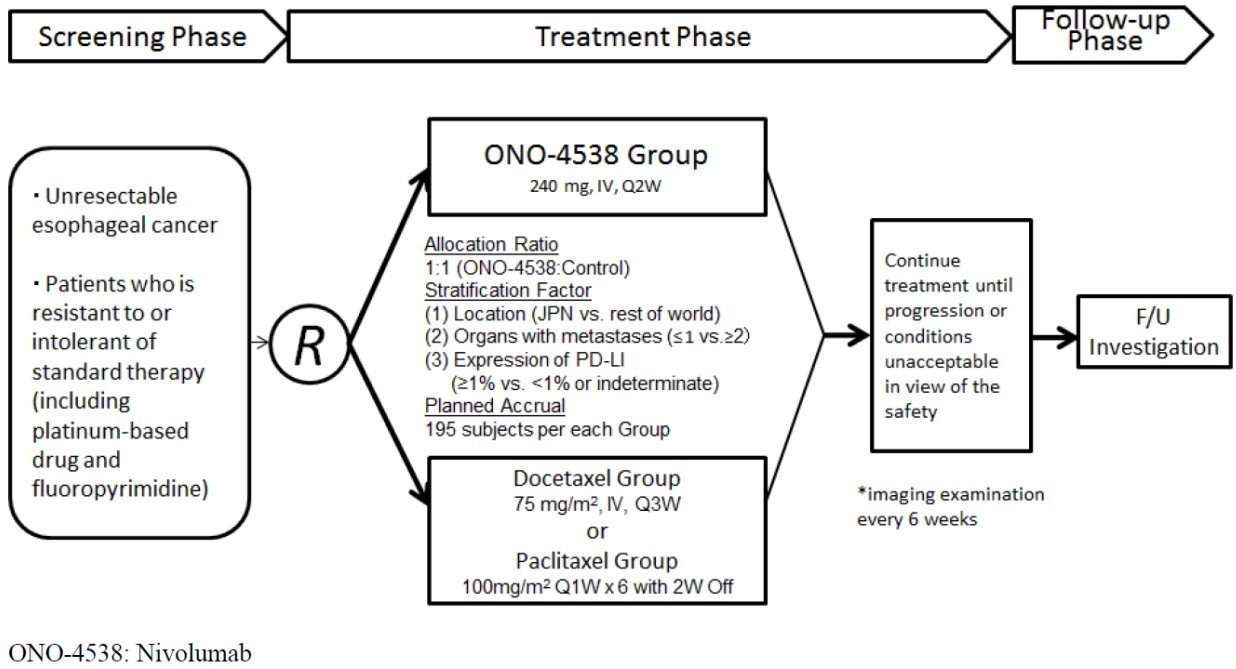
ONO-4538-24 (CA209473) Phase III Study, a multicentre, randomised, open-label study to evaluate efficacy and safety of nivolumab in patients with unresectable advanced, recurrent or metastatic esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs

Methods

Study **ONO-4538-24** (CA209473; NCT02569242; Kato et al. 2019) is a multicentre, randomised, open-label, docetaxel- or paclitaxel-controlled study to evaluate the efficacy and safety of nivolumab for the treatment of patients with unresectable advanced, recurrent or metastatic OSCC refractory to or intolerant of combination therapy with fluoropyrimidine- and platinum-based drugs. Patients were randomized (1:1) to receive either nivolumab or investigator's choice of docetaxel or paclitaxel

chemotherapy, all given intravenously. The entire study period consisted of 3 periods: screening period, treatment period, and post-treatment observation period, and a schema of the study design is provided in Figure 6.

Figure 6 Study design ONO-4538-24 (CA209473)



Abbreviations: 2W: 2 week; F/U: follow up; IV: intravenous; JPN: Japan; ONO-4538: nivolumab; QxW: every x weeks; R: randomization

Tumour assessments were conducted every 6 weeks for 1 year, and every 12 weeks thereafter. Thoraco-abdomino-pelvic computed tomography or other imaging examinations were performed, and the tumour response was assessed using the standard Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) and as assessed by the investigator. For patients with a response assessment other than PD per RECIST 1.1 who had discontinued the treatment phase for safety reasons, imaging was continued as far as possible until either initiation of post-study treatment for OSCC or until assessment of PD or recurrence.

Study participants

Patients with oesophageal cancer who were refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs were enrolled.

Having provided written consent before participation in the study, patients were required to fulfil all of the inclusion criteria and none of the exclusion criteria to be eligible for randomisation.

Key inclusion criteria:

- Patients aged ≥20 years with ECOG PS 0 or 1, with oesophageal cancer, a life expectancy of ≥3 months, and whose major lesion in the oesophagus (if already resected, the major lesion in the oesophagus prior to resection) satisfies the following criteria:

    - Major lesion located in the cervical oesophagus or thoracic oesophagus (upper, middle, or lower thoracic region; including the oesophagogastric junction); and
    - Histological type of major lesion squamous cell carcinoma or adenosquamous cell carcinoma.
- Patients who are refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs for oesophageal cancer, have previously received 1 treatment regimen, and are not indicated for a radical resection. The definition of refractory was to be defined as follows; and a therapy applicable to the following was to be counted as 1 regimen.
    - Patients whose progressive disease (PD)or recurrence was confirmed by imaging during their initial chemotherapy (including chemoradiation) or within 8 weeks after the last dose of chemotherapy were assessed as "refractory."
    - Patients who underwent a radical resection (R0 resection confirmed) in conjunction with chemotherapy including neo-adjuvant/adjuvant therapy and chemoradiation (including patients who underwent chemoradiation followed by salvage surgery) whose recurrence was confirmed by imaging within 24 weeks after the last dose of chemotherapy were determined to be "refractory."
    - If a complete response (CR) was assessed as a result of the initial chemotherapy (including chemoradiation), patients whose recurrence was confirmed by imaging during the initial chemotherapy (including chemoradiation) or within 24 weeks after the last dose of chemotherapy were determined to be "refractory."
- At least 1 measurable or non-measurable lesion per RECIST 1.1.
- Patients must provide tumour tissue (stored tissue or tissue from the last biopsy) for analysis of PD-L1 expression.

Key exclusion criteria:

- Patients with apparent tumour invasion in organs located adjacent to the oesophagus (e.g., the aorta or respiratory tract) and/or patients receiving stent therapy in the oesophagus or respiratory tract.
- Patients who had previously received taxane agents to treat oesophageal cancer. Patients who were not proven refractory (see the definition of refractory in the above inclusion criteria) or intolerant to taxane-based combination therapy, had subsequently received fluoropyrimidine- and platinum-based combination therapy, and then had been proven refractory or intolerant could be randomised.
- Metastasis in the brain or meninx that was symptomatic or required treatment.
- Concurrent autoimmune disease or history of chronic or recurrent autoimmune disease or medical conditions requiring systemic immunosuppression.
- Current or past history of interstitial lung disease or pulmonary fibrosis. Patients with radiation pneumonitis could be randomised if the radiation pneumonitis had been confirmed as stable (beyond the acute phase) without any concerns about recurrence.
- Concurrent diverticulitis or symptomatic gastrointestinal (GI) ulcerative disease.
- Pericardial fluid, pleural effusion, or ascites requiring treatment.

- A transient ischemic attack, cerebrovascular accident, thrombosis or thromboembolism (pulmonary arterial embolism or deep vein thrombosis) within 180 days before randomization.
- A history of uncontrollable or significant cardiovascular disease.

Treatments

Patients received either nivolumab or investigator's choice of chemotherapy (i.e. docetaxel or paclitaxel), as follows:

- Nivolumab 240 mg was administered intravenously over 30 minutes Q2W. Six weeks counted as 1 cycle of treatment.
- Docetaxel was administered intravenously at a dose of 75 mg/m^2 Q3W over at least 60 minutes in accordance with the package insert. Each treatment cycle lasted 3 weeks.
- Paclitaxel was administered intravenously over 60 minutes in accordance with the package insert at a 100 mg/m^2 dose weekly for 6 weeks followed by a 2-week washout period.

Treatment was continued until disease progression as assessed by the investigator per RECIST 1.1, or unacceptable toxicity. Treatment beyond initial investigator-assessed progression was permitted in patients receiving nivolumab with no rapid progression, investigator-assessed benefit, tolerance to treatment, stable ECOG PS, and for whom treatment beyond progression would not delay an imminent intervention to prevent serious complications associated with disease progression (e.g. brain metastasis). Prior to continuing nivolumab treatment beyond progression, a patient's written re-consent had to be obtained. Dose reductions were not permitted for nivolumab, whereas for paclitaxel and docetaxel dose reductions were permitted to manage the toxic effects of chemotherapy.

In regard to Nivolumab used in the main clinical study the MAH provided data to support that the batches used to support this extension of indication are comparable to the EU-commercial material. It should be noted that the clinical material and EU-commercial material are manufactured by the same drug substance (DS) manufacturing process and manufacturing site and that the Drug Substance is therefore the same. The clinical trial product used in the ONO-4538-24 (CA209473) study consists of four batches manufactured at the Ono facility as well as one batch manufactured at the approved BMS facility (Manati, Puerto Rico, USA). Nivolumab injection manufactured by both Ono and by BMS uses Process C drug substance of the same composition, made from the same cell line by the same approved commercial manufacturing site at Lonza Biologics, Inc. located in Portsmouth, New Hampshire, USA. The dosage form, formulation, and primary packaging of Ono and BMS drug products are the same. Therefore, the evaluation of comparability focused on (a) drug product manufacturing process, (b) analytical testing data between the BMS and Ono drug products, (c) stability comparability, and (d) an assessment of clinical pharmacokinetic (PK) data following administration of the BMS and Ono products in Asian patients. Minor differences between the Ono and Lonza/BMS drug product manufacturing process exist; these minor differences have been described in extensive detail between the approved (commercial) Lonza site and the Ono-facility (e.g. details of dilution and filtration process) (data not shown). These differences are considered technical adaptations with low risk and unlikely to have an impact on product quality. Minor differences exist with regard to the specifications/release tests. Although some differences exist in the exact list of tests, the batch analysis data from the clinical batches can be compared to specifications and historical data (in the form of TI/TLs) of the EU–commercial material.

This analysis does not suggest that any meaningful difference might exist between the clinical and EU-commercial material. Most results are comparable (either compared to the RS or within the TI/TL), except for the higher level of endotoxins which is actually considered worst-case and therefore not an issue when clinical trial results are interpreted.

All of the four Ono drug product batches and one BMS drug product batch used in this clinical study were manufactured from drug substance produced at approved Lonza Portsmouth, NH, USA using the approved Process C. (Table 2.3.2-8). The drug substance batches used to manufacture all five drug product batches were released according to the approved drug specifications in place at the time of testing and data for drug substance batches were provided.

The submitted data further confirm that the same DS was used.

Population PK (popPK) analyses were also provided which investigated whether the PK of nivolumab were similar in Asian patients administered nivolumab BMS and Ono drug products.

These PK analyses showed that using BMS or Ono product does not impact the Cl of nivolumab since the comparison of the Ono product to the reference product has a point estimate of nearly 1, and the 90% CI is within the 80% to 120% limits. In addition, a comparison of average nivolumab serum concentrations after the first dose following administration of BMS or Ono drug product in Asian patients demonstrates that the exposure estimates for the two drug products are similar.

Collectively, these PK analyses demonstrate that administration of the Ono and BMS drug products result in similar PK.

In conclusion, comparability of the clinical material from Ono to the EU-commercial material has been sufficiently substantiated for the purpose of this application.

Objectives

Primary objective

To compare overall survival (OS) between the nivolumab group and control group (docetaxel or paclitaxel) in patients with oesophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs.

Secondary objectives

To compare objective response rate (ORR) between the nivolumab group and control group.

To compare progression-free survival (PFS) between the nivolumab group and control group.

Outcomes/endpoints

Primary endpoint

Overall survival (OS) defined as the time from randomisation until death from any cause.

Secondary endpoints

- Objective response rate (ORR) defined as the percentage of patients whose best overall response is either confirmed complete response (CR) or partial response (PR) as assessed by the investigator per RECIST 1.1.
- Progression free survival (PFS) defined as the time from randomisation to the earlier date on which either the overall response was assessed as progressive disease (PD) by the investigator (per RECIST 1.1), or the patient died of any cause.
- Disease control rate (DCR) defined as the percentage of patients whose BOR was assessed as CR, PR, or stable disease (SD) by the investigator (per RECIST 1.1).

- Duration of response (DoR) defined as the time between the date of first confirmed response (complete response [CR] or partial response [PR]) and the date of the first documented progression as determined by the investigator (per RECIST 1.1), or death due to any cause, whichever occurs first. DoR was calculated in patients whose BOR was assessed as either confirmed CR or confirmed PR.
- Time to response (TTR) defined as the time from randomization to the date of first assessment of confirmed CR or confirmed PR.
- Best overall response (BOR) was determined solely by imaging assessment according to RECIST 1.1, and did not take into account any clinical/symptomatic progression. Evaluable imaging data was of those without an overall response of "not evaluable (NE)."
- Maximum percent change from baseline in the sum of diameters of target lesions in patients with target lesions, on the basis of the diameters of target lesions as measured by RECIST 1.1, but excluding the diameter data obtained after an overall response of PD, after start of subsequence anti-cancer therapy and after end of investigating subsequence anti-cancer therapy.

Exploratory biomarkers

Amongst others, tumour tissue examination (PD-L1 expression analysis, essential; other parameters, optional).

Other (exploratory) endpoints and test variables

Amongst others, patient reported outcomes (PROs) to assess health-related quality of life (QoL), i.e. general health status was measured using the EuroQol 5-dimension 3-level version (EQ-5D-3L, see EQ-5D-3L User Guide), a standardized instrument for use as a measure of self-reported health status. The EQ-5D-3L is comprised of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and each dimension has 3 levels: no problems, some problems, and extreme problems (labelled 1-3). These EQ-5D-3L health states may be converted into a single summary index (utility index [UI]) by applying a formula that attaches values (weights) to each of the levels in each dimension. The EQ-5D-3L UI, ranging from death (0; negative values indicate health states worse than dead) to full health (1), used utility weights for the UK population (Dolan. 1997). Additionally, the EQ-5D visual analog rating scale (VAS; EQ-VAS) allows patients to rate their own health state on a scale from 0 to100 (higher scores indicating better health).

Sample size

This study was intended to verify the superiority of the nivolumab group over the control groups (docetaxel or paclitaxel) in terms of OS. For the control arm an exponential distribution with 7.2 months median OS was assumed based on the phase II single-arm study of docetaxel (median OS 5.5-8.1 months) and the retrospective study of paclitaxel (median OS 6.1-10.4 months) as 2L treatment for patients with oesophageal cancer. Nivolumab was assumed to result in similar OS for the first 3 months and in long term survival in 5% of the patients based on a randomised phase 3 clinical trial of nivolumab vs. investigator's choice in recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (CA209141) and a phase 2 uncontrolled study of nivolumab in oesophageal cancer refractory or intolerant to standard therapy (ONO-4538-07). After the first 3 months, nivolumab was assumed to yield a HR of 0.65 for the non-long term survivors based on the following: a) in patients with stage IIIB/IV or recurrent squamous NSCLC who received a prior platinum-containing chemotherapy regimen (CA209017) a HR of 0.59 [96.85% confidence interval: 0.43, 0.81] for nivolumab over docetaxel was observed, and b) since no data of nivolumab versus paclitaxel was available, but c) an expected

average hazard ratio of the total nivolumab group (i.e., including HR = 1 over the first three months, and including 5% long term survivors) to the control groups was assumed to be 0.70 in this study.

The number of events required to detect superiority of the nivolumab group over the control groups with two-sided significance level of 5% and 90% or more power by the log-rank test was calculated to be 331. Assuming the enrolment period to be 16 months and the follow-up period after the last patient's enrolment to be 18 months, the number of patients required to ensure the required 331 events was estimated to be 390. For the calculation of the required events and sample size at the time of planning the study, the statistical analysis software SAS (version 9.3) was used.

Randomisation

Each patient was enrolled in the study by an interactive web response system (IWRS) and patients were randomised using a permuted block method in a 1:1 ratio to the nivolumab group or control group (docetaxel group or paclitaxel group). Randomisation was stratified by:

- location (Japan vs. the rest of the world);
- number of organs with metastases (at randomisation) (≤1 vs. ≥2); and
- expression of PD-L1 (≥1% vs. <1% or indeterminate).

On the IWRS and before randomisation, the investigator was to indicate whether they would use docetaxel or paclitaxel when the randomisation outcome would be the control arm.

Blinding (masking)

Not applicable, as study ONO-4538-24 is an open-label study. Patients and investigators were thus not masked to treatment allocation.

Statistical methods

Definitions of analysis populations/sets

For the primary endpoint OS and the secondary efficacy endpoint PFS, the intention-to-treat population (ITT) will be the analysis set, i.e. all randomised patients.

The response evaluable set (RES), i.e. all patients from the ITT who are not GCP non-compliant and have target lesion measurements at baseline, will be the primary analysis population for the secondary endpoint ORR, as well as for DCR, DoR, TTR, BOR, and maximum percent change from baseline in the sum of diameters of target lesions.

For safety endpoints, the safety set (SAF) will be the analysis set, i.e. all patients given at least one dose of the investigational product.

Type I error control and significance level to be used

Two-sided test will be performed with 5% significance level. If superiority in OS is determined, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 5%. The key secondary endpoints will be tested in the following hierarchical order: 1. ORR; 2. PFS.

Interactions will be tested with two-sided 15% significance level.

Data review

After data collection but before data is fixed a preliminary analysis in the ITT set will be performed to investigate the overall distribution of: patient background factors (descriptive statistics), subsequent anti-cancer therapy (surgery, radiotherapy, pharmacotherapy: frequencies), OS and primary definition PFS (number of events and censors, median and 95%CI, cross-tabulation of stratification factors by IWRS and eCRF), ORR (proportion and 95% CI by Clopper-Pearson method), AE (number of patients with AE, overall and drug-related, by System Organ Class, and Preferred Term, and Grade).

Primary endpoint OS: analysis

The primary hypothesis was that the nivolumab group is superior to the control group in terms of OS.

As primary analytical method, the distribution of OS will be compared between the two treatment groups using the stratified log-rank test with the randomization factors from IWRS (see Randomisation) as the stratification factors.

As sensitivity analyses, the distribution of OS will be compared between the two treatment groups by using the unstratified log-rank test, and by using the stratified log-rank test adjusted by the three stratification factors from test result source (location and the number of organs with metastases from eCRF source and PD-L1 expression), if there exists more than 10% discrepancy between stratification factors by IWRS source and stratification factors by eCRF source.

As secondary analytical methods, amongst others, the HR and the corresponding two-sided 95% confidence interval (CI) for the nivolumab group relative to the control group, docetaxel group and paclitaxel group will be estimated using a stratified Cox proportional hazards model with the IWRS randomization factors as the stratification factors. A Kaplan-Meier curve will be plotted for each treatment group and control regimen. Using the Kaplan-Meier method, the median OS and the corresponding two-sided Brookmeyer-Crowley 95% CI method will be estimated for each treatment group and control regimen.
Also, to examine the assumption of proportional hazards in the stratified Cox proportional hazards model, in addition to treatment, a time-dependent variable defined by treatment by time interaction will be added into the model. A two-sided Wald Chi-square p-value of less than 0.1 may indicate a potential non-constant treatment effect. In that case, additional exploratory analyses may be performed.

Subgroup analyses will be performed for OS and the interaction between treatment group and several demographic factors will be assessed using a Cox proportional-hazards model. For the analysis, each demographic factor, treatment group and interaction between each demographic variable and treatment group will be used for the factors. Adjusted analyses for OS will be performed using demographic factors. The HR and the corresponding two-sided 95% CI of the nivolumab group relative to the control group will be calculated using a multivariate stratified Cox proportional hazard model with the stratification factors (IWRS source) as the stratification factors, treatment groups and each demographic factor as the covariance factors.

Exploratory, the effect of nivolumab vs control will be investigated (Kaplan-Meier, hazard ratio) in each of the investigator's choice strata, i.e. in the stratum where the investigator before randomisation indicated that docetaxel would be used if the patient was randomized to control, and idem for paclitaxel.

Also exploratory, the effect of subsequent therapy could be investigated with Rank-preserving structural failure time models, inverse probability of weighting methods, or time-dependent Cox models.

Secondary endpoint ORR: analysis

Data will be compared between the two treatment groups using the Cochran-Mantel-Haenszel (CMH) test with the IWRS randomization factors as the stratification factors. The associated odds ratio (OR) and the corresponding two-sided 95% CI and the estimate of the difference and corresponding two-sided 95% CI

for the nivolumab group relative to the control group, docetaxel group, and paclitaxel group will be calculated using CMH methodology and adjusted by the same stratification factors. The proportions and the corresponding two-sided 95% CI will be estimated using the Clopper-Pearson method for each treatment group and control regimen. Subgroup analyses will be performed.

Regarding the other secondary endpoints DCR, DoR, TTR, BOR and maximum percent change from baseline in the sum of diameters of target lesions, the analytical methods are as follows.

- For DCR, the analytical items are the same as for ORR (see above).
- For DoR, the Kaplan-Meier curve will be plotted for each treatment group and control regimen. Using the Kaplan-Meier method, the median DoR and the corresponding two-sided 95% CI will be estimated for each treatment group and control regimen. CI for median DoR will be calculated using the Brookmeyer and Crowley method based on a log-log transformed CI for the survivor function. Additionally, summary statistics (minimum and maximum) will also be estimated for each treatment group and control regimen. This analysis will be performed on ITT/RES patients whose BOR is confirmed CR or confirmed PR.
- For TTR, summary statistics will be used, and the Kaplan-Meier curves will be plotted.
- Regarding BOR, the percentage of confirmed CR, confirmed PR, SD, PD and NE will be calculated for each treatment group and control regimen. For the percentages of CR, PR and SD, the corresponding 95% CI will be estimated using the Clopper-Pearson method for each treatment group.
- For maximum percent change from baseline in the sum of diameters of target lesions, a waterfall plot will be displayed by treatment group and control regimen.

Secondary endpoint PFS: analysis

PFS was analysed using the same primary and secondary analysis methods as OS.

According to the primary definition of PFS, patients who received or completed subsequent anticancer therapy before progressive disease or death data were censored on the last evaluable tumour assessment before initiation, or before the end of subsequent anti-cancer therapy, respectively. In contrast, patients that started (and possibly finished) subsequent anti-cancer therapy without experiencing a progression or death during the study period, would be censored at their last evaluable tumour assessment.

Whereas, by the secondary definition of PFS, an event of PD or death occurring after the start of any subsequent anti-cancer therapy (that was started before an event of PD or death) will be counted as an event, which is the EMA preferred analysis (CHMP/27994/2008 Rev. 1). Subgroup analyses will be performed.

Other (exploratory) endpoints and test variables analysis

The percentage of patients with PRO questionnaire completion in each investigational product will be summarized at each time point, with percentage defined as the proportion of questionnaires actually received out of the expected number (i.e. the number of patients still on treatment or in f/u at each time point). The EQ-5D-3L UI scores (UK based scoring) and EQ-VAS scores will be analysed using summary statistics. However, see below addition of change in EQ-5D-3L and EQ-VAS scores from baseline to the SAP and, more importantly, the (post-hoc) analytical methods actually used (refer to Outcomes and estimation – Other (exploratory) endpoints and test variables).

Safety

Not applicable because no statistical tests were performed on safety.

Changes in the planned analyses

Version 3.0 (dated 17-Dec-2018) of the statistical analysis plan (SAP) is the current version, as the original SAP was amended twice.

Major changes (dated 05-Mar-2018) from the SAP version 1.0 (dated 27-Jul-2015) included (amongst others):

- The hierarchical testing was added: OS, then ORR, then PFS.
- The interim analysis for OS was dropped.
- A test for examining the proportional hazards assumption for OS was added, to assess the proportional hazards assumption for OS.
- The above secondary definition of PFS was added, to evaluate the robustness of analysis result using PFS.
- Comparisons were added of nivolumab versus docetaxel in the patients where the investigator choice was docetaxel and idem for paclitaxel.
- Change in EQ-5D-3L and EQ-VAS scores from baseline were added, to evaluate - by means of summary statistics - health-related QoL with nivolumab relative to the control regimen from a multilateral perspective.

Major changes (thus dated 17-Dec-2018) from the SAP version 2.0 included (amongst others):

The analysis population to be used for OS, ORR and PFS when performing the test using the hierarchical hypothesis testing approach was added, in order to clarify which of the two analysis population populations of ITT and RES would be tested for each endpoint.

Results

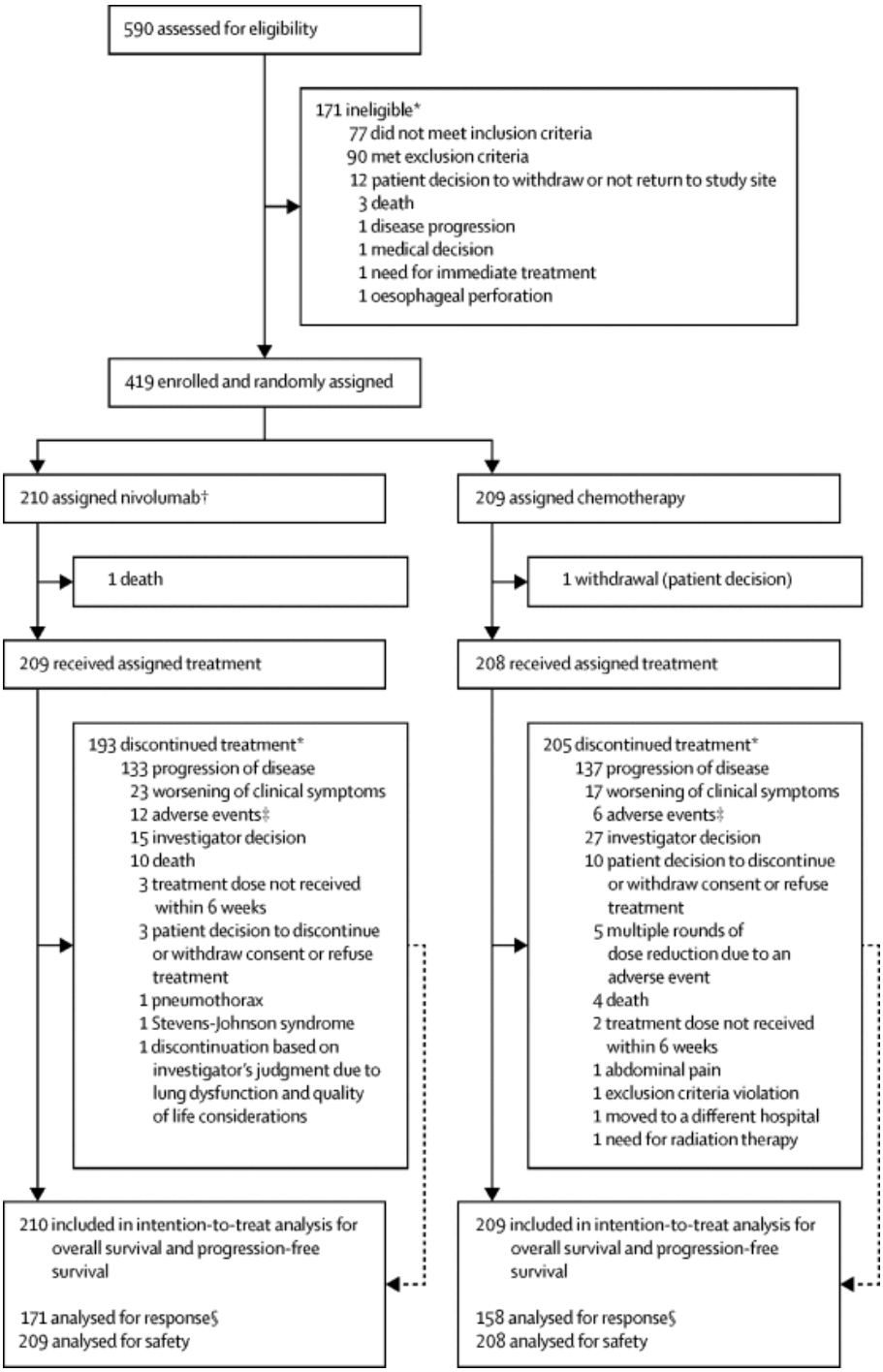
Recruitment and Participant flow

The clinical data cut-off date was 12-Nov-2018 for the ONO-4538-24 (CA209473). Final CSR and the database was locked on 28-Dec-2018. The last patient's first treatment (LPFT) occurred on 03-May-2017. The minimum follow-up (time from randomisation of the last patient to clinical data cut-off) was thus 17.6 months. The median follow-up (time from randomisation to last known date alive or death) for OS was 10·5 months (interquartile range [IQR]: 4·5, 19·0) in the nivolumab group and 8·0 months (IQR: 4·6, 15·2) in the control group.

The study was conducted at 90 study sites in 8 countries (Japan, Korea, Taiwan, UK, US, Germany, Italy, and Denmark). Therefore, the term Asian used in this assessment report will refer to the recruited patients from Japan, Korea and Taiwan. Note, although the UK is included as a participating country, no patients were randomised there. The enrolment period lasted approximately 18 months (Dec-2015 to May-2017).

A total of 590 patients provided informed consent, were enrolled in the study, and assessed for eligibility (Figure 7).

Figure 7 Patient flow



*Numbers do not always add up to the total because some patients had more than one reason for exclusion from randomization or discontinuation from treatment. ‡Discontinuation from treatment occurred due to pre-specified categories of either onset of grade 3 or higher peripheral neuropathy, grade 2 or higher interstitial lung disease (regardless of causal relationship with study drug); grade 3 or higher bronchospasm, diarrhoea, colitis, neurological toxicity, hypersensitivity reaction, infusion reaction, or uveitis, for which the causal relationship with nivolumab could not be ruled out; or any drug-related liver function test abnormality meeting protocol-defined criteria for discontinuation. §39 patients in the nivolumab group and 51 patients in the chemotherapy group were excluded from the response analysis because of non-measurable disease.

Note, figure taken from published article on study ONO-4538-24 (Kato et al. 2019)

Conduct of the study

Protocol amendments

The current version of the protocol is version 9.0 (dated 07-Nov-2017). The original protocol (version 1.0; dated 27-Jul-2015) was (thus) amended 8 times. Important amendments to the protocol were the following:

- In the 7th amendment (resulting in protocol v8.0 dated 12-Jul-2017), according to the MAH "*in consideration of the latest results of clinical trial ONO-4538*", required events for the interim analysis of OS and two-sided significance levels for the interim analysis and the final analysis were changed. I.e. the number of OS events required to have occurred for the interim analysis was increased from approximately 60% (199 events) of the required 331 events to approximately 80% (265 events). As a result, the nominal two-sided significance level of the OS interim analysis and the OS final analysis were changed from 0.77% and 4.76%, to 2.45% and 4.29%, respectively.
- In the 8th amendment (resulting in current protocol v9.0), due to cancellation of interim analysis, the two-sided significance level for the final analysis was changed to 5%.

Protocol deviations

Four patients (1.9%) in the nivolumab group had relevant protocol deviations. One patient did not meet an inclusion criterion (i.e. "*refractory or intolerant to combination therapy with fluoropyrimidine and platinum-based drugs for oesophageal cancer*", as the patient had no second CT confirming a CR as a result of initial chemotherapy). Another patient received prohibited medication while on treatment with nivolumab (i.e. intravitreal injection of bevacizumab for eye metastasis). Third patient received concurrent anti-cancer therapy while on treatment with nivolumab (i.e. surgical treatment of a progressed non-target lesion of the lung). Lastly, a serious adverse event (SAE) of the fourth patient was not reported within the safety follow-up time period required per the protocol, see also below safety section.

GCP

Study ONO-4538-24 was sponsored and conducted by the Sponsor Ono Pharmaceutical Co. Ltd in collaboration with the MAH (as Co-sponsor) according to good clinical practice (GCP) guidelines developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), in compliance with the protocol, and all applicable local regulations, as claimed by the MAH. However, a GCP non-compliant activity was identified in Taiwan after the 28-Dec-2018 database lock (DBL) and following the finalization of the ONO-4538-24 (CA209473) Final clinical study report (CSR) on 12-Mar-2019, but before 22-Mar-2019 (and thus between 12-Mar-2019 and 22-Mar-2019). This activity involved a contract research organization (CRO) clinical site monitor submitting false monitoring reports claiming the submission of some study-related documents to the relevant Institutional Review Board (IRB)/Independent Ethics Committees (IECs) of 4 clinical sites, even though these activities were never performed.

Linical Co., Ltd, the outsourcing contractor for monitoring work in Taiwan, on 22-Mar-2019 reported to Ono that this clinical site monitor who was in charge of 6 (out of the 11) Taiwanese investigational sites had submitted false monitoring reports claiming the submission of study-related documents to the relevant Institutional Review Board (IRB)/Independent Ethics Committees (IECs) of 3 investigational

sites, although these activities were never performed. Study-related documents that were not submitted for approval by IRB/IECs included among others, revised protocol versions 8 and 9, country-specific informed consent forms (ICFs) versions 10, 11, and 13 (including ICF addendums 1, 2 and 3), and nivolumab Investigator's Brochure (IB) versions 16 and 17. After receiving the report from Linical, Ono, as a sponsor of this study, carried out an investigation between 22-Mar-2019 and 03-Sep-2019 and confirmed this. In addition, in the course of this investigation, i.e. between 22-Mar-2019 and 03-Sep-2019, it was found that a serious adverse event (SAE) of diabetic ketoacidosis (nivolumab group; Grade 4; related) had not been reported in one study site (site code 3009), although this SAE should have been reported to the sponsor by the investigator.

The MAH (BMS) became aware of an issue concerning a fourth site, only after the 03-Sep-2019 pre-submission meeting with the EMA. This was due to a suspected unexpected serious adverse reaction (SUSAR) report not being submitted to the IRB at this site by the same clinical site monitor, although that submission had been reported as complete in the monitoring report.

The MAH acknowledges that these actions indeed constitute a GCP non-compliant activity. However, following an internal assessment of the impact of these actions, it has been concluded that neither patient safety nor the interpretation or scientific value of the reported trial results were adversely impacted by this matter. In total, 29 subjects were randomised at these 4 Taiwan sites, and among those 29, 8 subjects were alive (when the issue was discovered) and hence could have potentially signed the revised ICFs. At the time this issue was identified by the Sponsor and the revised ICF were to be signed, 5 out of the 8 subjects were still alive, and re-consented between May and August 2019. Nevertheless, an additional ancillary analysis was performed that was based on a modified ITT population, i.e. the ITT population excluding the 31 patients randomized at all 6 clinical sites in Taiwan handled by the Linical clinical site monitor (hereafter referred to as ITT-31; N = 388). The CSR based on this ITT-31 analysis is dated 25-Jun-2019.

Baseline data

The patient population in study ONO-4538-24 (CA209473) consisted of patients with OSCC who were refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs. The key demographic and other baseline characteristics for the ITT patient population are shown in Table 3.

Table 3 Key demographic and other baseline characteristics - ITT patient population

	Nivolumab N = 210	**Control**			**Total N = 419**
		Total N = 209	**Docetaxel N = 65**	**Paclitaxel N = 144**	
Sex, n (%)					
Male	179 (85.2)	185 (88.5)	56 (86.2)	129 (89.6)	364 (86.9)
Female	31 (14.8)	24 (11.5)	9 (13.8)	15 (10.4)	55 (13.1)
Age (years)					
<65	112 (53.3)	85 (40.7)	21 (32.3)	64 (44.4)	197 (47.0)
≥65	98 (46.7)	124 (59.3)	44 (67.7)	80 (55.6)	222 (53.0)

Table 3 Key demographic and other baseline characteristics - ITT patient population

	Nivolumab N = 210	Control			Total N = 419
		Total N = 209	Docetaxel N = 65	Paclitaxel N = 144	
65 - <75	84 (40.0)	96 (45.9)	37 (56.9)	59 (41.0)	180 (43.0)
≥75	14 (6.7)	28 (13.4)	7 (10.8)	21 (14.6)	42 (10.0)
Mean (SD)	62.8 (8.90)	64.9 (9.33)	65.5 (8.61)	64.6 (9.65)	63.8 (9.17)
Median	64.0	67.0	67.0	67.0	65.0
Min - Max	37 - 82	33 - 87	48 - 81	33 - 87	33 - 87
Race					
Asian	201 (95.7)	200 (95.7)	61 (93.8)	139 (96.5)	401 (95.7)
White[a]	9 (4.3)	9 (4.3)	4 (6.2)	5 (3.5)	18 (4.3)
Geographical location (IWRS source)					
Japan	136 (64.8)	138 (66.0)	44 (67.7)	94 (65.3)	274 (65.4)
Rest of the world	74 (35.2)	71 (34.0)	21 (32.3)	50 (34.7)	145 (34.6)
ECOG Performance Status					
0	101 (48.1)	107 (51.2)	38 (58.5)	69 (47.9)	208 (49.6)
1	109 (51.9)	102 (48.8)	27 (41.5)	75 (52.1)	211 (50.4)
Time from the date of diagnosis of the primary disease to randomization (Months)					
Mean (SD)	8.70 (12.20)	7.28 (5.70)	6.27 (4.50)	7.73 (6.13)	7.99 (9.54)
Median	6.31	5.65	5.36	5.78	6.01
Min - Max	0.1 - 150.2	0.1 - 38.7	0.7 - 23.1	0.1 - 38.7	0.1 - 150.2
Lesion site (TNM classification)					
Cervical Esophagus	5 (2.4)	7 (3.3)	3 (4.6)	4 (2.8)	12 (2.9)
Thoracic Esophagus	84 (40.0)	93 (44.5)	30 (46.2)	63 (43.8)	177 (42.2)
Upper Thorax	20 (9.5)	24 (11.5)	10 (15.4)	14 (9.7)	44 (10.5)
Middle Thorax	43 (20.5)	54 (25.8)	14 (21.5)	40 (27.8)	97 (23.2)
Lower Thorax	34 (16.2)	34 (16.3)	10 (15.4)	24 (16.7)	68 (16.2)
Cervical Esophagus and Thoracic Esophagus	3 (1.4)	7 (3.3)	1 (1.5)	6 (4.2)	10 (2.4)
Unknown	118 (56.2)	102 (48.8)	31 (47.7)	71 (49.3)	220 (52.5)
Histological classification					

Table 3 Key demographic and other baseline characteristics - ITT patient population

	Nivolumab N = 210	Control			Total N = 419
		Total N = 209	Docetaxel N = 65	Paclitaxel N = 144	
Squamous Cell Carcinoma	210 (100.0)	209 (100.0)	65 (100.0)	144 (100.0)	419 (100.0)
Recurrent					
No	107 (51.0)	120 (57.4)	34 (52.3)	86 (59.7)	227 (54.2)
Yes	103 (49.0)	89 (42.6)	31 (47.7)	58 (40.3)	192 (45.8)
Disease stage (TNM classification)[b]					
I-III	11 (5.2)	18 (8.6)	7 (10.8)	11 (7.6)	29 (6.9)
IV	172 (81.9)	168 (80.4)	49 (75.4)	119 (82.6)	340 (81.1)
Unknown	27 (12.9)	23 (11.0)	9 (13.8)	14 (9.7)	50 (11.9)
Sites of metastases					
Lymph Node	159 (75.7)	163 (78.0)	51 (78.5)	112 (77.8)	322 (76.8)
Peritoneum	5 (2.4)	11 (5.3)	3 (4.6)	8 (5.6)	16 (3.8)
Liver	57 (27.1)	54 (25.8)	18 (27.7)	36 (25.0)	111 (26.5)
Lung	98 (46.7)	92 (44.0)	28 (43.1)	64 (44.4)	190 (45.3)
Pleural Tissue	22 (10.5)	13 (6.2)	5 (7.7)	8 (5.6)	35 (8.4)
Adrenal Gland	6 (2.9)	7 (3.3)	0	7 (4.9)	13 (3.1)
Brain	5 (2.4)	1 (0.5)	0	1 (0.7)	6 (1.4)
Bone	23 (11.0)	25 (12.0)	8 (12.3)	17 (11.8)	48 (11.5)
Bone Marrow	0	0	0	0	0
Skin	1 (0.5)	1 (0.5)	1 (1.5)	0	2 (0.5)
Stomach	0	3 (1.4)	1 (1.5)	2 (1.4)	3 (0.7)
Other	26 (12.4)	28 (13.4)	6 (9.2)	22 (15.3)	54 (12.9)
Number of organs with metastases (IWRS source)					
≤1	89 (42.4)	91 (43.5)	30 (46.2)	61 (42.4)	180 (43.0)
≥2	121 (57.6)	118 (56.5)	35 (53.8)	83 (57.6)	239 (57.0)
PD-L1 expression (IWRS source)[c]					
<1% or indeterminate	109 (51.9)	108 (51.7)	31 (47.7)	77 (53.5)	217 (51.8)
≥1%	101 (48.1)	101 (48.3)	34 (52.3)	67 (46.5)	202 (48.2)
PD-L1 expression (CRF results)[c]					

Table 3 Key demographic and other baseline characteristics - ITT patient population

	Nivolumab N = 210	Control			Total N = 419
		Total N = 209	Docetaxel N = 65	Paclitaxel N = 144	
<1%	109 (51.9)	107 (51.2)	30 (46.2)	77 (53.5)	216 (51.6)
≥1%	101 (48.1)	102 (48.8)	35 (53.8)	67 (46.5)	203 (48.4)
Sum of reference diameters of target lesions (mm)					
N	172	159	49	110	331
Missing	38	50	16	34	88
Mean (SD)	49.59 (32.29)	51.23 (37.38)	42.09 (23.23)	55.30 (41.64)	50.38 (34.79)
Median	40.27	39.00	36.70	42.50	40.00
Min - Max	10.1 - 162.0	10.0 - 239.7	11.2 - 117.3	10.0 - 239.7	10.0 - 239.7

Abbreviations: CRF = case report form; ECOG = Eastern Cooperative Oncology Group; IWRS = interactive web response system; SD = standard deviation; PD-L1 = programmed death ligand 1; TNM = tumour node metastasis.

[a] Of the 18 "White" patients, 17 (8 nivolumab and 9 control) were from the EU (from Germany, Denmark and Italy) and 1 patient in the nivolumab group was from the USA.

[b] Summarized for patients at randomization

[c] Note: CRF results = test results. A discrepancy in the tumour cell PD-L1 expression results between IWRS and the CRF results was observed due to 1 patient who was randomized in absence of PD-L1 test results. There was a delay in processing the sample and reporting the test results by the central lab; therefore, the patient was randomized as 'indeterminate' (which is grouped along with PD-L1 <1%) and assigned to the control group. The PD-L1 test result, which was received after the randomization, suggested that the patient had tumour cell PD-L1 expression level ≥ 1%, and subsequently had data entered in the CRF.

Of the 18 white patients, in the nivolumab group four (44.4%) were male and five (55.6%) were female vs. in the control group 8 male patients (88.9%) and a single female patient (11.1%).

Biomarkers

Baseline PD-L1 expression results, both IWRS-sourced and CRF results, are depicted in Table 3.

Regarding microsatellite instability (MSI) status, out of the 419 randomised patients, 162 had tissue available for MSI testing, 80 from the nivolumab group and 82 from the control group. 26 samples were not sequenced due to pre-analytical failure and 9 samples had unknown MSI status due to quality control failure. A total of 127 patients had valid MSI results, 64 for the nivolumab group and 63 for the control group. There were no patients with microsatellite instability high (MSI-H tumours) identified. All the 127 patients with valid MSI results had tumours that were MSI-stable (MSS).

Prior systemic anti-cancer treatment

Per protocol, all patients in study ONO-4538-24 (CA209473) were required to be refractory or intolerant to at least 1 prior fluoropyrimidine- and platinum-based combination chemotherapy.

In the nivolumab group, all patients (100.0%) had received prior fluoropyrimidine-based chemotherapy and 206 patients (98.1%) had received prior platinum-based chemotherapy. In the control group, 206 patients (98.6%) had received prior fluoropyrimidine-based chemotherapy and 208 patients (99.5%) had received prior platinum-based chemotherapy.

The most frequently used prior fluoropyrimidine agent reported was fluorouracil (96.7% in the nivolumab group, 96.2% in the control group). The most frequently used prior platinum-based agent reported was cisplatin (88.1% in the nivolumab group, 90.4% in the control group).

The median number of prior systemic anti-cancer treatment regimens was 1.0 for both the nivolumab as well as the control group. In the nivolumab group, 138 (65.7%), 53 (25.2%), and 19 (9.0%) patients had received 1, 2, and ≥3 prior regimens, respectively. In the control group, 141 (67.5%), 57 (27.3%), and 11 (5.3%) patient had received 1, 2, and ≥3 prior regimens, respectively.

The best response to the most recent regimen was disease progression for 72 patients (34.3%) vs. 81 patients (38.8%) in the nivolumab and control groups, respectively.

Prior taxane therapy had been received by 13 (6.2%) patients in the nivolumab group and 16 (7.7%) patients in the control group.

Prior concomitant chemoradiotherapy had been received by 51 patients (24.3%) in the nivolumab group and 51 patients (24.4%) in the control group.

Concomitant other medication

Immune-modulating medications were used for management of AEs in 40.2% (84 patients) in the nivolumab group, 72.3% (47 patients) in the docetaxel group, and 44.8% (64 patients) in the paclitaxel group. The most common type of immune-modulating medication used in the nivolumab group was systemic hormonal preparations excluding sex hormones and insulins (23.9%), followed by dermatologicals (22.0%). The most common type of immune-modulating medication used in the docetaxel group was antineoplastic and immune-modulating agents (56.9%), followed by dermatologicals (20.0%). The most common type of immune-modulating medication used in the paclitaxel group was dermatologicals (21.7%), followed by systemic hormonal preparations excluding sex hormones and insulins (17.5%).

Post-discontinuation anti-cancer treatment

The percentage (number) of patients who received any subsequent anti-cancer therapy was 56.7% (119 patients) in the nivolumab group and 55.0% (115 patients) in the control group. Of the patients in the nivolumab group 14.3% (30 patients) received subsequent radiotherapy and 3.3% (7 patients) received subsequent surgery. Of the patients in the control group 11.0% (23 patients) received subsequent radiotherapy and 7.2% (15 patients) received subsequent surgery.

Subsequent systemic anti-cancer treatment was given to 53.3% (112 patients) in the nivolumab group and 47.4% (99 patients) in the control group. The most frequently received subsequent systemic anti-cancer treatment was a taxane, which was given to 47.6% (100 patients) in the nivolumab group and 20.6% (43 patients) in the control group. The second most frequently received subsequent systemic anti-cancer treatment was fluoropyrimidine-based chemotherapy, i.e. to 11.4% (24 patients) vs. 18.7% (39 patients), respectively. Immunotherapy was given to 0.5% (1 patient) in the nivolumab group and 6.2% (13 patients) in the control group.

Extrapolation of data across regions

The vast majority of the (ITT) patient population in the study ONO-4538-24 (CA209473) was Asian/from Asia and only a small minority (18/419 = 4.3%) was white/from non-Asian countries. During the pre-submission meeting held on 03-Sep-2019, the MAH put forward their view on why the results from study ONO-4538-24 (CA209473) are (also) applicable to the EU patient population and medical practice.

The MAH hereby referred to ICH Topic E 5 (R1) on Ethnic Factors in the Acceptability of Foreign Clinical Data (CPMP/ICH/289/95). This note for guidance describes how a sponsor developing a medicine can deal

with the possibility that ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. As described in this guidance, ethnic factors can consist of intrinsic and extrinsic factors.

Intrinsic ethnic factors are factors that help to define and identify a subpopulation and may influence the ability to extrapolate clinical data between regions. Examples of intrinsic factors include genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction.

Extrinsic ethnic factors are factors associated with the environment and culture in which a person resides. Extrinsic factors tend to be less genetically and more culturally and behaviourally determined. Examples of extrinsic factors include the social and cultural aspects of a region such as medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and sunshine, socioeconomic status, compliance with prescribed medications, and, particularly important to the reliance on studies from a different region, practices in clinical trial design and conduct.

The MAH discussed both intrinsic and extrinsic factors.

Intrinsic factors

Regarding the ***pharmacokinetics*** (PK) of nivolumab, the MAH argues that, as compared to small molecules there are fewer conventional concerns for ethnic differences in PK of mAbs between different races.

The MAH provided data that race had little effect on nivolumab clearance (CL) and exposure, suggesting that no dose adjustment is needed based on race.

The MAH thus concludes that race does not affect nivolumab PK following IV administration and that nivolumab exposures following IV administration are similar in Asian and non-Asian populations.

Regarding ***OSCC disease biology***, the MAH puts forward that current evidence indicates that OSCC is molecularly distinct from oesophageal adenocarcinoma. Although the disease and molecular biology of OSCC is not yet fully understood, the similarities in various molecular aspects of OSCC between Asian and Caucasian patients suggest that they have similar underlying disease biology.

Extrinsic factors

Regarding the ***risk factors for OSCC***, these are primarily tobacco smoking (including swallowed toxins from cigarette smoke) and alcohol overconsumption (Lagergren et al. 2017). According to the MAH, some risk factors such as betel quid chewing or consuming hot beverages appear to be region specific and differences in exposure to risk factors and/or different levels of exposure to risk factors may contribute to the observed regional differences in OSCC incidence.

Regarding a ***possible effect of region on overall survival*** in OSCC patients, there is some data/evidence in scientific literature.

Zhang *et al.* performed a(n observational) comparison of clinicopathologic features and survival between Eastern and Western population with OSCC, i.e. between the (Chinese) Shanghai Cancer Registries (n = 1,718) and the US SEER database (n = 1,624). They concluded that OSCC from Eastern and Western countries might have some different features (Zhang et al. 2015). They found that the Caucasian group had a significantly higher proportion of female patients than the Chinese group (38.24% vs. 18.68%; p <0.01). OSCC was diagnosed in Chinese patients at an earlier age and stage than in Caucasians. The Chinese patients had similar overall survival rate with Caucasian by both univariate and multivariate analysis. Median OS was 15.3 months for Chinese patients vs. 14.2 months in Caucasians (p=0.13). The difference in median OS was statistically significant for male patients (median OS 14.5 vs. 12.8 months; p <0.01), but not in female patients (median OS 18.5 vs. 16.9 months; p=0.14).

Lin *et al.* used the SEER database to compare the clinicopathologic characteristics and survival of 479 Chinese and 35,748 Caucasian patients with OSCC (*both*) residing in the US (Lin et al. 2015). They did find that, for patients with OSCC residing in the US, Chinese race was independently associated with a better OS compared to Caucasians (hazard ratio 1.330; 95% CI: 1.159, 1.527; p <0.001).

Although not presented by the MAH, the results of the ongoing global pembrolizumab (another PD-1 mAb) phase 3 study KEYNOTE-181 (NCT02564263) should also be taken into account on this matter. Study KEYNOTE-181 is a randomised, open-label study of pembrolizumab vs. physicians' choice of docetaxel, paclitaxel, or irinotecan in patients with advanced/metastatic adenocarcinoma and squamous cell carcinoma of the oesophagus that have progressed after 1L standard therapy. The subgroup of 2L OSCC patients in study KEYNOTE-181 is thus similar to the patient population included in study ONO-4538-24 (CA209473). In study KEYNOTE-181, however, a much larger percentage of non-Asian patients with OSCC was included compared to in study ONO-4538-24 (CA209473), i.e. 170/401 = 42.4% vs. 18/419 = 4.3%. Notably, the efficacy of pembrolizumab was lower in non-Asian patients when compared to Asia patients (Keytruda - Withdrawal assessment report [EMEA/H/C/003820/II/0072]). In a comment to the published article of study ONO-4538-24 (CA209473), it was therefore stated that this subgroup analysis of the more global KEYNOTE-181 trial suggests that anti-PD-1 therapy is more effective in Asian patients with OSCC than in non-Asian patients (Smyth and Lordick. 2019).

Regarding ***medical practice***, the implementation of early screening programs for gastric cancer in Japan and Korea may explain the larger proportion of patients diagnosed with early-stage disease in these countries compared to Western countries (Shin et al. 2018).

To further elucidate similarities and differences in disease between Western and Asian countries, the MAH conducted a real-world retrospective global treatment patterns study using patient charts among patients with 2L OSCC treated systemically or with best supportive care (BSC) (Jaffe et al. 2019a; Jaffe et al. 2019b). Data was provided for 1,049 OSCC patients who had initiated 1L or 2L systemic therapy. Of these, 387 patients (195 Western and 192 Asian) received 2L 'therapy', i.e. 58% (21.4% of total) received systemic treatment and 42% received BSC. Taxane monotherapy represented a common 2L systemic treatment option across regions, including Europe. The mean age was 63.4 years and 81.4% were male. A higher proportion of Western patients were diagnosed with metastatic disease (58.5% vs 37.5%; p < 0.001) than Asian patients. At initiation of 2L treatment, the ECOG PS was 0 in 7% of patients, 1 in 42%, and 2-4 in 50%. Only 8% of patients went on to 3L treatment.

In table 4, the MAH has summarized outcomes in advanced OSCC with standard of care chemotherapy from scientific literature. All of the included studies were either conducted in Japan or in Europe/a European country, no study included patients from both regions.

Table 4 Outcomes with standard of care in advanced OSCC

Line of treatment	Dataset	N	Regimen	ORR (%)	mPFS (mo)	mOS (mo)
1L	**Kato et al. 2014**	42 (Japanese)	5-FU + nedaplatin	40	2.5	8.8
	Iizuka et al. 1992	39 (Japanese)	5-FU + cis	36	Pts with response: 3.5	Pts with response: 9.5 Pts w/o response: 5.6

Table 4 Outcomes with standard of care in advanced OSCC

Line of treatment	Dataset	N	Regimen	ORR (%)	mPFS (mo)	mOS (mo)
	Bleiberg et al. 1997	44 (European)	5-FU + cis	35	6.2	7.6
	Lorenzen et al. 2009	30 (German)	5-FU + cis	13	3.6	5.5
	Moehler et al. 2017	73 (German)	5-FU + cis	43	5.8	10.2
2L	**Muro et al. 2004**	OSCC 46, other: 3 (Japanese)	Docetaxel	20	2.3[a]	8.1[a]
	Kato et al. 2011	52 (Japanese)	Paclitaxel	44	3.9	10.4

[a] Including 1L subjects (n = 14)

Abbreviations: 1L: first-line; 2L: second-line; 5-FU: 5-fluorouracil; cis: cisplatin; OSCC: oesophageal squamous cell carcinoma; mo: months; mOS: median overall survival; mPFS: median progression-free survival; ORR: overall response rate; pts: patients; w/o: without

To provide ***real-world data*** (RWD) of 2L therapy in patients with advanced or metastatic OSCC, the MAH conducted two retrospective studies using 2 US databases, i.e. the US SEER and Flatiron electronic health record databases.

In study CA2097E7, using the US SEER-Medicare population, 756 patients with advanced OSCC met all infusion criteria and were included. Of these, 448 patients (59%) initiated 1L, only 104 (14%) received 2L treatment, and a mere 26 (3%) went on to 3L treatment. The median duration of treatment for the 2L OSCC patients was 1.5 months, and the median age was 73.0 years. The median OS for 2L OSCC patients was 5.7 months (95% CI: 5.0, 8.5).

In study CA2098LY, using the Flatiron EHR database, 374 patients with advanced OSCC who met all inclusion criteria were included. Of these, 86 patients (23%) received 2L treatment and 29 (8%) 3L treatment. ECOG PS at the initiation of 2L treatment was 0-1 for 75.5% of patients. The median age of patients in this study was 64 years. Median OS in all patients who received ≥2 lines of treatment for advanced OSCC was 6.7 months (95% CI: 5.1, 8.3), with a median duration of treatment of 1.7 months.

Additionally, the MAH has summarized the results of five Japanese, real-world observational studies evaluating taxane monotherapy use in 2L OSCC in Table 5.

Table 5 Japanese real-world observational studies of taxane monotherapy in 2L OSCC

Study name	**Disease site (Histology %)**	**Treatment arms**	**Sample size**	**ECOG/WHO performance status (%)**	**Median OS (months)**

Table 5 Japanese real-world observational studies of taxane monotherapy in 2L OSCC

Study name	Disease site (Histology %)	Treatment arms	Sample size	ECOG/WHO performance status (%)		Median OS (months)
				0-1	2	
Comparative						
Mizota et al. 2011	OC (OSCC 95%)	Docetaxel	86	93%	7%	6.1
		Paclitaxel	38	90%	11%	7.2
Shirakawa et al. 2014	OC (OSCC 100%)	Docetaxel	132	92%	8%	5.5
		Paclitaxel	31	94%	7%	6.1
Nakatsumi et al. 2016	OC (OSCC 89%)	Docetaxel	25	84%	16%[a]	5.3
		Paclitaxel	14	93%	7%[a]	8.6
Single treatment						
Sakamoto et al. 2014	OC (OSCC 100%)	Paclitaxel	13	92.3	7.7	7.3
Tsushima et al. 2015[b]	OC (OSCC 100%)	Docetaxel/ paclitaxel	24	87.5	12.5	6.4

[a] Includes subjects with ECOG PS of 2-3

[b] Importantly, this study investigated re-introduction of taxane, i.e. all patients had previously been treated with fluorouracil, platinum and a taxane

Abbreviations: 2L: second-line treatment; ECOG: eastern cooperative oncology group; OC: oesophageal cancer; OSCC: oesophageal squamous cell carcinoma; OS: overall survival; WHO: World Health Organization

Further data were submitted during the procedure that included new preliminary results from nivolumab Study CA209577 in adjuvant EC or GEJC (see below) as well as new RWD analysis aimed at supporting extrapolation of the ONO-4538-24 (CA209473) results to the European patient population.

Numbers analysed

The ITT consisted of 210 patients in the nivolumab group and 209 patients in the control group, the RES consisted of 171 vs. 158 patients, and the SAF consisted of 209 vs. 208 patients, respectively (Table 6).

Table 6 Analysis populations

	Nivolumab	Control			Total
		Total	Docetaxel	Paclitaxel	
Intention-to-treat (**ITT**)[a]	210	209	65	144	419

	Nivolumab	Control			Total
		Total	Docetaxel	Paclitaxel	
Response Evaluable Set (**RES**)[b]	171	158	49	109	329
Incomplete target lesion measurements	39	51	16	35	90
Safety Set (**SAF**)[c]	209	208	65	143	417
Untreated patients	1	1	0	1	2

[a] The ITT consisted of all randomized patients.

[b] The RES consisted of the ITT patients who had target lesion measurements at baseline.

[c] The SAF consisted of all patients given at least one dose of the study treatment.

Outcomes and estimation

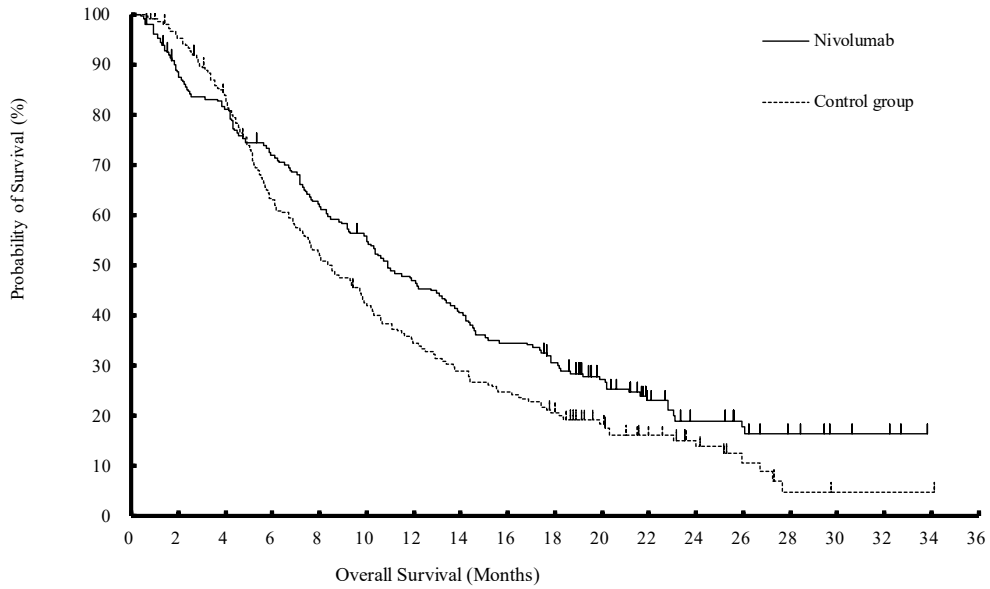
Primary endpoint OS

Primary analytical method

Study ONO-4538-24 (CA209473) met its primary endpoint. In the ITT patient population nivolumab demonstrated statistically significant benefit in OS over the control group (HR 0.77 [95% CI: 0.62, 0.96]; p=0.0189). Median OS was 10.91 months (95% CI: 9.23, 13.34) in the nivolumab group and 8.38 months (95% CI: 7.20, 9.86) in the control group (Δ 2.53 months; **Figure 8** and **Table 7**). There was an early crossing of the KM OS curves at approximately 5 months, only afterwards favouring nivolumab.

Fewer OS events (deaths) were reported in the nivolumab group (160 [76.2%] patients) compared with the control group (173 [82.8%] subjects) by the data cut-off date of 12-Nov-2018. There were 50 (23.8%) patients in the nivolumab group and 36 (17.2%) subjects in the control group that were censored. Forty-six (21.9%) and 31 (14.8%) of the patients in the nivolumab and control group, respectively, were still on-study (on-treatment or in follow-up).

Figure 8 Kaplan-Meier plot of overall survival - ITT patient population



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
Control group	209	196	169	126	105	84	68	57	49	40	27	17	12	6	2	1	1	1	0

Abbreviation: ITT - Intention to treat

Table 7 Summary of efficacy results - ITT patient population vs. subgroup of white patients

Efficacy Parameter	ITT patient population		Subgroup of white patients	
	Nivolumab	Control	Nivolumab	Control
ITT population (N)	**210**	**209**	**9**	**9**
Overall survival (OS)				
Events, n (%)	160 (76.2)	173 (82.8)	7 (77.8)	8 (88.9)
Median, months (95% CI)[a]	10.91 (9.23, 13.34)	8.38 (7.20, 9.86)	6.21 (1.41, 20.14)	6.11 (2.60, 13.24)
HR (95% CI)[b]	0.77 (0.62, 0.96)		0.53 (0.17, 1.65)	
p-value[c]	p=0.0189*		-	
Rate at 12 months (95% CI), %[d]	46.9 (39.9, 53.5)	34.4 (27.8, 40.9)	44.4 (13.6, 71.9)	25 (3.7, 55.8)
Rate at 18 months (95% CI), %[d]	30.5 (24.4, 36.9)	20.7 (15.4, 26.6)	29.6 (5.2, 60.7)	N.A

Table 7 Summary of efficacy results - ITT patient population vs. subgroup of white patients

Efficacy Parameter	ITT patient population		Subgroup of white patients	
	Nivolumab	Control	Nivolumab	Control
RES population (N)[e]	**171**	**158**	**7**	**8**
Investigator-assessed objective response rate (ORR)				
Responders, n (%)	33 (19.3%)	34 (21.5%)	1 (14.3%)	1 (12.5%)
95% CI[f]	(13.7, 26.0)	(15.4, 28.8)	(0.4, 57.9)	(0.3, 52.7)
Odds ratio (95% CI)[g]	0.88 (0.51, 1.50)		1.00 (0.06, 15.99)	
Difference (95% CI)[h]	-2.13 (-10.87, 6.61)		0.00 (-40.17, 40.17)	
p-value[c]	p=0.6323 N.S.		-	
ITT population (N)	**210**	**209**	**9**	**9**
Investigator-assessed progression-free survival (PFS)				
Events, n (%)	187 (89.0)	176 (84.2)	8 (88.9)	8 (88.9)
Progression	167 (79.5)	162 (77.5)	6 (66.7)	6 (66.7)
Death	20 (9.5)	14 (6.7)	2 (22.2)	2 (22.2)
Median, months (95% CI)[a]	1.68 (1.51, 2.73)	3.35 (2.99, 4.21)	1.45 (1.05, 6.21)	4.24 (1.51, 5.22)
HR (95% CI)[b]	1.08 (0.87, 1.34)		1.42 (0.50, 4.06)	
Rate at 12 months (95% CI), %[d]	11.9 (7.8, 16.8)	7.2 (3.8, 12.0)	N.A	N.A
Rate at 18 months (95% CI), %[d]	9.0 (5.5, 13.6)	4.0 (1.6, 8.2)	N.A	N.A

1 month = 30.4375 days

[a] This estimation was conducted by using the KM method.

[b] HR and the corresponding two-sided 95% CI for the nivolumab group relative to the each column group was calculated using the stratified Cox proportional-hazards model adjusted by the 3 stratification factors as mentioned in footnote 'c'. For white patients column, hazard ratio and the corresponding two-sided 95% CI for the nivolumab group relative to each column group was calculated by using the unstratified Cox proportional-hazards model.

[c] Nivolumab group and total of control group were used for the calculation of p-value. The calculation of p-value was conducted by using the two-sided stratified log-rank test adjusted by the following 3 factors (IWRS source):

1) location (Japan vs Rest of World)

2) the number of organs with metastases (≤ 1 vs ≥ 2)

3) PD-L1 expression (≥ 1% vs < 1% or indeterminate)

*: p<0.05; N.S.: p>=0.05

[d] The estimation was derived from the KM estimate and corresponding CI was derived based on Greenwood formula for variance and on log-log transformation.

[e] RES population consisted of the ITT patients with target lesion measurements at baseline.

[f] Exact 95% CI was calculated by using Clopper-Pearson method.

[g] Odds ratio and the corresponding CI for the nivolumab group relative to the each column group was calculated using Cochran-Mantel-Haenszel methodology with the 3 stratification factors as mentioned in footnote 'b'.

[h] Difference and the corresponding CI for the nivolumab group relative to the each column group was calculated using Cochran-Mantel-Haenszel methodology with the 3 stratification factors as mentioned in footnote 'b'.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; KM, Kaplan-Meier; N.S., not significant; RES, response evaluable set; SD, standard deviation.

Secondary endpoint ORR

Primary analysis

In Table 8 the ORR, DCR and BOR results are shown.

Table 8 Best overall response, objective response rate and disease control rate - RES patient population

	Nivolumab N = 171	**Control N = 158**
Objective response rate		
ORR (CR+PR), n (%)	33 (19.3)	34 (21.5)
(95% CI) [a]	(13.7, 26.0)	(15.4, 28.8)
Odds ratio (95% CI) [b]	0.88 (0.51, 1.50)	
Difference (95% CI) [c]	-2.13 (-10.87, 6.61)	
p-value[d]	p=0.6323	
Best overall response		
CR, n (%)	1 (0.6)	2 (1.3)
(95% CI)[a]	(0.0, 3.2)	(0.2, 4.5)
PR, n (%)	32 (18.7)	32 (20.3)
(95% CI) [a]	(13.2, 25.4)	(14.3, 27.4)
SD, n (%)	31 (18.1)	65 (41.1)
(95% CI)[a]	(12.7, 24.7)	(33.4, 49.2)
PD, n (%)	94 (55.0)	51 (32.3)
NE, n (%)	13 (7.6)	8 (5.1)
Disease control rate		
DCR (CR+PR+SD), n (%)	64 (37.4)	99 (62.7)
(95% CI) [a]	(30.2, 45.1)	(54.6, 70.2)

Table 8 Best overall response, objective response rate and disease control rate - RES patient population

	Nivolumab N = 171	Control N = 158
Odds ratio (95% CI) [b]	0.33 (0.21, 0.53)	
Difference (95% CI)[c]	-25.41 (-35.64, -15.19)	

Abbreviations: CR = complete response; DCR = disease control rate; NE = not evaluable; PD = progressive disease; PR = partial response; RES = response evaluable set; SD = stable disease.

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 for the nivolumab group relative to the each column group was calculated using Cochran-Mantel-Haenszel methodology with the three stratification factors (IWRS source) mentioned in footnote 'd'.

[c] Difference and the corresponding confidence interval was calculated by using Cochran-Mantel-Haenszel methodology with the three stratification factors (IWRS source) mentioned in footnote 'd'.

[d] Nivolumab group and total of control group were used for the calculation of p-value. The calculation of p-value was conducted by using Cochran-Mantel-Haenszel test stratified by the following three factors (IWRS source).

1) Location (Japan vs Rest of the world)

2) The number of organs with metastases (≤1 vs ≥2)

3) PD-L1 expression (≥1% vs <1% or indeterminate)

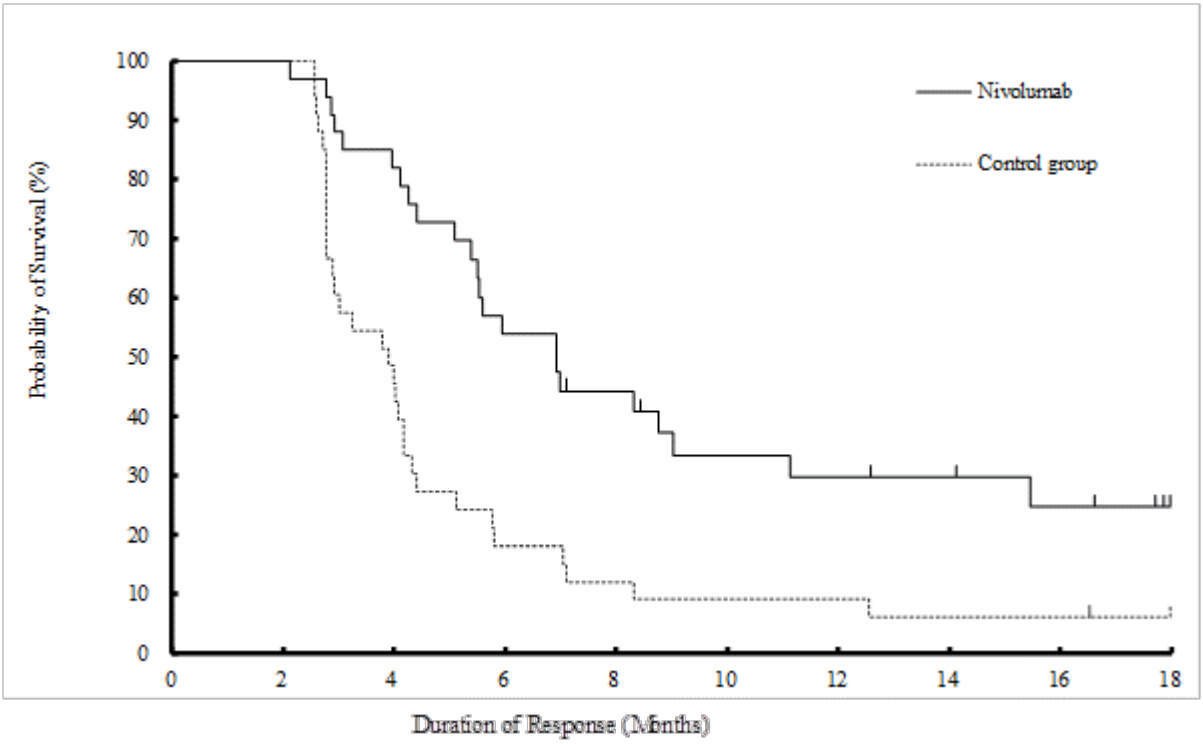
*: p<0.05, N.S.: p>=0.05

Secondary endpoint DoR

In the RES patient population, the median (investigator-assessed) DoR was 6.93 months (95% CI: 5.39, 11.14) for the 33 responders in the nivolumab group vs. 3.91 months (95% CI: 2.79, 4.17) for the 34 responders in the control group (Δ 3.02 months), see **Figure 9**.

Seven of the 33 responders (21.2%) in the nivolumab group and 2 of the 34 responders (5.9%) in the control group had a continuing response to treatment at the time of data cut-off.

Figure 9 Kaplan-Meier plot of duration of response - RES patient population



At risk	0	2	4	6	8	10	12	14	16	18
Nivolumab	33	33	27	17	13	9	8	7	5	0
Control group	34	34	16	6	4	3	3	2	2	0

Abbreviations: BOR = best overall response; CR = complete response; PR = partial response; RES = response evaluable set

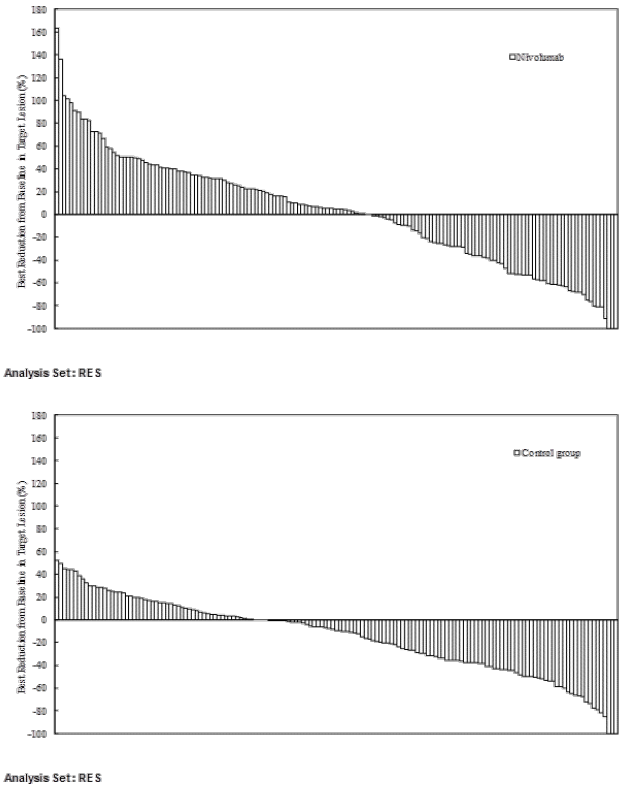
Note: Includes patients whose BOR was assessed as either CR or PR

Secondary Endpoint TTR

The median (investigator-assessed) TTR (for the RES patient population) was 2.60 months (range: 1.2 to 6.5) in the nivolumab group vs. 1.48 months (range: 1.2 to 5.6) in the control group.

Waterfall plots of the maximum percent change from baseline in the sum of diameters of target lesions for the RES patient population in the nivolumab and control groups are shown below in **Figure 10**.

Figure 10 Waterfall plots of maximum percent change from baseline in sum of diameters of target lesions for nivolumab group and control group - RES patient population



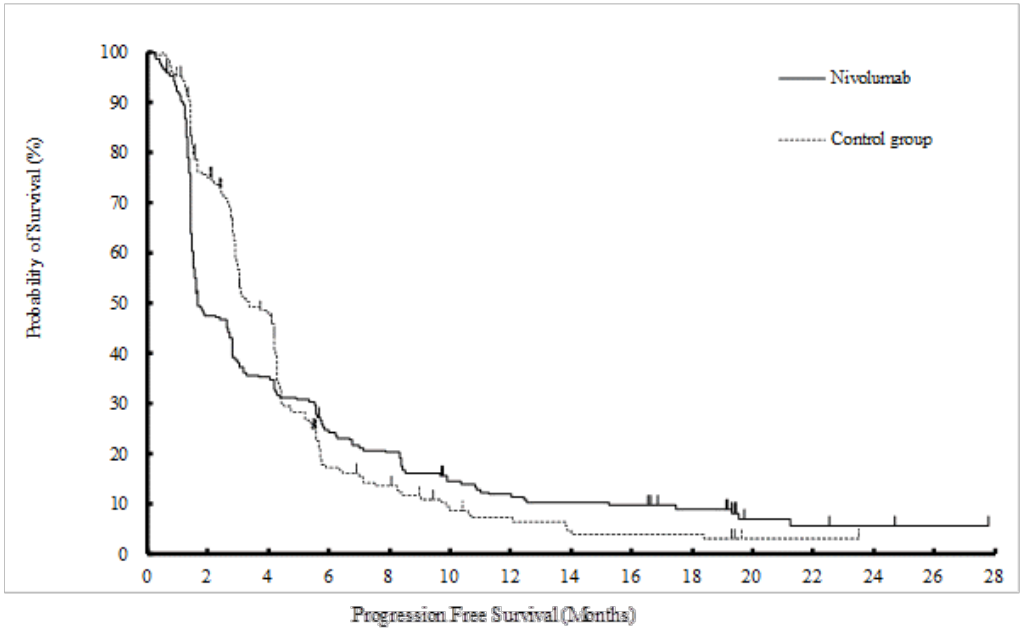
Secondary endpoint PFS

Because ORR did not pass the statistical boundary for significance, according to the hierarchical order, PFS was not formally tested.

The PFS HR for the nivolumab group vs. the control group was 1.08 (95% CI: 0.87, 1.34). Median PFS was 1.68 months (95% CI: 1.51, 2.73) vs. 3.35 months (95% CI: 2.99, 4.21), respectively (**Figure 11** and **Table 7**). There was an early crossing of the KM PFS curves between 4 and 6 months, only afterwards favouring nivolumab. PFS events (disease progression or death) had occurred in 187 (89.0%) subjects in the nivolumab group and 176 (84.2%) subjects in the control group by the data cut-off date (**Table 7**).

Median PFS in the docetaxel group was 3.02 months (95% CI: 2.46, 4.21; HR 0.97 [95% CI: 0.71, 1.33]) and median PFS in the paclitaxel group was 4.11 months (95% CI: 2.69, 4.21; HR 1.15 [95% CI: 0.91, 1.46]).

Figure 11 Kaplan-Meier plot of progression-free survival - ITT patient population



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Nivolumab	210	96	71	48	40	27	22	19	18	13	5	4	3	1	0
Control group	209	147	89	29	22	12	9	5	5	5	1	1	0	0	0

Abbreviation: ITT = intention-to-treat

Note, the PFS primary definition is used.

Other (exploratory) endpoints and test variables

As an exploratory endpoint, health-related QoL was assessed using the EQ-5D-3L UI score and the EQ-VAS. Changes from baseline and differences between treatment groups in health-related QoL were assessed post hoc using a longitudinal mixed model repeated measures (MMRM) approach. For time-to-event analyses, a stratified Cox regression model was used to estimate hazard ratios, and an un-stratified Kaplan-Meier method was used to estimate median times to event and the proportion of patients who were event-free. Significance testing was two-sided at the 0.05 level, with no adjustment for multiplicity.

Comparisons between treatment groups were made at all on-treatment time points (through week 42) where there were at least 10 patients in each treatment group with a valid EQ-5D-3L assessment.

Compliance rates were high, with >85% of expected assessments completed through week 42. The absolute number of completed EQ-5D-3L questionnaires in the control group, however, decreased to 20 (10%) and 13 (6%) at week 36 and week 42, respectively.

For EQ-5D-3L UI, the difference between treatment groups numerically favoured nivolumab at all time points and for the overall time-averaged least squares (LS) mean estimate (least squares means difference [LSMD]: 0.076; 95% CI: 0.011, 0.142). The estimated difference between treatment groups exceeded the threshold for meaningful change (≥0.08 points; Pickard et al. 2007) at week 24, 30, 36, and 42 (Kato et al. 2019).

For the EQ-VAS, the difference between treatment groups numerically favoured nivolumab at all time points as well as for the overall time-averaged LS mean estimate (LSMD: 6.9; 95% CI: 3.0, 10.9). The estimated difference between treatment groups exceeded the threshold for meaningful change (≥7 points; Pickard et al. 2007) at week 18, 24, and 30 (Kato et al. 2019).

Ancillary analyses

- **Primary endpoint OS**

Sensitivity analyses

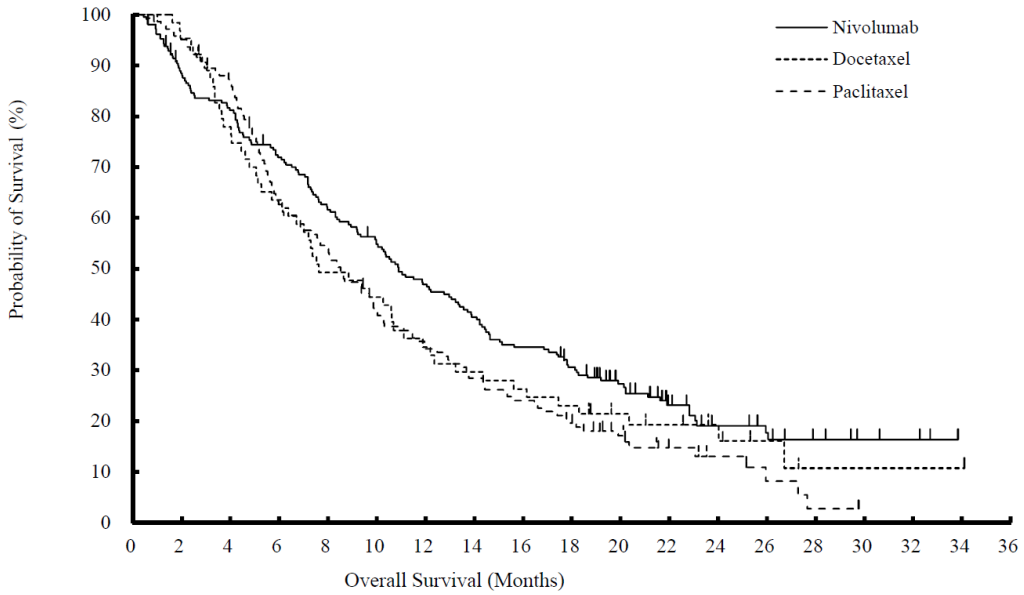
As a sensitivity analysis, an unstratified log-rank test was performed. The result was consistent with that of the primary analysis: p=0.0163; nivolumab median OS 10.91 months (95% CI: 9.23, 13.34) vs. control median OS 8.38 months (95% CI: 7.20, 9.86).

As there did not exist more than 10% discrepancy between IWRS-sourced stratification factors and eCRF-sourced stratification factors, a sensitivity analysis using the stratified log-rank test adjusted by the three stratification factors (location and the number of organs with metastases from eCRF source and PD-L1 expression from test result source) was not performed.

Secondary analytical methods

The HR and the corresponding two-sided 95% confidence interval (CI) for the nivolumab group relative to the docetaxel group and paclitaxel group was estimated using a stratified Cox proportional hazards model with the IWRS randomisation factors as the stratification factors. The OS HR of nivolumab vs. docetaxel or paclitaxel was 0.78 (95% CI: 0.56, 1.07) and 0.76 (95% CI: 0.60, 0.97), respectively, with median OS of 7.62 months (95% CI: 6.11, 10.68) in the docetaxel group and 8.51 months (95% CI: 6.87, 9.89) in the paclitaxel group (**Figure 12**).

Figure 12 Kaplan-Meier Plot of overall survival - nivolumab vs docetaxel and paclitaxel - ITT patient population



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	210	182	167	147	126	111	95	82	70	60	43	25	17	13	7	4	3	0	0
Docetaxel	65	61	49	40	31	27	21	18	16	14	10	8	6	3	1	1	1	1	0
Paclitaxel	144	135	120	86	74	57	47	39	33	26	17	9	6	3	1	0	0	0	0

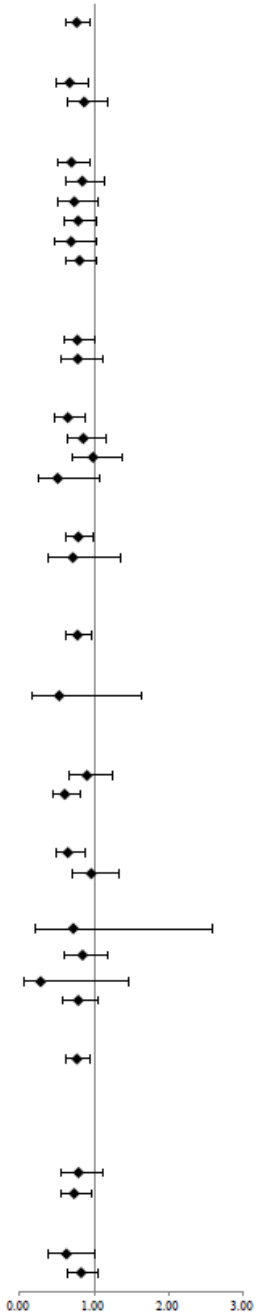
In this study, the observed OS curves crossed around 5 months, indicating non-proportional hazards. Furthermore, a pre-specified analysis to examine the assumption of proportional hazards of the Cox model indicated a violation of such assumption (p=0.0682). Therefore, the treatment difference in OS was assessed in a post-hoc analysis using a weighted log-rank test from the Fleming-Harrington G(ρ-γ) family with a ρ value of 1 and γ value of 1.18. For the ITT patient population, the p value for nivolumab vs. control was 0.0019, favouring nivolumab (compared to 0.0189 when using the primary analysis method).

Subgroup analyses

A forest plot summarizing the subgroup analyses for OS in the ITT patient population is presented in **Figure 13** and **Figure 14**.

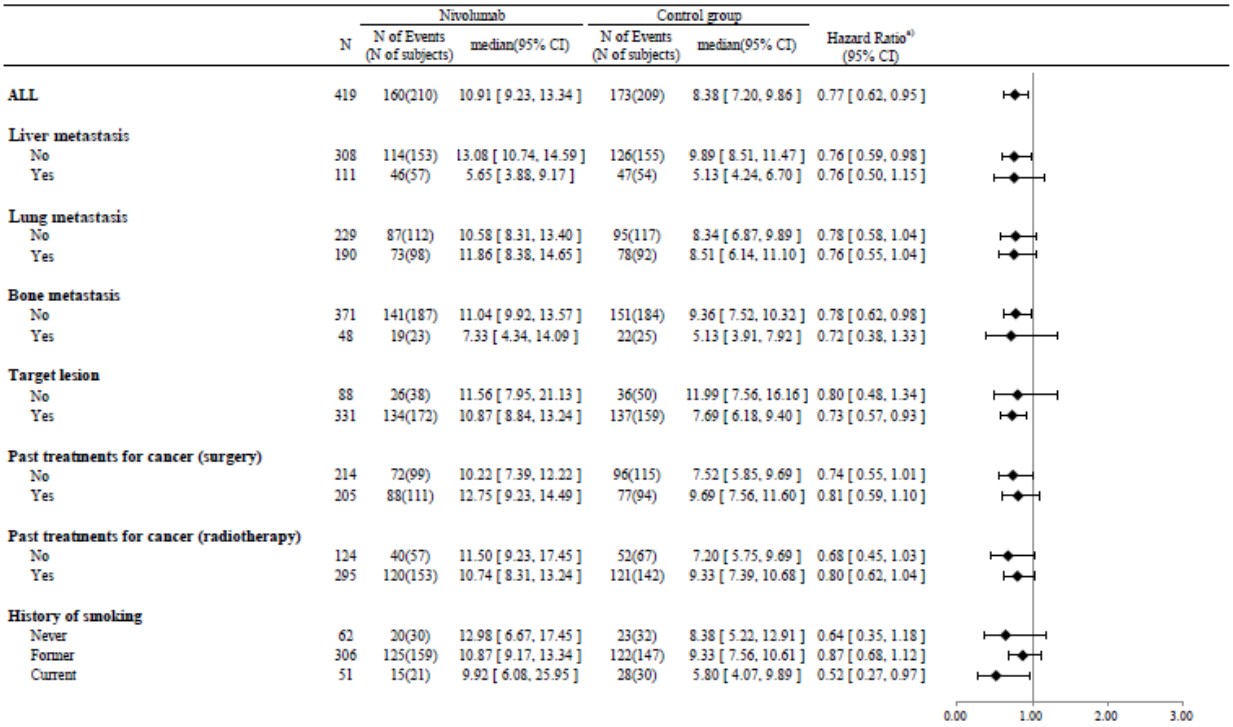
Figure 13 Forest plot of subgroup analysis for overall survival - ITT patient population

	N	Nivolumab N of Events (N of subjects)	Nivolumab median(95% CI)	Control group N of Events (N of subjects)	Control group median(95% CI)	Hazard Ratio[a] (95% CI)
ALL	419	160(210)	10.91 [9.23, 13.34]	173(209)	8.38 [7.20, 9.86]	0.77 [0.62, 0.95]
PD-L1 Expression (IWRS)						
>=1%	202	77(101)	10.91 [7.98, 14.23]	89(101)	8.05 [5.85, 9.69]	0.67 [0.49, 0.91]
<1% and indeterminate	217	83(109)	10.91 [8.38, 13.90]	84(108)	9.33 [7.20, 11.99]	0.87 [0.64, 1.18]
PD-L1 Expression (test results)						
>=1%	203	77(101)	10.91 [7.98, 14.23]	89(102)	8.05 [5.98, 9.86]	0.69 [0.51, 0.94]
<1%	216	83(109)	10.91 [8.38, 13.90]	84(107)	9.33 [7.20, 11.96]	0.84 [0.62, 1.14]
>=5%	146	56(74)	10.74 [7.33, 13.86]	61(72)	7.62 [5.68, 10.18]	0.73 [0.51, 1.06]
<5%	273	104(136)	11.04 [8.94, 14.09]	112(137)	9.33 [7.29, 10.32]	0.78 [0.60, 1.03]
>=10%	121	48(64)	11.50 [7.59, 14.23]	48(57)	7.62 [5.45, 10.25]	0.69 [0.46, 1.04]
<10%	298	112(146)	10.87 [8.84, 13.73]	125(152)	8.64 [7.29, 10.32]	0.80 [0.62, 1.04]
Not Quantifiable	0	-	-	-	-	-
Location (IWRS)						
Japan	274	101(136)	13.40 [10.35, 15.05]	109(138)	9.36 [7.39, 10.58]	0.77 [0.59, 1.01]
Rest of world	145	59(74)	8.31 [6.08, 10.87]	64(71)	7.29 [5.22, 10.18]	0.78 [0.55, 1.12]
Age						
<65	197	86(112)	10.74 [8.84, 13.40]	73(85)	8.08 [6.11, 10.02]	0.65 [0.47, 0.89]
>=65	222	74(98)	11.86 [7.39, 14.09]	100(124)	8.54 [6.70, 10.58]	0.86 [0.63, 1.16]
65 - <75	180	64(84)	11.17 [7.20, 14.23]	74(96)	9.86 [7.00, 12.85]	0.99 [0.71, 1.38]
>=75	42	10(14)	11.89 [4.27, 18.14]	26(28)	5.88 [4.60, 9.36]	0.51 [0.25, 1.07]
Sex						
Male	364	139(179)	10.74 [8.84, 13.24]	156(185)	8.08 [6.93, 9.86]	0.79 [0.63, 0.99]
Female	55	21(31)	14.09 [8.31, 17.81]	17(24)	9.36 [5.06, 13.24]	0.72 [0.38, 1.36]
Race						
American Indian or Alaska Native	0	-	-	-	-	-
Asian	401	153(201)	10.91 [9.33, 13.34]	165(200)	8.54 [7.29, 10.02]	0.78 [0.62, 0.97]
Black or African American	0	-	-	-	-	-
Native Hawaiian or Other Pacific Islander	0	-	-	-	-	-
White	18	7(9)	6.21 [1.41, 20.14]	8(9)	6.11 [2.60, 13.24]	0.53 [0.17, 1.65]
Other	0	-	-	-	-	-
ECOG Performance Status score at baseline						
0	208	73(101)	13.57 [10.38, 16.85]	81(107)	11.30 [8.64, 13.73]	0.90 [0.66, 1.24]
1	211	87(109)	9.20 [6.67, 11.50]	92(102)	6.11 [5.16, 7.92]	0.61 [0.45, 0.82]
Recurrent						
No	227	79(107)	10.35 [8.08, 14.23]	103(120)	7.36 [5.85, 8.54]	0.65 [0.48, 0.87]
Yes	192	81(103)	11.50 [9.20, 13.73]	70(89)	10.68 [8.38, 13.40]	0.96 [0.70, 1.32]
Lesion sites (TNM classification)						
Cervical Esophagus	12	4(5)	9.99 [5.95, N.A.]	6(7)	7.52 [1.15, 12.19]	0.72 [0.20, 2.59]
Thoracic Esophagus (Upper Thorax, Middle Thorax, Lower Thorax)	177	65(84)	8.48 [7.16, 10.91]	78(93)	7.36 [5.75, 9.79]	0.84 [0.61, 1.18]
Cervical Esophagus and Thoracic Esophagus	10	2(3)	10.87 [10.51, N.A.]	6(7)	5.54 [3.29, 15.51]	0.28 [0.05, 1.47]
Unknown	220	89(118)	13.34 [10.38, 14.65]	83(102)	9.86 [7.66, 11.99]	0.79 [0.58, 1.06]
Histological classification						
Squamous Cell Carcinoma	419	160(210)	10.91 [9.23, 13.34]	173(209)	8.38 [7.20, 9.86]	0.77 [0.62, 0.95]
Adenosquamous Cell Carcinoma	0	-	-	-	-	-
Other	0	-	-	-	-	-
Unknown	0	-	-	-	-	-
Number of organs with metastases (IWRS)						
<=1	180	63(89)	14.59 [11.17, 18.66]	67(91)	11.96 [9.89, 15.18]	0.79 [0.56, 1.12]
>=2	239	97(121)	8.84 [7.16, 10.74]	106(118)	5.78 [5.16, 7.39]	0.73 [0.55, 0.97]
Lymph Node metastasis						
No	97	33(51)	17.05 [9.17, 20.14]	36(46)	10.68 [7.56, 14.36]	0.63 [0.39, 1.01]
Yes	322	127(159)	10.35 [8.31, 12.06]	137(163)	7.92 [6.18, 9.69]	0.83 [0.65, 1.05]



Analysis Set : ITT

Figure 14 Forest plot of subgroup analysis for overall survival - ITT patient population (continued)



	N	Nivolumab: N of Events (N of subjects)	Nivolumab: median(95% CI)	Control group: N of Events (N of subjects)	Control group: median(95% CI)	Hazard Ratio[a] (95% CI)
ALL	419	160(210)	10.91 [9.23, 13.34]	173(209)	8.38 [7.20, 9.86]	0.77 [0.62, 0.95]
Liver metastasis						
No	308	114(153)	13.08 [10.74, 14.59]	126(155)	9.89 [8.51, 11.47]	0.76 [0.59, 0.98]
Yes	111	46(57)	5.65 [3.88, 9.17]	47(54)	5.13 [4.24, 6.70]	0.76 [0.50, 1.15]
Lung metastasis						
No	229	87(112)	10.58 [8.31, 13.40]	95(117)	8.34 [6.87, 9.89]	0.78 [0.58, 1.04]
Yes	190	73(98)	11.86 [8.38, 14.65]	78(92)	8.51 [6.14, 11.10]	0.76 [0.55, 1.04]
Bone metastasis						
No	371	141(187)	11.04 [9.92, 13.57]	151(184)	9.36 [7.52, 10.32]	0.78 [0.62, 0.98]
Yes	48	19(23)	7.33 [4.34, 14.09]	22(25)	5.13 [3.91, 7.92]	0.72 [0.38, 1.33]
Target lesion						
No	88	26(38)	11.56 [7.95, 21.13]	36(50)	11.99 [7.56, 16.16]	0.80 [0.48, 1.34]
Yes	331	134(172)	10.87 [8.84, 13.24]	137(159)	7.69 [6.18, 9.40]	0.73 [0.57, 0.93]
Past treatments for cancer (surgery)						
No	214	72(99)	10.22 [7.39, 12.22]	96(115)	7.52 [5.85, 9.69]	0.74 [0.55, 1.01]
Yes	205	88(111)	12.75 [9.23, 14.49]	77(94)	9.69 [7.56, 11.60]	0.81 [0.59, 1.10]
Past treatments for cancer (radiotherapy)						
No	124	40(57)	11.50 [9.23, 17.45]	52(67)	7.20 [5.75, 9.69]	0.68 [0.45, 1.03]
Yes	295	120(153)	10.74 [8.31, 13.24]	121(142)	9.33 [7.39, 10.68]	0.80 [0.62, 1.04]
History of smoking						
Never	62	20(30)	12.98 [6.67, 17.45]	23(32)	8.38 [5.22, 12.91]	0.64 [0.35, 1.18]
Former	306	125(159)	10.87 [9.17, 13.34]	122(147)	9.33 [7.56, 10.61]	0.87 [0.68, 1.12]
Current	51	15(21)	9.92 [6.08, 25.95]	28(30)	5.80 [4.07, 9.89]	0.52 [0.27, 0.97]

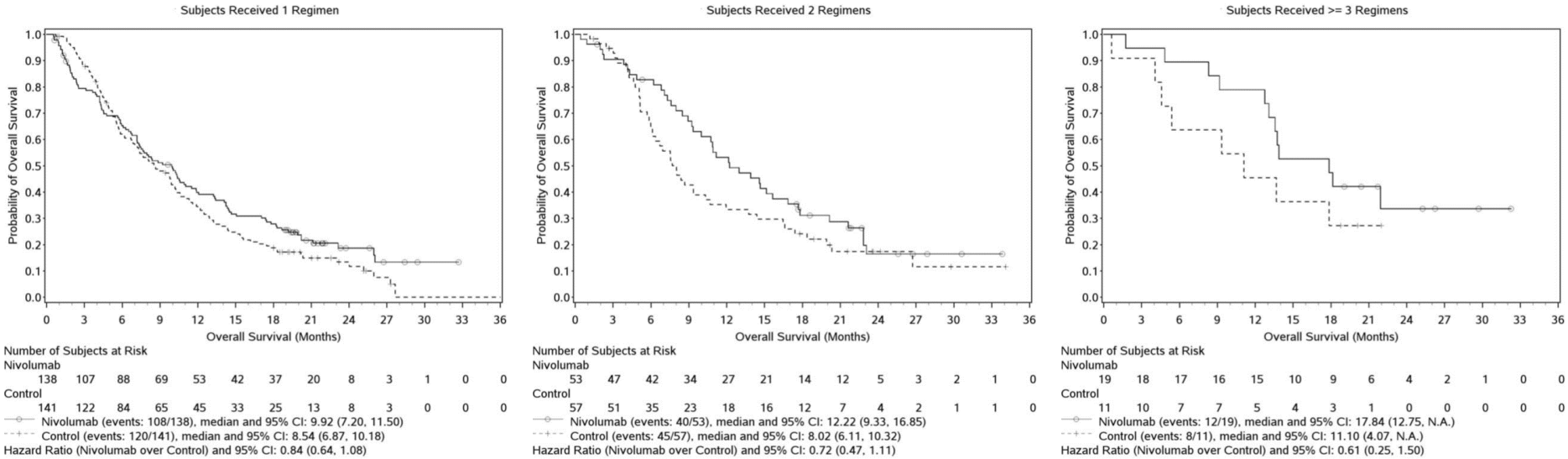
Analysis Set : ITT

a) Hazard ratios were estimated by using unstratified Cox proportional hazards model

Note: PD-L1 Expression (test results) refers to test CRF results

An exploratory, post-hoc subgroup analyses by number of prior systemic treatment regimens was conducted. The OS KM plots by number of prior systemic treatment regimens are depicted in **Figure 15**.

Figure 15 Kaplan-Meier plots of overall survival by number of prior systemic treatment regimens - ITT patient population



Another exploratory, post-hoc subgroup analyses by prior taxane therapy was conducted:

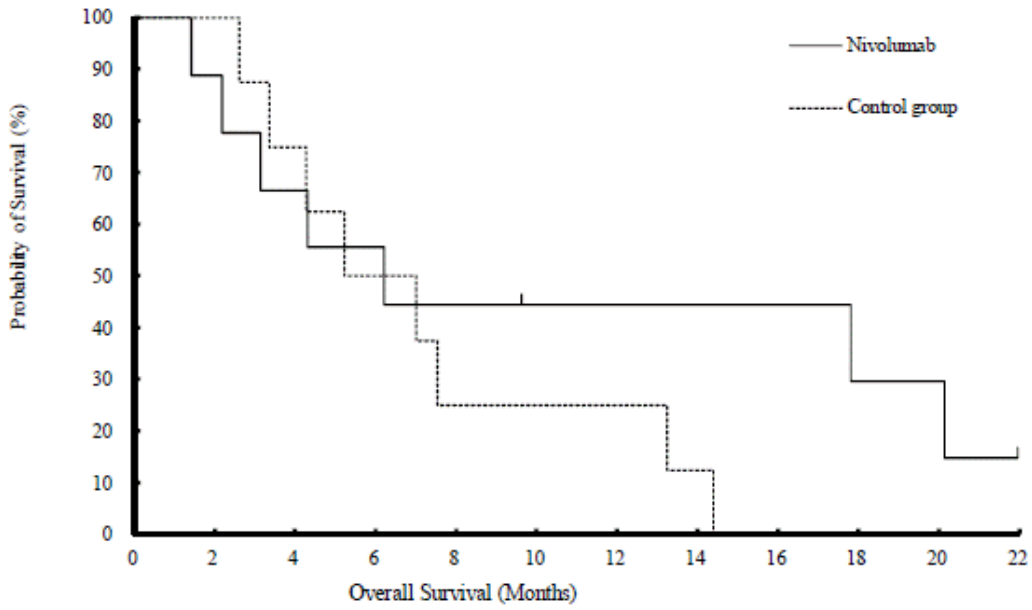
- Yes: events/patients = 9/13 vs. 13/16 ; HR = 0.85 (95% CI: 0.36, 2.02); nivolumab mOS = 12.75 months (95% CI: 2.18, 21.62) vs. control mOS = 13.70 months (95% CI: 5.98, 16.59); and
- No: events/patients = 151/197 vs. 160/193; HR = 0.75 (95% CI: 0.60, 0.94); nivolumab mOS = 10.91 months (95% CI: 9.17, 13.34) vs. control mOS = 8.02 months (95% CI: 6.87, 9.79).

Lastly, also not included in the figure is the (exploratory, post-hoc) subgroup analysis by prior chemoradiotherapy:

- Yes: events/patients = 40/51 vs. 45/51; HR = 0.83 (95% CI: 0.54, 1.27); nivolumab mOS = 8.84 months (95% CI: 4.86, 14.09) vs. control mOS = 7.52 months (95% CI: 5.06, 11.96); and
- No: events/patients = 120/159 vs. 128/158; HR = 0.75 (95% CI: 0.59, 0.97); nivolumab mOS = 11.86 months (95% CI: 9.99, 13.86) vs. control mOS = 8.64 months (95% CI: 7.00, 9.89).

Specifically regarding the subgroup of the 18 white/non-Asian patients in study ONO 4538-24 (CA209473), the OS (and other efficacy) results of this subgroup are presented side by side with the results of the total ITT (or RES) patient population in **Table 7**. The OS KM for the subgroup of white patients (only) is shown in **Figure 16**.

Figure 16 Kaplan-Meier plot of overall survival - white patient subgroup from ITT patient population



Analysis Set : ITT in western subjects

At risk	0	2	4	6	8	10	12	14	16	18	20	22
Nivolumab	9	8	6	5	4	3	3	3	3	2	2	0
Control group	9	8	6	4	2	2	2	1	0	0	0	0

Biomarker subgroup analysis

In addition to the results of the subgroup analysis by PD-L1 expression (CRF result) depicted in **Figure 13**, the OS (and other efficacy) results of this subgroup analysis are summarized in Table 9. The Kaplan-Meier plots of OS by PD-L1 expression (1% cut-off) are shown in **Figure 17**.

Table 9 Summary of efficacy results by PD-L1 expression subgroup (CRF results)

Efficacy result by baseline PD-L1 expression (using a 1% cut-off)	**Nivolumab patients**	**Control patients**
Patients with ≥1% PD-L1 expression		
ITT population (N)	**101**	**102**
Overall survival		
Events, n	77	89
Median OS (95% CI), months	10.91 (7.98, 14.23)	8.05 (5.98, 9.86)
HR (95% CI)[a]	0.69 (0.51, 0.94)	
RES population (N)	**87**	**80**
Objective response rate		
Events, n	21	20
Investigator-assessed ORR (95% CI)	24.14 (15.60, 34.50)	25.00 (15.99, 35.94)
Odds Ratio (95% CI) [b,c]	0.95 (0.47, 1.93)	
ITT population (N)	**101**	**102**
Progression-free Survival		
Events, n	88	86
Median, (95% CI), months	2.73 (1.51, 3.25)	3.06 (2.89, 4.17)
HR (95% CI) [a]	0.90 (0.67, 1.23)	
Patients with <1% PD-L1 expression		
ITT population (N)	**109**	**107**
Overall survival		
Events, n	83	84
Median OS (95% CI), months	10.91 (8.38, 13.90)	9.33 (7.20, 11.96)
HR (95% CI) [a]	0.84 (0.62, 1.14)	
RES population (N)	**84**	**78**
Objective response rate		
Events, n	12	14

Table 9 Summary of efficacy results by PD-L1 expression subgroup (CRF results)

Efficacy result by baseline PD-L1 expression (using a 1% cut-off)	Nivolumab patients	Control patients
Investigator-assessed ORR (95% CI)	14.29 (7.61, 23.62)	17.95 (10.17, 28.28)
Odds Ratio (95% CI) [b,c]	0.76 (0.33, 1.77)	
ITT population (N)	**109**	**107**
Progression-free survival		
Events, n	99	90
Median, (95% CI), months	1.61 (1.48, 2.63)	4.11 (3.02, 4.27)
HR (95% CI) [a]	1.30 (0.97, 1.73)	

[a] HR was estimated by using unstratified Cox proportional hazards model.

[b] Exact 95% CI was calculated by using Clopper-Pearson method. Items whose estimated value exceeded 10.00 were not plotted.

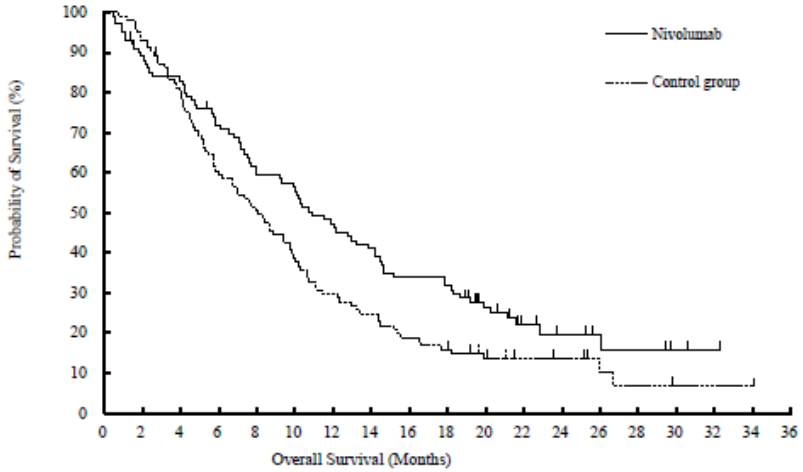
[c] Odds ratio was estimated by using the logistic regression model with the treatment group as the single covariate.

Note: CRF results = test results.

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intention-to-treat; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; RES, response evaluable set.

Figure 17 Kaplan-Meier plots of overall survival by PD-L1 Expression (1% cut-off) - ITT patient population

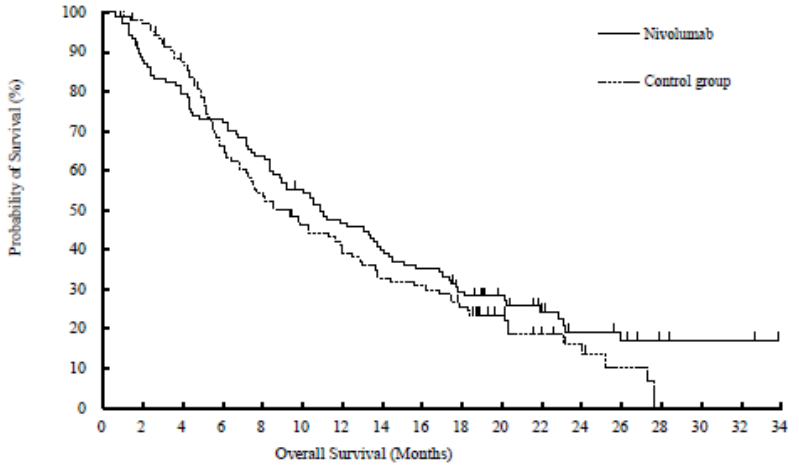
PD-L1 EXPRESSION ≥1%



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Nivolumab	101	88	82	70	58	54	46	40	33	31	21	10	7	5	4	2	1	0	0
Control group	102	95	81	60	51	39	30	25	19	16	11	8	6	3	2	1	1	1	0

PD-L1 EXPRESSION <1%



Analysis Set : ITT

At risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Nivolumab	109	94	85	77	68	57	49	42	37	29	22	15	10	8	3	2	2	0
Control group	107	101	88	66	54	45	38	32	30	24	16	9	6	3	0	0	0	0

The result of the interaction analyses with respect to OS between a treatment group and demographic factors is presented in **Table 10**. Covariates that were considered as interaction with a treatment group (p<0.15) were ECOG PS at baseline, recurrent, and history of smoking.

Table 10 Interaction analyses for overall survival

Analysis Set : ITT

Covariance factor	Chi-square [a)]	p-value [a)b)]
PD-L1 Expression (IWRS) x Treatment group	1.34	p=0.2472 N.S
PD-L1 Expression (test results, 1%) x Treatment group	0.78	p=0.3763 N.S
PD-L1 Expression (test results, 5%) x Treatment group	0.15	p=0.7017 N.S
PD-L1 Expression (test results, 10%) x Treatment group	0.52	p=0.4726 N.S
PD-L1 Expression (test results, Not Quantifiable) x Treatment group	N.A.	N.A.
Location(IWRS) x Treatment group	0.01	p=0.9055 N.S
Age x Treatment group	1.24	p=0.2645 N.S
Sex x Treatment group	0.17	p=0.6833 N.S
Race x Treatment group	0.37	p=0.5443 N.S
ECOG Performance Status score at baseline x Treatment group	4.22	p=0.0399*
Recurrent x Treatment group	3.71	p=0.0542*
Lesion sites (TNM classification) x Treatment group	0.13	p=0.7155 N.S
Histological classification x Treatment group	N.A.	N.A.
The number of organs with metastases(IWRS) x Treatment group	0.39	p=0.5345 N.S
Lymph Node metastasis x Treatment group	0.89	p=0.3447 N.S
Liver metastasis x Treatment group	0.33	p=0.5642 N.S
Lung metastasis x Treatment group	0.01	p=0.9054 N.S
Bone metastasis x Treatment group	0.31	p=0.5801 N.S
Target lesion x Treatment group	0.20	p=0.6552 N.S
Past treatments for cancer (surgery) x Treatment group	0.36	p=0.5470 N.S
Past treatments for cancer (radiotherapy) x Treatment group	0.49	p=0.4839 N.S
History of smoking x Treatment group	3.91	p=0.1414*

Location and the number of organs with metastases were extracted from IWRS. The other factors except for PD-L1 expression were extracted from eCRF. PD-L1 expression was extracted from test result.

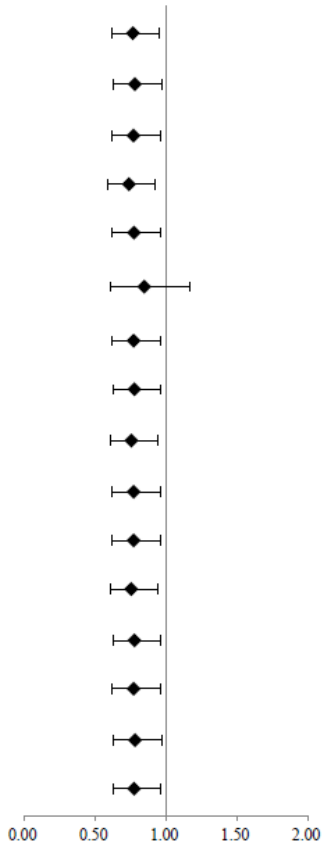
a) The multivariate Cox proportional hazards model stratified by each demographic factor was performed to assess the interaction between treatment group and each demographic factor.

b) *: p<0.15 N.S.: p>=0.15 (two-sided)

The results of the adjusted analyses for OS, i.e. adjusted by demographic factors, are presented in **Figure 18**.

Figure 18 Forest plots of adjusted analyses for overall survival - ITT patient population

Covariance factor	Hazard Ratio [a] (95% CI)	p value
Age	0.76 [0.61, 0.95]	p=0.0175 *
Sex	0.78 [0.62, 0.97]	p=0.0240 *
Race	0.77 [0.62, 0.96]	p=0.0179 *
ECOG Performance Status score at baseline	0.74 [0.59, 0.92]	p=0.0065 *
Recurrent	0.77 [0.62, 0.96]	p=0.0194 *
Lesion sites (TNM classification)	0.84 [0.61, 1.17]	p=0.3091 N.S.
Histological classification	0.77 [0.62, 0.96]	p=0.0187 *
Lymph Node metastasis	0.77 [0.62, 0.96]	p=0.0219 *
Liver metastasis	0.75 [0.61, 0.94]	p=0.0113 *
Lung metastasis	0.77 [0.62, 0.96]	p=0.0188 *
Bone metastasis	0.77 [0.62, 0.96]	p=0.0189 *
Target lesion	0.75 [0.60, 0.94]	p=0.0112 *
Past treatments for cancer (surgery)	0.77 [0.62, 0.96]	p=0.0219 *
Past treatments for cancer (radiotherapy)	0.77 [0.62, 0.96]	p=0.0183 *
History of alcohol consumption	0.78 [0.63, 0.97]	p=0.0257 *
History of smoking	0.77 [0.62, 0.96]	p=0.0208 *



Analysis Set : ITT

a) Hazard ratio for the Nivolumab group relative to the control group was calculated by using the stratified Cox proportional-hazards model with the startifiction factors (IWRS source) as the stratification factors, treatment groups and each demographic factor as the factors.

- **Secondary endpoint ORR and DoR**

Sensitivity analysis/analyses

For the ITT patient population, the ORR in the nivolumab group was 15.7% (95% CI: 11.1, 21.4) vs. 16.3% (95% CI: 11.5, 22.0) in the control group (OR 0.96; 95% CI: 0.57, 1.62). The DCR was 30.5% (95% CI: 24.3, 37.2) vs. 47.4% (95% CI: 40.4, 54.4).

Subgroup analyses

In general, the ORR subgroup analyses were unremarkable (data not shown).

For the ORR results of the subgroup of white patients, compared to the total RES patient population, see **Table 7**. The DoR for the single responder in the nivolumab group was 5.55 months and the DoR for the single responder in the control group was 5.13 months.

For the ORR results by PD-L1 expression subgroup (CRF result), see Table 9. The median DoR in the subgroup of patients with ≥1% PD L1 expression (CRF result) was 7.00 months (95% CI: 5.09, NA) for nivolumab patients vs. 4.17 months (95% CI: 2.79, 5.78) for control patients (Δ 2.83 months). The median DoR in the subgroup of patients with <1% PD L1 expression (CRF result) was 5.59 months (95% CI: 2.86, 9.03) for nivolumab patients vs. 2.96 months (95% CI: 2.63, 4.01) for control patients (Δ 2.63 months).

- **Secondary Endpoint PFS**

Sensitivity analysis

Using the secondary PFS definition, the PFS HR for the nivolumab group vs. the control group was 1.11 (95% CI: 090, 1.36). Median PFS was 1.68 months (95% CI: 1.51, 2.79) vs. 4.04 months (95% CI: 3.02, 4.21), respectively, and the early crossing of the KM PFS curves between 4 and 6 months, only afterwards favouring nivolumab, remained (figure not shown).

Subgroup analyses

In general, the PFS subgroup analyses were unremarkable (data not shown).

For the PFS results (primary definition) of the subgroup of white patients, compared to the total ITT patient population, see **Table 7**.

For the PFS results (primary definition) by PD-L1 expression subgroup (CRF result), see Table 9.

Modified ITT-31 patient population

An additional efficacy analysis was performed based on the modified ITT-31 patient population excluding the 31 patients randomised at the 6 clinical sites in Taiwan handled by the Linical clinical site monitor (N = 388, i.e. 193 patients in the nivolumab group and 195 patients in the control group; see also GCP - *Study conduct*).

In the ITT-31 patient population, nivolumab similarly demonstrated a benefit in OS over the control group (HR 0.79 [95% CI: 0.63, 0.99]; p=0.0381). Median OS was 11.17 months (95% CI: 9.99, 13.73) in the nivolumab group and 8.54 months (95% CI:7.20, 9.89) in the control group. There was an early crossing of the KM OS curves between 4 and 6 months, only afterwards favouring nivolumab (figure not shown).

In the modified RES patient population (N = 307, i.e. 158 patients in the nivolumab group and 149 patients in the control group), the ORR in the nivolumab group was 32/158 patients (20.3%; 95% CI: 14.3, 27.4) vs. 33/149 patients (22.1%; 95% CI: 15.8, 29.7) in the control group (odds ratio 0.88 [95% CI: 0.51, 1.52]; p=0.6490).

Using the primary PFS definition, the PFS HR for the nivolumab group vs. the control group was 1.07 (95% CI: 0.86, 1.34). Median PFS was 1.84 months (95% CI: 1.54, 2.83) vs. 3.75 months (95% CI: 3.02, 4.21), respectively. There was an early crossing of the KM PFS curves at approximately 4 months, only afterwards favouring nivolumab (figure not shown).

Secondly, several exploratory, post-hoc analyses of OS were performed, following feedback received from the EMA during pre-submission discussions.

Analyses of early deaths

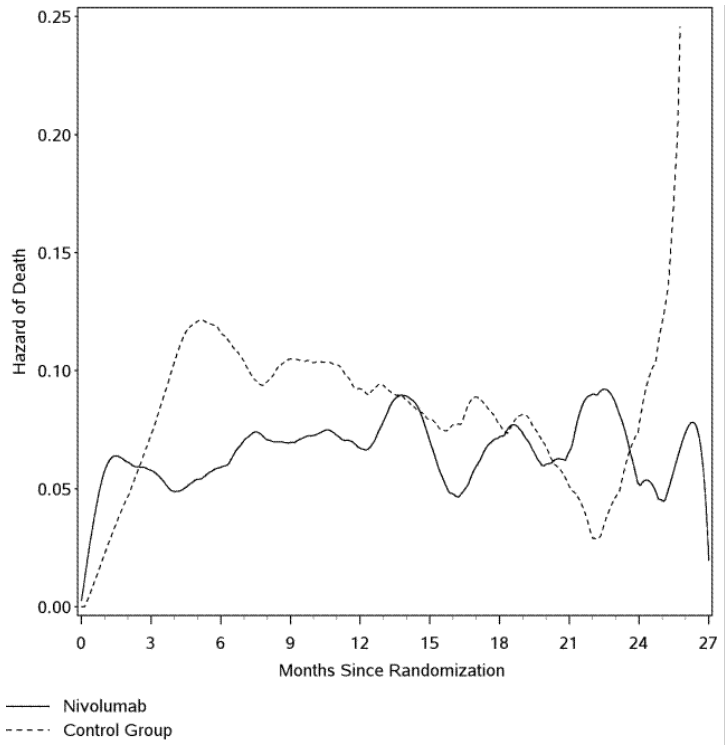
Additional exploratory, post-hoc analyses were conducted to further understand and/or characterize risks of early deaths in patients treated with nivolumab. Early death was defined as any death that occurred prior to the first timepoint when hazard for treatment arms were equal (first time-point of the crossing of the hazard curves).

Based on visual evaluation of the OS KM curves (

Figure **8**), the early crossing indicated an imbalance of deaths with the control group showing a higher survival rate for the first 3 months compared with the nivolumab group. A stratified piecewise Cox-regression model with treatment group as covariate was produced with the piecewise time intervals defined as 0-2, > 2-3, > 3-4, > 4-5, > 5-6, and > 6 months. The piece-wise hazard ratio of nivolumab over control was 2.48 in the first two months, 1.02 between 2 and 3 months, 0.44 between 3 and 4 months, 0.66 between 4 and 5 months, 0.20 between 5 and 6 months, and 0.77 after 6 months.

Also, the instantaneous hazard of death over time was plotted using Epanechnikov kernel for each treatment, see **Figure 19**. The first time point when the smoothened curves cross (i.e. hazards of death are equal) is at 2.49 months, but the curves cross at multiple later time points, the second time point being between 13 and 14 months.

Figure 19 Plot of smoothed instantaneous hazard of death over time - ITT patient population



Early death occurred in 32 (15.2%) patients in the nivolumab group and 15 (7.2%) patients in the control group. The most frequent cause of early death was initial disease (i.e. OSCC), accounting for 20/32 (62.5%) of cases vs. 10/15 (66.7%) of cases, respectively. Two (6.3%) patients in the nivolumab group and 2 (13.3%) patients in the control group had early deaths due to study drug toxicity.

Fifteen (pre-defined) baseline demographic and disease variables were identified with an imbalance ≥10% in early death between the nivolumab and control group. The sample sizes for early deaths within these identified subgroups were (however) small.

Overall survival by best overall response category

An exploratory, post-hoc analysis was performed of OS according to BOR (CR/PR; SD; PD; NE) in the RES patient population.

An OS benefit of nivolumab over control was observed in patients with a BOR of CR/PR (HR: 0.71 [95% CI: 0.39, 1.30]), SD (HR: 0.43 [95% CI: 0.27, 0.71]), or PD (HR: 0.49 [95% CI: 0.34, 0.72]). There was no OS benefit observed in (the small [nivolumab: 13; control 8] subgroup of) patients with a BOR of NE (HR: 1.81 [95% CI: 0.67, 4.86]).

Overall survival with censoring at the start of subsequent therapy

An exploratory, post-hoc sensitivity analysis was performed examining the impact of censoring at the start of subsequent therapy on OS in the ITT patient population.

Fewer OS events (deaths) were reported in the nivolumab group (61/210) compared with the control group (77/209). OS HR was 0.69 (95% CI: 0.49, 0.98) and the KM estimate of median OS was 14.65 months (95% CI: 13.24, N.A.) in the nivolumab group and 8.34 months (95% CI: 7.20, 10.61) in the control group.

Summary of main study

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

Table 1. Summary of Efficacy for trial ONO-4538-24 (CA209473)

Title: ONO-4538 Phase III Study, a multicenter, randomized, open-label study in patients with esophageal cancer refractory or intolerant to combination therapy with fluoropyrimidine- and platinum-based drugs			
Study identifier	ONO-4538-24 (CA209473; NCT02569242)		
Design	Phase 3, multicentre, randomised, open-label, docetaxel- or paclitaxel-controlled		
	Duration of enrolment period:		approximately 18 months (Dec-2015 to May-2017)
Hypothesis	Superiority		
Treatments groups	**Nivolumab**		240 mg IV Q2W until disease progression per RECIST 1.1, or unacceptable toxicity **N = 210**
	Control (investigator's choice of chemotherapy (docetaxel or paclitaxel)		Docetaxel 75 mg/m^2 IV Q3W Paclitaxel 100 mg/m^2 IV weekly for 6 weeks followed by a 2-week washout period Both until disease progression per RECIST 1.1, or unacceptable toxicity **N = 209**
Endpoints and definitions	Primary endpoint	Overall survival (**OS**)	Time from randomisation until death from any cause
	Secondary endpoint	Objective response rate (**ORR**)	Percentage of patients whose best overall response is either confirmed complete or partial response as assessed by investigator per RECIST 1.1
	Secondary endpoint	Disease control rate (**DCR**)	Percentage of patients whose best overall response is either confirmed complete or partial response, or stable disease as assessed by investigator per RECIST 1.1
	Secondary endpoint	Duration of response (**DoR**)	Time between date of first confirmed response (complete or partial) and date of first documented progression as determined by investigator (per RECIST 1.1) or death due to any cause, whichever occurs first

	Secondary endpoint	Progression free survival (**PFS**)	Time from randomisation to the earlier date on which either the overall response was assessed as progressive disease (PD) by the investigator (per RECIST 1.1), or the patient died of any cause
Database lock	28-Dec-2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) patient population for OS and PFS Response evaluable set (RES) patient population for ORR (i.e. all patients from the ITT with target lesion measurements at baseline) Clinical cut-off date: 12-Nov-2018 Minimum follow-up (time from randomisation of last patient to clinical data cut-off): 17.6 months Median follow-up (time from randomisation to last known date alive or death) for OS was 10·5 months in the nivolumab group and 8·0 months in the control group		
Descriptive statistics and estimate variability	Treatment group	**Nivolumab**	**Control**
	Number of patient	210	209
	Median **OS** (months)	10.91	8.38
	95% confidence interval (CI)	9.23, 13.34	7.20, 9.86
	ORR (%)	19.3	21.5
	95% CI	13.7, 26.0	15.4, 28.8
	DCR (%)	37.4	62.7
	95% CI	30.2, 45.1	54.6, 70.2
	Median **DoR** (months)	6.93	3.91
	95% CI	5.39, 11.14	2.79, 4.17
	Median **PFS** (months)	1.68	3.35
	95% CI	1.51, 2.73	2.99, 4.21

Effect estimate per comparison	Primary endpoint **OS**	Comparison groups	Nivolumab vs. control
		Hazard ratio (HR)	0.77
		95% CI	0.62, 0.96
		p-value (two-sided)	0.0189
	Secondary endpoint **ORR**	Comparison groups	Nivolumab vs. control
		Odds ratio	0.88
		95% CI	0.51, 1.50
		p-value (two-sided)	0.6323
	Secondary endpoint **DCR**	Comparison groups	Nivolumab vs. control
		Odds ratio	0.33
		95% CI	0.21, 0.53
		p-value	Not applicable
	Secondary endpoint **DoR**	Comparison groups	Nivolumab vs. control
		Hazard ratio (HR)	Not applicable
	Secondary endpoint **PFS**	Comparison groups	Nivolumab vs. control
		Hazard ratio (HR)	1.08
		95% CI	0.87, 1.34
		p-value	Not applicable
Notes	Because ORR did not pass the statistical boundary for significance, according to the hierarchical order, PFS was not formally tested.		

Clinical studies in special populations

The below table shows the number of elderly patients in the studies included in this application, further specified per age category (i.e. age 65-74, age 75-84, and age 85+). Notably, study ONO-4538-24

(CA209473) is the only study in this application. Refer also to the forest plot of OS subgroup analyses (**Figure 13**).

Table 11 Elderly patients in study ONO-4538-24 (CA209473)

	Age 65-74 (older patients number/total number)	**Age 75-84 (older patients number/total number)**	**Age 85+ (older patients number/total number)**
Controlled trials	180 / 419 (43.0%)	41 / 419 (9.8%)	1 / 419 (0.2%)
Non-controlled trials	Not applicable	Not applicable	Not applicable

Note: study ONO-4538-24 (CA209473) is the only study in this application.

Supportive study

In Japan, the open-label, single arm, multicentre, phase 2 study ONO-4538-07 was conducted (Kudo et al. 2017). Eligible patients had advanced OSCC refractory or intolerant to fluoropyrimidine-based, platinum-based, and taxane-based chemotherapy. Patients were treated with 3 mg/kg nivolumab IV Q2W. The primary endpoint was centrally-assessed ORR per RECIST 1.1.

The MAH did not submit the CSR of this phase 2 study, but the following key information was provided. A total of 65 patients were enrolled and 64 patients were assessable for the primary endpoint. ORR was 17.2% (95% CI: 9.9, 28.2; 11/64 patients), DCR was 42.2% (95% CI: 31, 54; 27/64), and median DoR was 11.17 months [95% CI: 3.02, NA]). Median PFS (centrally-assessed) was 1.5 months (95% CI: 1.4, 2.8). Median OS was 10.78 months (95% CI: 7.39, 13.93), with a 2-year survival rate of 17.2%.

These results from study ONO-4538-07 provided the rationale for the pivotal phase 3 study ONO-4538-24 (CA209473).

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study design. The randomised, open-label, docetaxel- or paclitaxel-controlled study design that was used in study ONO-4538-24 (CA209473) is considered adequate to evaluate the benefits and risks of nivolumab in patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine- and platinum-based combination chemotherapy, i.e. in the ≥2L treatment setting. In this disease setting, there are no approved therapies and in general the value of SoC palliative chemotherapy is less clear for OSCC than for oesophageal adenocarcinoma (Lordick et al. 2016).The study was open-label, but given that the primary endpoint is OS, this is acceptable.

Collectively, the PK analyses demonstrate that administration of the Ono and BMS drug products batches result in similar PK. In conclusion, comparability of the clinical material from Ono to the EU-commercial material has been sufficiently substantiated for the purpose of this application.

Patient population. The inclusion and exclusion criteria for study ONO-4538-24 (CA209473) appear overall acceptable. The enrolled patient population is considered a somewhat selected population compared to patients with OSCC treated in clinical practice since patients had to have an ECOG PS ≤1. Whereas, in the real-world retrospective global treatment patterns study conducted by the MAH, 50% of

patients at initiation of 2L treatment had an ECOG PS of 2-4 (Jaffe et al. 2019a; Jaffe et al. 2019b). Also, patients with apparent tumour invasion in organs located adjacent to the oesophagus (i.e. T4 tumours) were excluded from the study, but this information is adequately reflected in the SmPC.

Comparator. Taxane monotherapy (either docetaxel or paclitaxel) is recommended by current clinical guidelines (2019 NCCN Guidelines; Lordick et al. 2016) and is thus an acceptable comparator. The investigator's choice option is acknowledged. Nevertheless, the company could have also considered best supportive care (BSC) as control, as is suggested in EMA guidance ("*In cases where there is no established reference therapy, investigator's best choice or BSC with or without placebo are acceptable.*"; EMA/CHMP/205/95 Rev.5). Firstly, as it is also a recognised option in the same clinical guidelines, especially for patients with poor(er) performance status. Secondly, given the (expected) low efficacy of the taxane monotherapy, the increased toxicity, decrease in health related quality of life, and/or maybe even mortality associated with this comparator could - at least in theory - have biased the study results in favour of nivolumab (whereas BSC as a comparator would have not).

Endpoints. The choice for OS as the primary endpoint of the pivotal study is considered appropriate. Firstly, as convincingly demonstrated favourable effects on OS are from both a clinical and methodological perspective the most persuasive outcome of a clinical trial (EMA/CHMP/205/95 Rev.5). Secondly, it is considered appropriate specifically for the target patient population, as the life expectancy is rather short and results are unlikely to be influenced by next line therapies. The study design included ORR and PFS as key secondary endpoints, both as assessed by the investigator per RECIST 1.1. No (blinded) central evaluation of imaging was performed. As OS was the primary endpoint and the effect on OS will be most important in the assessment of efficacy, this lack of (blinded) central evaluation of the imaging endpoints is considered acceptable in this case. The exploratory endpoint health-related QoL was measured using the EQ-5D, which is a non-disease-specific instrument that is recommended for and commonly used in cost-effectiveness analysis/for economic appraisal. This could limit the value of the health-related QoL results for the benefit-risk assessment.

Statistical analysis. The used stratification factors (i.e. location, number of organs with metastases, and expression of PD-L1) are acceptable, although stratification by location preferably would have been Asia vs. non-Asia/the rest of the world (instead of Japan vs. the rest of the world).

Analyses were performed as outlined in the SAP and were appropriate given the type of endpoints.

Of note, ORR and PFS were added as key secondary endpoints in a hierarchical testing procedure in a later stage. As this did not affect the primary endpoint, the impact is considered limited for interpretation of the trial's results.

However, in the 7th protocol amendment (after recruitment was finished and when 2/3 of the patients had at least 6 months of follow-up) the interim analysis was postponed from 60% of the events to 80% of events. As a consequence, required events for the interim analysis of OS and two-sided significance levels for the interim and final OS analysis were changed (according to the MAH "*in consideration of the latest results of clinical trial ONO-4538*"), and in the 8th and final amendment of the protocol (when all patients had at least 6 months of follow-up and 2/3 even one year of follow-up) the OS interim analysis was cancelled. According to the MAH, the decision to change the interim analysis (7th protocol amendment) was not driven by data from the pivotal study ONO-4538-24 (CA209473) in 2L OSCC, but by data from study ONO-4538-11/CA209141 in 2L SCCHN which is thus *external* data. The MAH also clarified that the reason to drop the interim analysis (8th and final protocol amendment) was that monitoring of the observed pooled OS events in the pivotal study (performed by an independent statistician) suggested that the number of OS events necessary to trigger the final analysis would already be reached at about the same time of the planned interim analysis. Both decisions can be understood and are acceptable.

It is noted that for the analysis of ORR (DCR, DoR, TTR, BOR, and maximum percent change from baseline in the sum of diameters of target lesions) the RES patient population was used instead of the ITT patient population. This analysis may be biased as it only included patients with target lesion measurements at baseline. However, the MAH provided ORR results for the ITT patient population as a sensitivity analysis.

The censoring rules of the primary definition of PFS are not in accordance with the EMA preferred analysis (EMA/CHMP/27994/2008/Rev.1), and moreover make censoring dependent on success of subsequent anti-cancer therapy, which does not seem to address a meaningful question. However, the provided sensitivity analysis using the secondary definition of PFS *is* the EMA preferred analysis.

Whereas the SAP (v3.0) merely mentions analyses of the health-related QoL data using summary statistics, for the referred-to EQ-5D results (Kato et al. 2019) several other (more advanced) analytical methods were used post hoc, without adjustment for multiplicity. Some analytical methods also used thresholds for meaningful change, but these were (thus) not pre-defined. It is thus considered that the health-related QoL results are of less value for the assessment and are of a hypothesis-generating nature only.

Study conduct. The GCP non-compliant activities at 4 Taiwanese study sites are a cause of concern. In light of the nature of the activities (i.e. mostly failing to submit several study-related documents for approval by IRB/IECs) it can, however, be agreed with the MAH that the adverse impact on the interpretation or scientific value of the reported trial results are not major. Therefore, the (original) analyses of the complete ITT patient population of study ONO-4538-24 (CA209473) remains the primary analyses to be assessed. The fact that the MAH has performed additional ancillary analyses of the ITT-31 patient population is acknowledged.

Four patients in the nivolumab group had relevant protocol deviations. Given the small number of patients, these are not expected to have an impact on the overall interpretation of the efficacy outcomes.

Efficacy data and additional analyses

Demographics and other baseline characteristics. The majority of the ITT patient population was male (86.9%), the median age was 65.0 and almost all patients were Asian (95.7% with approximately two-thirds [65.4%] from Japan). Based on the SEER database; median age at diagnosis is 68 years of age, which is only marginally higher than observed in the clinical trial (SEER database). Of note, the vast majority of patients was Asian/from Asia and only a small subset of patients (n = 18; 4.3%) was white/from non-Asian countries. See *Extrapolation of data across regions* below. Study ONO-4538-24 included 222 patients (43.0%) ≥65 years of age and 42 patients (10.0%) ≥75 years of age.

In general, the demographics and other baseline characteristics were reasonably well balanced between both treatment arms, but there were some exceptions. Compared to the patients in the control group, the patients in the nivolumab group were slightly younger, had a slightly longer median time from diagnosis to treatment, and a higher proportion of patients had recurrent disease, previous tumour surgery, an R0 resection, and previous radiotherapy. Univariate adjustment for these factors showed treatment effects consistent with the primary OS analysis. Therefore, the observed slight imbalances in possibly prognostic baseline factors did not appear to have a relevant impact on the primary endpoint. In addition, the MAH conducted a *multivariate* analysis incorporating *all* baseline characteristics that were not completely balanced between both treatment arms (data not shown) and this analysis was also supportive of the result of the primary OS analysis.

Scrutinizing any differences in demographics and other baseline characteristics between the ITT patient population and the small white patient population, it is noted that the majority of patients (55.6%) in the

white nivolumab group is female. This is in contrast to the white control group (11.1%), the ITT patient population (see Table 3), and the male preponderance known from medical practice.

Prior systemic anti-cancer treatment was comparable in both treatment arms. It is, however, noted that66.6 % of patients had received one prior systemic therapy regimen, 26.3% had received two prior systemic therapy regimens and 7.2% had received ≥3 prior systemic regimens, irrespective of setting. In contrast, the real-world data provided by the MAH show that in clinical practice only a minority of OSCC patients actually proceed to 2L treatment (Jaffe et al. 2019: 21.4%; study CA2097E7: 14%; study CA2098LY: 23%) and even fewer patients receive 3L treatment (Jaffe et al. 2019: 8%; study CA2097E7: 3%; study CA2098LY: 8%). The study population thus appears to receive/have received more lines of treatment than is common in clinical practice and hence suggest a likely more fit study population compared to generally observed in clinical practice. It is, therefore, uncertain whether the obtained results are representative for medical practice. Moreover, approximately half of patients received subsequent systemic anti-cancer treatment, emphasizing the previous remark. It was given to slightly more patients in the nivolumab group (53.3%) than in the control group (47.4%). However, an exploratory, post-hoc sensitivity analysis of OS was performed by the MAH, censoring at the start of subsequent therapy. The results of this analysis suggest confirmation of benefit of nivolumab over control and are considered of informative nature.

Primary endpoint - OS. Mature OS data (event rate nivolumab: 76.2%; control: 82.8%) show a statistically significant benefit for nivolumab over control (HR = 0.77; p=0.0189; median OS 10.91 vs. 8.38 months; Δ 2.53 months). This treatment effect could be regarded as being clinically relevant given the poor prognosis of patients with advanced OSCC. Importantly however, there was an early crossing of the OS KM curves at approximately 5 months. Afterwards OS rates consistently favoured nivolumab with differences around 5-10%.

A pre-planned sensitivity analysis confirmed the primary analysis and there was hardly any difference in the effect on OS of nivolumab vs. either docetaxel or paclitaxel, as expected. A post-hoc analysis of OS by non-proportional hazards that weighted events later in time (i.e. later onset of effect) not surprisingly also showed a p-value favouring nivolumab.

The OS result for the ITT-31 patient population was confirmatory, although here statistical significance was more borderline compared to the ITT analysis (HR = 0.79 [95% CI: 0.63, 0.99]; p=0.0381).

Regarding the other (exploratory, post-hoc) ancillary OS analyses, based on the analysis of early deaths unfortunately no definite conclusion could be drawn on any particular predictive factor in nivolumab-treated OSCC patients. The primary reason for this were the small sample sizes within the baseline demographics and disease characteristics variables that were identified with an imbalance ≥10% in early death between the nivolumab and control group, limiting the interpretation of results. In general, perhaps the well-known delayed treatment effect of immunotherapy vs. chemotherapy may have led to risk of early death. The results of another ancillary OS analysis, i.e. an analysis of OS according to BOR, could suggest that OS benefit was not limited to responders, but could also be subject to selection bias.

The subgroup analyses of OS consistently favoured nivolumab over control, represented by a HR <1. Nevertheless, the treatment effect of nivolumab seems to be more apparent when it is given in a later line of therapy, as the OS HR over control for patients who had received 1, 2, and ≥3 prior regimens (irrespective of setting) was 0.84, 0.72, and 0.61, respectively. Patients fulfilling the eligibility criteria of the pivotal study (that are clearly reflected in the SmPC) *do* exist in clinical practice in non-Asian (including European) countries.

Regarding the subgroup analysis by PD-L1 expression (one of the stratification factors), on the one hand the OS HR for both patients with ≥1% PD-L1 expression (0.69) as well as for patients with PD-L1 expression <1% (0.84) favoured nivolumab over control, and in an interaction analysis for OS the

covariate PD-L1 expression (with a 1% cut-off) was not considered as interaction with a treatment group (p=0.3763). On the other hand, however, the OS benefit in patients with PD-L1 expression <1% could be considered somewhat less apparent (than in patients with ≥1% PD-L1 expression) from the gain in median OS (Δ 1.58 vs. 2.86 months), when looking at the subgroup OS KM curves (**Figure 17**; although the difference appears to be driven by the control group curves with poorer outcome in patients with ≥1% PD-L1 expression), and when taking into account the subgroup analyses in the secondary endpoints ORR and PFS, see below. The MAH has included the OS results of the subgroup analysis by PD-L1 expression in section 5.1 of the SmPC. This is agreed and this issue is not pursued further.

Secondary endpoints – ORR, DCR, DoR and PFS. There was no support for the primary endpoint OS from the secondary endpoints ORR and PFS, only DoR numerically favoured nivolumab over control.

The **ORR** in the RES patient population was numerically higher in the control group than in the nivolumab group (21.5% vs. 19.3%; p=0.6323), also for the (very low) rate of complete responses (1.3% vs. 0.6). For **DCR**, the difference was even bigger (62.7% vs. 37.4). In contrast, **DoR** (median DoR 6.93 vs. 3.91 months) did numerically favour nivolumab over control.

The numerically longer TTR for the nivolumab group (median TTR 2.60 vs. 1.48 months for control) is as expected, given the delayed treatment effect of immunotherapy when compared to chemotherapy.

Because ORR did not pass the statistical boundary for significance, **PFS** was not formally tested. Nonetheless, mature PFS data (event rate nivolumab: 89.0%; control: 84.2%) numerically favoured control over nivolumab (HR = 1.08; median PFS 1.68 vs. 3.35 months). Here also, there was an early crossing of the KM PFS curves between 4 and 6 months, only afterwards favouring nivolumab with differences around 5%.

The sensitivity analysis using the secondary PFS definition (EMA preferred analysis) showed similar results to the analysis using the primary PFS definition.

The PFS subgroup analyses were unremarkable. For the few white patients, the subgroup of white patients is too small to base any conclusions. Regarding the PFS subgroup analysis by PD-L1 expression, again the unfavourable trend for nivolumab was more apparent in patients with PD-L1 expression <1% (than in patients with ≥1% PD-L1 expression, with PFS HRs of 1.30 and 0.90, respectively).

Other endpoints - health-related QoL. The MAH's presentation of the health-related QoL results in the dossier is rather brief when compared to in the published article on study ONO-4538-24 (Kato et al. 2019). It is (however) considered that the open-label study design, the exploratory nature of this endpoint, and the fact that the statistical analysis was post-hoc (see above) do not allow health-related QoL results to be considered in the benefit-risk assessment.

Special populations. *Elderly patients:* The OS subgroup analysis on age consistently favoured nivolumab over control across age categories, represented by a HR <1 (see **Figure 13**).

Proposed indication. The proposed indication is:

Oesophageal Squamous Cell Carcinoma (OSCC)

OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

The proposed indication adequately reflects the studied patient population and the wording is in line with the wording of the other, already approved indications for OPDIVO.

Extrapolation of data across regions

As very few white/non-Asian patients were included in the pivotal study, EMA guidance on multi-regional clinical trials and the extrapolation of foreign data should be taken into account (CPMP/ICH/289/95; EMEA/CHMP/EWP/692702/2008; EMA/CHMP/ICH/453276/2016 Rev.1).

The acceptability of the foreign (in this case Asian) clinical data component of the complete data package (in this case 95.7% of the ITT patient population) depends upon whether it can be extrapolated to the population of the new region (CPMP/ICH/289/95). There is a need to understand the differences and concerns that may arise in the extrapolation of study results to the EU population, and intrinsic as well as extrinsic factors are important to consider when extrapolating data obtained in a study population to the EU setting (EMEA/CHMP/EWP/692702/2008). Nevertheless, region can be an indicator for other, often unknown (or unanticipated) factors causing regional differences in treatment effects (EMA/CHMP/ICH/453276/2016 Rev.1). Therefore, multi-regional clinical trials are usually stratified by region and should be planned to include an evaluation of the consistency of treatment effects among regions (where consistency is defined as a lack of clinically relevant differences between treatment effects in different regions).

In the pivotal study, the MAH applied proportional allocation, i.e. facilitating recruitment by allocating patients to the regions with the greatest disease burden (Asia), thereby minimizing the time needed to complete enrolment. The disadvantage is that some regions may end up with too few or no patients, while other regions may dominate the outcome of the trial. This was clearly the case in study ONO-4538-24 with 95.7% Asian patients vs. 4.3% non-Asian patients. With equal allocation, i.e. allocation of equal numbers of patients to each region, or a balance between proportional and equal allocation, as is recommended in EMA guidance (EMA/CHMP/ICH/453276/2016 Rev.1), the MAH could have prevented the current uncertainty on extrapolation of data. In practical terms, the MAH could have alternatively used an approach with a fixed minimum number (or percentage) and/or with capping of the number (or percentage) of Asian patients to be enrolled.

MAH's view on extrapolation of data across regions. The MAH's effort to justify extrapolation of the efficacy (and safety) results from the Asian patient majority in the pivotal study to the EU patient minority, by discussing the different intrinsic and extrinsic factors, is acknowledged.

Based on the data provided it is agreed that PK is sufficiently comparable between Asian and non-Asian OSCC patients. Even though the disease and molecular biology of OSCC is not yet fully understood, the similarities in various molecular aspects of OSCC between Asian and non-Asian patients suggest that they could have similar underlying disease biology, while this notion is not unequivocally recognised, e.g. "*the biology … might substantially vary in different regions of the world*" (van Laarhoven. 2020; referencing Deng et al. 2017). Apart from the two primary *risk factors for OSCC* globally being tobacco smoking and alcohol overconsumption, some other risk factors for OSCC appear to be region specific and differences therein may contribute to the regional differences in OSCC incidence. Regarding the *possible effect of region on overall survival* in OSCC patients, there *does* appear to be evidence from two comparative observational studies hinting at better OS in (male) Asian patients when compared to (male) non-Asian patients upon immunotherapy (Zhang et al. 2015; Lin et al. 2015). Moreover, there is contemporary data that the effect of anti-PD-1 therapy on OS is greater in Asian patients with OSCC than in non-Asian patients (Smyth and Lordick. 2019; Keytruda - Withdrawal assessment report [EMEA/H/C/003820/II/0072]). The outcomes in advanced OSCC with *medical practice* SoC chemotherapy in scientific literature do not seem to differ across regions. Median OS in the so-called *real-world* studies does not appear to differ significantly, but the uncertain quality of RWD should be considered.

In summary, the scarce data available for the non-Asian patient population which severely hampered the extrapolation of data across regions, i.e. from the majority of Asian patients in the pivotal study to the

to-be-treated EU patient population in clinical practice. On this issue additional expert consultation has been requested and an Oral explanation with the company has taken place (see below outcome)

Additional expert consultation

A Scientific Advisory Group in Oncology (SAG-O) was asked to provide their view on the following question:

"*Does the SAG consider aetiology, biology and clinical characteristics, such as incidence, response to treatment and prognosis of the disease, in the European population and the Asian population sufficiently similar to justify an extrapolation of the OS benefit observed in the ONO-4538-24 study?*"

This SAG-O meeting was held on 07-Oct-2020 and the final minutes were as follows:

> A number of differences have been reported in terms of incidence, histology, risk factors, cancer biology, and cancer survival across regions or populations for oesophageal or other cancers. Some of such differences, may in theory be associated with higher or lower response to cancer immunotherapy (see for example, Deng et al, Nature Comm 2017). However, the SAG unanimously agreed that there are no strong data to support this hypothesis and that the factors associated with response to nivolumab in this setting are not well understood (see also below). In conclusion, the SAG agreed that there are no strong reasons in favour (or against) questioning that the effects associated with nivolumab in the ONO-4538-24 study can be generalised to the European population, at least in qualitative terms.
>
> Although a qualitative interaction seems unlikely, a quantitative difference cannot be excluded. In a meta-analysis, the efficacy of PD-L1 or PD-1 antibodies was higher in the Asian versus non-Asian cancer patients (Peng L, et al. Oncoimmunology. 2020). "A total of 11,020 cancer patients from 19 prospective randomised controlled clinical trials were included. The overall estimated HR for OS was 0.69 with 95% CI of 0.61–0.77 in Asian versus 0.82 with 95% CI of 0.77–0.88 in non-Asian patients. The estimated hazard ratio (HR) for PFS measured 0.54 (95% CI, 0.32–0.76) and 0.69 (95% CI, 0.54–0.85) in Asian and non-Asian patients, respectively." This meta-analysis shows for the first time that Asian cancer patients have a significantly improved survival benefit than non-Asian patients receiving PD-1/PD-L1 inhibitor-based therapy.
>
> In particular, looking at the results of trial ONO-4538-24, the SAG agreed that the magnitude of the effect in the subgroup of patients from US, Germany, Italy, and Denmark (n=18) could not be determined precisely due to the small number of patients (HR=0.53; 95%CI: 0.17; 1.65). Based on visual exploration of the survival curves, one cannot exclude that the effect on OS could overall be smaller compared to the rest of the trial population. A similar pattern has been observed for pembrolizumab, with a similar mechanism of action, in the same second-line metastatic setting based on the KN-181 study. Admittedly though, cross trial and product comparisons are difficult. Also, an adjuvant trial of nivolumab v. placebo did not show a smaller effect in the European population. However, two large studies in first line metastatic oesophageal and gastric cancers combining chemotherapy with or without either nivolumab (Checkmate 649) or pembrolizumab (Keynote 590) supported the benefit of the association in both Asians and Caucasians patients. (ESMO, September 2020; admitting the difficult to use abstracts as reference and cross-study comparisons in different settings.)
>
> The SAG also agreed that nivolumab was associated with a better toxicity profile compared to the control group receiving docetaxel or paclitaxel. Apart from the uncertainties about the precise magnitude of the benefit, the SAG agreed that there are no reasons to doubt generalisability of trial results in terms of benefits and harms to the European population purely on the basis of

geographic origin. However, some SAG members argued that remaining uncertainties would need to be resolved prior to approval (see below).

According to some SAG members, given the overall results compared to active control, the favourable toxicity profile compared to chemotherapy, the lack of reasons to suspect important qualitative differences in pharmacodynamic effects, the efficacy was considered convincing and relevant for the EU population.

However, some SAG members disagreed and considered that the lack of a clear improvement compared to chemotherapy (especially in PD-L1 negative patients that represent ~ 50% of the population and will most likely not profit from this treatment), as observed also with pembrolizumab, and the many other uncertainties about role of biomarkers, and most importantly, risk factors for early death associated with nivolumab monotherapy (early lack of efficacy vs chemo has been observed a number of times in the specific situation of mono-immuno vs chemotherapy), in the European population, and the unclear differences in magnitude of effects, question the benefit for non-Asian patients until these uncertainties are properly addressed.

The SAG generally regretted the very small proportion of patients from Europe included in the trial. Clearly, recruitment had not been carefully planned in this respect, to provide a better understanding of any quantitative differences. Furthermore, there is lack of comprehensive information about biomarkers associated with survival (including early deaths) that should ideally be studied using biopsies just before the start and over the course of treatment.

Thus in conclusion, the SAG agreed that there are no strong reasons to question that the effects observed with nivolumab in the pivotal study can be generalised to the European population, at least in qualitative terms, though a quantitative difference cannot be excluded. Whereas some SAG members disagreed, according to other SAG members the efficacy was thus considered convincing and relevant for the EU population.

Oral Explanation at the October 2020 CHMP meeting

During the Oral Explanation the MAH further discussed the uncertainty regarding the extrapolation of the study results to the European/non-Asian patient population. The MAH, among other, elaborated on the intrinsic and extrinsic factors and real world data (characteristics and outcomes across regions), see above. Furthermore, the MAH mentioned that key results from other clinical trials investigating anti-PD-1 therapies in oesophageal cancer have very recently become available, which provide proof of concept for efficacy of nivolumab across regions (e.g. Study CA209577 [NCT02743494; presentation at 2020 ESMO meeting].

2.4.3. Conclusions on the clinical efficacy

In the single pivotal study ONO-4538-24 (CA209473), treatment with nivolumab resulted in an OS benefit vs. chemotherapy control. However, only a few white/non-Asian patients were included in the study ((4.3% [18/419 randomized subjects]), which is considered a limitation of the study.

The intrinsic and extrinsic factors have been sufficiently discussed by the MAH. It should, however, be noted that even if there is somewhat limited information on this matter, the available data do not indicate that there are important differences between regions (Asian vs Western) that would hamper generalisation. However, importantly, the effect of anti-PD-1 therapy on OS could be smaller in non-Asian patients than in Asian patients. New data became available from other studies, and the MAH shared key data from Study CA209577 (nivolumab in the adjuvant setting) during the oral explanation. Preliminary results indicate proof of concept for efficacy of nivolumab in Western patients with OSCC. With this

information it is understood that the currently available results from Study ONO-4538-24 can be considered generalisable to Western patients, at least in qualitative terms.

Overall, based on the totality of data it is expected that Western patients with OSCC will also benefit from 2L nivolumab, albeit the magnitude of benefit in Western patients has not been fully established.

2.5. Clinical safety

Introduction

To date, nivolumab has been approved by the EC for the treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell cancer of the head and neck and urothelial carcinoma. The known safety profile of nivolumab is mostly characterized by immune-related reactions.

To support the addition of a new therapeutic indication, the MAH provided efficacy and safety data from study ONO-4538-24 (CA209473). The safety analysis was based on the safety set (SAF), which consisted of all patients given at least one dose of the investigational product (**Table 6**). At the 12-Nov-2018 data cut-off date, 417 of the 419 randomised patients (209 patients in the nivolumab group and 208 patients in the control group [65 patients in the docetaxel group and 143 patients in the paclitaxel group]) were administered at least one dose of the investigational product and were thus included in the SAF.

Patient exposure

The extent of exposure is summarized in Table 12.

Table 12 Extent of exposure and administration of study treatment - all treated ONO-4538-24 (CA209473) patients

Analysis Set : SAF

		Nivolumab	Control group		
			Total	Docetaxel	Paclitaxel
Analysis item (unit)		n (%)	n (%)	n (%)	n (%)
	N	209	208	65	143
Number of Dose Received (times)					
Mean (SD)		10.8 (11.7)	-	4.8 (4.1)	12.0 (10.4)
Median		6.0	-	3.0	10.0
Min - Max		1 - 60	-	1 - 22	1 - 75
Duration of Treatment (Months) [a]					
>6		54 (25.8)	24 (11.5)	6 (9.2)	18 (12.6)
>12		21 (10.0)	7 (3.4)	3 (4.6)	4 (2.8)
Mean (SD)		4.89 (5.90)	3.33 (3.31)	2.92 (3.32)	3.51 (3.31)
Median		2.56	2.56	2.10	2.79
Min - Max		0.0 - 29.2	0.0 - 21.4	0.0 - 18.9	0.0 - 21.4
Number of Cycle [b]					
1		59 (28.2)	48 (23.1)	4 (6.2)	44 (30.8)
2 - <=3		73 (34.9)	99 (47.6)	29 (44.6)	70 (49.0)
4 - <=6		42 (20.1)	44 (21.2)	20 (30.8)	24 (16.8)
>=7		35 (16.7)	17 (8.2)	12 (18.5)	5 (3.5)
Mean (SD)		4.1 (4.2)	3.3 (3.0)	4.8 (4.1)	2.6 (1.9)
Median		2.0	3.0	3.0	2.0
Min - Max		1 - 20	1 - 22	1 - 22	1 - 13
Cumulative Dose (mg, mg/m^2) [c]					
Mean (SD)		2585.148 (2816.066)	-	303.491 (240.131)	1039.129 (856.917)
Median		1440.000	-	224.988	863.905
Min - Max		240.00 - 14400.00	-	72.49 - 1215.10	94.27 - 6578.86
Relative Dose Intensity (%) [d]					
<50		0	7 (3.4)	0	7 (4.9)
50 - <70		2 (1.0)	51 (24.5)	10 (15.4)	41 (28.7)
70 - <90		33 (15.8)	84 (40.4)	30 (46.2)	54 (37.8)
90 - <110		173 (82.8)	66 (31.7)	25 (38.5)	41 (28.7)
>=110		1 (0.5)	0	0	0
Mean (SD)		95.42 (7.78)	80.00 (16.25)	84.65 (13.52)	77.89 (16.97)
Median		100.00	80.53	86.64	77.61
Min - Max		63.8 - 112.0	43.8 - 107.7	50.4 - 104.0	43.8 - 107.7

a) Duration of Treatment (Months)=("Date of the last dose" - "Date of the first dose" +1)/30.4375

b) The number of cycle will be calculated for the cycle proceeding to the next cycle. The discontinued cycle or the cycle receiving no investigational product also will be calculated.
Each treatment cycle consists of following weeks.
Nivolumab : 6 weeks.
Docetaxel : 3weeks.
Paclitaxel : 6 weeks administered and 2 weeks rested.

SAF: Safety

Dose modifications and interruptions

Six patients in the nivolumab group (2.9%) experienced at least 1 infusion interruption vs. 10 in the control group (4.8%); see Table 13. Reasons for infusion interruptions included AE (4 patients) and 'other' (2 patients) in the nivolumab group. No patients in the nivolumab group experienced an infusion rate reduction. Fewer patients in the nivolumab group (41.6%) experienced dose delay than in the control group (63.9%). Most patients with dose delay experienced only 1 delay (23.4% and 29.8% in the nivolumab and control groups, respectively). AEs leading to dose delay were reported in 27.3% of patients in the nivolumab group and 57.7% of patients in the control group.

Table 13 Infusion interruption, infusion rate reduction, and dose delay of study therapy - all treated ONO-4538-24 (CA209473) patients

	Nivolumab N = 209	Control N = 208
PATIENTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	6 (2.9)	10 (4.8)
NUMBER OF INFUSION INTERRUPTED PER PATIENT (%)		
0	203 (97.1)	198 (95.2)
1	6 (2.9)	9 (4.3)
2	0	1 (0.5)
3	0	0
>=4	0	0
TOTAL NUMBER DOSE INTERRUPTED/ TOTAL NUMBER DOSE RECEIVED (%)	6/2252 (0.3)	11/2027 (0.5)
REASON FOR INFUSION INTERRUPTION (%) (A)		
ADVERSE EVENT	4 (66.7)	9 (81.8)
OTHER	2 (33.3)	2 (18.2)
PATIENTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	0	129 (62.0)
NUMBER OF INFUSIONS WITH IV RATE REDUCTION PER PATIENT (%)		
0	209 (100.0)	79 (38.0)
1	0	78 (37.5)
2	0	50 (24.0)
3	0	0
>=4	0	1 (0.5)
TOTAL NUMBER IV RATE REDUCED/ TOTAL NUMBER DOSE RECEIVED (%)	0/2252	182/2027 (9.0)
REASON FOR IV RATE REDUCTION (%) (B)		
ADVERSE EVENT	0	153 (84.1)
OTHER	0	28 (15.4)
NOT REPORTED	0	1 (0.5)
PATIENTS WITH AT LEAST ONE DOSE DELAYED (%) (C)	87 (41.6)	133 (63.9)
NUMBER OF DOSE DELAY PER PATIENT (%) (C)		
0	122 (58.4)	75 (36.1)
1	49 (23.4)	62 (29.8)
2	16 (7.7)	25 (12.0)
3	8 (3.8)	21 (10.1)
>=4	14 (6.7)	25 (12.0)
TOTAL NUMBER DOSE DELAYED/ TOTAL NUMBER DOSE RECEIVED (%) (D)	184/2043 (9.0)	328/1819 (18.0)
LENGTH OF DELAY (%) (E)		
4-<8 DAYS	109 (59.2)	227 (69.2)
8-<15 DAYS	44 (23.9)	73 (22.3)
15-<42 DAYS	26 (14.1)	28 (8.5)
>= 42 DAYS	5 (2.7)	0

(A) Percentages are computed out of the total number of Dose Interrupted.
(B) Percentages are computed out of the total number of infusions with IV rate reduction.
(C) A dose was considered as actually delayed if the delay is exceeding 3 days. Based on calculated dose delay. No reason collected in CRF.
(D) TOTAL NUMBER DOSE RECEIVED is excluding first dose.
(E) Percentages are computed out of the total number of Dose Delayed.

Adverse events

A summary of AEs is presented in Table 14.

Table 14 Summary of adverse events

Analysis Set : SAF

		Nivolumab			Control group		
		Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	N	209	209	209	208	208	208
Number of subjects with AEs		189 (90.4)	80 (38.3)	7 (3.3)	205 (98.6)	147 (70.7)	5 (2.4)
Number of subjects with SAEs		68 (32.5)	43 (20.6)	7 (3.3)	77 (37.0)	63 (30.3)	5 (2.4)
Number of subjects with AEs leading to discontinuation of study treatment		29 (13.9)	11 (5.3)	5 (2.4)	33 (15.9)	22 (10.6)	4 (1.9)
Number of subjects with AEs leading to dose delay		57 (27.3)	33 (15.8)	0	120 (57.7)	90 (43.3)	0
Number of subjects with AEs leading to dose reduction		0	0	0	77 (37.0)	38 (18.3)	0
Number of subjects with drug-related AEs [a)]		137 (65.6)	38 (18.2)	0	198 (95.2)	131 (63.0)	2 (1.0)
Number of subjects with drug-related SAEs [a)]		33 (15.8)	20 (9.6)	0	47 (22.6)	39 (18.8)	2 (1.0)
Number of subjects with drug-related AEs leading to discontinuation of study treatment [a)]		18 (8.6)	8 (3.8)	0	19 (9.1)	12 (5.8)	1 (0.5)
Number of subjects with drug-related AEs leading to dose delay [a)]		34 (16.3)	15 (7.2)	0	104 (50.0)	81 (38.9)	0
Number of subjects with drug-related AEs leading to dose reduction [a)]		0	0	0	75 (36.1)	37 (17.8)	0

AEs, drug-related AEs occurring between the start date of the first administration of the investigational product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.

a) Drug-related AEs were defined as any AEs with causal relationship with the investigational product is "Related" or missing.

All causality AEs

Any grade

AEs were reported in 90.4% (189 patients) in the nivolumab group and 98.6% (205 patients) in the control group. Common AEs (incidence ≥5%) at PT level are summarized in **Table 15**.

AEs with a higher incidence in the nivolumab group than in the control group (difference ≥5%) were hypothyroidism (10.0% [nivolumab] vs. 1.4% [control]) and pruritus (12.4% vs. 7.2%).

AEs with a lower incidence in the nivolumab group than in the control group (difference ≥5%) were alopecia (1.4% [nivolumab] vs. 48.1% [control]), neutrophil count decreased (1.4% vs. 37.0%), white blood cell count decreased (1.0% vs. 34.6%), peripheral sensory neuropathy (0.5% vs. 23.1%), neutropenia (0.5% vs. 19.2%), malaise (6.2% vs. 24.0%), anaemia (12.4% vs. 29.3%), fatigue (9.6% vs. 25.0%), decreased appetite (20.6% vs. 34.6%), neuropathy peripheral (0% vs. 11.1%), febrile neutropenia (0% vs. 10.6%), stomatitis (3.3% vs. 12.5%), nausea (11.0% vs. 19.7%), leukopenia (0% vs. 8.7%), myalgia (2.9% vs. 10.6%), lymphocyte count decreased (2.4% vs. 10.1%), arthralgia (4.8% vs. 12.0%), and rash (12.4% vs. 19.2%).

Grade 3-4

Grade 3-4 AEs were reported in 38.3% and 70.7% of patients in the nivolumab and control groups, respectively.

- In the nivolumab group, the only common grade 3-4 AE (incidence ≥5%) was anaemia (8.1%).
- In the control group, common grade 3-4 AEs (incidence ≥5%) were neutrophil count decreased (28.4%), white blood cell count decreased (22.1%), neutropenia (13.9%), anaemia (11.5%), febrile neutropenia (10.6%), lymphocyte count decreased (7.2%), leukopenia (6.7%), and decreased appetite (5.3%).

Table 15 Summary of any (all causality) adverse events by worst CTC grade with 5% cut-off - all treated patients ONO-4538-24 (CA209473)

	AEs					
	Nivolumab			Control		
SOC	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
PT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
N	209	209	209	208	208	208
Total	**189 (90.4)**	**80 (38.3)**	**7 (3.3)**	**205 (98.6)**	**147 (70.7)**	**5 (2.4)**
Gastrointestinal disorders	96 (45.9)	10 (4.8)	0	116 (55.8)	11 (5.3)	0
Diarrhoea	37 (17.7)	3 (1.4)	0	36 (17.3)	3 (1.4)	0
Constipation	35 (16.7)	0	0	40 (19.2)	0	0
Nausea	23 (11.0)	0	0	41 (19.7)	1 (0.5)	0
Dysphagia	15 (7.2)	5 (2.4)	0	5 (2.4)	3 (1.4)	0
Abdominal pain	12 (5.7)	2 (1.0)	0	10 (4.8)	3 (1.4)	0
Vomiting	12 (5.7)	0	0	19 (9.1)	1 (0.5)	0
Stomatitis	7 (3.3)	1 (0.5)	0	26 (12.5)	1 (0.5)	0
General disorders and administration site conditions	63 (30.1)	5 (2.4)	0	121 (58.2)	10 (4.8)	0
Pyrexia	33 (15.8)	1 (0.5)	0	38 (18.3)	1 (0.5)	0
Fatigue	20 (9.6)	2 (1.0)	0	52 (25.0)	9 (4.3)	0
Chest pain	13 (6.2)	2 (1.0)	0	4 (1.9)	0	0
Malaise	13 (6.2)	0	0	50 (24.0)	0	0
Metabolism and nutrition disorders	51 (24.4)	16 (7.7)	0	82 (39.4)	24 (11.5)	0
Decreased appetite	43 (20.6)	4 (1.9)	0	72 (34.6)	11 (5.3)	0
Hypercalcaemia	14 (6.7)	9 (4.3)	0	9 (4.3)	3 (1.4)	0
Hyponatraemia	5 (2.4)	3 (1.4)	0	11 (5.3)	10 (4.8)	0
Skin and subcutaneous tissue disorders	49 (23.4)	1 (0.5)	0	119 (57.2)	2 (1.0)	0
Pruritus	26 (12.4)	0	0	15 (7.2)	0	0
Rash	26 (12.4)	1 (0.5)	0	40 (19.2)	2 (1.0)	0
Alopecia	3 (1.4)	0	0	100 (48.1)	0	0
Infections and infestations	46 (22.0)	8 (3.8)	2 (1.0)	54 (26.0)	16 (7.7)	2 (1.0)
Pneumonia	17 (8.1)	5 (2.4)	2 (1.0)	23 (11.1)	9 (4.3)	2 (1.0)
Upper respiratory tract infection	16 (7.7)	1 (0.5)	0	13 (6.3)	0	0
Nasopharyngitis	13 (6.2)	0	0	9 (4.3)	0	0
Lung infection	6 (2.9)	2 (1.0)	0	13 (6.3)	7 (3.4)	0
Respiratory, thoracic and mediastinal disorders	43 (20.6)	3 (1.4)	0	34 (16.3)	1 (0.5)	0
Cough	32 (15.3)	0	0	25 (12.0)	1 (0.5)	0
Dyspnoea	15 (7.2)	3 (1.4)	0	9 (4.3)	0	0
Investigations	36 (17.2)	11 (5.3)	0	110 (52.9)	74 (35.6)	0
Aspartate aminotransferase increased	13 (6.2)	2 (1.0)	0	7 (3.4)	0	0

Table 15 Summary of any (all causality) adverse events by worst CTC grade with 5% cut-off - all treated patients ONO-4538-24 (CA209473)

	AEs					
	Nivolumab			Control		
SOC	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
PT	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
N	209	209	209	208	208	208
Alanine aminotransferase increased	11 (5.3)	2 (1.0)	0	7 (3.4)	1 (0.5)	0
Weight decreased	11 (5.3)	2 (1.0)	0	11 (5.3)	1 (0.5)	0
Lymphocyte count decreased	5 (2.4)	3 (1.4)	0	21 (10.1)	15 (7.2)	0
Neutrophil count decreased	3 (1.4)	1 (0.5)	0	77 (37.0)	59 (28.4)	0
White blood cell count decreased	2 (1.0)	1 (0.5)	0	72 (34.6)	46 (22.1)	0
Blood and lymphatic system disorders	27 (12.9)	17 (8.1)	0	99 (47.6)	65 (31.3)	0
Anaemia	26 (12.4)	17 (8.1)	0	61 (29.3)	24 (11.5)	0
Neutropenia	1 (0.5)	0	0	40 (19.2)	29 (13.9)	0
Febrile neutropenia	0	0	0	22 (10.6)	22 (10.6)	0
Leukopenia	0	0	0	18 (8.7)	14 (6.7)	0
Endocrine disorders	21 (10.0)	0	0	3 (1.4)	0	0
Hypothyroidism	21 (10.0)	0	0	3 (1.4)	0	0
Musculoskeletal and connective tissue disorders	14 (6.7)	0	0	42 (20.2)	2 (1.0)	0
Arthralgia	10 (4.8)	0	0	25 (12.0)	1 (0.5)	0
Myalgia	6 (2.9)	0	0	22 (10.6)	1 (0.5)	0
Psychiatric disorders	11 (5.3)	0	0	13 (6.3)	0	0
Insomnia	11 (5.3)	0	0	13 (6.3)	0	0
Nervous system disorders	6 (2.9)	0	0	80 (38.5)	2 (1.0)	0
Dysgeusia	5 (2.4)	0	0	14 (6.7)	0	0
Peripheral sensory neuropathy	1 (0.5)	0	0	48 (23.1)	1 (0.5)	0
Neuropathy peripheral	0	0	0	23 (11.1)	1 (0.5)	0

MedDRA version 21.1. CTCAE version 4.0.

AEs and drug-related AEs occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.

Drug-related AEs were defined as any AEs with causal relationship with the product "Related" or missing.
Source: Table 14.3.1.1.9-1 in the ONO-4538-24 (CA209473) final CSR

Drug-related AEs

Any grade

Drug-related AEs were reported in 65.6% (137 patients) in the nivolumab group and 95.2% (198 patients) in the control group. Common drug-related AEs (incidence ≥5%) at PT level are summarized in **Table 16**.

The drug-related AE PT with a higher incidence in the nivolumab group than in the control group (difference ≥5%) was hypothyroidism (8.1% [nivolumab] vs. 0.5% [control]).

Drug-related AEs with a lower incidence in the nivolumab group than in the control group (difference ≥5%) were alopecia (1.4% vs. 47.1%), neutrophil count decreased (1.4% vs. 36.5%), white blood cell count decreased (1.0% vs. 34.6%), peripheral sensory neuropathy (0.5% vs. 22.6%), anaemia (2.4% vs. 23.6%), decreased appetite (7.7% vs. 26.9%), neutropenia (0.5% vs. 19.2%), malaise (4.3% vs. 21.6%), nausea (1.9% vs. 16.3%), fatigue (7.2% vs. 20.7%), febrile neutropenia (0% vs. 10.6%), neuropathy peripheral (0% vs. 10.6%), stomatitis (2.4% vs. 12.0%), arthralgia (1.4% vs. 10.1%), leukopenia (0% vs. 8.2%), myalgia (1.4% vs. 8.7%), lymphocyte count decreased (1.9% vs. 8.7%), vomiting (0.5% vs. 6.7%), constipation (1.9% vs. 7.7%), and dysgeusia (1.4% vs. 6.7%).

Plots showing the comparison of drug-related AEs (≥5% of any grade) between the nivolumab group and total chemotherapy group, and nivolumab vs. either the docetaxel or paclitaxel group are provided **Figure 20** and **Figure 21** respectively.

Grade 3-4

Fewer drug-related grade 3-4 AEs were reported in the nivolumab group (18.2%) than in the control group (63.0%).

- In the nivolumab group, no grade 3-4 drug-related AEs occurred with incidence ≥5%.
- In the control group, common grade 3-4 drug-related AEs (incidence ≥5%) were neutrophil count decreased (28.4%), white blood cell count decreased (22.1%), neutropenia (13.9%), anaemia (9.1%), febrile neutropenia (10.6%), lymphocyte count decreased (5.8%), and leukopenia (6.7%)

Table 16 Summary of drug-related adverse events by worst CTC grade with 5% cut-off - all treated ONO-4538-24 (CA209473) patients

		AEs					
		Nivolumab			Control		
SOC		Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
PT		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	N	209	209	209	208	208	208
Total		**137 (65.6)**	**38 (18.2)**	**0**	**198 (95.2)**	**123 (63.0)**	**2 (1.0)**
Skin and subcutaneous tissue disorders		37 (17.7)	1 (0.5)	0	112 (53.8)	2 (1.0)	0
Rash		23 (11.0)	1 (0.5)	0	31 (14.9)	2 (1.0)	0
Pruritus		17 (8.1)	0	0	11 (5.3)	0	0
Alopecia		3 (1.4)	0	0	98 (47.1)	0	0
Gastrointestinal disorders		33 (15.8)	3 (1.4)	0	76 (36.5)	4 (1.9)	0
Diarrhoea		22 (10.5)	2 (1.0)	0	20 (9.6)	2 (1.0)	0
Stomatitis		5 (2.4)	1 (0.5)	0	25 (12.0)	1 (0.5)	0
Constipation		4 (1.9)	0	0	16 (7.7)	0	0
Nausea		4 (1.9)	0	0	34 (16.3)	1 (0.5)	0
Vomiting		1 (0.5)	0	0	14 (6.7)	1 (0.5)	0
General disorders and administration site conditions		33 (15.8)	2 (1.0)	0	94 (45.2)	9 (4.3)	0
Fatigue		15 (7.2)	1 (0.5)	0	43 (20.7)	9 (4.3)	0
Pyrexia		15 (7.2)	1 (0.5)	0	17 (8.2)	0	0
Malaise		9 (4.3)	0	0	45 (21.6)	0	0
Endocrine disorders		17 (8.1)	0	0	1 (0.5)	0	0
Hypothyroidism		17 (8.1)	0	0	1 (0.5)	0	0
Metabolism and nutrition disorders		16 (7.7)	2 (1.0)	0	56 (26.9)	10 (4.8)	0
Decreased appetite		16 (7.7)	2 (1.0)	0	56 (26.9)	10 (4.8)	0
Investigations		8 (3.8)	4 (1.9)	0	101 (48.6)	70 (33.7)	0

Lymphocyte count decreased	4 (1.9)	2 (1.0)	0	18 (8.7)	12 (5.8)	0
Neutrophil count decreased	3 (1.4)	1 (0.5)	0	76 (36.5)	59 (28.4)	0
White blood cell count decreased	2 (1.0)	1 (0.5)	0	72 (34.6)	46 (22.1)	0
Blood and lymphatic system disorders	6 (2.9)	4 (1.9)	0	88 (42.3)	61 (29.3)	0
Anaemia	5 (2.4)	4 (1.9)	0	49 (23.6)	19 (9.1)	0
Neutropenia	1 (0.5)	0	0	40 (19.2)	29 (13.9)	0
Febrile neutropenia	0	0	0	22 (10.6)	22 (10.6)	0
Leukopenia	0	0	0	17 (8.2)	14 (6.7)	0
Musculoskeletal and connective tissue disorders	5 (2.4)	0	0	34 (16.3)	2 (1.0)	0
Arthralgia	3 (1.4)	0	0	21 (10.1)	1 (0.5)	0
Myalgia	3 (1.4)	0	0	18 (8.7)	1 (0.5)	0
Nervous system disorders	4 (1.9)	0	0	78 (37.5)	2 (1.0)	0
Dysgeusia	3 (1.4)	0	0	14 (6.7)	0	0
Peripheral sensory neuropathy	1 (0.5)	0	0	47 (22.6)	1 (0.5)	0
Neuropathy peripheral	0	0	0	22 (10.6)	1 (0.5)	0
Infections and infestations	3 (1.4)	1 (0.5)	0	11 (5.3)	6 (2.9)	0
Lung infection	3 (1.4)	1 (0.5)	0	11 (5.3)	6 (2.9)	0

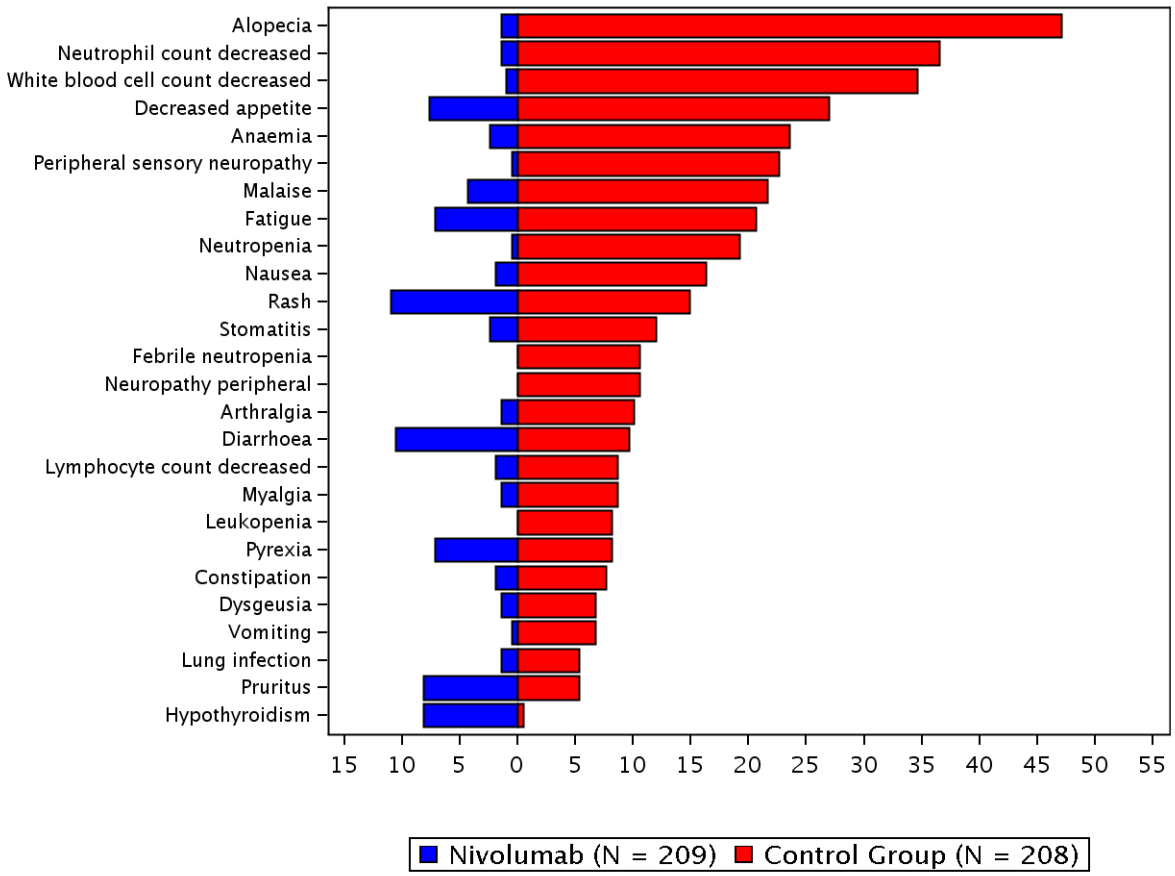
MedDRA version 21.1. CTCAE version 4.0.

AEs and drug-related AEs occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.

Drug-related AEs were defined as any AEs with causal relationship with the product "Related" or missing.

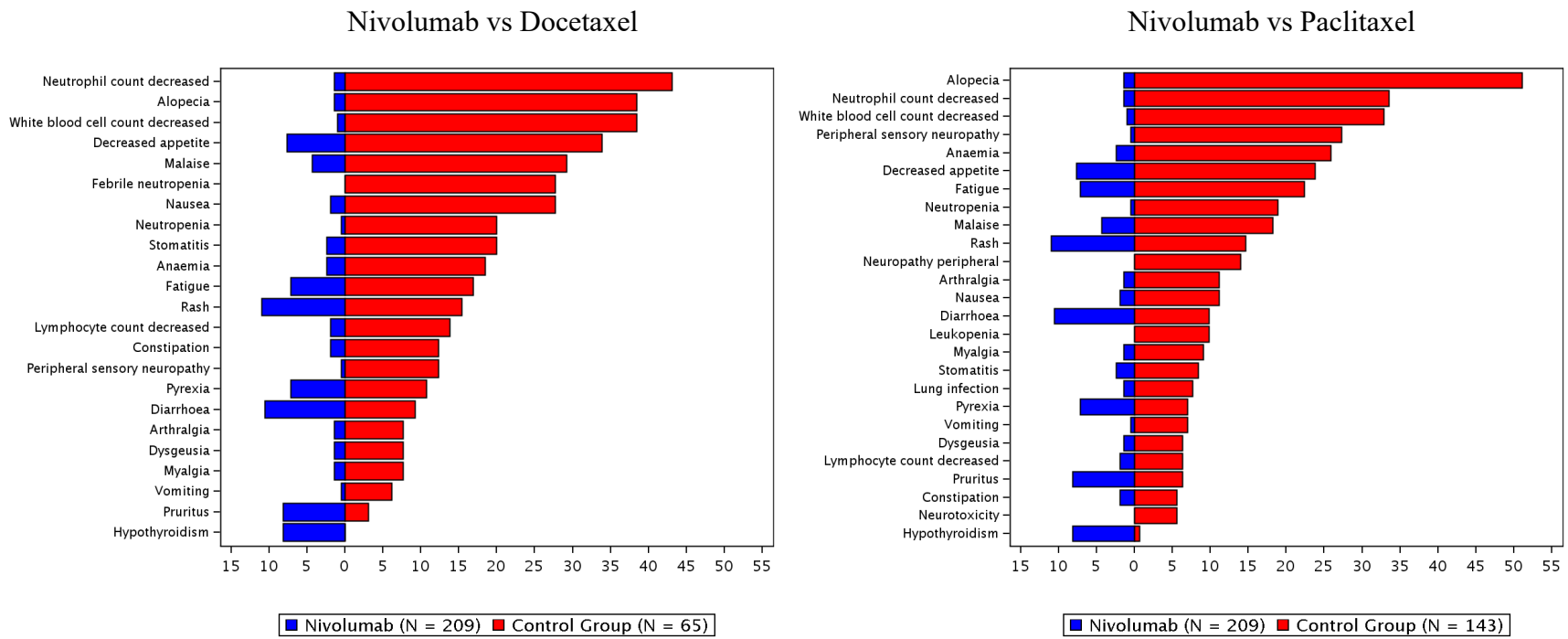
Source: Table 14.3.1.1.9-4 in the ONO-4538-24 (CA209473) final CSR

Figure 20 Bar graph of any grade drug-related adverse events – with incidence rate ≥5% - all treated patients



MedDRA Version: 21.1, CTC Version 4.0
Includes events reported between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.
Drug-related AEs were defined as any AEs with causal relationship with the product is ``Related`` or missing.

Figure 21 Bar graph of any grade drug-related adverse events - with incidence rate ≥5% - All treated with nivolumab or chemotherapy patients



MedDRA Version: 21.1, CTC Version 4.0
Includes events reported between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.
Drug-related AEs were defined as any AEs with causal relationship with the product is =Related or missing.
Source: Figure 5.3.1 (nivolumab vs docetaxel) and Figure 5.4.1 (nivolumab vs paclitaxel) in Appendix 2

Select adverse events

In order to characterize AEs of special clinical interest, which are potentially associated with the use of nivolumab, the MAH identified select AEs based on the following 4 guiding principles:

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

Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each of these were grouped into endocrine, GI, hepatic, pulmonary, renal, skin and hypersensitivity/infusion reaction select AE categories, respectively.

Endocrine events

Endocrine select AEs were reported in 28 patients (13.4%) in the nivolumab group and 5 patients (2.4%) in the control group. Grade 3-4 endocrine select AEs (all-causality) were reported in 0 and 1 patient (0.5%) in the nivolumab and control groups, respectively. The most commonly reported all-causality endocrine select AE in the nivolumab group was hypothyroidism (21 patients, 10.0%), followed by hyperthyroidism (3 patients, 1.4%), blood thyroid stimulating hormone increased (2 patients, 1.0%), diabetes mellitus (1 patient, 0.5%), and hypopituitarism (1 patient, 0.5%). All-causality endocrine select AEs reported in the control group were hypothyroidism (3 patients, 1.4%) and diabetes mellitus (2 patients, 1.0%).

Drug-related endocrine select AEs were reported in 23 patients (11.0%) in the nivolumab group and 1 patient (0.5%) in the control group (**Table 17**).The most commonly reported drug-related endocrine AE in the nivolumab group was hypothyroidism (17 patients, 8.1%), followed by hyperthyroidism (3 patients, 1.4%), blood thyroid stimulating hormone increased (2 patients, 1.0%), and hypopituitarism (1 patient, 0.5%). The only drug-related endocrine select AE in the control group was hypothyroidism (1 patient). No grade 3-4 drug-related endocrine select AEs were reported in either group.

In the nivolumab group, the median time to onset of drug-related endocrine AEs was 17.57 weeks (**Table 17**). Two patients were treated with IMM for a median duration of 32.14 weeks. Overall, 6 of the 23 nivolumab treated patients with drug-related endocrine select AEs had resolution of the event; the median time to resolution was not reached (range 1.7+ to 104.9+ weeks). Fourteen patients with drug-related endocrine select AEs were treated with hormone replacement therapy. These AEs did not resolve by the time of data cut-off.

Endocrine select AEs leading to discontinuation of study treatment were reported in 2 patients in the nivolumab group and 0 patient in the control group. The only endocrine select AE leading to discontinuation of study treatment by PT reported in the nivolumab group was hypothyroidism (1.0%, 2 patients). All of the endocrine select AEs leading to discontinuation of study treatment reported in the nivolumab group were drug-related.

Table 17 Summary of drug-related endocrine select adverse events by worst CTC grade reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) patients

Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Treatment Group: Nivolumab 240mg N = 209							
TOTAL PATIENTS WITH AN EVENT	11 (5.3)	12 (5.7)	0	0	0	0	23 (11.0)
THYROID DISORDER	11 (5.3)	11 (5.3)	0	0	0	0	22 (10.5)
Hypothyroidism	7 (3.3)	10 (4.8)	0	0	0	0	17 (8.1)
Hyperthyroidism	2 (1.0)	1 (0.5)	0	0	0	0	3 (1.4)
Blood thyroid stimulating Hormone increased	2 (1.0)	0	0	0	0	0	2 (1.0)
PITUITARY DISORDER	0	1 (0.5)	0	0	0	0	1 (0.5)
Hypopituitarism	0	1 (0.5)	0	0	0	0	1 (0.5)
Treatment Group: Control N = 208							
TOTAL PATIENTS WITH AN EVENT	1 (0.5)	0	0	0	0	0	1 (0.5)
THYROID DISORDER	1 (0.5)	0	0	0	0	0	1 (0.5)
Hypothyroidism	1 (0.5)	0	0	0	0	0	1 (0.5)

MedDRA Version: 21.1; CTC Version 4.0
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.

Table 18 Onset, treatment, and resolution of drug-related endocrine select adverse events reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) patients

	Nivolumab 240mg		Control	
Category: ENDOCRINE ADVERSE EVENT	Any Grade N = 23	Grade 3-5 N = 0	Any Grade N = 1	Grade 3-5 N = 0
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	17.57 (4.0-61.3)	N.A. (N.A.-N.A.)	32.57 (32.6-32.6)	N.A. (N.A.-N.A.)
PATIENTS WHO RECEIVED IMMUNE MODULATING MEDICATION(A) (%)	2/23 (8.7)	N.A.	0/1	N.A.
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	32.14 (0.9-63.4)			
PATIENTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	2 (8.7)			
NUMBER OF PATIENTS WHO RESOLVED (%)	6 (26.1)	0	1 (100.0)	0
TIME TO RESOLUTION (WEEKS)				
MEDIAN(B) (95% CI)	N.A. (20.14 - N.A.)		2.00 (N.A. - N.A.)	
RANGE(C) (MIN - MAX)	1.7+ - 104.9+		2.0 - 2.0	

MedDRA Version: 21.1
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.
Drug-related AEs were defined as any AEs with causal relationship with the product is "related" or missing.
Select AEs are defined in the SAP (Appendix 16.1.9) for analyses from the ONO-4538-24 (CA209473) final CSR.
Select AEs are defined in Appendix E.141a-EUSCS in Appendix 2 for BMS-generated analyses (analyses from an integrated database).
(A) Denominator is based on the number of patients who experienced the event.
(B) This estimation was conducted by using the Kaplan-Meier method. The CI was calculated using the Brookmeyer and Crowley method based on a log-log transformed CI for the survivor function.
(C) Symbol + indicates a censored value.

Immune-related endocrinopathies in the pooled safety analysis

In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 9.7% (270/2787). The majority of cases were Grade 1 or 2 in severity reported in 4.2% (118/2787) and 5.4% (150/2787) of patients, respectively. Grade 3 thyroid disorders were reported in < 0.1% (2/2787) of patients. Hypophysitis (1 Grade 1, 2 Grade 2, 5 Grade 3, and 1 Grade 4), hypopituitarism (5 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency) (1 Grade 1, 9 Grade 2, and 5 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus) (3 Grade 2 and 1 Grade 3), and diabetic ketoacidosis (2 Grade 3) were reported. No Grade 5 cases were reported in these studies. Median time to onset of these endocrinopathies was 2.8 months (range: 0.3-29.1). Resolution occurred in 123 patients (41.6%). Time to resolution ranged from 0.4 to 144.1+ weeks.

Gastrointestinal (GI) events

GI select AEs (all-causality, any grade) were reported in 38 patients (18.2%) in the nivolumab group and 36 patients (17.3%) in the control group. Grade 3-4 GI select AEs (all causality) were reported in 4 (1.9%) nivolumab and 3 (1.4%) control treated patients, respectively. The most commonly reported all causality GI select AE in the nivolumab group was diarrhoea (37 patients, 17.7%), followed by colitis (1 patient). The only reported all causality GI select AE in the control group was diarrhoea (36 patients).

Drug-related GI select AEs were reported in 22 patients (10.5%) and 20 patients (9.6%) in the nivolumab and control groups, respectively (**Table 19**). The only reported drug-related GI select AE in each group was diarrhoea. Drug-related grade 3-4 GI select AEs were reported in 2 patients (1.0%) in the nivolumab group and 2 patients (1.0%) the control group.

GI select AEs leading to discontinuation of study treatment were reported in 1 patient (0.5%) in each the nivolumab group and the control group (both events diarrhoea and considered drug-related).

In the nivolumab group, the median time to onset of drug-related GI select AE (any grade) was 6.00 weeks (**Table 20**). Four patients were treated with IMM for a median duration of 2.29 weeks, with 2 of these treated with high-dose corticosteroids. Overall, 15 of the 22 patients with drug related GI select AEs had resolution of the event, with a median time to resolution of 8.00 (95% CI: 1.57, 63.86) weeks.

Table 19 Summary of drug-related GI select adverse events by worst CTC grade reported up to 28 days after Last Dose - all treated ONO-4538-24 (CA209473) patients

Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Treatment Group: Nivolumab 240mg N = 209							
TOTAL PATIENTS WITH AN EVENT	10 (4.8)	10 (4.8)	2 (1.0)	0	0	0	22 (10.5)
DIARRHOEA	10 (4.8)	10 (4.8)	2 (1.0)	0	0	0	22 (10.5)
Treatment Group: Control N = 208							
TOTAL PATIENTS WITH AN EVENT	15 (7.2)	3 (1.4)	2 (1.0)	0	0	0	20 (9.6)
DIARRHOEA	15 (7.2)	3 (1.4)	2 (1.0)	0	0	0	20 (9.6)

MedDRA Version: 21.1; CTC Version 4.0
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.

Table 20 Onset, treatment, and resolution of drug-related GI select adverse events reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) Patients

	Nivolumab 240mg		Control	
Category: GASTROINTESTINAL ADVERSE EVENT	Any Grade N = 22	Grade 3-5 N = 2	Any Grade N = 20	Grade 3-5 N = 2
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	6.00 (0.3 - 43.6)	21.93 (0.3 - 43.6)	1.50 (0.1 - 15.7)	5.14 (0.7 - 9.6)
PATIENTS WHO RECEIVED IMMUNE MODULATING MEDICATION(A) (%)	4/22 (18.2)	1/2 (50.0)	0/20	0/2
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	2.29 (0.3-8.7)	8.71 (8.7-8.7)		
PATIENTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	2 (9.1)	1 (50.0)		
NUMBER OF PATIENTS WHO RESOLVED (%)	15 (68.2)	2 (100.0)	20 (100.0)	2 (100.0)
TIME TO RESOLUTION (WEEKS)				
MEDIAN(B) (95% CI)	8.00 (1.57 - 63.86)	5.71 (0.71 - 10.71)	0.79 (0.29 - 1.71)	1.07 (0.43 - 1.71)
RANGE(C) (MIN - MAX)	0.1 - 111.3+	0.7 - 10.7	0.1 - 19.4	0.4 - 1.7

MedDRA Version: 21.1
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.
Drug-related AEs were defined as any AEs with causal relationship with the product is "related" or missing.
Select AEs are defined in the SAP (Appendix 16.1.9) for analyses from the ONO-4538-24 (CA209473) final CSR.
Select AEs are defined in Appendix E.141a-EUSCS in Appendix 2 for BMS-generated analyses (analyses from an integrated database).
(A) Denominator is based on the number of patients who experienced the event.
(B) This estimation was conducted by using the Kaplan-Meier method. The CI was calculated using the Brookmeyer and Crowley method based on a log-log transformed CI for the survivor function.
(C) Symbol + indicates a censored value.

Immune-related colitis in the pooled analysis

In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 13% (361/2787). The majority of cases were Grade 1 or 2 in severity reported in 8.3% (230/2787) and 3.2% (88/2787) of patients respectively. Grade 3 cases were reported in 1.5% (43/2787) of patients. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.8 months (range: 0.0-26.6). Resolution occurred in 311 patients (86.9%) with a median time to resolution of 2.1 weeks (range: 0.1-124.4+).

Hepatic events

Hepatic select AEs (all-causality, any grade) were reported in 26 patients (12.4%) in the nivolumab group and 14 patients (6.7%) in the control group. Grade 3-4 hepatic select AEs (all-causality) were reported in 7 patients (3.3%) in the nivolumab group and 5 patients (2.4%) in the control group. The most commonly reported all-causality hepatic select AE in the nivolumab group was AST increased (13 patients, 6.2%), followed by ALT increased (11 patients, 5.3%). The most commonly reported all causality hepatic select AEs in the control group were ALT increased (7 patients, 3.4%) and AST increased (7 patients, 3.4%), followed by gamma-glutamyltransferase increased (6 patients, 2.9%).

Drug-related hepatic select AEs were reported in 14 patients (6.7%) in the nivolumab group and 8 patients (3.8%) in the control group (**Table 21**). Drug-related hepatic select AEs in the nivolumab group were AST increased (10 patients, 4.8%), ALT increased (6 patients, 2.9%), gamma-glutamyltransferase increased (4 patients, 1.9%), blood alkaline phosphatase increased (2 patients, 1.0%), blood bilirubin increased (1 patient, 0.5%), and hepatitis (1 patient, 0.5%). Drug-related hepatic select AEs in the control group were ALT increased (2.4%, 5 patients), AST increased (2.4%, 5 patients), gamma-glutamyltransferase increased (1.9%, 4 patients), blood alkaline phosphatase increased (1.4%, 3 patients), blood bilirubin increased (0.5%, 1 patient), and hepatic enzyme increased (0.5%, 1 patient).Most drug-related hepatic select AEs were Grade 1-2. Drug-related Grade 3-4 hepatic select AEs were reported in 1 patient (0.5%) in the nivolumab group (AST increased) and 4 patients (1.9%) in the chemotherapy group (gamma glutamyltransferase increased, ALT increased, and blood alkaline phosphatase increased). No drug-related hepatic select AEs leading to discontinuation of study treatment were reported in either group.

In the nivolumab group, the median time to onset of drug-related hepatic event was 10.50 weeks (**Table 22**). 1 patient was treated with IMM (not high-dose corticosteroids) for a duration of 0.86 weeks. Overall, 10 of the 14 patients with drug related hepatic select AEs had resolution of the event, with a median time to resolution of 12.14 (95% CI: 2.29, 46.00) weeks.

Table 21 Summary of drug-related hepatic select adverse events by worst CTC grade reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) patients

Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Treatment Group: Nivolumab 240mg N = 209							
TOTAL PATIENTS WITH AN EVENT	7 (3.3)	6 (2.9)	1 (0.5)	0	0	0	14 (6.7)
Aspartate aminotransferase increased	7 (3.3)	2 (1.0)	1 (0.5)	0	0	0	10 (4.8)
Alanine aminotransferase increased	4 (1.9)	2 (1.0)	0	0	0	0	6 (2.9)
Gamma-glutamyltransferase increased	2 (1.0)	2 (1.0)	0	0	0	0	4 (1.9)
Blood alkaline phosphatase increased	2 (1.0)	0	0	0	0	0	2 (1.0)
Blood bilirubin increased	1 (0.5)	0	0	0	0	0	1 (0.5)
Hepatitis	0	1 (0.5)	0	0	0	0	1 (0.5)
Treatment Group: Control N = 208							
TOTAL PATIENTS WITH AN EVENT	2 (1.0)	2 (1.0)	3 (1.4)	1 (0.5)	0	0	8 (3.8)
Alanine aminotransferase increased	4 (1.9)	0	1 (0.5)	0	0	0	5 (2.4)
Aspartate aminotransferase increased	4 (1.9)	1 (0.5)	0	0	0	0	5 (2.4)
Gamma-glutamyltransferase increased	0	1 (0.5)	2 (1.0)	1 (0.5)	0	0	4 (1.9)
Blood alkaline phosphatase increased	2 (1.0)	0	1 (0.5)	0	0	0	3 (1.4)
Blood bilirubin increased	1 (0.5)	0	0	0	0	0	1 (0.5)
Hepatic enzyme increased	0	1 (0.5)	0	0	0	0	1 (0.5)

MedDRA Version: 21.1; CTC Version 4.0
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.
Source: Appendix E.113.b-EUSCS in Appendix 2

Table 22 Onset, treatment, and resolution of drug-related hepatic select adverse events reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) patients

	Nivolumab 240mg		Control	
Category: HEPATIC ADVERSE EVENT	Any Grade N = 14	Grade 3-5 N = 1	Any Grade N = 8	Grade 3-5 N = 4
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	10.50 (1.4 - 43.1)	22.14 (22.1 - 22.1)	2.00 (1.1 - 4.7)	3.29 (1.1 - 7.9)
PATIENTS WHO RECEIVED IMMUNE MODULATING MEDICATION(A) (%)	1/14 (7.1)	0/1	0/8	0/4
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	0.86 (0.9-0.9)			
PATIENTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	0			
NUMBER OF PATIENTS WHO RESOLVED (%)	10 (71.4)	1 (100.0)	4 (50.0)	1 (25.0)
TIME TO RESOLUTION (WEEKS)				
MEDIAN(B) (95% CI)	12.14 (2.29 - 46.00)	10.14 (N.A. - N.A.)	12.57 (6.14 - N.A.)	N.A. (9.43 - N.A.)
RANGE(C) (MIN - MAX)	0.7 - 94.3+	10.1 - 10.1	1.0+ - 46.7+	5.7+ - 46.7+

MedDRA Version: 21.1
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.
Drug-related AEs were defined as any AEs with causal relationship with the product is "related" or missing.
Select AEs are defined in the SAP (Appendix 16.1.9) for analyses from the ONO-4538-24 (CA209473) final CSR.
Select AEs are defined in Appendix E.141a-EUSCS in Appendix 2 for BMS-generated analyses (analyses from an integrated database).
(A) Denominator is based on the number of patients who experienced the event.
(B) This estimation was conducted by using the Kaplan-Meier method. The CI was calculated using the Brookmeyer and Crowley method based on a log-log transformed CI for the survivor function.
(C) Symbol + indicates a censored value.

Immune-related hepatitis in the pooled analysis

In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 6.7% (187/2787). The majority of cases were Grade 1 or 2 in severity reported in 3.5% (98/2787) and 1.4% (38/2787) of patients respectively. Grade 3 and 4 cases were reported in 1.5% (42/2787) and 0.3% (9/2787) of patients, respectively. No Grade 5 cases were reported in these studies. Median time to onset was 2.1 months (range: 0.0-27.6). Resolution occurred in 142 patients (76.3%) with a median time to resolution of 5.9 weeks (range: 0.1-94.3+)

Pulmonary events

Pulmonary select AEs (all-causality, any grade) were reported in 8.1% (17 patients) in the nivolumab group and 5.8% (12 patients) in the control group. Grade 3-4 pulmonary select AEs (all-causality) were reported in 1.0% (2 patients) in the nivolumab group and 2.4% (5 patients) in the control group. All-causality, any grade pulmonary select AEs reported in the nivolumab group were pneumonitis (8 patients, 3.8%), ILD (7 patients, 3.3%), and lung infiltration (2 patients, 1.0%), and in the control group were ILD (6 patients, 2.9%) and pneumonitis (6 patients, 2.9%).

Drug-related pulmonary select AEs were reported in 5.7% (12 patients) in the nivolumab group and 4.3% (9 patients) in the control group (**Table 23**). Drug-related grade 3-4 pulmonary select AEs were reported in 1.0% (2 patients) in the nivolumab group and 1.9% (4 patients) in the control group. Drug-related pulmonary select AEs in the nivolumab group were ILD (7 patients, 3.3%) and pneumonitis (5 patients, 2.4%). Drug-related pulmonary select AEs in the control group were ILD (6 patients, 2.9%) and pneumonitis (3 patients, 1.4%). Grade 3-4 drug-related pulmonary select AEs reported in the nivolumab group were ILD (1 patient, 0.5%) and pneumonitis (1 patient, 0.5%). Grade 3-4 drug-related pulmonary select AEs reported in the control group were pneumonitis (3 patients, 1.4%) and ILD (1 patient, 0.5%).

Drug-related pulmonary select AEs leading to discontinuation of study treatment reported in the nivolumab group were ILD (5 patients, 2.4%) and pneumonitis (4 patients, 1.9%), and in the chemotherapy group were ILD (3 patients, 1.4%) and pneumonitis (2 patients, 1.0%).

In patients in the nivolumab group, the median time to onset of drug-related pulmonary select AEs was 6.14 weeks (**Table 24**). 9 patients were treated with IMM (6 of these with high-dose corticosteroids), for a median duration of 7.71 weeks. Overall, 3 of the 12 patients with drug related pulmonary select AEs had resolution of the event; the median time to resolution was not reached.

Table 23 Summary of drug-related pulmonary select adverse events by worst CTC grade reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) patients

Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Treatment Group: Nivolumab 240mg N = 209							
TOTAL PATIENTS WITH AN EVENT	3 (1.4)	7 (3.3)	2 (1.0)	0	0	0	12 (5.7)
Interstitial lung disease	2 (1.0)	4 (1.9)	1 (0.5)	0	0	0	7 (3.3)
Pneumonitis	1 (0.5)	3 (1.4)	1 (0.5)	0	0	0	5 (2.4)
Treatment Group: Control N = 208							

TOTAL PATIENTS WITH AN EVENT	2 (1.0)	3 (1.4)	4 (1.9)	0	0
0	9 (4.3)				
Interstitial lung disease	2 (1.0)	3 (1.4)	1 (0.5)	0	0
0	6 (2.9)				
Pneumonitis	0	0	3 (1.4)	0	0
0	3 (1.4)				

MedDRA Version: 21.1; CTC Version 4.0
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.

Table 24 Onset, treatment, and resolution of drug-related pulmonary select adverse events reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) patients

	Control		Nivolumab 240mg		
			Any Grade	Grade 3-5	Any Grade
Category: PULMONARY ADVERSE EVENT	Grade 3-5 N = 9		N = 12	N = 2	N = 4
TIME TO ONSET (WEEKS)					
MEDIAN (MIN - MAX)	6.14 (1.1 - 36.4)	3.57 (3.1 - 4.0)	6.14 (3.9 - 12.7)	5.50 (3.9 - 9.1)	
PATIENTS WHO RECEIVED IMMUNE MODULATING MEDICATION(A) (%)	9/12 (75.0)	2/2 (100.0)	6/9 (66.7)	3/4 (75.0)	
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)					
MEDIAN (MIN-MAX)	7.71 (1.4-58.7)	2.50 (1.4-3.6)	13.07 (0.4-71.3)	8.00 (1.9-18.6)	
PATIENTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	6 (50.0)	2 (100.0)	4 (44.4)	2 (50.0)	
NUMBER OF PATIENTS WHO RESOLVED (%)	3 (25.0)	0	5 (55.6)	3 (75.0)	
TIME TO RESOLUTION (WEEKS)					
MEDIAN(B) (95% CI)	N.A. (10.14 - N.A.)	N.A. (N.A. - N.A.)	13.29 (1.43 - N.A.)	6.29 (1.43 - N.A.)	
RANGE(C) (MIN - MAX)	1.7+ - 78.7+	1.7+ - 3.9+	1.4 - 104.0+	1.4 - 19.9+	

MedDRA Version: 21.1
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.
Drug-related AEs were defined as any AEs with causal relationship with the product is "related" or missing.
Select AEs are defined in the SAP (Appendix 16.1.9) for analyses from the ONO-4538-24 (CA209473) final CSR.
Select AEs are defined in Appendix E.141a-EUSCS in Appendix 2 for BMS-generated analyses (analyses from an integrated database).
(A) Denominator is based on the number of patients who experienced the event.
(B) This estimation was conducted by using the Kaplan-Meier method. The CI was calculated using the Brookmeyer and Crowley method based on a log-log transformed CI for the survivor function.
(C) Symbol + indicates a censored value.

Immune-related pneumonitis in the polled analysis

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.6% (99/2787). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (24/2787) and 1.8% (51/2787) of patients respectively. Grade 3 and 4 cases were reported in 0.8% (21/2787) and <0.1% (1/2787) of patients respectively. Grade 5 cases were reported in < 0.1% (2/2787) of patients in these studies. Median time to onset was 3.3 months (range: 0.2-19.6). Resolution occurred in 66 patients (66.7%) with a median time to resolution of 6.6 weeks (range: 0.1+-96.7+); + denotes a censored observation.

Renal events

Renal select AEs (all-causality, any grade) were reported in 4.3% (9 patients) in the nivolumab group and 1.0% (2 patients) in the control group. One grade 3 renal select AE was reported in the nivolumab group (acute kidney injury). Renal select AEs (all-causality, any grade) in the nivolumab group were blood creatinine increased (7 patients, 3.3%), blood urea increased (1 patient, 0.5%), and acute kidney injury (1 patient, 0.5%), and in the control group were acute kidney injury (1 patient, 0.5%) and blood creatinine increased (1 patient, 0.5%).

Drug-related renal select AEs were reported in 1.4% (3 patients [2 grade 2 blood creatinine increased; 1 grade 3 acute kidney injury) in the nivolumab group and 0 patients in the control group.

No renal select AEs leading to discontinuation of study treatment were reported in either group.

In patients in the nivolumab group, the median time to onset of drug-related renal events was 4.14 weeks. No patients were treated with IMM. All 3 of the patients with drug related renal select AEs had resolution of the event; the median time to resolution was 3.43 (95% CI: 2.57, 6.14) weeks.

Immune-related nephritis and renal dysfunction in the poled analysis

In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.7% (74/2787). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (41/2787) and 0.7% (20/2787) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (12/2787) and <0.1% (1/2787) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies. Median time to onset was 2.3 months (range: 0.0-18.2). Resolution occurred in 45 patients (63.4%) with a median time to resolution of 12.1 weeks (range: 0.3-79.1+).

Skin events

Skin select AEs (all-causality, any grade) were reported in 28.7% (60 patients) in the nivolumab group and 29.3% (61 patients) in the control group. Grade 3-4 all-causality skin select AEs were reported in 1.9% (4 patients) in the nivolumab group and 1.0% (2 patients) in the control group. The most commonly reported skin select AEs in the nivolumab group were pruritus (25 patients, 12.0%) and rash (25 patients, 12.0%), followed by urticaria (4 patients, 1.9%). The most common skin select AE in the control group was rash (38 patients, 18.3%), followed by pruritus (15 patients, 7.2%).

Drug-related skin select AEs were reported in 20.6% (43 patients) in the nivolumab group and 20.2% (42 patients) in the control group (table 26). Drug-related grade 3-4 skin select AEs were reported in 1.9% (4 patients) in the nivolumab group and 1.0% (2 patients) in the control group. The most commonly reported drug-related skin select AE in the nivolumab group was rash (22 patients, 10.5%), followed by

pruritus (16 patients, 7.7%). The most common drug related skin select AEs in the control group were rash (29 patients, 13.9%), followed by pruritus (11 patients, 5.3%).

Skin select AEs leading to discontinuation of study treatment were reported in 0.5% (1 patient; Stevens-Johnson syndrome; drug-related) in the nivolumab group and 0 patients in the control group.

In patients in the nivolumab group, the median time to onset of the drug-related skin events was 3.29 weeks (table 27). 31 patients were treated with IMM (2 of these with high-dose corticosteroids), for a median duration of 9.14 weeks. Overall, 21 of the 43 patients with drug related skin select AEs had resolution of the event, with a median time to resolution of 40.14 (95% CI: 8.71, N.A.) weeks.

Table 25 Summary of drug-related skin select adverse events by worst CTC grade reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) patients

Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Treatment Group: Nivolumab 240mg N = 209							
TOTAL PATIENTS WITH AN EVENT	29 (13.9)	10 (4.8)	4 (1.9)	0	0	0	43 (20.6)
Rash	19 (9.1)	2 (1.0)	1 (0.5)	0	0	0	22 (10.5)
Pruritus	12 (5.7)	4 (1.9)	0	0	0	0	16 (7.7)
Urticaria	1 (0.5)	2 (1.0)	1 (0.5)	0	0	0	4 (1.9)
Drug eruption	1 (0.5)	1 (0.5)	1 (0.5)	0	0	0	3 (1.4)
Blister	1 (0.5)	0	0	0	0	0	1 (0.5)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.5)	0	0	0	0	0	1 (0.5)
Pruritus generalised	0	1 (0.5)	0	0	0	0	1 (0.5)
Rash generalised	0	1 (0.5)	0	0	0	0	1 (0.5)
Rash maculo-papular	1 (0.5)	0	0	0	0	0	1 (0.5)
Stevens-Johnson syndrome	0	0	1 (0.5)	0	0	0	1 (0.5)
Treatment Group: Control N = 208							
TOTAL PATIENTS WITH AN EVENT	31 (14.9)	9 (4.3)	2 (1.0)	0	0	0	42 (20.2)
Rash	21 (10.1)	6 (2.9)	2 (1.0)	0	0	0	29 (13.9)
Pruritus	7 (3.4)	4 (1.9)	0	0	0	0	11 (5.3)
Rash maculo-papular	3 (1.4)	1 (0.5)	0	0	0	0	4 (1.9)
Palmar-plantar erythrodysaesthesia syndrome	2 (1.0)	1 (0.5)	0	0	0	0	3 (1.4)
Erythema	2 (1.0)	0	0	0	0	0	2 (1.0)
Eczema	1 (0.5)	0	0	0	0	0	1 (0.5)
Rash generalised	1 (0.5)	0	0	0	0	0	1 (0.5)
Urticaria	0	1 (0.5)	0	0	0	0	1 (0.5)

MedDRA Version: 21.1; CTC Version 4.0
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.

Table 26 Onset, treatment, and resolution of drug-related skin select adverse events reported up to 28 days after last dose - all treated ONO-4538-24 (CA209473) patients

	Nivolumab 240mg		Control	
Category: SKIN ADVERSE EVENT	Any Grade N = 43	Grade 3-5 N = 4	Any Grade N = 42	Grade 3-5 N = 2
TIME TO ONSET (WEEKS)				
MEDIAN (MIN - MAX)	3.29 (0.1 - 93.1)	2.86 (2.1 - 22.1)	1.36 (0.3 - 34.1)	6.57 (3.0 - 10.1)
PATIENTS WHO RECEIVED IMMUNE MODULATING MEDICATION(A) (%)	31/43 (72.1)	3/4 (75.0)	25/42 (59.5)	1/2 (50.0)
TOTAL DURATION OF IMMUNE MODULATING MEDICATION (WEEKS)				
MEDIAN (MIN-MAX)	9.14 (0.1-114.9)	19.14 (0.4-36.1)	6.14 (0.1-52.6)	8.14 (8.1-8.1)
PATIENTS WHO RECEIVED CORTICOSTEROID AT A DOSE >= 40 MG PREDNISONE OR EQUIVALENT (%)	2 (1.7)	2 (50.0)	1 (2.4)	0
NUMBER OF PATIENTS WHO RESOLVED (%)	21 (48.8)	2 (50.0)	29 (69.0)	2 (100.0)
TIME TO RESOLUTION (WEEKS)				
MEDIAN(B) (95% CI)	40.14 (8.71 - N.A.)	20.86 (2.14 - N.A.)	7.07 (2.57 - 14.14)	6.71 (2.29 - 11.14)
RANGE(C) (MIN - MAX)	0.3 - 93.7+	1.0+ - 29.1+	0.1 - 78.7+	2.3 - 11.1

MedDRA Version: 21.1
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.
Drug-related AEs were defined as any AEs with causal relationship with the product is "related" or missing.
Select AEs are defined in the SAP (Appendix 16.1.9) for analyses from the ONO-4538-24 (CA209473) final CSR.
Select AEs are defined in Appendix E.141a-EUSCS in Appendix 2 for BMS-generated analyses (analyses from an integrated database).
(A) Denominator is based on the number of patients who experienced the event.
(B) This estimation was conducted by using the Kaplan-Meier method. The CI was calculated using the Brookmeyer and Crowley method based on a log-log transformed CI for the survivor function.
(C) Symbol + indicates a censored value.

Immune-related skin adverse reactions in the pooled analysis

In patients treated with nivolumab monotherapy, the incidence of rash was 25.9% (722/2787). The majority of cases were Grade 1 in severity reported in 19.6% (546/2787) of patients. Grade 2 and Grade 3 cases were reported in 5.0% (139/2787) and 1.3% (37/2787) of patients respectively. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.4 months (range: 0.0-27.9). Resolution occurred in 448 patients (62.8%) with a median time to resolution of 17.4 weeks (0.1-150.0^{+}).

Hypersensitivity/Infusion reactions

Hypersensitivity/infusion reactions (all-causality, any grade) were reported in 1.4% (3 patients) in the nivolumab group and 1.0% (2 patients) in the chemotherapy group; all were considered drug-related. One grade 4 event (anaphylactic shock) was reported in the nivolumab group.

No hypersensitivity/infusion reaction select AEs leading to discontinuation of study treatment were reported in either group.

In patients in the nivolumab group, the time to onset of the drug-related hypersensitivity/infusion reaction was 0.14 weeks. 1 patient was treated with IMM for a duration of 0.14 weeks. All 3 of the patients with drug-related hypersensitivity/infusion reaction had resolution of the event, with a time to resolution of 0.14 (95% CI: 0.14, 0.29) weeks.

Infusion reactions in the pooled analysis

In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.4% (123/2787), including 6 Grade 3 and 3 Grade 4 cases.

Other events of special interest

OESIs are events that do not fulfill 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. OESIs included the following PTs: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, pancreatitis, rhabdomyolysis, uveitis, autoimmune neuropathy, and graft vs host disease.

No OESIs were reported in ONO-4538-24 (CA209473).

Serious adverse event/deaths/other significant events

Serious Adverse Events

All causality SAEs

Any Grade

SAEs of any grade were reported in 32.5% of patients in the nivolumab group and 37.0% of patients in the control group (Table 27).

- In the nivolumab group, common SAEs (incidence ≥ 2%) were pneumonia (10 patients, 4.8%) and pyrexia (6 patients, 2.9%).

- In the control group, common SAEs (incidence ≥ 2%) were febrile neutropenia (16 patients, 7.7%), pneumonia (13 patients, 6.3%), decreased appetite (6 patients, 2.9%), and lung infection (5 patients, 2.4%).

Grade 3-4

Grade 3 to 4 SAEs were reported in 20.6% and 30.3% of patients in the nivolumab and control groups, respectively.

- In the nivolumab group, the most common grade 3-4 SAEs were pneumonia (5 patients, 2.4%) and hypercalcaemia (4 patients, 1.9%).
- In the control group, the most common grade 3-4 SAEs were febrile neutropenia (16 patients, 7.7%), pneumonia (9 patients, 4.3%), and decreased appetite (6 patients, 2.9%).

Drug-related SAEs

Any Grade

Drug-related SAEs were reported in 15.8% of nivolumab-treated patients and 22.6% of chemotherapy treated patients, respectively.

- In the nivolumab group, the following drug-related SAEs were reported in ≥2 patients: pyrexia (5 patients, 2.4%), ILD (4 patients, 1.9%), tumour haemorrhage (3 patients, 1.4%), pneumonia and pneumonitis (each 2 patients, 1.0%).
- In the control group, the following drug-related SAEs were reported in ≥2 patients: febrile neutropenia (16 patients, 7.7%), decreased appetite (6 patients, 2.9%), lung infection (5 patients, 2.4%), pneumonia, neutrophil count decreased, and ILD (each 3 patients, 1.4%), and diarrhoea, nausea, vomiting, pneumonia aspiration, and pneumonitis (each 2 patients, 1.0%).

Grade 3-4

Drug-related grade 3-4 SAEs were reported in 9.6% and 18.8% of patients in the nivolumab and control groups, respectively:

- In the nivolumab group, drug-related grade 3-4 SAEs were tumour haemorrhage (3 patients, 1.4%), and anaemia, inappropriate antidiuretic hormone secretion, adrenocorticotropic hormone deficiency, diarrhoea, dysphagia, pyrexia, abnormal hepatic function, anaphylactic shock, appendicitis, pneumonia, bacterial pneumonia, increased blood creatinine phosphokinase, hyponatraemia, acute kidney injury, ILD, pneumonitis, oesophagobronchial fistula, tracheal fistula, and Stevens-Johnson syndrome (each 1 patient, 0.5%).
- In the control group, drug-related grade 3-4 SAEs were febrile neutropenia (16 patients, 7.7%), decreased appetite (6 patients, 2.9%), lung infection (4 patients, 1.9%), decreased neutrophil count (3 patients, 1.4%), aspiration pneumonia and pneumonitis (each 2 patients, 1.0%), pancytopenia, bone marrow failure, cardiac failure, diarrhoea, nausea, upper GI haemorrhage, vomiting, asthenia, fatigue, infection, pneumonia, sepsis, neck abscess, bacterial pneumonia, dehydration, hyponatraemia, ILD, hypotension, and embolism (each 1 patient, 0.5%).

The docetaxel group had more grade 3-4 drug-related SAEs (26.2% of patients) compared to the paclitaxel group (15.4% of patients).

Table 27 Summary of serious adverse events by worst CTC grade with 2% cut-off - all treated ONO-4538-24 (CA209473) patients

SOC		SAEs					
		Nivolumab			Control		
		Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
PT		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	N	209	209	209	208	208	208
Total		68 (32.5)	43 (20.6)	7 (3.3)	77 (37.0)	63 (30.3)	5 (2.4)
Blood and lymphatic system disorders		2 (1.0)	2 (1.0)	0	17 (8.2)	17 (8.2)	0
Febrile neutropenia		0	0	0	16 (7.7)	16 (7.7)	0
General disorders and administration site conditions		9 (4.3)	2 (1.0)	1 (0.5)	7 (3.4)	5 (2.4)	1 (0.5)
Pyrexia		6 (2.9)	1 (0.5)	0	1 (0.5)	1 (0.5)	0
Infections and infestations		20 (9.6)	15 (7.2)	2 (1.0)	28 (13.5)	22 (10.6)	3 (1.4)
Pneumonia		10 (4.8)	5 (2.4)	2 (1.0)	13 (6.3)	9 (4.3)	2 (1.0)
Lung infection		1 (0.5)	1 (0.5)	0	5 (2.4)	4 (1.9)	0
Metabolism and nutrition disorders		12 (5.7)	10 (4.8)	0	8 (3.8)	8 (3.8)	0
Decreased appetite		3 (1.4)	0	0	6 (2.9)	6 (2.9)	0

Any AEs were coded using MedDRA version 21.1.
CTCAE version 4.0.
AEs occurring between the start date of the first administration of the product and 28 days after the last dose or the start date of subsequent anti-cancer therapy after the last dose, whichever comes first, were tabulated.

Additional safety information: Drug-related SAE

During the course of investigations of a GCP non-compliant activity in Taiwan, the MAH identified one SAE of diabetic ketoacidosis (nivolumab group; grade 4; related; date of onset: 11 Apr-2017) that occurred prior to the clinical cut-off date (12-Nov-2018) but was not reported by the DBL date of 28-Dec-2018. Since diabetic ketoacidosis is defined as a Select AE (Category; Endocrine/ Subcategory; Diabetes mellitus) for this study, information on this AE and the protocol deviation was discussed in the ONO-4538-24 [CA209473] final CSR.

Since diabetic ketoacidosis is a known side effect of nivolumab and this occurrence represented the only such event in study ONO-4538-24 (CA209473), the MAH concluded that this does not alter the safety evaluation of the study results and the subsequent risk and benefit assessment.

Deaths

As of the CSR data cut-off date (12-Nov-2018), deaths from any cause during the study were reported in 159 patients (76.1%) in the nivolumab group and 173 patients (83.2%) in the control group (Table 28). Progression of initial disease was the most common reason for death in each group (141 nivolumab patients [67.5%] and 151 control patients [72.6%]). A total of 15 (7.2%) patients in the nivolumab group and 19 (9.1%) patients in the control group had a reason for death noted as 'other'.

Two deaths (1.0%) were attributed to study drug toxicity with nivolumab; both occurred after 28 and within 100 days of permanent drug discontinuation. With chemotherapy, 3 deaths (1.4%) were attributed to study drug toxicity; all in the paclitaxel group. Two of these occurred within 28 days of last dose and 1 occurred beyond 100 days of last dose.

The treatment-related AEs resulting in death in both treatment groups were the following:

- Nivolumab group: pneumonitis and ILD (1 patient each)
- Control group: pneumonia, spinal cord abscess, and ILD (1 patient each)

Details regarding the 2 patients who died in the nivolumab group due to drug toxicity are provided:

- One patient was a 72-year-old male who died of pneumonitis 32 days after the first dose of study therapy with nivolumab. The diagnosis was supported by findings on CT scan and the patient received treatment with high dose steroids and antibiotics.
- Another patient was a 58-year-old male with recurrent laryngeal nerve paralysis who died of ILD 54 days after the first dose of study therapy with nivolumab. The patient was admitted to the hospital 14 days after the last dose of nivolumab (28 days after the first dose) with progressively worsening dyspnoea, productive cough and remittent fever. CT scan and bronchoscopy with bronchoalveolar lavage were suggestive of interstitial pneumonia and the patient received corticosteroid treatment. The course of illness was complicated with aspergillus infection, pneumonocystitis carinii and bacterial pneumonia, for which the patient received treatment with antibiotics. The death was attributed to drug-induced interstitial pneumonia and worsening of the underlying malignancy by the Investigator. No biopsy was performed.

Deaths occurring during the treatment period or within 28 days after the last dose of investigational product (or by the start date of subsequent anti-cancer therapy after the end of the treatment period, if used, whichever came first) were reported in 18 subjects (8.6%) in the nivolumab group and 9 subjects (4.3%) in the control group. Among these, reasons for death were 'initial disease' for 11 subjects (5.3%) and 'other' for 7 subjects (3.3%) in the nivolumab group. Ten of the 11 patients (with initial disease as reason for death) in the nivolumab arm and 1 of the 3 patients (with initial disease as reason for death) in the control arm represent cases of early deaths, with early death defined as death prior to or on 2.49 months after randomisation [crossing time point per smoothed instantaneous hazard of death overtime for each treatment arm]. Using the criterion 'Deaths occurring within 28 days after the last dose of investigational product' (irrespective of start date of subsequent anti-cancer therapy), 1 additional death was captured in the nivolumab group (19 patients [9.1%]) with reason for death 'initial disease' (Table 28).

In the nivolumab group, AEs of any cause leading to death occurring between first administration of study product and the earlier of either 28 days after the end of the treatment period or the start date of subsequent anti-cancer therapy after the end of the treatment period were: pneumonia (2 patients each), pneumonitis (2 patients each), and gastrointestinal haemorrhage, sudden death, metastases to lymph nodes, malignant neoplasm progression, ILD, pulmonary embolism, respiratory failure, and oesophageobronchial fistula (1 patient each). Of these AEs, 2 (pneumonitis and ILD) were considered drug-related (see above).

In the control group, AEs leading to death were reported only in paclitaxel-treated patients. In the paclitaxel group, AEs leading to death occurring during the treatment period or within 28 days after the last dose of investigational product (or by the start date of subsequent anti-cancer therapy after the end of the treatment period, if used, whichever came first) were: pneumonia (2 patients), and sudden death, disease progression, sepsis, spinal cord abscess, hypercalcaemia, tumour haemorrhage, and ILD (1

patient each). Of these AEs, 3 (pneumonia, spinal cord abscess, and ILD) were considered drug related (see above).

Table 28 Death summary - all treated ONO-4538-24 (CA209473) patients

	n (%)	
	Nivolumab	**Control**
N	209	208
Number of patients who died (%)[a]	159 (76.1)	173 (83.2)
Primary reason for death (%)		
Initial Disease	141 (67.5)	151 (72.6)
Drug Toxicity[b]	2 (1.0)	3 (1.4)
Other Cancer	1 (0.5)	0
Other	15 (7.2)	19 (9.1)
Number of patients who died within 28 days of last dose (%)	19 (9.1)	9 (4.3)
Primary reason for death (%)		
Initial Disease	12 (5.7)	3 (1.4)
Drug Toxicity[b]	0	2 (1.0)
Other Cancer	0	0
Other	7 (3.3)	4 (1.9)
Number of patients who died within 100 days of last dose (%)	60 (28.7)	65 (31.3)
Primary reason for death (%)		
Initial Disease	46 (22.0)	50 (24.0)
Drug Toxicity[b]	2 (1.0)	2 (1.0)
Other Cancer	0	0
Other	12 (5.7)	13 (6.3)

[a] Deaths until data cutoff (28-Dec-2018).
[b] Deaths which result from drug-related AEs were counted.
Safety analysis set

Laboratory findings

Haematology

Haematology was assessed via laboratory evaluation of haemoglobin, platelet count, leukocytes, lymphocytes, and absolute neutrophils.

The majority of patients in the nivolumab group did not have on-study worsening of haematology values. In the nivolumab group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ grade 3 for: lymphocyte count decreased (20 patients), haemoglobin decreased (10 patients), neutrophil count decreased (2 patients), and lymphocyte count increased (1 patient). In the control group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ grade 3 for: neutrophil count decreased (104 patients), white blood cell decreased (90 patients), lymphocyte count decreased (53 patients), and haemoglobin decreased (22 patients).

Serum chemistry

Liver function tests

The majority of patients in the nivolumab group did not have on-study worsening of liver function test (LFT) values. In the nivolumab group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ grade 3 for: alkaline phosphatase increased (8 patients), aspartate aminotransferase increased (13 patients), alanine aminotransferase increased (10 patients), and blood bilirubin increased (4 patients). In

the control group, CTCAE was worsened by at least 2 grades from baseline to ≥ grade 3 for: alanine aminotransferase increased (4 patients), alkaline phosphatase increased (2 patients), aspartate aminotransferase increased (2 patients), and blood bilirubin increased (2 patients).

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 4 patients (1.9%) in the nivolumab group and 2 patients (1.0%) in the control group (Table 29).

Table 29 Summary of on-treatment laboratory abnormalities in specific liver tests, SI units - all treated ONO-4538-24 (CA209473) patients

	n (%)	
	Nivolumab (N = 209)	**Control (N = 208)**
ALT or AST > 3× ULN	25 (12.0)	13 (6.3)
ALT or AST > 5× ULN	16 (7.7)	4 (1.9)
ALT or AST > 10× ULN	4 (1.9)	1 (0.5)
ALT or AST > 20× ULN	2 (1.0)	0
Total bilirubin > 2× ULN	5 (2.4)	2 (1.0)
ALT or AST > 3× ULN as well as total bilirubin collected 1day before and after > 2× ULN	4 (1.9)	1 (0.5)
ALT or AST > 3× ULN as well as total bilirubin collected 30 days before and after > 2× ULN	4 (1.9)	2 (1.0)
ALT or AST > 3× ULN as well as total bilirubin collected 1 day before and after ≥ 2× ULN, ALP < 2× ULN	1 (0.5)	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.

Kidney function tests

CTCAE grade was worsened by at least 2 grades from baseline to ≥ grade 3 for creatinine increased in 1 patient in the nivolumab group and 1 patient in the control group.

Thyroid function tests

The majority of patients in both treatment groups had normal thyroid-stimulating hormone (TSH) values throughout the reporting period (Table 30).

Table 30 Summary of on-treatment laboratory abnormalities in specific thyroid tests, SI units - all treated ONO-4538-24 (CA209473) patients

	n (%)	
	Nivolumab Group (N = 209)	**Control Group (N = 208)**
TSH > ULN	66 (31.6)	56 (26.9)
TSH > ULN as well as TSH ≤ ULN at the baseline	39 (18.7)	28 (13.5)
TSH > ULN as well as either free T3 or free T4 < LLN	50 (23.9)	40 (19.2)

TSH > ULN as well as both free T3 and free T4 ≥ LLN	16 (7.7)	16 (7.7)
TSH > ULN as well as either free T3 or free T4 is missing value	0	0
TSH < LLN	29 (13.9)	10 (4.8)
TSH < LLN as well as TSH ≥ LLN at the baseline	25 (12.0)	7 (3.4)
TSH < LLN as well as either free T3 or free T4 > ULN	11 (5.3)	2 (1.0)
TSH < LLN as well as both free T3 and free T4 ≤ ULN	18 (8.6)	8 (3.8)
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.

Electrolytes

In the nivolumab group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ grade 3 for: hyponatremia (22 patients), hypercalcemia (12 patients), hypokalaemia (6 patients), hypocalcaemia (1 patient), and hyperkalaemia (1 patient). In the control group, CTCAE grade was worsened by at least 2 grades from baseline to ≥ grade 3 for: hyponatremia (25 patients), hypokalaemia (7 patients), hypercalcemia (5 patients), hyperkalaemia (2 patients), and hypocalcaemia (1 patient).

Safety in special populations

Intrinsic and extrinsic factors

The overall incidences of AEs in subgroups were generally similar to those in the all treated patient population, suggesting no effects of the examined demographic and other baseline factors.

Age groups

In ONO-4538-24 (CA209473), the frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group in nivolumab monotherapy treated patients (N = 209) are presented in Table 31. Interpretation is limited by the small number of patients in the 75 to 84 years of age subgroup (n = 14). There were no patients ≥ 85 years of age.

Safety by age across integrated monotherapy studies, including ONO-4538-24 (CA209473)

Safety by age, integrated across indications (melanoma, NSCLC, RCC, cHL, SCCHN, urothelial cancer, and OSCC) in pooled nivolumab monotherapy treated patients (N = 2787), is presented in Table 32. Frequencies of SAEs, AEs leading to discontinuation, 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 patients (and there were no OSCC patients in this age group).

Table 31 Summary of on-treatment AEs by age group - all nivolumab monotherapy treated patients in ONO-4538-24 (CA209473)

MedDRA Terms (%)	Age group (Years) < 65 N = 112	65-74 N = 83	75-84 N = 14	>= 85 N = 0	Total N = 209
TOTAL PATIENTS WITH AN EVENT	100 (89.3)	75 (90.4)	14 (100.0)	0	189 (90.4)
SERIOUS AE - TOTAL	36 (32.1)	29 (34.9)	3 (21.4)	0	68 (32.5)
FATAL (DEATH)	8 (7.1)	3 (3.6)	0	0	11 (5.3)
HOSPITALIZATION/PROLONGATION	33 (29.5)	29 (34.9)	3 (21.4)	0	65 (31.1)
LIFE THREATENING	2 (1.8)	2 (2.4)	0	0	4 (1.9)
CANCER	0	0	0	0	0
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	1 (0.9)	2 (2.4)	0	0	3 (1.4)
AE LEADING TO DISCONTINUATION	15 (13.4)	12 (14.5)	2 (14.3)	0	29 (13.9)
PSYCHIATRIC DISORDERS	6 (5.4)	11 (13.3)	2 (14.3)	0	19 (9.1)
NERVOUS SYSTEM DISORDERS	15 (13.4)	9 (10.8)	3 (21.4)	0	27 (12.9)
ACCIDENT AND INJURIES	2 (1.8)	4 (4.8)	0	0	6 (2.9)
CARDIAC DISORDERS	1 (0.9)	3 (3.6)	0	0	4 (1.9)
VASCULAR DISORDERS	8 (7.1)	4 (4.8)	1 (7.1)	0	13 (6.2)
CEREBROVASCULAR DISORDERS	0	1 (1.2)	1 (7.1)	0	2 (1.0)
INFECTIONS AND INFESTATIONS	34 (30.4)	29 (34.9)	6 (42.9)	0	69 (33.0)
ANTICHOLINERGIC SYNDROME	31 (27.7)	24 (28.9)	5 (35.7)	0	60 (28.7)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	10 (8.9)	3 (3.6)	0	0	13 (6.2)

CTC Version 4.0; MedDRA Version: 21.1. 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.

Table 32 Summary of on-treatment AEs by age group - all treated patients - nivolumab monotherapy data integrated across indications, including ONO-4538-24 (CA209473)

MedDRA Terms (%)	Age group (Years) < 65 N = 1743	65-74 N = 784	75-84 N = 235	>= 85 N = 25	Total N = 2787
TOTAL PATIENTS WITH AN EVENT	1702 (97.6)	762 (97.2)	229 (97.4)	25 (100.0)	2718 (97.5)
SERIOUS AE - TOTAL	749 (43.0)	382 (48.7)	117 (49.8)	14 (56.0)	1262 (45.3)
FATAL (DEATH)	184 (10.6)	92 (11.7)	28 (11.9)	3 (12.0)	307 (11.0)
HOSPITALIZATION/PROLONGATION	660 (37.9)	339 (43.2)	106 (45.1)	11 (44.0)	1116 (40.0)
LIFE THREATENING	31 (1.8)	14 (1.8)	2 (0.9)	0	47 (1.7)
CANCER	26 (1.5)	19 (2.4)	10 (4.3)	2 (8.0)	57 (2.0)
DISABILITY/INCAPACITY	1 (<0.1)	1 (0.1)	0	0	2 (<0.1)
IMPORTANT MEDICAL EVENT	67 (3.8)	33 (4.2)	8 (3.4)	1 (4.0)	109 (3.9)
AE LEADING TO DISCONTINUATION	247 (14.2)	140 (17.9)	55 (23.4)	5 (20.0)	447 (16.0)
PSYCHIATRIC DISORDERS	320 (18.4)	124 (15.8)	39 (16.6)	7 (28.0)	490 (17.6)
NERVOUS SYSTEM DISORDERS	602 (34.5)	240 (30.6)	80 (34.0)	14 (56.0)	936 (33.6)
ACCIDENT AND INJURIES	132 (7.6)	68 (8.7)	26 (11.1)	3 (12.0)	229 (8.2)
CARDIAC DISORDERS	153 (8.8)	70 (8.9)	19 (8.1)	5 (20.0)	247 (8.9)
VASCULAR DISORDERS	270 (15.5)	135 (17.2)	40 (17.0)	10 (40.0)	455 (16.3)
CEREBROVASCULAR DISORDERS	22 (1.3)	26 (3.3)	9 (3.8)	1 (4.0)	58 (2.1)
INFECTIONS AND INFESTATIONS	737 (42.3)	341 (43.5)	92 (39.1)	14 (56.0)	1184 (42.5)
ANTICHOLINERGIC SYNDROME	626 (35.9)	258 (32.9)	79 (33.6)	11 (44.0)	974 (34.9)

QUALITY OF LIFE DECREASED	1 (<0.1)	0	0	0	1 (<0.1)
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	194 (11.1)	86 (11.0)	31 (13.2)	4 (16.0)	315 (11.3)

CTC Version 4.0; MedDRA Version: 21.1. Includes events reported between first dose and 30 days after last dose of study therapy, except for ONO-4538-24. For ONO-4538-24 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 CA209066, CA209037, CA209063, CA209017, CA209057, CA209067 (monotherapy arm), CA209025, CA209205, CA209039 (cHL patients), CA209141, CA209275, CA209032 (UC patients), and ONO-4538-24.

White patients

The MAH stated that the safety profile of the subgroup of white patients was comparable to that of the overall treated population in ONO-4538-24 (CA209473).

Adverse Events

A summary of AEs in white patients is presented in Table 33.

Table 33 Summary of adverse events – all treated Western patients in ONO-4538-24 (CA209473)

	Nivolumab			Control		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
N	9	9	9	8	8	8
Number of patients with AEs	9 (100.0)	4 (44.4)	0	8 (100.0)	7 (87.5)	0
Number of patients with SAEs	4 (44.4)	3 (33.3)	0	6 (75.0)	6 (75.0)	0
Number of patients with AEs leading to discontinuation of study treatment	3 (33.3)	1 (11.1)	0	1 (12.5)	1 (12.5)	0
Number of patients with drug-related AEs [a)]	5 (55.6)	1 (11.1)	0	8 (100.0)	5 (62.5)	0
Number of patients with drug-related SAEs [a)]	1 (11.1)	0	0	2 (25.0)	2 (25.0)	0
Number of patients with drug-related AEs leading to discontinuation of study treatment [a)]	1 (11.1)	0	0	0	0	0

AEs, drug-related AEs occurring between the start date of the first administration of the investigational product and 28 days after the last dose or the start date of subsequence anti-cancer therapy after the last dose whichever comes first were tabulated.
a) Drug-related AEs were defined as any AEs with causal relationship with the investigational product is "Related" or missing.

Safety related to drug-drug interactions and other interactions

The MAH stated that there was no new information regarding safety related to drug-drug interactions and other interactions.

Discontinuation due to adverse events

All causality AEs leading to discontinuation

Any grade

AEs leading to discontinuation of study treatment were reported in 13.9% of patients in the nivolumab group and 15.9% of patients in the control group.

- In the nivolumab group, AEs leading to discontinuation of study treatment, excluding disease progression (incidence ≥2%), were ILD and pneumonitis (each 5 patients, 2.4%).

- In the control group, no AEs leading to discontinuation of study treatment were reported at an incidence of ≥2%.

Grade 3-4

Grade 3-4 AEs leading to treatment discontinuation were reported in 5.3% and 10.6% of patients in the nivolumab and control groups, respectively.

- In the nivolumab group, no AEs leading to discontinuation of study treatment were reported at an incidence of ≥2%; the only grade 3-4 AE leading to discontinuation reported in >1 patient was dysphagia (2 patients).
- In the control group, no AEs leading to discontinuation of study treatment were reported at an incidence of ≥2%; grade 3-4 AEs leading to discontinuation reported in >1 patient were pneumonia, infectious pleural effusion, decreased neutrophil count, and pneumonitis (each 2 patients).

Drug-related AEs leading to discontinuation

Any grade

Drug-related AEs leading to discontinuation of study treatment were reported in 8.6% of patients in the nivolumab group and 9.1% of patients in the control group.

- In the nivolumab group, the only reported drug-related AE leading to discontinuation at an incidence ≥2% was ILD (5 patients, 2.4%). Other drug-related AEs leading to discontinuation were pneumonitis (4 patients, 1.9%), hypothyroidism (2 patients, 1.0%), and adrenocorticotropic hormone deficiency, diarrhoea, dysphagia, abnormal hepatic function, pneumothorax, tracheal fistula, and Stevens-Johnson syndrome (each 1 patient, 0.5%).
- In the control group, no drug-related AEs leading to discontinuation of study treatment were reported at an incidence of ≥ 2%. Drug-related AEs leading to discontinuation of study treatment were ILD (3 patients, 1.4%), neutrophil count decreased, neuropathy peripheral, and pneumonitis (each 2 patients, 1.0%), and neutropenia, diarrhoea, fatigue, pneumonia, lung infection, muscular weakness, neurotoxicity, peripheral motor neuropathy, peripheral sensory neuropathy, dyspnoea, pleural effusion, and pneumonia aspiration (each 1 patient, 0.5%).

Grade 3-4

Drug-related grade 3-4 AEs leading to discontinuation of study treatment were reported in 3.8% and 5.8% of nivolumab and chemotherapy-treated patients, respectively.

- In the nivolumab group, drug-related grade 3-4 AEs leading to discontinuation of study treatment were adrenocorticotropic hormone deficiency, diarrhoea, dysphagia, abnormal hepatic function, ILD, pneumonitis, tracheal fistula, and Stevens-Johnson syndrome (each 1 patient, 0.5%).

In the control group, drug-related grade 3-4 AEs leading to discontinuation of study treatment were neutrophil count decreased and pneumonitis (1.0%, 2 patients each), and neutropenia, diarrhoea, fatigue, lung infection, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, ILD, and pneumonia aspiration (each 1 patient, 0.5%).

Post marketing experience

Not applicable

2.5.1. Discussion on clinical safety

To support the extension of indication, the MAH provided efficacy and safety data from the ONO-4538-24 study. The safety data set (patients that received at least 1 dose of investigational product) consisted of 209 patients in the nivolumab group and 208 patients in the control group. No new safety signals were identified in the ONO-4538-24 study. Of note, in Europe best supportive care (BSC) is an acceptable and commonly used 2L treatment option in OSCC. This should be taken into account when hereafter comparing the toxicity profile of nivolumab with that of chemotherapy.

Regarding exposure, most patients (83.3%) in the nivolumab group received >90% of the planned dose intensity. Median duration of treatment was short and similar between groups (2.56 months in both the nivolumab and control group), in line with the short mPFS observed in both treatment arms.

Most patients had an all causality AE in both treatment groups (>90%). In the nivolumab group, commonly reported AEs (incidence ≥10%) were decreased appetite, diarrhoea, constipation, pyrexia, cough, anaemia, pruritus, rash, nausea, and hypothyroidism. Except for anaemia (which is not uncommon in patients with OSCC and likely disease-related), these AEs are known adverse drug reactions (ADRs) of nivolumab, although not every single event was assigned treatment-related by the investigator and occurrence could in some cases have other reasons, such as the disease itself. Commonly observed AEs were as expected in the control group, including, among other, alopecia, (febrile) neutropenia, neuropathy, arthralgia/myalgia.

Treatment-related AEs were less often reported in the nivolumab group than in the control group (49.8% vs 95.2%, respectively). Hypothyroidism was the only AE more often reported in the nivolumab group than in the control group (difference ≥5%). Not unexpectedly, AEs such as, but not limited to, myelosuppression, neuropathy, alopecia and myalgia/arthralgia were more often reported in the control group than the nivolumab group (difference ≥5%), which are common ADRs of taxanes (WHO[WWW]).

Even though there are some differences in incidence of AEs between taxanes (also observed in the ONO-4538-24 study), common ADRs are generally shared and the safety discussion will focus on the overall toxicity observed in the control group.

When comparing the percentage of patients with (drug-related) fatigue and nausea between the ONO-4538-24 study and the pooled dataset, both fatigue and nausea are less frequently reported in the ONO-4538-24 study (treatment-related fatigue [7.7% ONO-4538-24; 28.8% pooled dataset], treatment-related nausea [1.9% ONO-4538-24; 11.1% pooled dataset]. The same can be said for other AEs, but the difference was less pronounced. Hence, patients in the ONO-4538-24 study seemed to be less susceptible towards some of the most frequently reported ADRs of nivolumab. During the 2nd round, the MAH explained that the differences in frequencies of the AEs may be caused by several factors, such as exposure, physician reporting, or disease population. This might indeed have contributed to these differences, although this cannot be fully confirmed.

Grade 3-4 AEs were less frequently reported in the nivolumab group than in the control group (38.3% vs 70.7%). In the nivolumab group, the only common grade 3-4 AE (incidence ≥5%) was anaemia. As mentioned above, anaemia is not uncommon in patients with OSCC, and only a few of these events were assigned treatment-related. Common grade 3-4 AEs (incidence ≥5%) in the chemotherapy group were predominately within the SOC 'Blood and lymphatic system disorders' (e.g. neutropenia, febrile neutropenia, leukopenia, anaemia), which is not surprising given the myelosuppressive nature of taxanes.

As the safety profile of nivolumab observed in the ONO-4538-24 study was consistent with the already known safety information, section 4.8 of the SmPC remains largely unchanged.

Endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are considered selected AEs for nivolumab. In the nivolumab group, the most frequently reported (treatment-related) select AE categories were endocrine (predominately hypothyroidism), gastrointestinal (predominately diarrhoea) and skin (mostly rash and pruritus). When comparing treatment groups, most noticeable differences were endocrine events (11.0 % nivolumab; 0.5% chemotherapy), driven by hypothyroidism. This is not unexpected, given that hypothyroidism is a common ADR of nivolumab (Opdivo - Product Information). For other select AE categories the difference between treatment groups was small (difference <3%), but numerically favouring the control group. Overall, the majority of selected AEs were of low grade (grade 1-2). In the nivolumab group, half of the selected AEs (61/120) resolved with or without immune modulating medication (e.g. corticosteroids). However, the majority of endocrine and pulmonary events did not resolve. According to the MAH, not all endocrine events were considered resolved due to the continuing need for hormone replacement therapy. Select AEs seldom led to discontinuation of therapy, with the exception of pulmonary events (9 out of 12 patients discontinued therapy due to a pulmonary event).

In general, the reported selected AEs were consistent with the nivolumab monotherapy pooled safety dataset (n = 2787). Despite only a couple of patients had a pulmonary selected AE, this seems to be slightly more frequent observed in the ONO-4538-24 ONO study compared with the pooled dataset. However, pneumonitis was reported in a similar frequency in the control group and might also have been caused by other factors (e.g. previous radiation therapy).

The MAH informed that 1 patient had a grade 4 diabetic ketoacidosis before the DBL, but this was not reported at first. This event was identified during the course of investigations of a GCP non-compliant activity in Taiwan (refer to clinical efficacy). Although rare, diabetic ketoacidosis is a known adverse drug reaction of nivolumab. Based on the narrative it seems that diabetic ketoacidosis was not confirmed. This uncertainty will however not have an impact on the overall safety analysis and therefore will not be further pursued.

There were less (treatment-related) SAEs reported in the nivolumab group compared to the chemotherapy group.

Disease progression was the most common reason for death in each treatment group. AEs leading to death were reported in 11 patients in the nivolumab group and in 9 patients in the control group. Of these, only a few were considered treatment-related (2 deaths in the nivolumab group [pneumonitis and ILD] and 3 deaths in the control group [pneumonia, spinal cord abscess, and ILD]). Immune-related pneumonitis is an important identified risk of nivolumab and fatal outcomes have been reported in other studies. It could be questioned whether nivolumab might also have contributed to the other case of grade 5 pneumonitis that was reported in the study (narrative indicates that pneumonitis occurred after initiation of therapy, but not much additional information was provided). However, the investigator assigned this AE as unrelated to study drug.

In the nivolumab group approximately 1 in 7 patients had an AE leading to discontinuation of study treatment, which was slightly lower than in the chemotherapy group.

Regarding laboratory evaluations, in the nivolumab group, the majority of patients did not have on-study worsening of laboratory values for the clinical laboratory evaluations (or worsened by only one grade). As expected, changes in haematological values (worsened by at least 2 grades from baseline to ≥ grade 3) were more pronounced in the chemotherapy group compared with the nivolumab group. Changes in liver values (worsened by at least 2 grades from baseline to ≥ grade 3) were (slightly) more often observed in the nivolumab group than in the chemotherapy group. As increased AST, increased ALT, increased alkaline phosphatase are very common ADRs for nivolumab (Opdivo - Product Information), these findings are not unexpected.

Subgroup analyses for special populations were also performed. According to the MAH, the overall incidences of AEs in subgroups (including demographic and other baseline factors such as gender) were generally similar to those in the all treated patient population. A slightly higher percentage of all causality grade 3-4 AE were reported in the female subgroup than the male subgroup (45.2% vs 37.1%, respectively), but this difference was absent for treatment-related AEs (16.1 % vs 18.5%, respectively). Regarding age, relatively few patients older than 75 years of age (n = 14) were enrolled in the nivolumab arm of the ONO-4538-24 study, limiting the interpretably of the data. No consistent trend between age and incidence of AEs (AEs, serious AEs, AEs leading to discontinuation) was observed. Based on the pooled dataset (data integrated across indications), frequencies of serious AEs, hospitalizations and AEs leading to discontinuation increased slightly with increasing age, suggesting that (frail) elderly patients are slightly more prone to experiencing an AE. Despite that the effort of the MAH to discuss the safety in the subgroup of white patients in study ONO-4538-24 is appreciated, the sample size is too small to draw any conclusions. However, the safety profile of nivolumab has been well characterized in white patients based on previous experiences, and it is not expected that safety in white patients with OSCC will be considerably different.

Additional expert consultations

After consultation with Scientific Advisory Group in Oncology it is considered that nivolumab is associated with a better and more favourable toxicity profile compared to the control group receiving docetaxel or paclitaxel.

2.5.2. Conclusions on clinical safety

The commonly reported AEs in the ONO study were consistent with the known safety profile of nivolumab. Regarding the incidence of AEs (any grade and grade 3-4) and SAEs (any grade and grade 3-4), nivolumab compares favourably with chemotherapy. Nivolumab and chemotherapy have a distinct safety profile; nivolumab is mostly characterised by immune-related toxicity, while for instance haematological toxicity, neurotoxicity and alopecia are more characteristic of taxane-based chemotherapy. Selected AEs observed with nivolumab are often of low grade and are generally manageable with immune-modulating therapy. Nonetheless, treatment with nivolumab is not without risks, and two patients died due to drug-related pneumonitis. Experience with nivolumab in Western patients with OSCC is limited, and the safety profile is predominantly based on a selected population of Asian patients. However, the safety profile of nivolumab has been well characterized in white patients based on previous procedures (in other tumour types). Overall, there is increasing experience with this medicinal product and guidance (e.g. Product Information, EMSO guideline) exist to improve early detection and allow for adequate management of nivolumab-induced adverse reactions. Hence, the safety profile of nivolumab in the applied indication for target population is considered acceptable.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 16.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 16.2 with the following content:

Safety concerns

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

Data provided as part of this extension of indication did not lead to any changes to the safety concerns.

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 3 - Required additional pharmacovigilance activities				
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis,	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024

Ongoing and Planned Additional Pharmacovigilance Activities

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

No changes to the pharmacovigilance plan.

Risk minimisation measures

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

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

The risk minimisation measures are unchanged and remain sufficient to mitigate the risks of OPDIVO in all approved indications.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

For full reference to the changes included please see the attached PI

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet

has been submitted by the MAH and has been found acceptable for the following reasons:

- the readability of the PL (QRD template Version 9.0) of OPDIVO (nivolumab), in English, was assessed during the assessment of the initial MAA;
- the new indication in adults that is hereby applied for concerns the same route of administration and has a similar safety profile as the previously approved indications;
- administration of OPDIVO (nivolumab) is done by a health care professional, and the instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL (and were also successfully tested as part of the user consultation performed for the initial MAA) remain unchanged;
- the general design and layout of the proposed PL have not changed compared to the tested one; and
- overall, the proposed leaflet shares large text sections with the reference one and the modifications now proposed in the PL (i.e., those relevant to the new indication) do not represent major changes.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The purpose of the current submission was to seek marketing approval for OPDIVO as monotherapy for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

3.1.1. Disease or condition

Oesophageal cancer is the 7th most common cancer worldwide and the 6th most common cause of death from cancer in 2018, with an estimated 572,034 new cases (3.2% of all cancers) and 508,585 cancer deaths (5.3% of all cancer deaths) (GLOBOCAN 2018 [accessed on 24-Jan-2020]). Oesophageal cancer has two main subtypes - oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC). In general, the prognosis of OSCC is considered to be poorer compared to OAC. Although OSCC accounts for ~90% of cases of oesophageal cancer worldwide, mortality rates associated with OAC are rising and have surpassed those of OSCC in several regions in the EU (Castro et al. 2014).

The main risk factors for OSCC are tobacco smoking and alcohol overconsumption (Lagergren et al. 2017).

3.1.2. Available therapies and unmet medical need

Patients with advanced (metastatic or disseminated) and recurrent OSCC - and with good performance status (PS) - are generally treated with palliative intent with platinum-based doublet chemotherapy. The combination of platinum and a fluoropyrimidine is a widely accepted first-line (1L) treatment option. However, as for OSCC the value of palliative chemotherapy is less clear (than for OAC), best supportive care (BSC) could also be considered, especially for unfit patients (Lordick et al. 2016).

For 2L treatment of OSCC, there are no approved therapies in Europe. Moreover, treatment decisions are made in the absence of evidence from randomized controlled trials. However, single-agent chemotherapy

is an established option and taxane (docetaxel or paclitaxel) monotherapy is recommended by various clinical guidelines (Lordick et al. 2016; 2019 NCCN Guidelines). As, nonetheless, median OS with this therapy is <1 year, there is a clear unmet need for new treatment options in this disease setting.

3.1.3. Main clinical studies

The single pivotal (and only submitted) study in this application is **ONO-4538-24** (CA209473; NCT02569242), a multicentre, randomized, open-label study to evaluate the efficacy and safety of nivolumab for the treatment of patients with unresectable advanced, recurrent or metastatic OSCC refractory to or intolerant of combination therapy with fluoropyrimidine- and platinum-based drugs. Patients were randomised (1:1) to receive either nivolumab or investigator's choice of docetaxel or paclitaxel chemotherapy. The primary endpoint was OS. Key secondary endpoints were ORR and PFS. The hierarchical hypothesis testing order was as follows: OS - ORR - PFS.

A total of 419 patients were randomised to receive either nivolumab (n = 210) or control (n = 209), i.e. docetaxel (n = 65) or paclitaxel (n = 144).

3.2. Favourable effects

Regarding the primary endpoint OS, median OS was 10.91 months (95% CI: 9.23, 13.34) for the nivolumab group vs. 8.38 months (95% CI: 7.20, 9.86) for the control group (Δ 2.53 months). The HR was 0.77 (95% CI: 0.62, 0.96). This difference was statistically significant (p=0.0189).

The subgroup analyses of OS consistently favoured nivolumab over control, represented by a HR <1.

The results of all sensitivity analyses (both pre-defined as well as post-hoc) and secondary analytical methods of the primary endpoint OS were consistent with the primary analysis method.

Regarding the key secondary endpoint ORR, this was rather comparable between the nivolumab group (19.3%) and the control group (21.5%). Nevertheless, median DoR was numerically higher in the nivolumab group (6.93 months [95% CI: 5.39, 11.14]) than in the control group (3.91 months [95% CI: 2.79, 4.17]).

3.3. Uncertainties and limitations about favourable effects

There was an early crossing of the KM OS curves at approximately 5 months, only afterwards favouring nivolumab and no predictive factor for patients (most) at risk for an early death could be identified . This information is reflected in the SmPC.

There was no clear support for the primary endpoint OS from the key secondary endpoints ORR and PFS; only DoR numerically favoured nivolumab over control.

Even though the OS HR was <1 in both patients with PD-L1 expression <1% as well as ≥1%, the benefit seems less apparent in the first than in the latter subgroup, also considering the subgroup analyses in the secondary endpoints ORR and PFS. The MAH has included the OS results of the subgroup analysis by PD-L1 expression in section 5.1 of the SmPC.

3.4. Unfavourable effects

When compared to the control group, the incidence of all causality AEs, Grade 3-4 AEs, and SAEs was lower in the nivolumab group, i.e. 90.4% vs. 98.6%, 38.3% vs. 70.7%, and 32.5% vs. 37.0%, respectively.

The most commonly reported AEs in the nivolumab group were decreased appetite (20.6%), diarrhoea (17.7%), constipation (16.7%), pyrexia (15.8%), cough (15.3%), anaemia (12.4%), pruritus (12.4%), rash (12.4%), nausea (11%), and hypothyroidism (10%).

AEs leading to discontinuation were reported in 13.9% of the nivolumab-treated patients.

Deaths due to an AE were reported in 5.3% of the patients in the nivolumab group. Of these, 2 were assigned treatment-related.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile of nivolumab in OSCC is predominately based on a selected population of Asian patients; only 9 white/non-Asian patients were treated with this medicinal product. However, the safety profile of nivolumab has been well characterized in white patients based on previous procedures (in other tumour types). Overall, there is increasing experience with this medicinal product and guidance (e.g. Product Information, ESMO guideline) exist to improve early detection and allow for adequate management of nivolumab-induced adverse reactions.

Median exposure was 2.56 months, in line with the short median PFS observed in both treatment arms.

The toxicity of nivolumab was compared to that of chemotherapy, while in European clinical practice BSC is also an acceptable and commonly used 2L treatment option in OSCC.

3.6. Effects Table

Table 34 Effects Table for OPDIVO (nivolumab) in "*the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy*" (data cut-off: 12-Nov-2018)

Effect	Short description	Unit	Nivolumab	Control (docetaxel or paclitaxel)	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Overall survival, i.e. time from randomization until death from any cause	Median in months (95% CI)	10.91 (9.23, 13.34)	8.38 (7.20, 9.86)	Uncertainty regarding the OS benefit of nivolumab treatment in white/non-Asian patient population in European clinical practice Early crossing OS KM curves	
			Hazard ratio (HR) 0.77 (95% CI: 0.62, 0.96) p=0.0189			
ORR	Objective response rate, i.e. either confirmed complete or partial response	% (95% CI)	19.3 (13.7, 26.0)	21.5 (15.4, 28.8)	Results numerically favour control over nivolumab Open-label study design and lack of	
			Odds ratio 0.88 (95% CI: 0.51, 1.50)			

Effect	Short description	Unit	Nivolumab	Control (docetaxel or paclitaxel)	Uncertainties / Strength of evidence	References
	(investigator-assessed per RECIST 1.1)		p=0.6323		(blinded) central evaluation of imaging	
PFS	Progression-free survival, i.e. time until progressive disease (investigator-assessed per RECIST 1.1) or death from any cause, whichever occurs first	Median in months (95% CI)	1.68 (1.51, 2.73)	3.35 (2.99, 4.21)	Results numerically favour control over nivolumab Open-label study design and lack of (blinded) central evaluation of imaging	
			HR 1.08 (95% CI: 0.87, 1.34) p not applicable			
Unfavourable Effects						
Any grade AEs	Percentage of patients with an <u>all causality</u> adverse event	%	90.4	98.6		
	Percentage of patients with a <u>treatment-related</u> adverse event	%	65.6	95.2		
Grade 3-4 AEs	Percentage of patients with an <u>all causality</u> grade 3-4 adverse event	%	38.3	70.4		
	Percentage of patients with a <u>treatment-related</u> grade 3-4 adverse event	%	18.2	63.0		
SAEs	Percentage of patients with an <u>all causality</u> serious adverse event	%	32.5%	37.0%		
	Percentage of patients with a <u>treatment-related</u> serious adverse event	%	15.8%	22.6%		
Deaths	Percentage of patients with an <u>all causality</u> adverse event leading to death	%	5.3	4.3		
	Percentage of patients with a <u>treatment-related</u> adverse event leading to death	%	1.0	1.4		
Discontinuations	Percentage of patients with an <u>all causality</u> adverse event leading to	%	13.9	15.9		

Effect	Short description	Unit	Nivolumab	Control (docetaxel or paclitaxel)	Uncertainties / Strength of evidence	References
	discontinuation					
	Percentage of patients with a treatment-related adverse event leading to discontinuation	%	8.6	9.1		

Abbreviations: RECIST 1.1: Response Evaluation Criteria In Solid Tumours version 1.1

Notes: PFS result not statistically tested because ORR did not pass statistical boundary for significance.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In study ONO-4538-24 treatment with nivolumab resulted in a statistically significant OS benefit over the control of investigator's choice of paclitaxel or docetaxel chemotherapy. This OS benefit could be regarded as being clinically relevant given the poor prognosis of patients with advanced OSCC.

However, there was uncertainty regarding the OS benefit of nivolumab treatment in the white/non-Asian patient population in European clinical practice. The primary reason for this uncertainty was that the subgroup of white patients in the pivotal study is too small to draw any conclusion and extrapolation of the results of the Asian patient population to the white/non-Asian patient population was hampered. As a result, the MAH was asked to provide evidence showing that the study results are generalizable. The intrinsic and extrinsic factors have been sufficiently discussed by the MAH. Furthermore, even though the effect of anti-PD-1 therapy on OS can be expected to be smaller in non-Asian patients than in Asian patients, new data became available from other studies (MAH shared key data from Study CA209577 (nivolumab in the adjuvant setting)) in which preliminary results indicate proof of concept for efficacy of nivolumab in Western patients with OSCC. Overall, based on the totality of data it is expected that Western patients with OSCC will also benefit from 2L nivolumab, albeit the magnitude of benefit in Western patients has not fully been established.

Regarding safety, the AEs that were commonly reported in the study were those that can be expected when being treated with nivolumab. No new safety signals were reported. Nivolumab and chemotherapy have a distinct safety profile; nivolumab is mostly characterised by immune-related toxicity, while for instance haematological toxicity, neurotoxicity and alopecia are more characteristic of taxane-based chemotherapy. Considering the frequency of AEs (any grade, grade 3-4) and SAEs (any grade, grade 3-4), nivolumab compares favourably to chemotherapy. Select AEs were mostly of low grade (grade 1-2), and half of the events resolved with or without immune-modulating medication (hence were in many cases manageable). Yet, treatment with nivolumab is not without risks and two fatal treatment-related pulmonary events were reported. Nivolumab is already approved for several indications, and experience with this medicinal product has grown over the years, resulting in guidelines for adequate management of anti-PD-1 agents to minimize risks. Conclusion regarding the safety profile in white/non-Asian patients with OSCC is limited by the small sample size in the pivotal study. However, the safety profile of nivolumab has been well characterized in white patients based on previous experiences, and it is not expected that safety in white patients with OSCC will be considerably different.

3.7.2. Balance of benefits and risks

Based on the totality of data it is concluded that the results from the pivotal ONO-4538-24 study support benefit of nivolumab in OSCC patients. Furthermore, the data are considered generalisable and therefore it is expected that OSCC Western patients will also benefit from receiving nivolumab in the intended line of treatment albeit the magnitude of benefit in that particular group of patients has not been fully established. As there was no critical issue regarding the safety/toxicity of nivolumab in the indication applied therefore, the benefit/risk balance for nivolumab in "*the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy*" is positive.

3.8. Conclusions

The overall B/R of OPDIVO (nivolumab) is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.2 of the RMP has also been submitted. In addition, the Marketing Authorisation holder (MAH) took the opportunity to update the list of local representatives for Sweden and Denmark in the Package Leaflet.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module

8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion “Opdivo-H-C-3985-II-0080”.