EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/CHMP/271863/2017

Assessment report

Invented name: OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0017

Marketing authorisation holder (MAH): Bristol-Myers Squibb Pharma EEIG

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

5-FU	5-fluorouracil
ADR	Adverse drug reaction
AE	Adverse event
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMS	Bristol-Myers Squibb
BOR	Best overall response
BSC	Best supportive care
Cavgss	Time-averaged steady-state concentration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Total body clearance
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CP	Chronic phase
CR	Complete response
CSR	Clinical study report
CTC-AE	Common terminology criteria for adverse events
DBL	database lock
DC	discontinuation
DMC	Data Monitoring Committee
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FPFV	First patient first visit
GCP	Good clinical practice
GI	Gastrointestinal

HLGT MedDRA High-Level Group Term

HNSCC Head and neck squamous cell carcinoma (also: SCCHN)

HPV human papilloma virus

HR hazard ratio

IC investigator's choice

IEC Independent Ethics Committee

IMAE immune-mediated adverse event

IMM immune-modulating medication

IRB Institutional Review Board

ITT Intent-to-treat

IV Intravenous

LDH Lactate dehydrogenase

LLN Lower limit of normal

LPLV Last patient last visit

Max maximum

MedDRA Medical Dictionary for Regulatory Activities

Min minimum

mDOR median duration of response

mOS median OS

mPFS median PFS

NA not available

NR not reported

NSCLC non-small cell lung cancer

ORR objective response rate

OS overall survival

PD Progressive disease

PD-1/2 programmed death receptor 1/2

PD-L1/2 programmed cell death ligand 1/2

PMBL Primary mediastinal B cell lymphoma

PFS progression-free survival

PK pharmacokinetics

PPK population pharmacokinetics

PR Partial response

PS performance status

PT	preferred term
Q2W	every two weeks
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumours
ROW	Rest of world
RSDV	Reduced source data verification
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries;
SOC	system organ class
TL	transformed lymphoma,
TNBC	triple negative breast cancer
TSH	thyroid stimulating hormone
TTR	time to resolution
ULN	upper limit of normal
US	United States

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 21 June 2016 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 recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) after platinum-based therapy in adults for OPDIVO.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, of the SmPC are updated in order to add the proposed new indication, add a warning that patients with a baseline performance score ≥ 2, untreated brain metastasis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the SCCHN clinical trial and update the undesirable effect and safety information.
LabellingPackage leaflet is updated in accordance.
Moreover, the updated RMP version 6.0 has been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0064/2014 on the agreement of a paediatric investigation plan (PIP) and CW/1/2011 on the granting of a class waiver.

At the time of submission of the application, the PIP P/0064/2014 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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Aranzazu Sancho-Lopez Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	21 June 2016
Start of procedure:	16 July 2016
CHMP Rapporteur Assessment Report	19 September 2016
CHMP Co-Rapporteur Assessment Report	6 September 2016
PRAC Rapporteur Assessment Report	16 September 2016
PRAC members comments	21 September 2016
Updated PRAC Rapporteur Assessment Report	22 September 2016
PRAC Outcome	29 September 2016
CHMP members comments	3 October 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 October 2016
Request for supplementary information (RSI)	13 October 2016
CHMP Rapporteur Assessment Report	23 December 2016
PRAC Rapporteur Assessment Report	3 January 2017
PRAC members comments	4 January 2017
Updated PRAC Rapporteur Assessment Report	6 January 2017
PRAC Outcome	12 January 2017
CHMP members comments	16 January 2017
Updated CHMP Rapporteur Assessment Report	20 January 2017
Request for supplementary information (RSI)	26 January 2017
PRAC Rapporteur Assessment Report	24 February 2017
PRAC members comments	1 March 2017
CHMP Rapporteur Assessment Report	20 March 2017
PRAC Outcome	9 March 2017
CHMP members comments	13 March 2017
Updated CHMP Rapporteur Assessment Report	17 March 2017
Opinion	23 March 2017

2. Scientific discussion

2.1. Introduction

Nivolumab is a programmed death receptor 1 (PD-1) immune checkpoint inhibitor. The PD-1 receptor is a key regulator of T-cell activity that has been shown to control tumour-specific inhibition of T-cell responses to tumours. Engagement of the PD-1 co-inhibitory receptor on activated T cells through programmed death ligands 1 and 2 (PD-L1 and PD-L2) results in inhibition of T-cell proliferation, survival and cytokine secretion.

Opdivo is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that potentiates in vitro T-cell responses through dual ligand blockade of PD-L1 and PD-L2, and does not mediate antibody-dependent cell-mediated cytotoxicity (ADCC). Expression of PD-L1 and PD-L2 by malignant cells or other cells, including immune cells, allows multiple tumour types to evade immune-mediated destruction. Nivolumab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Problem statement

Head and neck carcinomas are the sixth most common cancer in the world, accounting for approximately 550,000 new cases and around 300,000 deaths each year[1,2,3]. In Europe, there were approximately 140,000 new cases per year with 63,500 deaths reported[4,5]. About ~90% of all head and neck cancer cancers are squamous cell carcinomas. Most SCCHN arise from the epithelial lining of the oral cavity, larynx and hypopharynx. The most important risk factors identified in SCCHN include tobacco and alcohol use, and in a subgroup of SCCHN (particularly oropharynx tumours), human papilloma virus (HPV) has been identified as a strong independent prognostic factor, with HPV positive infected tumours associated with more favourable clinical outcomes[6].

At initial diagnosis, about a third of patients present with early stage (33%; Stage I/II), whereas the majority present with locally advanced disease (52-60%; Stage III/IV-A/IV-B). Only a small minority presents with metastatic disease initially (~10%; Stage IV-C). With standard of care treatment, the 5-year survival is 80%, 50%, and 25% for early stage, locally advanced, and metastatic disease, respectively.

Approximately 50% of the population initially treated with curative intent will either have refractory disease or will eventually develop recurrent disease. For these patients, the 1-year survival rate is 5-33% by various estimates with a median OS (mOS) of 6 to 9 months[7]. Patients with metastatic and recurrent SCCHN that is no longer amenable to local surgical/radiation therapy experience substantial morbidity and high mortality. Treatment choice is mostly determined by prior treatment, progression-free interval since last platinum-based therapy, and comorbidities.

In patients without prior platinum treatment, or with a progression-free interval of > 6 months since last platinum, the current standard of care was established in 2008 with results from the EXTREME study[8]. The addition of cetuximab to platinum-based chemotherapy with 5-fluorouracil (5-FU) significantly prolonged the mOS from 7.4 months in the chemotherapy alone group to 10.1 months in the group that received

[1] Siegel RL, Miller KD, Jemal A. Cancer Statistics 2016. Cancer J Clin 2016; 7-30.
[2] Argiris A, Karamouzis MV, Raben D, et al. Head and neck cancer. Lancet 2008;371:1695-709.
[3] Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.
[4] Gatta G, Botta L, Sanchez MJ, et al. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. Eur J Cancer. 2015;51:2130.
[5] Gregoire V, Lefebvre JL, Licitra L, et al. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment, and follow-up. Annals Oncol 2010; 21 (Suppl 5): v184-v186.
[6] Leemans CR, Braakhuis B, Brakenhoff R. Molecular biology of head and neck cancer. Nature Reviews Cancer Vol 11 Jan 2011
[7] NCCN Guidlines 2015 Head and Neck Cancers. http://oralcancerfoundation.org/treatment/pdf/head-and-neck.pdf
[8] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008; 359(11):1116–1127.

chemotherapy plus cetuximab. Patients whose disease progresses within 6 months of platinum-based therapy, regardless of whether it was given for locally advanced or metastatic disease, have a poor prognosis[9]. In this patient population, no OS benefit has ever been demonstrated, and thus the choice of chemotherapy is not well defined. Treatment choice is based on several factors including previous chemotherapy exposure, performance status, and comorbid conditions. In the US and the EU, recommendations include best supportive care, clinical trials, and single agents including paclitaxel, docetaxel, 5-FU, methotrexate, cetuximab, ifosfamide, bleomycin, gemcitabine, capecitabine, and vinorelbine[10].

In Europe, no drugs have been approved for patients progressing on or after platinum based therapy. For patients not eligible for combination chemotherapy, European Society of Medical Oncology (ESMO) guidelines consider weekly methotrexate as the accepted treatment, and state that is unclear whether taxanes are useful in this context or not. The guidelines further mention that cetuximab alone has a favourable toxicity profile with activity that is comparable to methotrexate alone[5].

Several small, single arm studies have evaluated the treatment of platinum-refractory disease with best supportive care or other therapies. In a retrospective study analysing clinical records from 151 patients with SCCHN refractory to platinum-based chemotherapy treated between 1990 and 2000 at 7 different centres around Europe, most patients (45%) received only best supportive care and had a median survival of 56 days[11]. A total of 28.5% of the patients received second-line chemotherapies, without any objective response, and a median survival of 103 days. In platinum-refractory patients treated with cetuximab and cisplatin regimen, a mOS of 4.3 months and response rate of 6% has been reported[11]. Docetaxel monotherapy treatment of 20 patients with platinum-refractory disease with documented tumour progression during platinum-based treatment or recurrence within 6 months after platinum-based chemoradiotherapy resulted in an overall response rate of 10% (2/20) and tumour control rate of 25% (5/20)[12]. Median PFS (mPFS) and mOS were 1.7 and 4.6 months, respectively.

Table 1: Single Agents Recommended in US and EU for the Treatment of Recurrent and/or Metastatic SCCHN in the Platinum-refractory Setting

Agent	Date of Approval	Indication
Cetuximab	EU approval: Dec-2008	In combination with RT for the treatment of locally or regionally advanced SCCHN or in combination with platinum-based chemotherapy for recurrent and/or metastatic SCCHN
	US approval: Mar-2006	In combination with RT for the treatment of locally or regionally advanced SCCHN or monotherapy for treatment of patients with recurrent or metastatic SCCHN after failure of platinum-based therapy
	US approval: Nov-2011	In combination with platinum-based therapy + 5-FU for the first line treatment of patients with recurrent locoregional disease and/or metastatic SCCHN
Docetaxel	US approval: Oct-2006	In combination with cisplatin and 5-FU for the induction treatment of inoperable, locally advanced SCCHN
	EU approval: Nov-2006	In combination with cisplatin and 5-FU for the induction treatment of locally advanced SCCHN
Methotrexate	US approval: Jan-2004	Alone or in combination with other anti-cancer agents is the treatment of epidermoid cancers of the head and neck
	EU approval: various[a]	For the treatment of head and neck cancer (not centrally authorized, national approvals only)

[a] Approved via National procedures in several EU member states for over 30 years

Abbreviations: 5-FU: 5-fluorouracil; EU: European Union, RT: radiotherapy; SCCHN: squamous cell carcinoma of the head and neck; US: United States

[9] Colevas AD. Systemic therapy for metastatic or recurrent squamous cell carcinoma of the head and neck. J Natl Compr Canc Netw 2015; 13:e37-e48.

[10] Mesıa R, Pastor M, Grau JJ, et al. SEOM clinical guidelines for the treatment of head and neck cancer (HNC) 2013. Clin Transl Oncol 2013 Aug 27 [Epub ahead of print].

[11] Herbst RS, Arquette M, Shin DM, et al., Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 2005;23:5578-87.

[12] Zenda S, Onozawa Y, Boku N, et al. Single-agent Docetaxel in Patients with Platinum-refractory Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN). Jpn. J. Clin. Oncol. 2007;37(7): 477-481. (doi: 10.1093/jjco/hym059).

Table 2: Clinical Efficacy of Treatments in Recurrent and/or Metastatic SCCHN

Study/Treatment Reference	mOS (months)	mPFS (months)	ORR (mDOR)
Mixed patient population of pre-treated/untreated[11]			
Methotrexate	NA	NA	21%-66%
Docetaxel	3.9-11.3	1.8-2.1	7%-42%
Platinum-refractory			
Cetuximab monotherapy[10,13]	178 days (~5.8 months)	NA	13.0% (5.8 months)
Cetuximab+cisplatin[14]	4.3	NA	6%
Docetaxel monotherapy[15]	4.6	1.7	10%
Zalutumumab[16]	5.3	2.1	5.7%

Abbreviations: BSC: best supportive care; mDOR: median duration of response; FU: 5-fluorouracil; mOS: median overall survival; mPFS: median progression-free survival; NA: not available; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PT: platinum.

The proposed indication for nivolumab in SCCHN

"Opdivo is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck after platinum-based therapy in adults."

The final indication as adopted by the CHMP is:

"Opdivo as monotherapy is indicated for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1)."

The recommended dose and schedule of nivolumab monotherapy for the SCCHN indication is 3 mg/kg administered as IV infusion over 60 minutes Q2W, which is consistent with existing approved dose and schedule of nivolumab monotherapy in adults.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Nivolumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), nivolumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on the non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), an ERA justifying the lack of ERA studies is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Table 3 Tabular overview of clinical studies

Study Type	Study Identifier/Report Location (Study Status)	Study Objective	Study Design	Treatment Cohorts	No. of Treated Subjects (No. of Nivolumab-treated subjects)	Study Population
Efficacy, Safety	CA209141/ Module 5.3.5.1 (study completed, final report available)	To compare the OS of nivolumab to investigator's choice therapy in subjects who have tumor progression within 6 months of last dose of platinum therapy in the primary, recurrent, or metastatic setting	Phase 3, open-label randomized study of nivolumab monotherapy vs investigator's choice therapy	Randomized in 2:1 ratio to: **Nivolumab** - 3 mg/kg IV Q2W Or **Investigators choice of**: Cetuximab - 400 mg/m² IV once, then 250 mg/m² weekly(where approved for use as monotherapy for recurrent SCCHN) Methotrexate - 40 mg/m² IV weekly Docetaxel 30 mg/m² IV weekly	347 (236)	Adult (≥ 18 years) subjects with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) that has progressed on or within 6 months of the last dose of a platinum-containing therapy

Abbreviations: BMS: Bristol-Myers Squibb, IV: intravenous, No: number, NSCLC: non-small cell lung cancer, rate, OS: overall survival, Q2W: every 2 weeks;

2.3.2. Pharmacokinetics

The nivolumab clinical pharmacology profile has been well characterised and described in previously submitted clinical pharmacology package.

The clinical pharmacology data in this application support the proposed use of nivolumab as monotherapy for the treatment of recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN) at the recommended dose and schedule of 3 mg/kg infusion over 60 minutes every 2 weeks (Q2W).

The recommended dose and schedule of nivolumab monotherapy for SCCHN is the same as that approved for melanoma, NSCLC, and RCC.

Pharmacokinetic characteristics of nivolumab as previously described for patients with solid tumours melanoma, NSCLC and RCC is summarised in Table 4.

Table 4 Summary statistics of individual pharmacokinetic parameters of nivolumab in subjects with solid tumours (n= 1484)

Parameter	Mean (SD)	Geometric Mean (%CV)	Median (Min, Max)
Clearance (L/h)	0.01 (0.00455)	0.00921 (45.4)	0.00909 (0.00138,0.0438)
Volume of the Central Cmt (L)	4.15 (1.27)	3.95 (30.7)	4.01 (0.141,9.86)
Volume of the Peripheral Cmt (L)	3.92 (1.68)	3.65 (43)	3.68 (0.794,22.7)
Volume of Distribution (L)[a]	8.06 (2.35)	7.76 (29.1)	7.77 (2.49,27.6)
Alpha Half-life (h)	41.7 (10.9)	40.2 (26.3)	40.7 (2.58,103)
Beta Half-life (d)	28.8 (20.7)	26.4 (72)	26.3 (5.72,564)

Source: M:\bms\nivolumab\002522\d1pk\tables\rtf\sumstat-exp.rtf

[a] Volume of Distribution (L) at steady-state = Volume of the Central Cmt (L) + Volume of the Peripheral Cmt (L)

SD: standard deviation; %CV: coefficient of variation expressed as a percentage; Min: minimum; Max: maximum; Cmt: compartment

Results from a nivolumab population pharmacokinetics (PPK) analysis was used to characterise the nivolumab serum concentration-time profile in subjects with SCCHN from Phase 3 Study CA209141.

Population PK

Model

The purpose of the current popPK analysis was to characterise the nivolumab concentration-time data in subjects with SCCHN relative to NSCLC subjects. This was achieved by assessing the effect of SCCHN tumour type as a covariate of nivolumab CL, relative to subjects with NSCLC.

The PPK analysis was performed using data from 2 Phase 1 studies (MDX1106-01, MDX1106-03), 1 Phase 2 study (CA209063) and 3 Phase 3 studies (CA209017, CA209057, and CA209141), with a total of 1035 subjects included. These studies were chosen as nivolumab PK in SCCHN and NSCLC subjects was available from these studies, as well as in which nivolumab PK was sampled intensively.

The PPK model development consisted of: 1) Base Model to re-estimate the PK parameters using a previously developed final model, and 2) Full Model to assess the tumour type effect (SCCHN vs NSCLC) on nivolumab CL. The base model was a 2-compartment model with zero order IV infusion input and first-order elimination with a combined additive and proportional residual error model. It included effects of baseline body weight, eGFR, ECOG, tumour type on CL, baseline body weight and gender on VC.

Parameter estimates from the full PPK model are provided in Table 5.

Table 5: Parameter estimates of the full PPK model

Name[a,b] [Units]	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects			
Proportional error (-)	0.208	0.00600 (2.88)	0.195 - 0.220
Additive error (-)	0.286	0.0766 (26.8)	0.164 - 0.484
CL (L/h)	0.00858	2.59E-04 (3.02)	0.00806 - 0.00915
VC (L)	3.78	0.0692 (1.83)	3.65 - 3.92
Q (L/h)	0.0355	0.00229 (6.45)	0.0311 - 0.0407
VP (L)	3.85	0.107 (2.78)	3.65 - 4.07
CL_{BW}	0.665	0.0646 (9.71)	0.543 - 0.794
CL_{eGFR}	0.200	0.0527 (26.4)	0.0981 - 0.306
CL_{ECOG}	0.156	0.0316 (20.3)	0.0905 - 0.219
VC_{BW}	0.756	0.0479 (6.34)	0.665 - 0.854
VC_{SEX}	0.101	0.0226 (22.4)	0.0554 - 0.146
CL_{SCCHN}	0.0129	0.0444 (344)	-0.0758 - 0.108
CL_{Other}	0.0615	0.0399 (64.9)	-0.0182 - 0.140
Random Effects[f]			
ω^2 *CL [-]*[g]	0.163 (0.404)	0.0138 (8.47)	0.132 - 0.195
ω^2 *VC [-]*	0.0573 (0.239)	0.00580 (10.1)	0.0457 - 0.0685
ω^2 *VP [-]*	0.216 (0.465)	0.0262 (12.1)	0.167 - 0.270
ωCL:ωVC	0.0474 (0.490)	0.00593 (12.5)	0.0359 - 0.0592

[a] Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

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

[e] The confidence interval values are taken from 2000 bootstrap runs (1635 minimization successful runs) executed through PsN bootstrap procedure (including the minimization terminated runs due to rounding errors)

[f] Eta shrinkage: ETA_CL: 12.1%, ETA_VC: 23.8%, ETA_VP: 35.7%

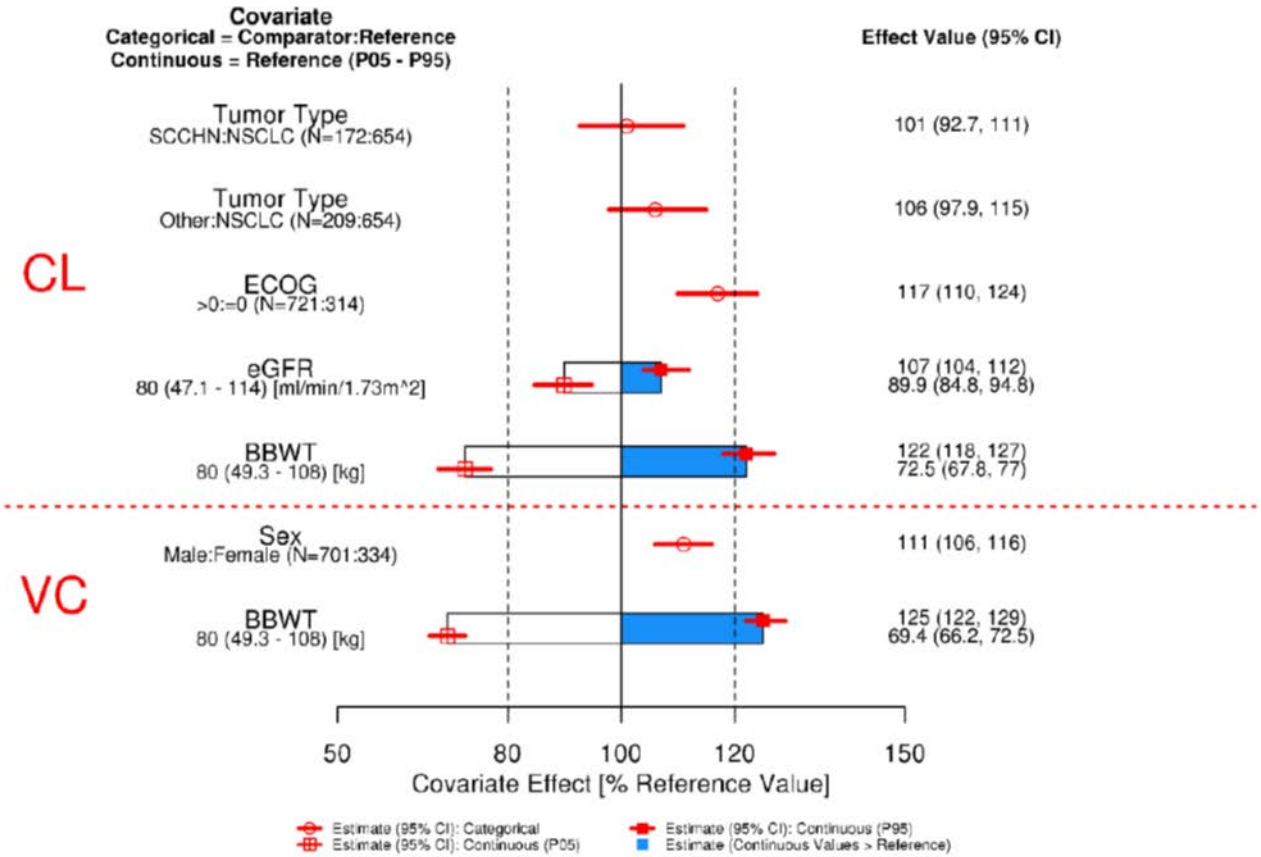
[g] Inter-individual variability

CL_{Other}: Effect of other types of tumor relative to NSCLC on CL.

Analysis of Covariate Effects

The effect of categorical and continuous covariates on the typical value of the structural model parameters of CL and VC and the estimated covariate effects (and 95% confidence intervals) are presented in Figure 1.

The magnitude of effect of the tested covariates on CL, accounting for uncertainty, was within the ±20% boundaries for all covariates, except BW. The magnitude of the effect of ECOG, body weight and eGFR on CL, and the effect of gender and body weight on central volume of distribution in this SCCHN population are comparable to what was previously reported in other solid tumour populations including RCC, NSCLC and melanoma. The SCCHN tumour type was associated with a non-statistically significant increase of approximately 1% in nivolumab CL.



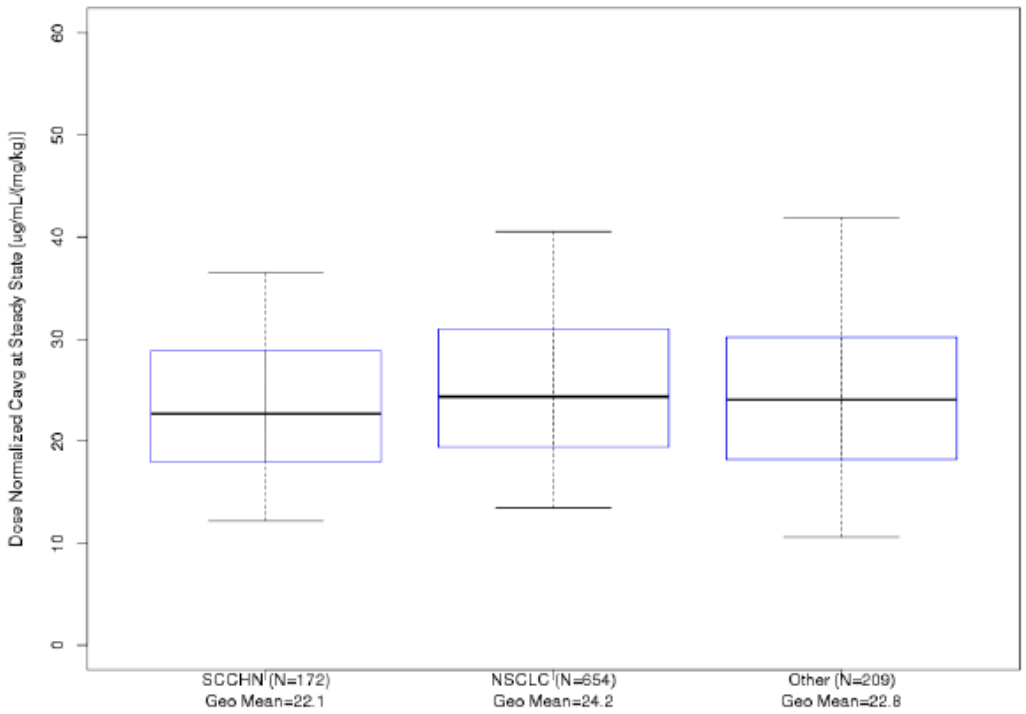
Analysis-Directory: /global/pkms/data/CA/209/C15/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/cov-eff-plot-fullmodel.r
Source: Analysis-Directory/R/plots/full-ppk-cov-eff-plot.png

Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal red lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal red lines). Open/Blue area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is female, ECOG=0, eGFR=80 m>/min/1.73m^2, body weight=80kg, NSCLC tumor type. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Figure 1: Covariate effects on PPK model parameters (full PPK model)

Evaluation of the Effect of Tumour Type on Nivolumab Exposure

Nivolumab exposure (measured as dose-normalized Cavgss, other exposure measurements are highly correlated with Cavgss) appears to be similar across SCCHN, NSCLC, and other solid tumour types (which include subjects with melanoma, prostate, renal, and colorectal cancer in phase 1 studies) as shown in Figure 2. SCCHN tumour type was not associated with any clinically or statistically different nivolumab CL relative to the NSCLC reference value determined in the population PK analysis.



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Program Source: Analysis Directory/R/scripts/reporting-tables-individual-exposures.r
Source: Analysis Directory/R/plots/CAVGSS by Tumor Type Q2W.png
The boxes represent the 25th, 50th, and 75th percentiles of the distribution. The whiskers extend from the 5th to 95th percentiles.

Figure 2: Distribution of nivolumab exposure (dose-normalised Cavgss) by tumour type

2.3.3. Pharmacodynamics

Exposure response analyses of efficacy were not conducted as data in subjects with SCHNN are only available from a single nivolumab dosing regimen. Previous exposure-response analyses of efficacy in RCC, lung cancer and melanoma indicated that high nivolumab Cl but not Cavgss was associated with less efficacy.

Exposure response analysis of safety were also not conducted for subjects with SCHNN, as nivolumab 3 mg/kg Q2W has been shown to be safe and well tolerated in several other tumour types and previous analyses in advanced melanoma, NSCLC, and RCC patients have shown that AE-DC/D does not increase with Cavgss produced by nivolumab doses of 1 to 10 mg/kg Q2W.

Immunogenicity

Anti-nivolumab antibody (ADA) was analysed using the previously described assay (ICDIM 140).

Immunogenicity Results from Study CA209141

A summary of the ADA assessments for nivolumab subjects on Study CA209141 who had evaluable ADA data at baseline and on treatment is presented in Table 6.

From 240 patients treated with nivolumab in CA209141 (SCCHN trial) only 148 (61.7%) were evaluable subjects for immunogenicity.

Thirteen subjects (8.8%) were ADA positive following administration of nivolumab. No subject was considered persistent positive and one subject was neutralizing ADA positive. The highest titer value observed in ADA positive subjects was 128, which occurred in 2 subjects. Both subjects were positive for ADA only at the last sample. One subject was also neutralising antibody positive. All other ADA positive subjects had low titer values of 32 or less.

Out of all nivolumab-treated subjects who were evaluable for ADA, none experienced select AEs in the hypersensitivity/infusion reaction category.

Table 6 Summary of nivolumab antibody assessments in study CA209141-All nivolumab treated subjects and at least one positive post-baseline assessment.

	Number of Subjects (%)
	CA209141 (N=148)
Baseline ADA Positive	13 (8.8)
ADA Positive	13 (8.8)
Persistent Positive	0
Only Last Sample Positive	9 (6.1)
Other Positive	4 (2.7)
Neutralizing ADA Positive[a]	1 (0.7)
ADA Negative	135 (91.2)

[a] See the narrative for Subject CA209141-27-198 in Appendix 7.4b of the CA209141 CSR[6]

Source: Table 8.13.1-1 of the CA209141 CSR[6]

Integrated Immunogenicity Analysis for Nivolumab (Monotherapy)

A pooled analysis of nivolumab ADA assessments was performed with data available from the following BMS-sponsored studies in which ADA was assessed by the current assay (ICDIM 140 V1.00/V2.02): CA209037, CA209063, CA209066, CA209017, CA209057, CA209067 (nivolumab monotherapy arm), CA209025, CA209039, CA209205 and CA209141 (see Table 7).

Of 1734 subjects who were treated with nivolumab 3 mg/kg every 2 weeks (Q2W) and evaluable for the presence of anti-drug antibodies (ADA), 170 subjects (9.8%) were ADA positive. Of those who were ADA positive, only 2 subjects (0.1% of the total) were persistent positive, and neutralising antibodies were detected in only 10 subjects (0.6% of the total). There were no acute infusion reactions, hypersensitivity events, or new or additional AEs observed in subjects with neutralising antibodies. Neutralising antibodies were not detectable in subsequent ADA assessments in 8/10 of these subjects; one of the subjects with neutralising ADA had a subsequent assessment which was ADA positive with a lower titre and neutralising antibody positive.

Table 7: Summary of nivolumab antibody assessments using method ICDIM 140 including study CA209141

	Number of Subjects (%)		
Study Number	Summary of Previous Studies[a] (N=1586)	CA209141 (N=148)	Pooled Summary (N=1734)
Baseline ADA Positive	79 (4.98)	13 (8.8)	92 (5.3)
ADA Positive	157 (9.9)	13 (8.8)	170 (9.8)
Persistent Positive[b]	2 (0.1)	0	2 (0.1)
Only Last Sample Positive	54 (3.4)	9 (6.1)	63 (3.6)
Other Positive	101 (6.4)	4 (2.7)	105 (6.1)
Neutralizing ADA Positive	9 (0.6)	1 (0.7)	10 (0.6)
ADA Negative	1429 (90.1)	135 (91.2)	1564 (90.2)

Source: See note a and Table 8.13.1-1 of the CA209141 CSR[6]

[a] Previous studies includes studies CA209-063, -037, -066, -017, -057, -067, -025, -039, -205 summarized in Module 2.7.2 Summary of Clinical Pharmacology for Classical Hodgkin Lymphoma[17]

[b] Persistent positive subject defined as a subject with ADA-positive samples at 2 or more consecutive time points, where the first and last ADA positive samples were at least 16 weeks apart.

Effect of Immunogenicity on Safety

To further explore the relationship between immunogenicity and safety, an integrated assessment of the potential impact of ADA on immunogenicity-related effects was performed by summarising the select adverse events in the hypersensitivity/infusion reaction category by anti-nivolumab antibody status (positive or negative) for those subjects who were treated with nivolumab monotherapy. Data was available from studies CA209063, CA209037, CA209066, CA209017, CA209057, CA209067, CA209025, CA209039 (cHL all), CA209205 (cohorts A+B+C), and CA209141 (Table **8**). Of the subjects evaluable for the presence of anti-nivolumab antibody, a total of 109 experienced hypersensitivity/infusion reactions. Of the 109 subjects who experienced hypersensitivity/infusion reactions, 4 were positive for anti-nivolumab antibody and 105 were negative for anti-nivolumab antibody during the study. A total of 4/180 (2.2%) anti-nivolumab antibody positive subjects experienced adverse events in the hypersensitivity/infusion reaction category.

One subject that was ADA positive (in Study CA209037) had an ADA positive status only for the last sample and experienced a Grade 1 hypersensitivity reaction after the first nivolumab dose when the ADA status was negative. One subject from Study CA209067 (monotherapy arm) had one ADA positive sample after one dose of nivolumab. This subject then continued nivolumab treatment, but ADA samples that were collected after 4 and 7 weeks of treatment were negative. This subject experienced bronchospasm prior to the last ADA sample at 7 weeks after initiation of treatment. Thus, the bronchospasm was not associated with the positive ADA status. Two subjects from Study CA209057 were ADA positive and had Grade 1-2 infusion related reactions on the same day. These subjects went on to receive additional nivolumab doses and ADA were not detectable in subsequent assessments.

Table 8: Summary of hypersensitivity / infusion reactions by nivolumab anti-nivolumab antibody status across studies - all treated subjects receiving nivolumab monotherapy with anti-nivolumab antibody Positive or anti-nivolumab antibody negative

	Number of Subjects (%)	
Select AE Category: Hypersensitivity/Infusion Reaction	Nivolumab ADA Positive (N = 180)	Nivolumab ADA Negative (N = 1603)
Total Subjects with an Event	4 (2.22)	105 (6.55)
Anaphylactic Shock	0	1 (0.06)
Bronchospasm	1 (0.56)	10 (0.62)
Hypersensitivity	1 (0.56)	42 (2.62)
Infusion Related Reaction	2 (1.11)	58 (3.62)

Note: Integrated data from studies CA209063, CA209037, CA209066, CA209017, CA209057, CA209067 (monotherapy arm), CA209025, CA209039 (all cHL), CA209205 (Cohort A+B+C), and CA209141

The impact of immunogenicity on nivolumab clearance has been assessed as part of previous PPK analyses as a time-varying covariate, and was associated with a 13% to 25% increase in clearance.

Effect of Immunogenicity on Efficacy

In previous integrated immunogenicity analyses it was demonstrated that the presence of neutralising antibodies was transient and did not recur in subsequent samples, and that there was no evidence of loss of efficacy in subjects with neutralising antibodies

2.3.4. Discussion on clinical pharmacology

No dose finding study was conducted for nivolumab monotherapy for treatment of HNSCC. The recommended dose and schedule of nivolumab monotherapy for treatment of HNSCC is the same as that approved for melanoma, NSCLC, and renal cell carcinoma monotherapy: 3 mg/kg IV infusion over 60 minutes Q2W. This is considered acceptable.

An updated popPK model has been developed for the evaluation of the PK in subjects with SCCHN. The popPK model has been based on the one initially developed for the characterisation of the PK in NSCLC. The same covariates as the ones included to characterise NSCLC have been considered in this new model for SCCHN: Baseline body weight, baseline ECOG, and baseline eFGR for CL and Baseline body weight and sex for VC.

One hundred seventy two (79.63%) out of 216 patients in the PK database from study CA209141 (SCCHN) were included in the popPK analysis dataset. Subjects with no serum concentrations available and subjects with PK samples that could not be associated with clinical data were excluded, which is acceptable. The estimated parameters were similar to the estimated parameters from the previous final models and remain in line with what could be expected for an IgG MoAb (CL=0.000858 L/h; VC=3.75 l; VP=3.85 L). The popPK model parameters were estimated with an acceptable precision (shrinkages are <30% from Cl and VC and slightly above this threshold for VP; ETA_VP: 35.7%).

Overall the model showed an acceptable agreement between model predictions and observations. Having said that, pharmacokinetic data for study CA209141 is limited and sparse, thus results should be interpreted with caution.

No clinically relevant differences in clearance and exposure were observed in patients with SCCHN vs. NSCLC vs. other tumours.

The absence of exposure response analysis for efficacy and safety for subjects with HNSCC has been sufficiently justified. Previous exposure-response relationships had shown that Cavgss was not a significant predictor of hazard of death after accounting for nivolumab CL. As in HNSCC, only one nivolumab dose was administered, relationships with Cavgss are confounded by nivolumab CL. Nivolumab 3 mg/kg Q2W has been shown to be safe and well tolerated in several other tumour types and previous analyses in advanced melanoma, NSCLC, and RCC patients have shown that AE-DC/D does not increase with Cavgss produced by nivolumab doses of 1 to 10 mg/kg Q2W. No unexpected safety issues in subjects with HNSCC were observed.

From 240 patients treated with nivolumab in CA209141 (SCCHN trial) 148 (61.7%) were evaluable subjects for immunogenicity. Nivolumab has low immunogenic potential; pooled analysis of all tumour types showed that approximately 10% of subjects who were treated with nivolumab 3 mg/kg every 2 weeks (Q2W) monotherapy tested positive for treatment-emergent anti-nivolumab antibody. Of those who were anti-nivolumab antibody positive, only 2 subjects (0.1% of the total) were persistent positive, and neutralising antibodies were detected in 10 subjects (0.6% of the total). The safety profiles of persistent positive or neutralising positive subjects were no different than those in other subjects. There was no evidence of loss of efficacy in subjects with neutralising antibodies.

2.3.5. Conclusions on clinical pharmacology

Pharmacokinetics and immunogenicity of nivolumab have been sufficiently investigated for the extension of the indication of nivolumab 3 mg/kg every 2 weeks for treatment of SCCHN.

Overall, the popPK analysis indicated that there are no major differences in pharmacokinetics of nivolumab in HNSCC compared to other solid tumour types.

Nivolumab has low immunogenic potential. The safety profiles of persistent positive or neutralising positive subjects were no different than those in other subjects. There was no evidence of loss of efficacy in subjects with neutralizing antibodies.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The dose of nivolumab, 3 mg/kg Q2W, was selected for CA209141 based upon collective experience of nivolumab monotherapy across multiple tumour types. The analyses of safety, efficacy, and exposure-response (E-R) data from the Phase 1 study CA209003, evaluating anti-tumour activity over a dose range of 0.1 mg/kg to 10 mg/kg Q2W in several tumour types including RCC, NSCLC, and melanoma has shown that nivolumab 3 mg/kg Q2W is active across multiple-tumour types. Clinical observations and E-R analyses of these tumour types showed that the probability of a tumour response approached a plateau for nivolumab trough concentrations achieved following administration of 3 mg/kg and 10 mg/kg Q2W. Although broadly similar, review of safety data for 10 mg/kg Q2W indicated a moderately greater incidence of Grade 3/4 drug-related adverse events leading to discontinuation. In an E-R analysis of the relationship between nivolumab exposure (Cavgss) and OS over the 1 mg/kg Q2W to 10 mg/kg Q2W dose range, which included 3 mg/kg Q2W, nivolumab Cavgss was not a significant predictor of hazard of death in melanoma, NSCLC, and RCC, indicating that, over this dose range, there is a flat E-R relationship. Based upon the totality of experience across immunogenic and non-immunogenic tumour types, 3 mg/kg Q2W was selected as the dose anticipated to achieve an appropriate balance of benefit and risk in CA209141.

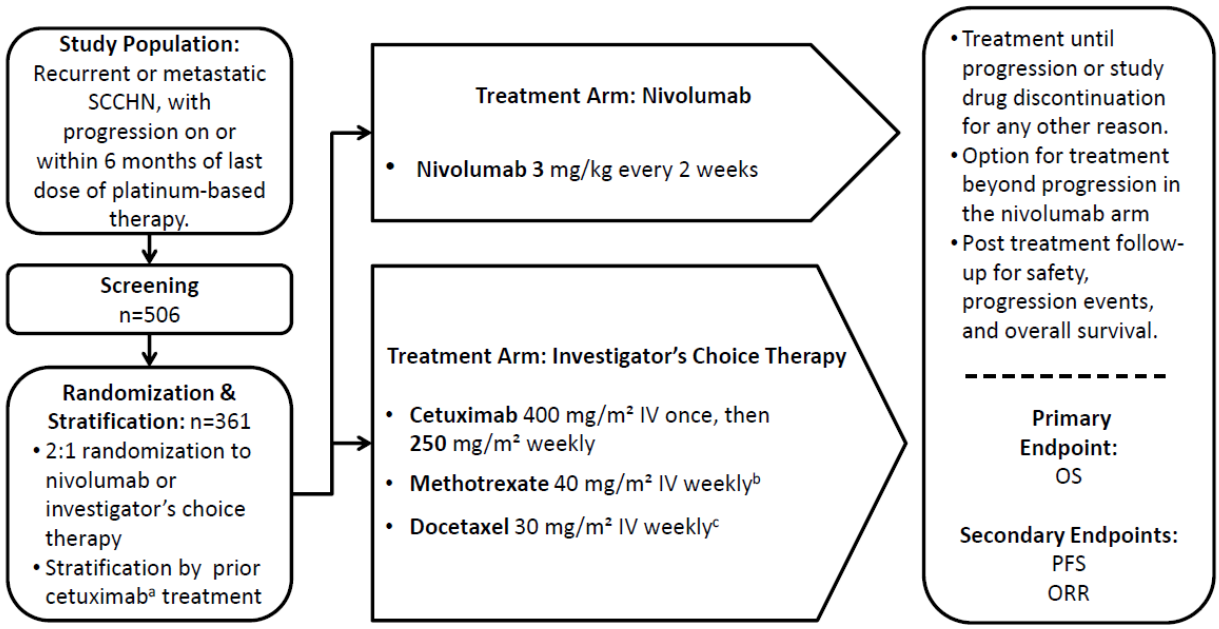
Nivolumab exposure (measured as dose-normalized Cavgss) at 3 mg/kg Q2W in SCCHN subjects in CA209141 appeared to be similar to that in NSCLC. SCCHN tumour type was not associated with a clinical or statistically significant difference in nivolumab clearance relative to the reference value for NSCLC as determined by population pharmacokinetic analysis.

Collectively, these results support the recommended dose of nivolumab 3 mg/kg Q2W in the treatment of recurrent or metastatic platinum-refractory SCCHN.

2.4.2. Main study

Study CA209141: An Open Label, Randomized Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's Choice in Recurrent or Metastatic Platinum-Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN)

The study consisted of 3 phases: screening, treatment, and follow-up. Tumour response was assessed by investigators according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 at week 9 (±1 week) and every 6 weeks (±1 week) thereafter until disease progression. Subjects were treated until progression, unacceptable toxicity, or other protocol-defined reasons (e.g. dose delay beyond a defined time period). Treatment beyond initial investigator-assessed RECIST v1.1-defined progression was permitted for nivolumab if the subject had investigator-assessed clinical benefit and was tolerating the study drug. Subjects were followed for OS every 3 months until death, lost to follow-up, or withdrawal of study consent. An independent Data Monitoring Committee (DMC) provided oversight of safety and efficacy considerations.



[a] Prior cetuximab Yes = 221 (61.2%), No = 140 (38.8%)
[b] Methotrexate could be increased to 60 mg/m^2 if tolerated per local practices
[c] Docetaxel could be increased to 40 mg/m^2 if tolerated per local practices
Dose reductions were not permitted for nivolumab, but were permitted for investigator's choice therapies.

Abbreviations: IV = intravenous; Nivo = nivolumab; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks; SCCHN = squamous cell carcinomas of head and neck.

Source: Figure 3.1-1 of the CA209141 CSR

Figure 3: Study design schematic

Methods

Study participants

Main inclusion criteria:

a) Histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).

b) Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

c) Documentation of p16-positive or p16-negative disease to determine human papillomavirus (HPV) status of tumour for SCCHN of the oropharynx. Note: If results are not available, then a sample (tissue on microscopic slides, tissue block or a fresh tissue biopsy in formalin) should be sent to the central laboratory for analysis.

d) Tumour progression or recurrence within 6 months of last dose of platinum therapy in the adjuvant (ie with radiation after surgery), primary (i.e., with radiation), recurrent, or metastatic setting. Clinical progression after platinum therapy is an allowable event for entry and is defined as progression of a lesion at least 10 mm in size that is amenable to caliper measurement (e.g. superficial skin lesion as per RECIST 1.1) or a lesion that has been visualised and photographically recorded with measurements and shown to have progressed.

e) Measurable disease by CT or MRI per RECIST 1.1 criteria.

f) Tumour tissue (archival or fresh biopsy specimen) must be available for PD-L1 expression analysis and other biomarker correlative studies. For subjects where a fresh biopsy is not feasible, archival tumour material must be made available. The subject must not have received systemic therapy subsequent to obtaining the archived biopsy and prior to screening. Tumour tissue must have been obtained in the metastatic setting or from an unresectable site of disease.

g) Prior curative radiation therapy must have been completed at least 4 weeks prior to study drug administration. Prior focal palliative radiotherapy must have been completed at least 2 weeks before study drug administration.

Tumour PD-L1 expression was quantitatively assessed using the Dako PD-L1 IHC 28-8 pharmDx with cut-off values of 1%.

Main exclusion criteria

a) Active brain metastases or leptomeningeal metastases are not allowed. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (except where contraindicated in which CT scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. Cases, including base of skull lesions without definitive evidence of dural or brain parenchymal involvement, should be discussed with the medical monitor. There must also be no requirement for immunosuppressive dose of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

b) Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary, and salivary gland or non-squamous histologies (e.g. mucosal melanoma) are not allowed.

Treatments

In subjects randomised to the nivolumab group, nivolumab 3 mg/kg was administered as a 60-minute IV infusion Q2W.

In subjects randomised to the investigator's choice group, subjects received one of the following treatments (as selected by the investigator):

- Cetuximab 400 mg/m^2 IV once, then 250 mg/m^2 weekly (where approved for use as monotherapy for recurrent SCCHN).
- Methotrexate 40 mg/m^2 IV weekly (could be increased to 60 mg/m^2 if tolerated as per local practices).
- Docetaxel 30 mg/m^2 IV weekly (could be increased to 40 mg/m^2 if tolerated as per local practices).

Dose reductions were not permitted for nivolumab but were permitted for cetuximab, methotrexate, and docetaxel.

Dose delays were permitted in both groups.

The following medications were prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event).
- Systemic corticosteroids > 10 mg daily prednisone equivalent (with defined exceptions).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy or standard or investigational agents for treatment of cancer).

Investigators may choose to resect solitary lesions in patients with unresectable or metastatic SCCHN and render the subject free of macroscopic disease. Subjects treated in this study may have lesions surgically resected only following consultation with the Medical Monitor and following the Week 21 re-staging assessments. If tumour shrinkage of the solitary lesion is noted on the Week 21 assessment, it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage. Subjects with a PR who go on to have surgical resection of remaining disease will be considered a PR.

Objectives

Primary

To compare OS of nivolumab to investigator's choice therapy in subjects who have tumour progression within 6 months of last dose of platinum therapy in the primary, recurrent, or metastatic setting.

Secondary

To compare progression-free survival (PFS) of nivolumab to investigator's choice.

To compare objective response rate (ORR) of nivolumab to investigator's choice.

Outcomes / endpoints

Objective	Endpoint	Endpoint Description
PRIMARY		
To compare OS of nivolumab to investigator's choice therapy	OS	OS was defined as the time from randomization to the date of death from any cause. The survival time for subjects who had not died was censored at the last known alive date. OS was censored at the date of randomization for subjects who were randomized but had no follow-up.
SECONDARY		
To compare progression-free survival PFS of nivolumab to investigator's choice.	PFS	The primary definition of PFS was the time between the date of randomization and the first date of documented progression, as determined by the investigator (as per RECIST v1.1 criteria). Subjects who die without a reported progression were considered to have progressed on the date of their death. Subjects who did not progress or die were censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessments and did not die were censored on the date they were randomized. Subjects who received subsequent systemic anti-cancer therapy prior to documented progression were censored at the date of the last tumor assessment prior to the initiation of the new therapy. The secondary definition of PFS, also known as the ITT definition, was the same as the primary definition, except there was no censoring for receipt of subsequent anti-cancer therapy prior to documented progression.
To compare objective response rate (ORR) of nivolumab to investigator's choice.	ORR	ORR was defined as the proportion of randomized subjects who achieved a best response of complete response (CR) or partial response (PR) using the RECIST v1.1 criteria as per investigator assessment. To achieve a best response of CR or PR, confirmation was required. BOR was defined as the best response designation, recorded between the date of randomization and the date of progression, as assessed by the investigator per RECIST v1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first.

Sample size

Approximately 360 subjects were to be randomised. The study required at least 278 OS events (deaths) to ensure that a 2-sided, α=0.05 level, sequential log-rank test procedure with one interim look after 70% of OS events (195) had 90% power when the true OS hazard ratio of the experimental to the control arm was 0.6667. This is equivalent to demonstrating a 50% improvement in median OS in the nivolumab group relative to the investigator's choice group.

Randomisation

After initial eligibility was established and the informed consent obtained, subjects were enrolled into the study via an IVRS. Once enrolled in the IVRS, subjects who met all eligibility criteria were randomized by IVRS in a 2:1 ratio to the nivolumab group or the investigator's choice group, with stratification by prior cetuximab treatment (yes vs no). The investigator's intended choice of therapy (cetuximab, methotrexate, or docetaxel) was entered in the IVRS for every subject prior to randomisation.

Blinding (masking)

The study was open-label.

Statistical methods

A hierarchical testing procedure was used for the comparisons of secondary endpoints to preserve the study-wise type I error rate at 0.05. If a statistically significant improvement in OS was demonstrated for nivolumab compared with investigator's choice, then PFS would be compared between treatment groups at the 5% level. If a statistically significant improvement in PFS was also demonstrated for nivolumab compared with investigator's choice, then ORR would be compared between treatment groups at the 5% level.

The comparisons of OS and PFS between treatment groups were carried out using log-rank tests stratified by prior cetuximab (yes, no), as reported in the IVRS. The primary comparison of response rate between arms was carried out using a Cochran-Mantel-Haenszel (CMH) test, stratified by prior cetuximab (yes, no).

Changes to the Planned Statistical Analyses

The following ad hoc exploratory analyses were added after database lock to help further characterise the study results:

- Cross tabulation of "intended investigator choice agent" (as recorded in the IVRS) versus investigator's choice agent actually received. Prior to randomization, investigators were asked to state which of the 3 investigator choice agents they would give if the subject were randomized to the investigator's choice arm. This information, the so called "intended investigator's choice regimen," was recorded for all randomized subjects in the IVRS.
- Demographic and baseline disease characteristics by individual agent – nivolumab, cetuximab, methotrexate, and docetaxel.
- Efficacy of nivolumab (using all subjects randomized to the nivolumab arm) versus that of cetuximab, methotrexate, and docetaxel individually.
- Efficacy of nivolumab versus that of cetuximab, restricted to subjects whose intended investigator choice prior to randomization was cetuximab. These analyses were repeated on subjects whose intended investigator choice was docetaxel and methotrexate. These analyses were intended to remove any selection bias associated with the choice of agent when comparing nivolumab to cetuximab, methotrexate, and docetaxel.
- Efficacy of nivolumab versus that of the investigator choice group by HPV p-16 status, positive or negative.
- Efficacy of nivolumab versus investigator choice group in subsets formed by crossing PD-L1 expression (< 1%, ≥ 1%) and HPV status (positive, negative).

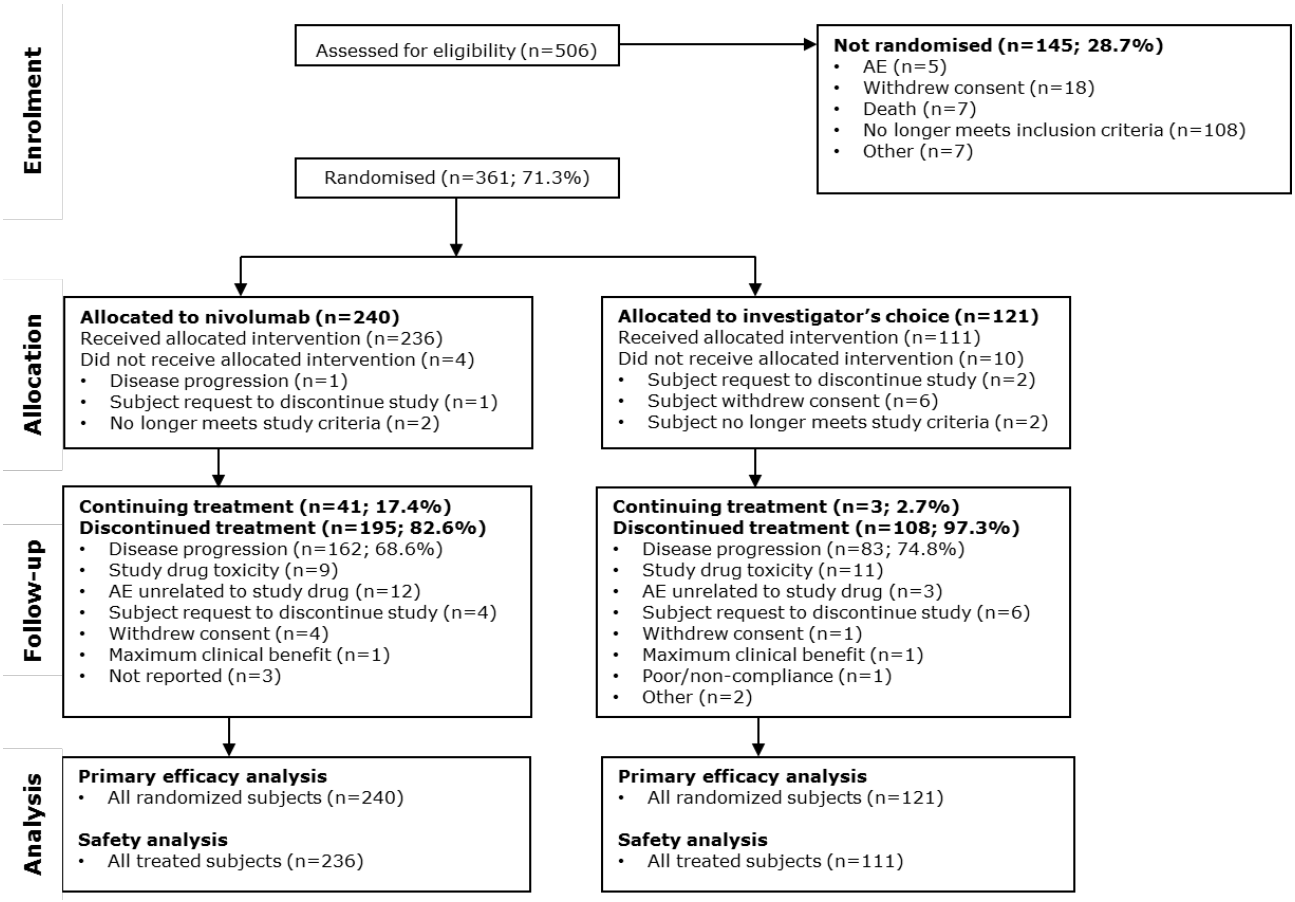
Efficacy data presented are based on 3 different database locks:

- **18-Dec-2015 Database Lock**: This lock was performed when the pre-planned number of events (deaths) was reached for the interim analysis. Analyses of demographics and other baseline characteristics, dosing, and OS were based on this lock.
- **03-Feb-2016 Database Lock**: This lock was used for PD-L1 data only. Since not all PD-L1 measurements were available at time of the original lock, a lock was performed on 03-Feb-2016 to update PD-L1 measurements (survival was not updated at this time, i.e., all OS analyses by PD-L1 status are based on clinical data as of 18-Dec-2015).
- **05-May-2016 Database Lock**: Tumour assessments, investigator-assessed best overall response (BOR), response and progression dates, and subsequent therapy are based on this lock.
  - ORR is based on this lock and includes information up until this lock.
  - PFS analyses are also based on this lock; however, since death information was not updated for this lock, and since PFS depends on both progression and death, PFS analyses were restricted to progression events (deaths or radiographic progressions) prior to the primary lock of 18-Dec-2015.

During review, updated efficacy (OS, progression-free survival [PFS], objective response rate [ORR], and duration of response [DOR]) and safety results based on the 20-Sep-2016 database lock were submitted.

Results

Participant flow



Recruitment

The enrolment period lasted approximately 14 months (May-2014 to Jul-2015). The last subject was randomised on 28-Aug-2015, and the last patient last visit date (primary clinical cut-off) for this CSR occurred on 06-Nov-2015, providing a minimum follow-up for survival of approximately 2.3 months. A total of 55 sites in 15 countries randomised subjects. Of the 361 randomised subjects, 171 (47.4%) were in Europe, 145 (40.2%) were in North America, and 45 (12.5%) were in Rest of World.

Conduct of the study

The original protocol for this study was dated 05-Feb-2014. As of 18-Dec-2015, 3 global amendments and 6 country-specific amendments were issued for this study. In addition, 1 administrative letter was issued for this study (22-Apr-2015) that corrected the title page of Amendment 08 to be country specific (Argentina) instead of global (all sites).

Table 9: Summary of Changes to Protocol CA209141

Document (Sites)	Date	Summary of Change
Amendment 01 (DE)	02-Jan-2014	Based on recommendations by the German health authorities, HIV testing was added as a safety assessment at screening and a positive test for HIV was added as an exclusion criterion (3b).
Amendment 02 (FR)	04-Jun-2014	Based on a request from the French competent authority, an inclusion criterion (5c, contraindications for subjects treated with methotrexate) and prohibited medications for subjects treated with methotrexate were added.
Amendment 03 (All)	10-Jul-2014	Table 4-1 of the protocol was updated to ensure that details for investigational product were described accurately. In addition, the dose recalculation rules as a function of body weight for the nivolumab arm were clarified, and the collection schedule for PK samples was modified. Typos were removed and other details were modified to increase comprehensibility.
Amendment 04 (JP)	10-Jul-2014	Local regulatory requirements for Japanese sites were added.
Amendment 05 (CA, FR, DE, IT, ES, CH, NL, UK, HK, TW, and KR)	26-Nov-2014	At the end of February 2015, the source and potency of the investigational product methotrexate was changed. Methotrexate 25 mg/mL, 250 mg solution for infusion used for this study would no longer be available. Methotrexate 25 mg/mL, 1000 mg solution for infusion was to be used instead.
Amendment 06 (JP)	11-Dec-2014	At the end of February 2015, the source and potency of the investigational product methotrexate was changed. Methotrexate 25 mg/mL, 250 mg solution for infusion used for this study would no longer be available. Methotrexate 25 mg/mL, 1000 mg solution for infusion was to be used instead.
Amendment 07 (All)	30-Jan-2015	Data external to the trial suggest that assumptions for co-primary outcomes of PFS and OS in CA209141 were underestimated for both treatment arms. Hence, the sample size was increased to target a hazard ratio that is in line with the available data. PFS was changed from a co primary endpoint to a secondary endpoint, leaving OS as the sole primary endpoint. This modification was based on external data which suggest that median PFS is comparable in both arms. PFS was now the first secondary endpoint to be tested in the statistical hierarchy if OS was positive. The amendment also contained administrative changes and clarifications of procedures, concomitant treatments, and eligibility criteria. This amendment was implemented prior to the Sponsor being unblinded to the data.
Amendment 08 (AR)	25-Mar-2015	Based on a request from the Argentinean health authority, study drug should be permanently discontinued in case of pregnancy.
Amendment 09 (All)	09-Jun-2015	The interim analysis was to occur 2 months after the last subject was randomized. However, because of a faster than expected accrual rate, it was projected that there would be only 55% of the required number of deaths at that time. For this reason, the stopping rule was changed to "after 70% of events or 6 months after the end of accrual, whichever occurs earlier." The amendment also contained clarification of eligibility criteria and survival data collection.

Relevant protocol deviations (significant protocol deviations that were programmable and could potentially affect the interpretability of study results) were reported in 11.9% of subjects (13.3% nivolumab and 9.1% investigator's choice). The most common relevant protocol deviation at study entry was progression associated with last prior platinum regimen > 6 months after last dose. Subjects with insufficient information to determine refractoriness to their prior platinum regimen were considered to be not refractory.

The most common relevant protocol deviation during the treatment period was receipt of concurrent anti-cancer therapy (other than palliative radiation to non-target lesions), affecting 3.3% of subjects in the nivolumab group and 1.7% of subjects in the investigator's choice group.

Table 10: Relevant Protocol Deviations

	Number of Subjects (%)		
	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)	Total (N=361)
SUBJECTS WITH AT LEAST ONE DEVIATION	32 (13.3)	11 (9.1)	43 (11.9)
AT ENTRANCE			
ECOG PS > 1 (1)	2 (0.8)	4 (3.3)	6 (1.7)
DID NOT HAVE MEASUREABLE DISEASE AT BASELINE	5 (2.1)	1 (0.8)	6 (1.7)
PROGRESSION ASSOCIATED WITH LAST PRIOR PLATINUM REGIMEN > 6 MONTHS AFTER LAST DOSE OF PLATINUM (2)	18 (7.5)	4 (3.3)	22 (6.1)
ON-TREATMENT DEVIATIONS			
RECEIVED CONCURRENT ANTI-CANCER THERAPY (3)	8 (3.3)	2 (1.7)	10 (2.8)
SUBJECT TREATED WITH THE WRONG (NOT RANDOMIZED TO) REGIMEN THROUGHOUT THE STUDY	0	0	0

(1) There was no ECOG PS reported at baseline for subjects 29-227 and 40-364. These subjects were included in the count.
(2) 9 subjects (1-316, 17-509, 42-443, 48-470, 58-424, 6-342, 61-257, 8-469, and 8-499) had insufficient information to determine time from last dose of prior platinum to progression. These subjects were counted as deviators.
(3) Palliative radiation to non-target lesions is not counted as a deviation.

Baseline data

Baseline demographic and disease characteristics and tumour assessments were generally well balanced between the nivolumab and investigator's choice groups. There was a higher proportion of former/current smokers in the nivolumab group (79.6%) than in the investigator's choice group (70.2%).

Among all randomised subjects, the median age was 60.0 years and the majority of subjects were white and male. At baseline, 90.0% had Stage IV disease, 76.5% were either former or current smokers, and 66.2% had 2 or more disease sites.

Table 11: Baseline Demographic Characteristics - All Randomized Subjects

	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)	Total (N=361)
AGE			
N	240	121	361
MEAN	59.0	59.4	59.1
MEDIAN	59.0	61.0	60.0
MIN, MAX	29, 83	28, 78	28, 83
STANDARD DEVIATION	10.15	11.00	10.43
AGE CATEGORIZATION (%)			
Grouping 1			
< 65	172 (71.7)	76 (62.8)	248 (68.7)
>= 65 AND < 75	56 (23.3)	39 (32.2)	95 (26.3)
>= 75	12 (5.0)	6 (5.0)	18 (5.0)
Grouping 2			
< 65	172 (71.7)	76 (62.8)	248 (68.7)
>= 65	68 (28.3)	45 (37.2)	113 (31.3)
GENDER (%)			
MALE	197 (82.1)	103 (85.1)	300 (83.1)
FEMALE	43 (17.9)	18 (14.9)	61 (16.9)
RACE (%)			
WHITE	196 (81.7)	104 (86.0)	300 (83.1)
BLACK OR AFRICAN AMERICAN	10 (4.2)	3 (2.5)	13 (3.6)
ASIAN	29 (12.1)	14 (11.6)	43 (11.9)
OTHER	5 (2.1)	0	5 (1.4)
ETHNICITY (%)			
HISPANIC/LATINO	9 (3.8)	4 (3.3)	13 (3.6)
NOT HISPANIC/LATINO	132 (55.0)	60 (49.6)	192 (53.2)
NOT REPORTED	99 (41.3)	57 (47.1)	156 (43.2)
REGION (%)			
NORTH AMERICA	101 (42.1)	44 (36.4)	145 (40.2)
EUROPE	109 (45.4)	62 (51.2)	171 (47.4)
REST OF WORLD	30 (12.5)	15 (12.4)	45 (12.5)

Between the 2 treatment groups, the most frequent site of the primary tumour was the oral cavity. The lymph node and lung were the most common site of disease reported outside of the head and neck.

Per protocol, and in keeping with clinical practice and guidelines, investigators were instructed to test the HPV-p16 ("HPV") status of subjects when they identified the primary site to be oropharynx. Among all randomised subjects, the proportion of subjects with HPV-positive status was balanced between the nivolumab (26.3%) and investigator's choice groups (24.0%).

Table 12: Baseline Disease Characteristics and Tumour Assessments – All Randomized Subjects

	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)	Total (N=361)
ECOG PS (%)			
0	49 (20.4)	23 (19.0)	72 (19.9)
1	189 (78.8)	94 (77.7)	283 (78.4)
>= 2	1 (0.4)	3 (2.5)	4 (1.1)
NOT REPORTED	1 (0.4)	1 (0.8)	2 (0.6)
TOBACCO USE (%)			
NEVER	39 (16.3)	31 (25.6)	70 (19.4)
FORMER/CURRENT	191 (79.6)	85 (70.2)	276 (76.5)
UNKNOWN	10 (4.2)	5 (4.1)	15 (4.2)
Stage of Disease at Study Entry			
STAGE III	25 (10.4)	10 (8.3)	35 (9.7)
STAGE IV	214 (89.2)	111 (91.7)	325 (90.0)
NOT REPORTED	1 (0.4)	0	1 (0.3)
Site of Primary Tumor (a)			
ORAL CAVITY	108 (45.0)	67 (55.4)	175 (48.5)
PHARYNX	92 (38.3)	36 (29.8)	128 (35.5)
LARYNX	34 (14.2)	15 (12.4)	49 (13.6)
OTHER	6 (2.5)	3 (2.5)	9 (2.5)
HPV-16 Status			
POSITIVE	63 (26.3)	29 (24.0)	92 (25.5)
NEGATIVE	50 (20.8)	36 (29.8)	86 (23.8)
UNKNOWN (b)	127 (52.9)	56 (46.3)	183 (50.7)
TIME FROM INITIAL DIAGNOSIS (YEARS)			
N	240	121	361
MEDIAN (MIN - MAX)	2.1 (0.2-17.5)	1.5 (0.1-19.9)	1.9 (0.1-19.9)
TIME FROM INITIAL DIAGNOSIS (%)			
< 1 YEAR	62 (25.8)	29 (24.0)	91 (25.2)
1- < 2 YEARS	55 (22.9)	43 (35.5)	98 (27.1)
2- < 3 YEARS	48 (20.0)	16 (13.2)	64 (17.7)
3- < 4 YEARS	26 (10.8)	9 (7.4)	35 (9.7)
4- < 5 YEARS	17 (7.1)	7 (5.8)	24 (6.6)
>= 5 YEARS	32 (13.3)	17 (14.0)	49 (13.6)
SUBJECTS WITH AT LEAST ONE LESION (b) (%)	239 (99.6)	120 (99.2)	359 (99.4)
SITE OF LESION (c) (d) (%)			
SKIN/SOFT TISSUE	41 (17.1)	11 (9.1)	52 (14.4)
LUNG	113 (47.1)	58 (47.9)	171 (47.4)
LIVER	34 (14.2)	19 (15.7)	53 (14.7)
VISCERAL, OTHER	1 (0.4)	5 (4.1)	6 (1.7)
LYMPH NODE	122 (50.8)	69 (57.0)	191 (52.9)
ADRENAL GLAND	3 (1.3)	2 (1.7)	5 (1.4)
CENTRAL NERVOUS SYSTEM	1 (0.4)	0	1 (0.3)
MEDIASTINUM	9 (3.8)	6 (5.0)	15 (4.2)
ORAL CAVITY	66 (27.5)	32 (26.4)	98 (27.1)
EFFUSION	1 (0.4)	2 (1.7)	3 (0.8)
SPLEEN	1 (0.4)	0	1 (0.3)
BRAIN	2 (0.8)	1 (0.8)	3 (0.8)
BREAST	1 (0.4)	0	1 (0.3)
PELVIS	2 (0.8)	0	2 (0.6)
PERITONEUM	4 (1.7)	0	4 (1.1)
ESOPHAGUS	0	1 (0.8)	1 (0.3)
PANCREAS	1 (0.4)	0	1 (0.3)
KIDNEY	2 (0.8)	3 (2.5)	5 (1.4)
PLEURA	4 (1.7)	2 (1.7)	6 (1.7)
GASTRIC	1 (0.4)	1 (0.8)	2 (0.6)
CHEST WALL	8 (3.3)	3 (2.5)	11 (3.0)
BONE WITH SOFT TISSUE COMPONENT	9 (3.8)	8 (6.6)	17 (4.7)

	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)	Total (N=361)
SITE OF LESION (c) (d) (%), continued			
BONE, NO SOFT TISSUE COMPONENT	7 (2.9)	7 (5.8)	14 (3.9)
OTHER	67 (27.9)	36 (29.8)	103 (28.5)
NUMBER OF DISEASE SITES Per Subject (%)			
1	78 (32.5)	42 (34.7)	120 (33.2)
2	82 (34.2)	31 (25.6)	113 (31.3)
3	60 (25.0)	32 (26.4)	92 (25.5)
4	17 (7.1)	10 (8.3)	27 (7.5)
>= 5	2 (0.8)	5 (4.1)	7 (1.9)
SUBJECTS WITH AT LEAST ONE TARGET LESION (%)	238 (99.2)	120 (99.2)	358 (99.2)
SITE OF TARGET LESION (c) (%)			
SKIN/SOFT TISSUE	38 (15.8)	11 (9.1)	49 (13.6)
LUNG	95 (39.6)	48 (39.7)	143 (39.6)
LIVER	29 (12.1)	17 (14.0)	46 (12.7)
VISCERAL, OTHER	1 (0.4)	4 (3.3)	5 (1.4)
LYMPH NODE	78 (32.5)	55 (45.5)	133 (36.8)
ADRENAL GLAND	0	1 (0.8)	1 (0.3)
CENTRAL NERVOUS SYSTEM	1 (0.4)	0	1 (0.3)
MEDIASTINUM	7 (2.9)	6 (5.0)	13 (3.6)
ORAL CAVITY	64 (26.7)	30 (24.8)	94 (26.0)
SPLEEN	1 (0.4)	0	1 (0.3)
BREAST	1 (0.4)	0	1 (0.3)
PELVIS	2 (0.8)	0	2 (0.6)
PERITONEUM	3 (1.3)	0	3 (0.8)
ESOPHAGUS	0	1 (0.8)	1 (0.3)
PANCREAS	1 (0.4)	0	1 (0.3)
KIDNEY	0	2 (1.7)	2 (0.6)
PLEURA	4 (1.7)	2 (1.7)	6 (1.7)
GASTRIC	1 (0.4)	1 (0.8)	2 (0.6)
CHEST WALL	7 (2.9)	2 (1.7)	9 (2.5)
BONE WITH SOFT TISSUE COMPONENT	8 (3.3)	4 (3.3)	12 (3.3)
OTHER	60 (25.0)	26 (21.5)	86 (23.8)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)			
N	238	120	358
MEDIAN (MIN - MAX)	72.0 (11-490)	66.0 (10-198)	70.0 (10-490)

(a) Each was not subcategorized to capture a more precise primary tumor site (eg, oropharynx)
(b) Baseline 'unknown' HPV status included 180 subjects who were not tested (per protocol, HPV status testing was only required for patients with oropharyngeal disease), 2 subjects whose sample was collected after baseline, and 1 nivolumab subject who was tested for HPV, but had a non-evaluable test result.
(c) Subjects may have lesions at more than one site.
(d) Includes both target and non-target lesions.

Table 13: Summary of Tumour Specimen Acquisition and Characteristics and Frequencies of PD-L1 Expression at Baseline - All Randomized Subjects

	Nivolumab 3 mg/kg N = 240	Investigator's Choice N = 121	TOTAL N = 361
SUBJECTS WITH TUMOR TISSUE SAMPLE COLLECTED AT BASELINE	213 (88.8)	114 (94.2)	327 (90.6)
SITE OF COLLECTION (b)			
PRIMARY	66 (31.0)	31 (27.2)	97 (29.7)
METASTASIS	107 (50.2)	63 (55.3)	170 (52.0)
NOT REPORTED	40 (18.8)	20 (17.5)	60 (18.3)
OTHER	0	0	0
SUBJECTS WITH QUANTIFIABLE PD-L1 EXPRESSION AT BASELINE (c)	161 (67.1)	99 (81.8)	260 (72.0)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	88/161 (54.7)	61/99 (61.6)	149/260 (57.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	73/161 (45.3)	38/99 (38.4)	111/260 (42.7)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	54/161 (33.5)	43/99 (43.4)	97/260 (37.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	107/161 (66.5)	56/99 (56.6)	163/260 (62.7)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 10%	43/161 (26.7)	34/99 (34.3)	77/260 (29.6)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 10%	118/161 (73.3)	65/99 (65.7)	183/260 (70.4)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE	79 (32.9)	22 (18.2)	101 (28.0)
SUBJECTS WITHOUT TUMOR TISSUE SAMPLE (a1)	25 (10.4)	7 (5.8)	32 (8.9)
SUBJECTS WITH TUMOR TISSUE SAMPLE COLLECTED AFTER BASELINE ONLY (a2)	2 (0.8)	0	2 (0.6)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE (a3) (d)	0	0	0
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (a4) (e)	52 (21.7)	15 (12.4)	67 (18.6)

(a1)+(a2)+(a3)+(a4): Subjects without quantifiable tumor PD-L1 expression at baseline.
(b) Percentages are based on subjects with tumor tissue sample collected at baseline.
(c) Subjects with at least one tumor sample collected at baseline, with number viable tumor cells >=100 and percentage of viable tumor cells exhibiting PD-L1 membrane staining >= 0%.
(d) Indeterminate = tumor cell membrane staining hampered for reasons attributed to the biology of the tumor biopsy specimen and not because of improper sample preparation or handling.
(e) Not evaluable = Tumor biopsy specimen was not optimally collected or prepared (eg, PD-L1 expression is neither quantifiable nor indeterminate).

Table 14: Prior Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)	Total (N=361)
NUMBER OF LINES OF PRIOR SYSTEMIC CANCER THERAPY			
1	106 (44.2)	58 (47.9)	164 (45.4)
2	80 (33.3)	45 (37.2)	125 (34.6)
>= 3	54 (22.5)	18 (14.9)	72 (19.9)
NUMBER OF LINES OF PRIOR SYSTEMIC CANCER THERAPY FOR METASTATIC DISEASE			
0 (a)	128 (53.3)	62 (51.2)	190 (52.6)
1	74 (30.8)	37 (30.6)	111 (30.7)
2	27 (11.3)	13 (10.7)	40 (11.1)
>= 3	11 (4.6)	9 (7.4)	20 (5.5)
PRIOR SYSTEMIC THERAPY REGIMEN SETTING			
ADJUVANT	37 (15.4)	21 (17.4)	58 (16.1)
NEO-ADJUVANT	17 (7.1)	16 (13.2)	33 (9.1)
PRIMARY	173 (72.1)	83 (68.6)	256 (70.9)
METASTATIC DISEASE	112 (46.7)	59 (48.8)	171 (47.4)
TYPE OF PRIOR SYSTEMIC THERAPY RECEIVED (b)			
ANY PRIOR SYSTEMIC THERAPY	240(100.0)	121(100.0)	361(100.0)
PRIOR PLATINUM BASED THERAPY	240(100.0)	121(100.0)	361(100.0)
PRIOR MONOCLONAL ANTIBODIES	153 (63.8)	73 (60.3)	226 (62.6)
PRIOR FOLIC ACID ANALOGUE	7 (2.9)	3 (2.5)	10 (2.8)
PRIOR TAXANES	131 (54.6)	62 (51.2)	193 (53.5)
OTHER SYSTEMIC CANCER THERAPY - EXPERIMENTAL DRUGS	23 (9.6)	13 (10.7)	36 (10.0)
OTHER SYSTEMIC CANCER THERAPY - APPROVED	140 (58.3)	69 (57.0)	209 (57.9)
BEST RESPONSE TO MOST RECENT PRIOR SYSTEMIC THERAPY REGIMEN			
CR OR PR	44 (18.3)	19 (15.7)	63 (17.5)
SD	47 (19.6)	37 (30.6)	84 (23.3)
PD	112 (46.7)	48 (39.7)	160 (44.3)
UNKNOWN/NOT REPORTED	37 (15.4)	17 (14.0)	54 (15.0)
MOST RECENT PRIOR PLATINUM THERAPY			
CARBOPLATIN	123 (51.3)	61 (50.4)	184 (51.0)
CISPLATIN	115 (47.9)	60 (49.6)	175 (48.5)
NEDAPLATIN	1 (0.4)	0	1 (0.3)
PLATINUM COMPOUND	1 (0.4)	0	1 (0.3)
BEST RESPONSE TO MOST RECENT PRIOR PLATINUM- CONTAINING REGIMEN			
CR OR PR	54 (22.5)	24 (19.8)	78 (21.6)
SD	48 (20.0)	30 (24.8)	78 (21.6)
PD	100 (41.7)	46 (38.0)	146 (40.4)
UNKNOWN/NOT REPORTED	38 (15.8)	21 (17.4)	59 (16.3)
TIME FROM LAST DOSE OF MOST RECENT PLATINUM REGIMEN TO PROGRESSION			
<= 2 MONTHS	119 (49.6)	57 (47.1)	176 (48.8)
>2- <= 4 MONTHS	67 (27.9)	40 (33.1)	107 (29.6)
>4- <= 6 MONTHS	36 (15.0)	20 (16.5)	56 (15.5)
>6- <= 8 MONTHS	6 (2.5)	2 (1.7)	8 (2.2)
> 8 MONTHS	4 (1.7)	1 (0.8)	5 (1.4)
UNKNOWN/NOT REPORTED	8 (3.3)	1 (0.8)	9 (2.5)
PRIOR SURGERY RELATED TO CANCER			
YES	207 (86.3)	109 (90.1)	316 (87.5)
NO	33 (13.8)	12 (9.9)	45 (12.5)
PRIOR RADIOTHERAPY			
YES	216 (90.0)	114 (94.2)	330 (91.4)
NO	24 (10.0)	7 (5.8)	31 (8.6)

(a) The percentage of patients with 0 prior therapies for metastatic disease cannot necessarily be interpreted as the percentage of first-line patients in this study, as some patients may have received first-line therapy for non-metastatic disease, which was not amenable to surgery and/or radiation. 93.9% of patients in the randomized population had progressed on or within 6 months of prior platinum therapy.
(b) Some subjects may have been treated with more than 1 type of therapy.

Table 15: Subsequent Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)	
	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	84 (35.0)	46 (38.0)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	29 (12.1)	12 (9.9)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	1 (0.4)	2 (1.7)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	71 (29.6)	39 (32.2)
FOLIC ACID ANALOGUE	17 (7.1)	7 (5.8)
METHOTREXATE	17 (7.1)	7 (5.8)
IMMUNOTHERAPY	5 (2.1)	9 (7.4)
PEMBROLIZUMAB	1 (0.4)	8 (6.6)
URELUMAB	4 (1.7)	1 (0.8)
MONOCLONAL ANTIBODIES	26 (10.8)	11 (9.1)
BEVACIZUMAB	1 (0.4)	0
CETUXIMAB	23 (9.6)	10 (8.3)
NIVOLUMAB	2 (0.8)	1 (0.8)
OTHER SYSTEMIC CANCER THERAPY - APPROVED	20 (8.3)	16 (13.2)
AFATINIB	0	1 (0.8)
ANTINEOPLASTIC	0	1 (0.8)
CAPECITABINE	3 (1.3)	5 (4.1)
FLUOROURACIL	4 (1.7)	8 (6.6)
GEMCITABINE	1 (0.4)	2 (1.7)
GIMER/TEGFUR/OTERA	7 (2.9)	1 (0.8)
HYDROXYUREA	1 (0.4)	0
MITOMYCIN	1 (0.4)	1 (0.8)
OLAPARIB	1 (0.4)	0
TEGAFUR	2 (0.8)	0
TEGFUR/URACIL	0	1 (0.8)
TEMSIROLIMUS	1 (0.4)	0
VINORELBINE	2 (0.8)	0
OTHER SYSTEMIC CANCER THERAPY - EXPERIMENTAL DRUGS	9 (3.8)	2 (1.7)
ABBV 221	1 (0.4)	0
AZD6738	2 (0.8)	0
BAY 16443	1 (0.4)	0
BKM120	2 (0.8)	0
BUPARLISIB	1 (0.4)	0
BUPARLISIB/PLACEBO	1 (0.4)	0
FICLATUZUMAB	1 (0.4)	0
GSK200980	0	1 (0.8)
INVESTIGATIONAL ANTINEOPLASTIC DRUG	1 (0.4)	0
MEDI0562	1 (0.4)	0
MLN0128	1 (0.4)	0
MLN1117	1 (0.4)	0
MLN4924	1 (0.4)	0
MSB0010718C	0	1 (0.8)
PLATINUM-BASED CHEMOTHERAPY	12 (5.0)	9 (7.4)
CARBOPLATIN	9 (3.8)	6 (5.0)
CISPLATIN	3 (1.3)	3 (2.5)
TAXANES	28 (11.7)	10 (8.3)
DOCETAXEL	10 (4.2)	4 (3.3)
PACLITAXEL	19 (7.9)	6 (5.0)
UNASSIGNED	1 (0.4)	1 (0.8)
UNASSIGNED	1 (0.4)	1 (0.8)

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as non-study anticancer therapy started on or after first dosing date (randomization date if subject never treated).
Based on 05-May-2016 database lock.

Numbers analysed

The all-randomised population was the primary population used for the primary efficacy analysis and the all-treated population was the primary population for safety analyses.

Table 16: Analysis Populations

Population	Nivolumab Group N	Investigator's Choice Group N	Total N
Enrolled subjects: All subjects who signed an ICF and were registered into the IVRS. This is the population for pre-treatment disposition.	NA	NA	506
Randomized subjects: All enrolled subjects who were randomized. This is the population for baseline demographics and efficacy analyses.	240	121	361
Treated subjects: All randomized subjects who received at least one dose of study drug. This is the population for the safety and dosing evaluation.	236	111	347
Biomarker subjects: All randomized subjects with available biomarker data.			
All randomized subjects with quantifiable PD-L1 expression at baseline: See definitions of baseline and quantifiable PD-L1 expression in Table 3.5.1-1.	161	99	260
Immunogenicity (ADA evaluable) subjects: All nivolumab-treated subjects with baseline and at least 1 post-baseline assessment for ADA	148	NA	148

Source: Table S.2.5 (enrolled), Table S.2.6 (randomized), Table S.2.7 (treated), Table S.10.2 (PD-L1 quantifiable), and Table S.7.10a (immunogenicity).

Outcomes and estimation

Primary endpoint: Overall survival

In all randomised subjects, nivolumab demonstrated superior OS compared with investigator's choice therapy (HR = 0.70 [97.73% CI: 0.51, 0.96]; stratified log-rank test p-value = 0.0101. Median OS was higher in the nivolumab group than the investigator's choice group (7.49 vs 5.06 months).

At the cut-off date of 6 November 2015, median follow-up for OS (time between randomisation date and last known date alive or death) was 5.3 months (range: 0.0 to 16.8 months) in the nivolumab group and 4.6 months (range: 0.0 to 15.2 months) in the investigator's choice group.

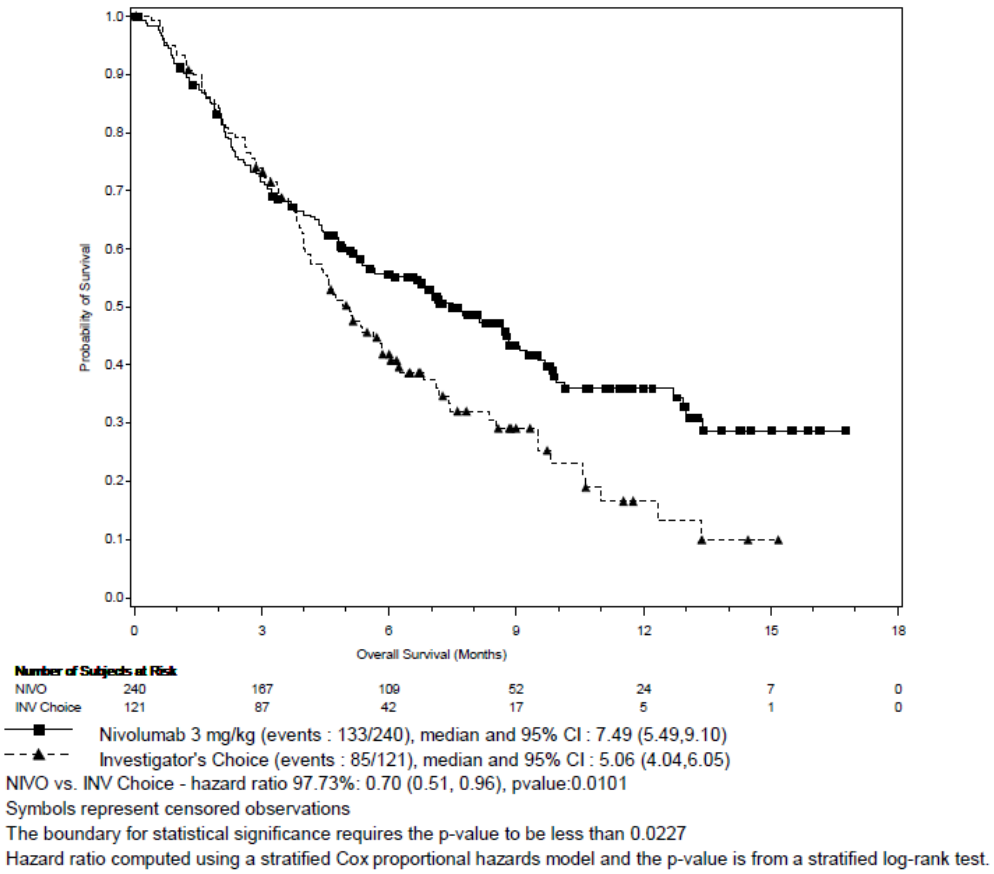


Figure 4: Kaplan-Meier Overall Survival Plot - All Randomized Subjects (cut-off 18 December 2015)

The minimum follow-up for survival for all randomised subjects in the updated analysis was approximately 11.4 months. As of the 20-Sep-2016 database lock, 16 (6.8%) subjects in the nivolumab group and 1 (0.9%) subject in the investigator's choice group were continuing on study therapy.

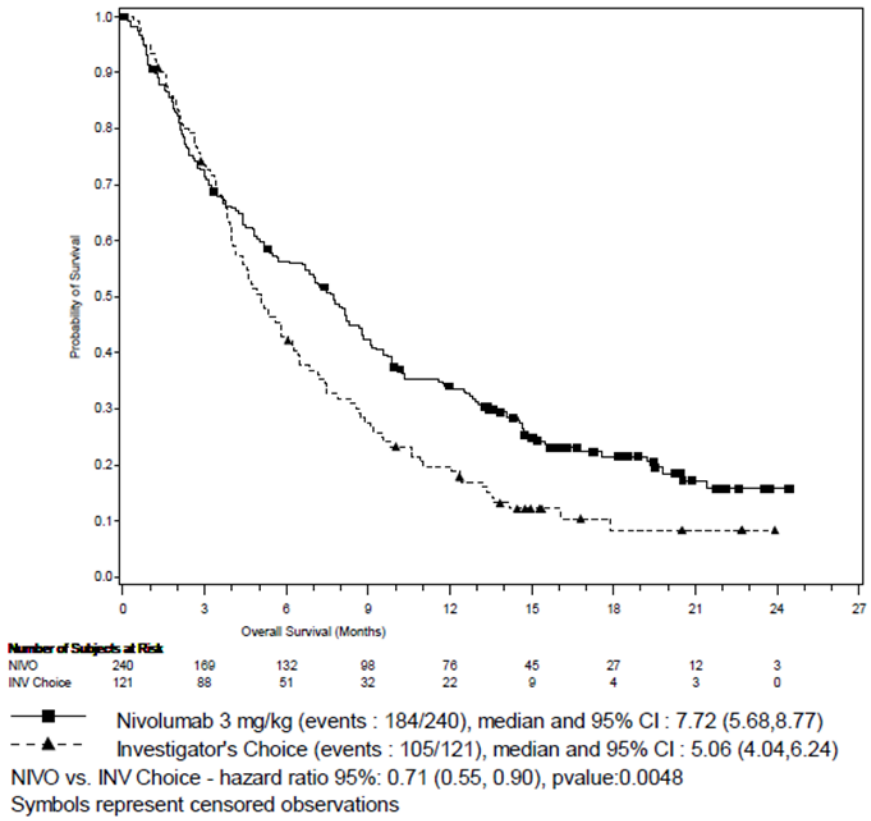


Figure 5: Kaplan-Meier Overall Survival Plot- All Randomised Subjects- CA209141 (Cut-off 20 Sep 2016)

Table 17: Status of censored subjects, OS primary analysis. All Randomised Subjects.

Status of Censored Subjects, OS Primary Analysis
All Randomized Subjects

	Number of Subjects (%)	
	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)
NUMBER OF DEATHS(%)	133 (55.4)	85 (70.2)
NUMBER OF SUBJECTS CENSORED(%)	107 (44.6)	36 (29.8)
STATUS OF CENSORED SUBJECTS (%)		
STILL ON-TREATMENT	41 (17.1)	3 (2.5)
NOT PROGRESSED	35 (14.6)	3 (2.5)
PROGRESSED (1)	6 (2.5)	0
IN FOLLOW-UP	55 (22.9)	29 (24.0)
OFF STUDY	11 (4.6)	4 (3.3)
SUBJECT WITHDREW CONSENT	5 (2.1)	3 (2.5)
LOST TO FOLLOW-UP	4 (1.7)	1 (0.8)
OTHER	2 (0.8)	0
NOT REPORTED	0	0

Table 18: Overall Survival Rates - All Randomized Subjects - CA209141 (Cut-off 20 Sep 2016)

Survival Rate (95% CI)	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)
3-MONTH	71.3 (65.1, 76.6)	74.2 (65.4, 81.1)
6-MONTH	56.5 (49.9, 62.5)	43.0 (34.0, 51.7)
9-MONTH	42.3 (35.9, 48.5)	27.5 (19.8, 35.8)
12-MONTH	34.0 (28.0, 40.1)	19.7 (13.0, 27.3)
18-MONTH	21.5 (16.2, 27.4)	8.3 (3.6, 15.7)
24-MONTH	15.8 (10.3, 22.3)	NA

Based on Kaplan-Meier Estimates.
Source: Table 6.1-1 of Addendum 01 to the CA209141 Final CSR[2]

Sensitivity analyses

Table 19: OS Sensitivity Analyses - All Randomized Subjects

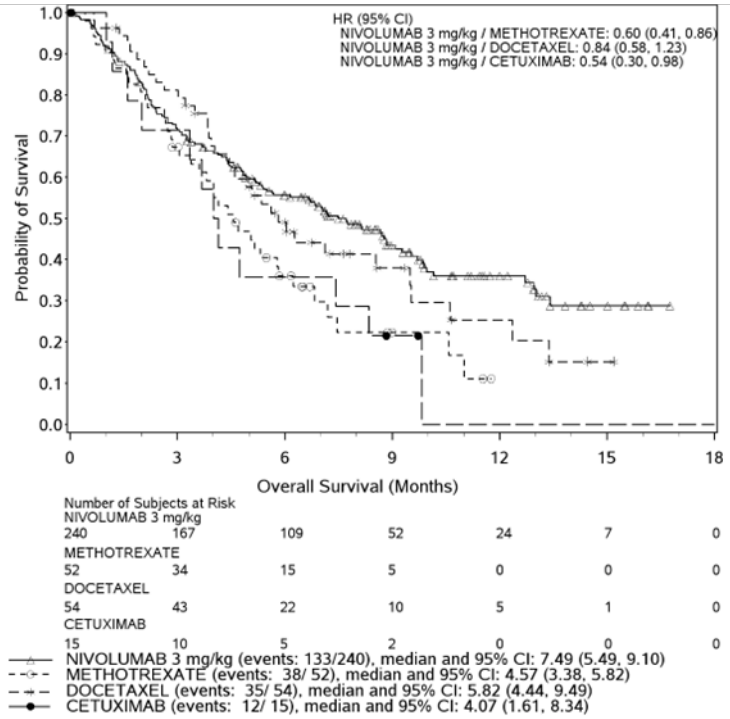
	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)	HR(1) (95% CI)	P-Value (2)
Unstratified Analysis:				
# EVENTS / # SUBJECTS (%)	133/240 (55.4)	85/121 (70.2)	0.69	0.00780
MEDIAN OS (MONTHS) (95% CI)	7.49 (5.49-9.10)	5.06 (4.04-6.05)	(0.53-0.91)	
Analysis Based on Subjects with No Relevant Deviations:				
# EVENTS / # SUBJECTS (%)	116/208 (55.8)	76/110 (69.1)	0.71	0.0180
MEDIAN OS (MONTHS) (95% CI)	7.49 (5.39-9.26)	5.06 (4.04-6.28)	(0.53-0.94)	

In a multivariate analysis of OS, the treatment effect when adjusted for HPV-p16 status, baseline ECOG PS, and prior chemotherapy for metastatic disease was consistent with the primary OS analysis. ECOG PS was a significant prognostic variable for OS.

Table 20: Overall survival, multivariate Analysis - All randomised subjects

	HR(2) (95% CI)	P-Value (2)
TREATMENT NIVO. VS INV. CHOICE (1)	0.71 (0.53 - 0.93)	0.0144
HPV-16 STATUS BY P-16 TESTING		
POSITIVE VS NEGATIVE	0.92 (0.62 - 1.36)	0.6780
UNKNOWN VS NEGATIVE	1.06 (0.76 - 1.48)	0.7462
ECOG PS		
0 VS >=1	0.51 (0.35 - 0.75)	0.000675
PRIOR CHEMOTHERAPY FOR METASTATIC DISEASE		
NO VS YES	0.88 (0.66 - 1.17)	0.3925

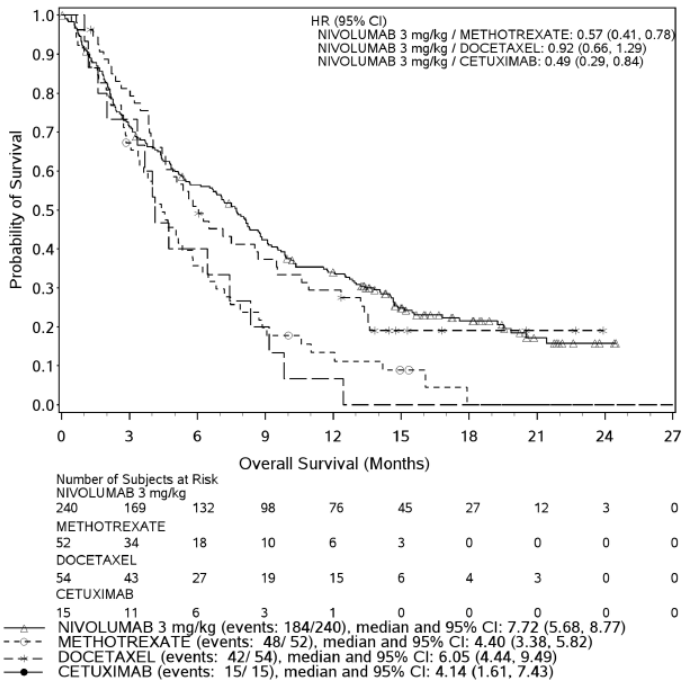
(1) Effect of treatment adjusted for HPV-16 status, baseline ECOG, prior chemotherapy for metastatic disease.
(2) P-values and HRs from multivariate Cox Model stratified by prior treatment with cetuximab (yes, no) as entered into the IVRS.



Symbols represent censored observations.

Hazard ratio is based on unstratified Cox proportional hazards model with regimen – Nivolumab, Cetuximab, Methotrexate or Docetaxel - as the sole covariate.

Figure 6: Kaplan-Meier Overall Survival Plot by Agent (Nivolumab, Cetuximab, Methotrexate, or Docetaxel) - All randomized subjects (cut-off 18 December 2015)



Symbols represent censored observations

Hazard ratio is based on unstratified Cox proportional hazards model with regimen – Nivolumab, Cetuximab, Methotrexate or Docetaxel - as the sole covariate.

Figure 7: Kaplan-Meier Overall Survival Plot by Agent (Nivolumab, Cetuximab, Methotrexate, or Docetaxel) - All randomized subjects (data cut-off: 20 September 2016)

Per protocol, investigators were to indicate their choice of therapy (cetuximab, methotrexate, or docetaxel) for each patient prior to randomisation.

Secondary endpoints:

- Progression free survival (PFS)

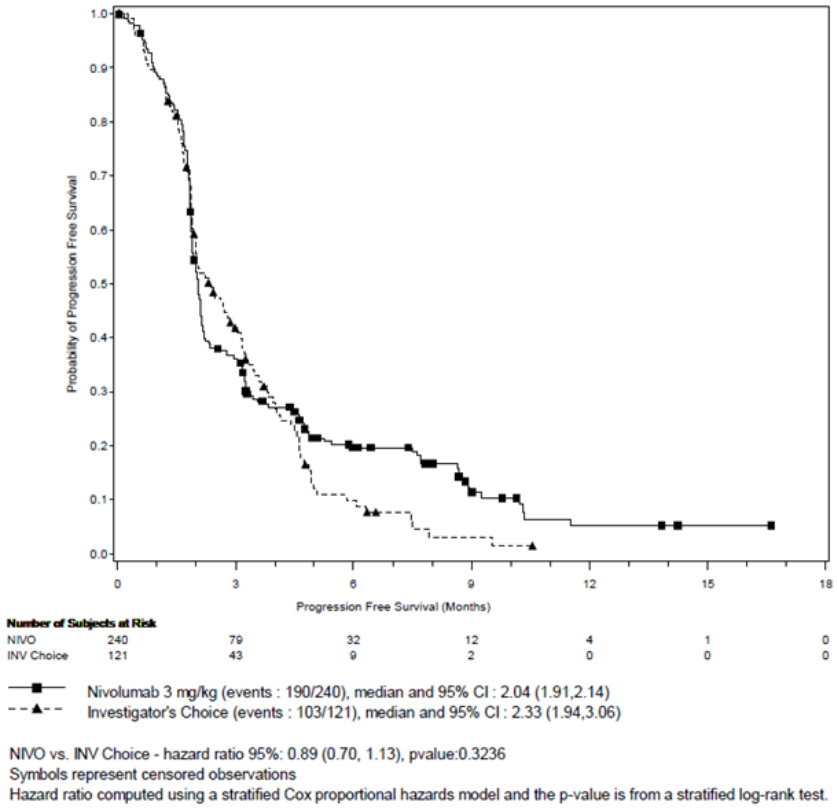
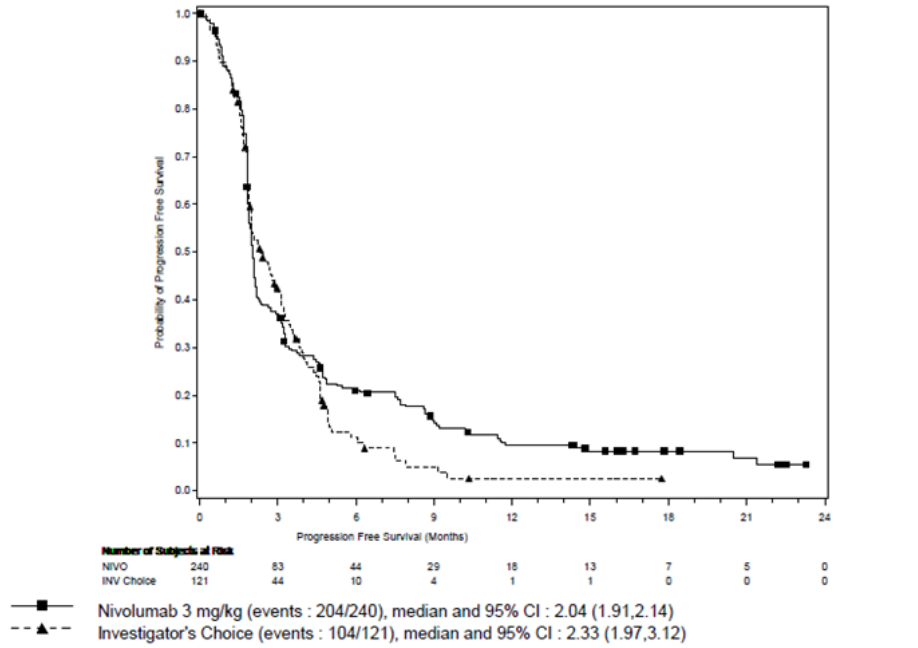


Figure 8: Kaplan-Meier Plot of Progression-free Survival (Primary Definition, cut-off 18 December 2015) - All Randomized Subjects

Updated PFS results (20-Sep-2016 database lock) were consistent with those reported in the CA209141 Final CSR.



NIVO vs. INV Choice - hazard ratio 95%: 0.87 (0.69, 1.11), pvalue:0.2597
Symbols represent censored observations
Hazard ratio computed using a stratified Cox proportional hazards model and the p-value is from a stratified log-rank test.

Figure 9: Kaplan-Meier Plot of Progression-free Survival (Primary Definition) -All Randomized Subjects

Table 21: Reason for censoring PFS, primary definition – All randomised subjects

	Number of Subjects (%)	
	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)
NUMBER OF EVENTS (%)	190 (79.2)	103 (85.1)
TYPE OF EVENT (%)		
PROGRESSION (1)	139 (57.9)	71 (58.7)
DEATH	51 (21.3)	32 (26.4)
NUMBER OF SUBJECTS CENSORED (%)	50 (20.8)	18 (14.9)
CENSORED ON DATE OF RANDOMIZATION	7 (2.9)	1 (0.8)
NO BASELINE TUMOR ASSESSMENT AND NO DEATH (2)	1 (0.4)	1 (0.8)
NEVER TREATED	1 (0.4)	1 (0.8)
OTHER	0	0
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	6 (2.5)	0
NEVER TREATED	2 (0.8)	0
OTHER	4 (1.7)	0
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY OR LAST ASSESSMENT PRIOR TO SUBSEQUENT ANTI-CANCER THERAPY	43 (17.9)	17 (14.0)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (3)	14 (5.8)	10 (8.3)
STILL ON-TREATMENT	24 (10.0)	1 (0.8)
IN FOLLOW-UP	4 (1.7)	4 (3.3)
OFF STUDY	1 (0.4)	2 (1.7)
SUBJECT WITHDREW CONSENT	0	2 (1.7)
LOST TO FOLLOW-UP	1 (0.4)	0
OTHER	0	0
NOT REPORTED	0	0

A pre-specified sensitivity analysis was performed for PFS in which there was no censoring for systemic anti-cancer therapy prior to a progression event.

- ORR

Table 22: Best Overall Response - All Randomized Subjects

	Number of Subjects (%)	
	Nivolumab 3 mg/kg (N=240)	Investigator's Choice (N=121)
BEST OVERALL RESPONSE:		
COMPLETE RESPONSE (CR)	6 (2.5)	1 (0.8)
PARTIAL RESPONSE (PR)	26 (10.8)	6 (5.0)
STABLE DISEASE (SD)	55 (22.9)	43 (35.5)
PROGRESSIVE DISEASE (PD)	100 (41.7)	42 (34.7)
UNABLE TO DETERMINE (UTD)	53 (22.1)	29 (24.0)
NEVER TREATED	4 (1.7)	8 (6.6)
WRONG CANCER DIAGNOSIS	0	0
DEATH PRIOR TO DISEASE ASSESSMENT	30 (12.5)	11 (9.1)
EARLY DISCONTINUATION DUE TO TOXICITY	2 (0.8)	1 (0.8)
OTHER	15 (6.3)	8 (6.6)
NOT REPORTED	2 (0.8)	1 (0.8)
OBJECTIVE RESPONSE RATE (1,2) (95% CI)	32/240 (13.3) (9.3, 18.3)	7/121 (5.8) (2.4, 11.6)
DIFFERENCE OF OBJECTIVE RESPONSE RATES (3) (95% CI)	7.55 (1.55, 13.56)	
CMH ESTIMATE OF COMMON ODDS RATIO (4,5) (95% CI)	2.49 (1.07, 5.82)	

(1) Number of responders (CR + PR)/number of subjects;
(2) Confidence interval computed using the Clopper and Pearson method.
(3) Stratum adjusted difference in response rates (Nivolumab - Investigator's Choice) based on the Cochran-Mantel-Haenszel (CMH) method of weighting.
(4) Stratified by Prior Cetuximab (yes,no) as recorded in the IVRS.
(5) Stratum adjusted odds ratio (Nivolumab - Investigator's Choice) using Mantel-Haenszel Method.
Includes data reported until 05-May-2016.

In the updated analysis (20-Sep-2016 database lock), the investigator-assessed confirmed ORR (using RECIST v1.1) was unchanged from what was reported in the Final CSR: 13.3% for nivolumab and 5.8% for investigator's choice.

- Time to response (exploratory endpoint)

Table 23: Time to Objective Response - All Randomized Subjects with Response

	Nivolumab 3 mg/kg (N=32)	Investigator's Choice (N=7)
TIME TO RESPONSE (MONTHS)		
NUMBER RESPONDERS	32	7
MEAN	3.0	2.4
MEDIAN	2.1	2.0
MIN, MAX	1.8, 7.4	1.9, 4.6
Q1, Q3	1.9, 3.6	2.0, 2.3
STANDARD DEVIATION	1.55	0.99

Includes data reported until 05-May-2016

In the updated analysis (20-Sep-2016 database lock), median TTR was unchanged from what was reported in the CA209141 Final CSR: 2.1 months in the nivolumab group and 2.0 months in the investigator's choice group.

- Duration of the response

Table 24: Time to Response and Duration of Response - All Responders

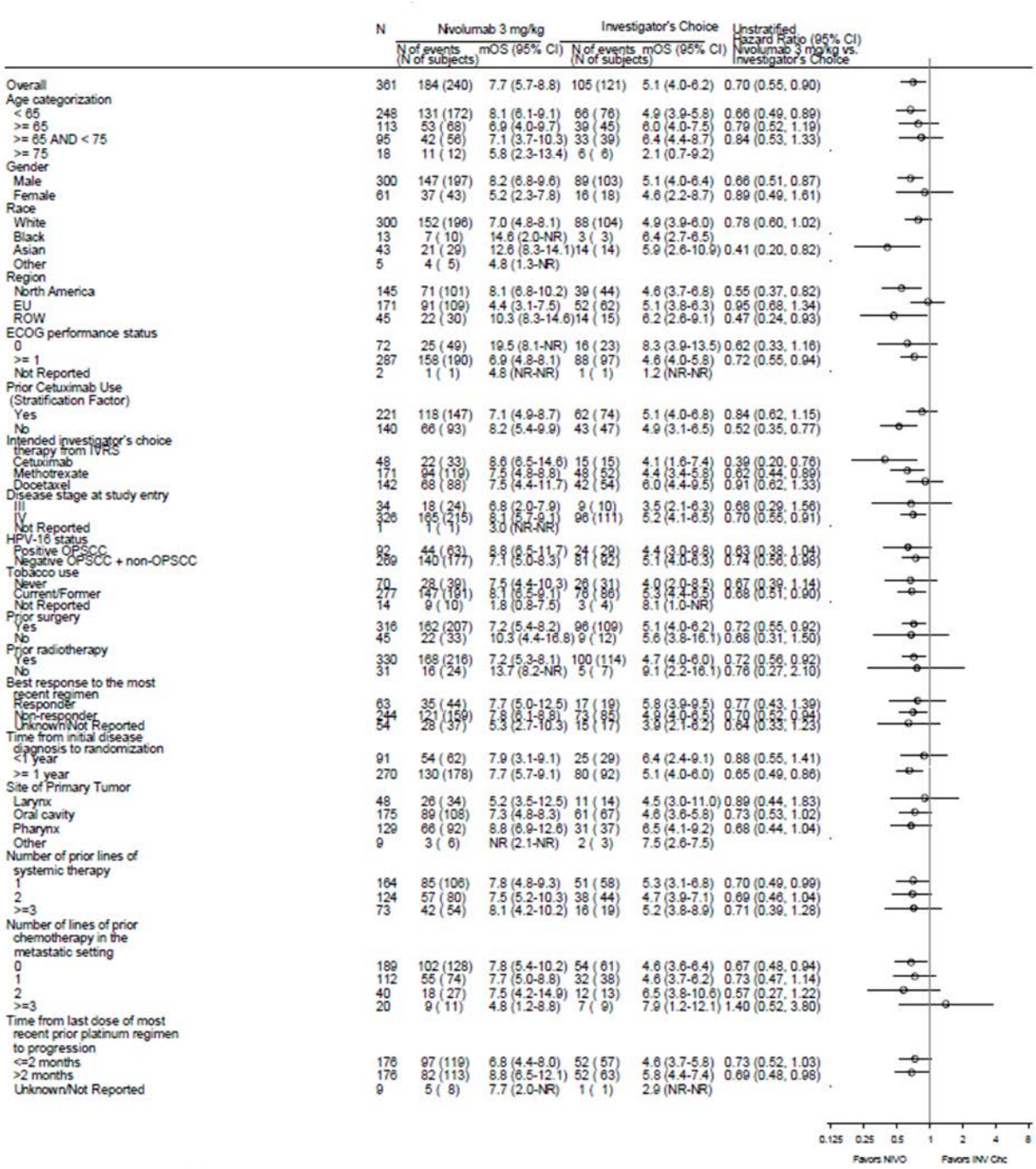
	Nivolumab 3 mg/kg (N=32)	Investigator's Choice (N=7)
TIME TO RESPONSE (MONTHS)		
NUMBER RESPONDERS	32	7
MEAN	3.0	2.4
MEDIAN	2.1	2.0
MIN, MAX	1.8, 7.4	1.9, 4.6
Q1, Q3	1.9, 3.6	2.0, 2.3
STANDARD DEVIATION	1.55	0.99
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (a)	2.8, 20.3+	1.5+, 8.5+
MEDIAN (95% CI) (b)	9.7 (5.6, NR)	4.0 (2.9, NR)
Q1, Q3	5.6, NR	3.0, NR
N EVENT/N RESP (%)	16/32 (50.0)	3/7 (42.9)

(a) Symbol + indicates a censored value.
(b) Median computed using Kaplan-Meier method.

At the time of the 20-Sep-2016 database lock, 16/32 (50.0%) subjects in the nivolumab group and 4/7 (57.1%) subjects investigator's choice group had an ongoing response (as of the last available tumour assessment).

Ancillary analyses

- Efficacy outcomes in Subpopulations



HR is not computed for subsets (except age, race, region, and gender) with 20 or fewer subjects in total (across treatment groups). HRs are computed using unstratified Cox Proportional Hazards models with treatment as the sole covariate.

Figure 10: Forest Plot of Treatment Effect on Overall Survival in Baseline Subgroups - All Randomised Subjects - CA209141 (20-Sep-2016 Database Lock)

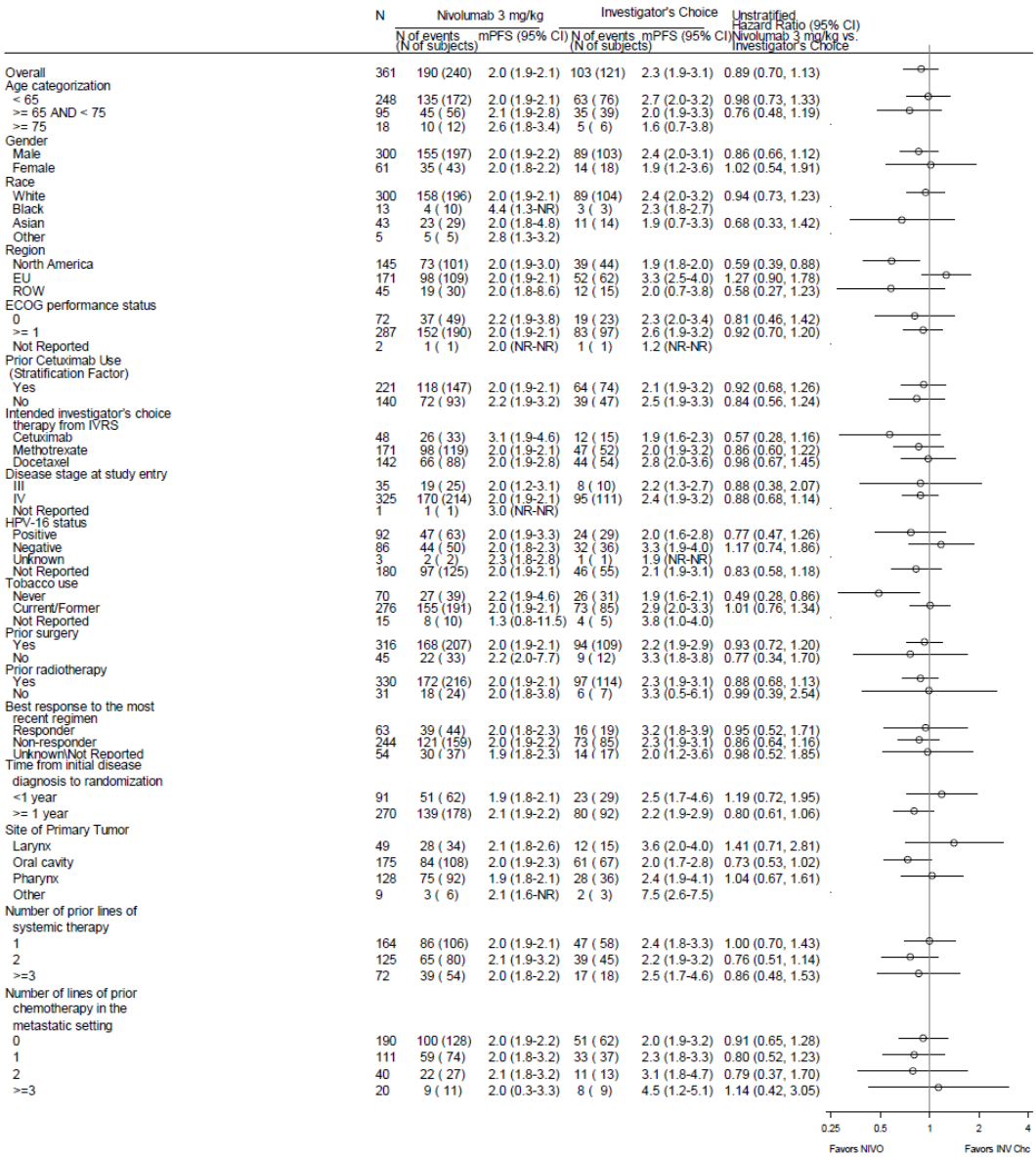


Figure 11: Forest Plot of Treatment Effect on PFS in Baseline Subgroups - All Randomised Subjects - CA209141 (20-Sep-2016 Database Lock)

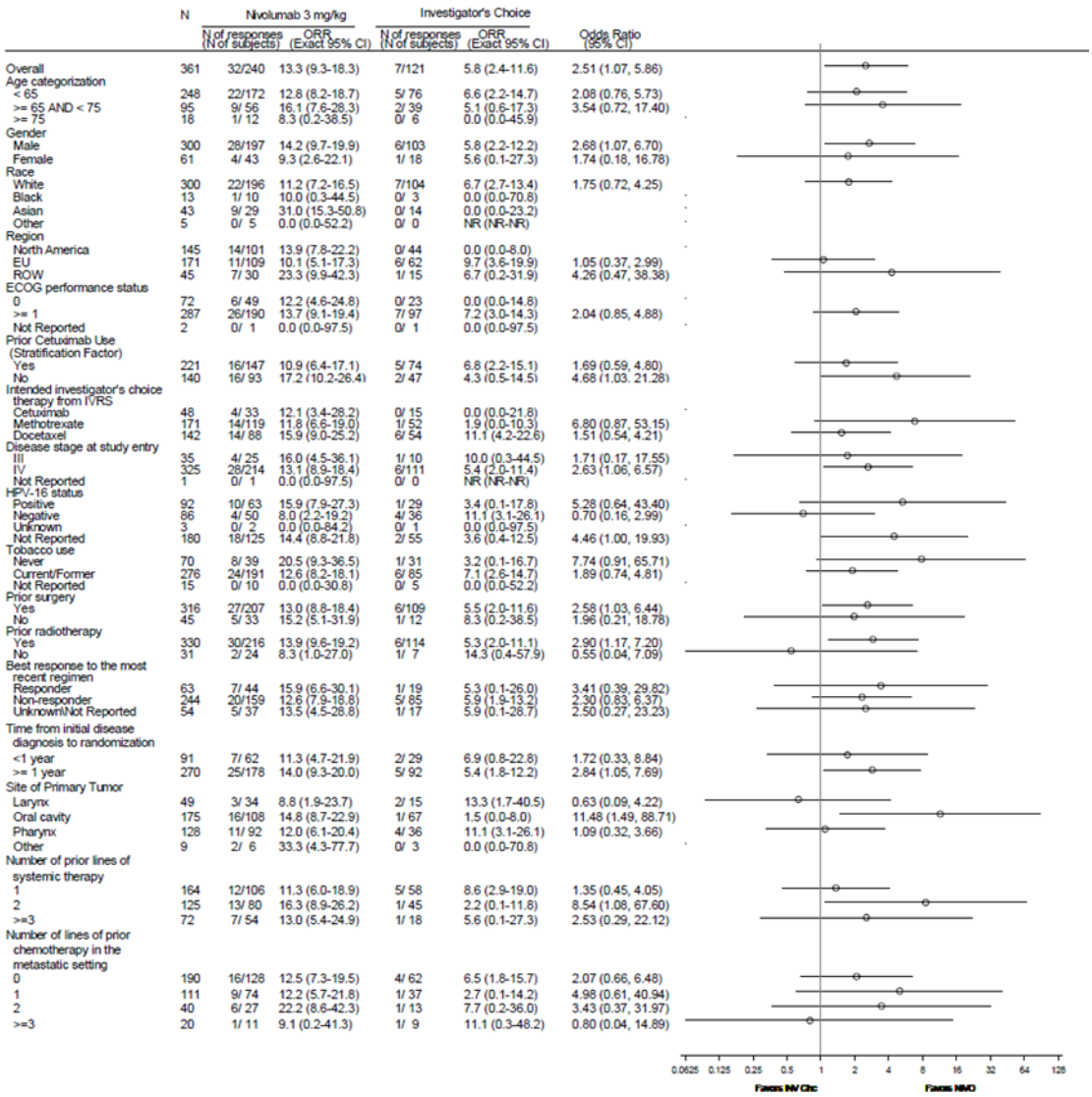


Figure 12: Forest Plot of Treatment Effect on ORR in Baseline Subgroups - All Randomised Subjects - CA209141 (20-Sep-2016 Database Lock)

- PD-L1 expression

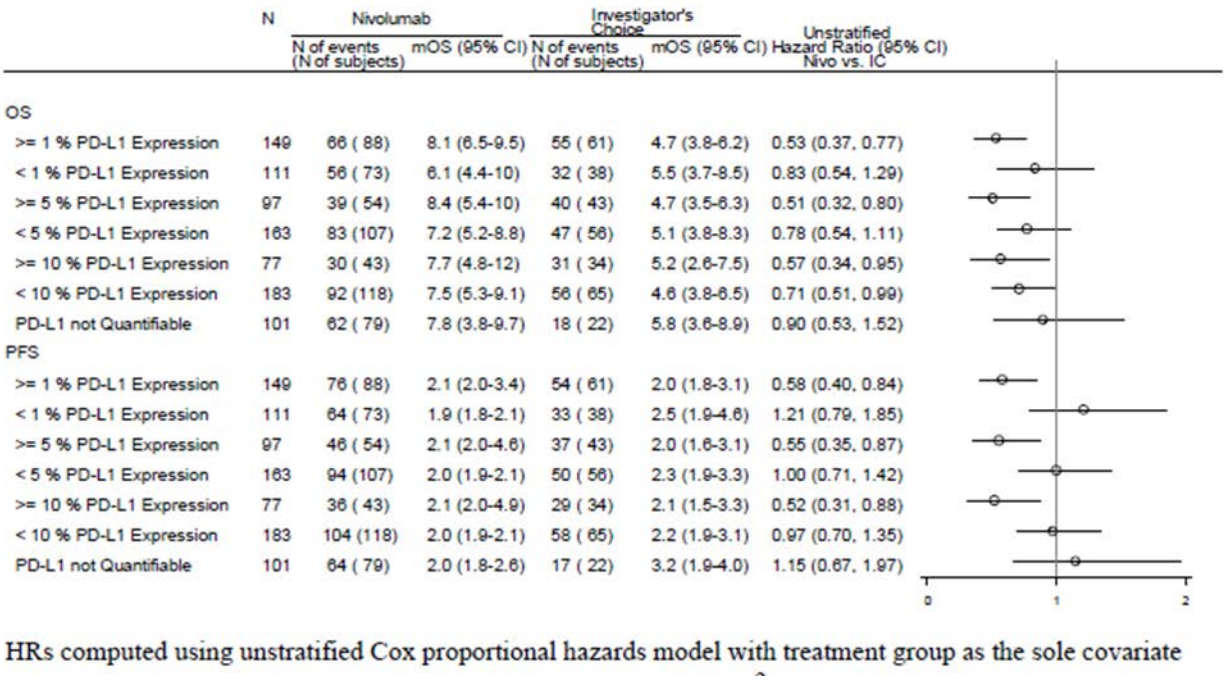
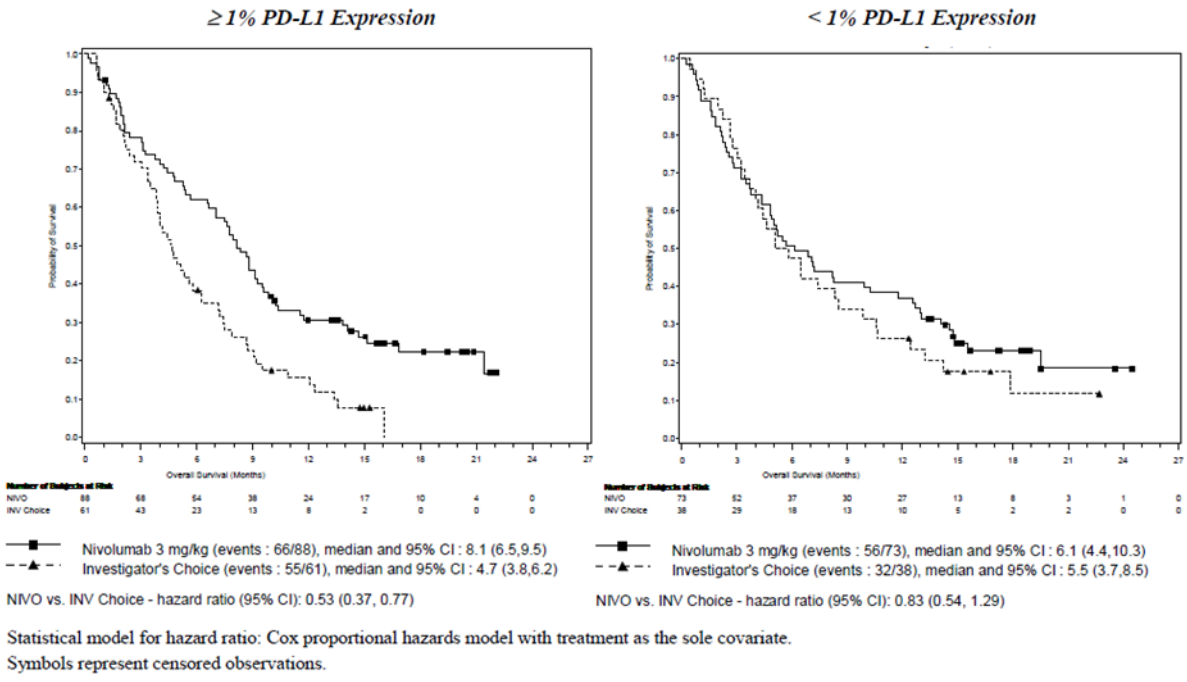


Figure 13: Forest Plot of OS Hazard Ratios by Baseline tumour PD-L1 Expression – All Randomized Subjects - CA209141 (20-Sep-2016 Database Lock)



Statistical model for hazard ratio: Cox proportional hazards model with treatment as the sole covariate.
Symbols represent censored observations.

Figure 14: Kaplan-Meier Plot of OS by Baseline tumour PD-L1 Expression (1% Expression Level) - All Randomized Subjects with Quantifiable PD-L1 Expression at Baseline - CA209141 (20-Sep-2016 Database Lock)

PD-L1 expression on tumour cells and tumour-associated immune cells (TAICs) was analysed on baseline samples and assessed for association with clinical outcome (OS, PFS and ORR) using data from the 20-Sep-2016 database lock. These were exploratory post-hoc analysis using a non-validated assay.

PD-L1+ TAIC abundance in the tumour microenvironment were qualitatively assessed, and characterised as “abundant” and “rare” based on pathologist assessments. Amongst 254 subjects analysed, TAICs were detected in all but 1 patient, and 98% of the subjects had TAIC PD-L1 expression.

PD-L1+ TAIC location in the tumour microenvironment were qualitatively assessed and defined based on pathological assessment as:

- Intra-tumoural defined as being within the tumour
- Intra-peritumoural defined as being within the tumour and surrounding stroma
- Peritumoural defined as being outside the tumour in the tumour stromal only

Table 25: Efficacy in subjects with <1 % tumour PD-L1 expression by abundance or location of TAICs

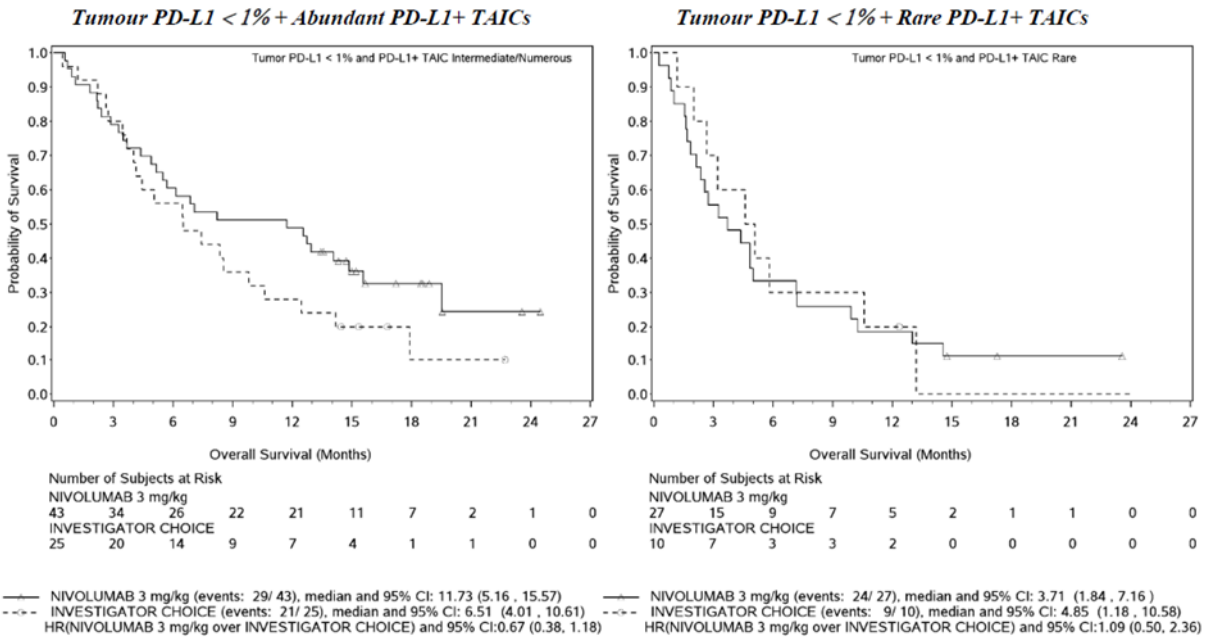
	Median OS, Months HR (95% CI)		Median PFS, Months HR (95% CI)		ORR, % (95% CI)	
	Nivo	IC	Nivo	IC	Nivo	IC
PD-L1<1%, PD-L1+ TAIC Abundant (43 Nivo, 25 IC)	11.73	6.51	2.10	2.73	18.6	12.0
	0.67 (0.38, 1.18)		0.96 (0.55, 1.67)		(8.4, 33.4)	(2.5, 31.2)
PD-L1<1%, PD-L1+ TAIC Rare (27 Nivo, 10 IC)	3.71	4.85	1.84	2.12	3.7	10.0
	1.09 (0.50, 2.36)		1.91 (0.84, 4.36)		(<0.1, 19.0)	(0.3, 44.5)
PD-L1<1%, Intra/Intra-peritumoural PD-L1+ TAICs (44 Nivo, 27 IC)	9.07	5.09	2.07	2.63	18.2	11.1
	0.65 (0.38, 1.13)		1.03 (0.61, 1.74)		(8.2, 32.7)	(2.4, 29.2)
PD-L1<1%, Peritumoural PD-L1 TAICs (22 Nivo, 7 IC)	4.27	6.47	2.04	1.84	4.5	14.3
	1.16 (0.46, 2.94)		1.58 (0.57, 4.34)		(0.1, 22.8)	(0.4, 57.9)

OS and PFS were estimated using Kaplan-Meier method.

HR is nivolumab over IC.

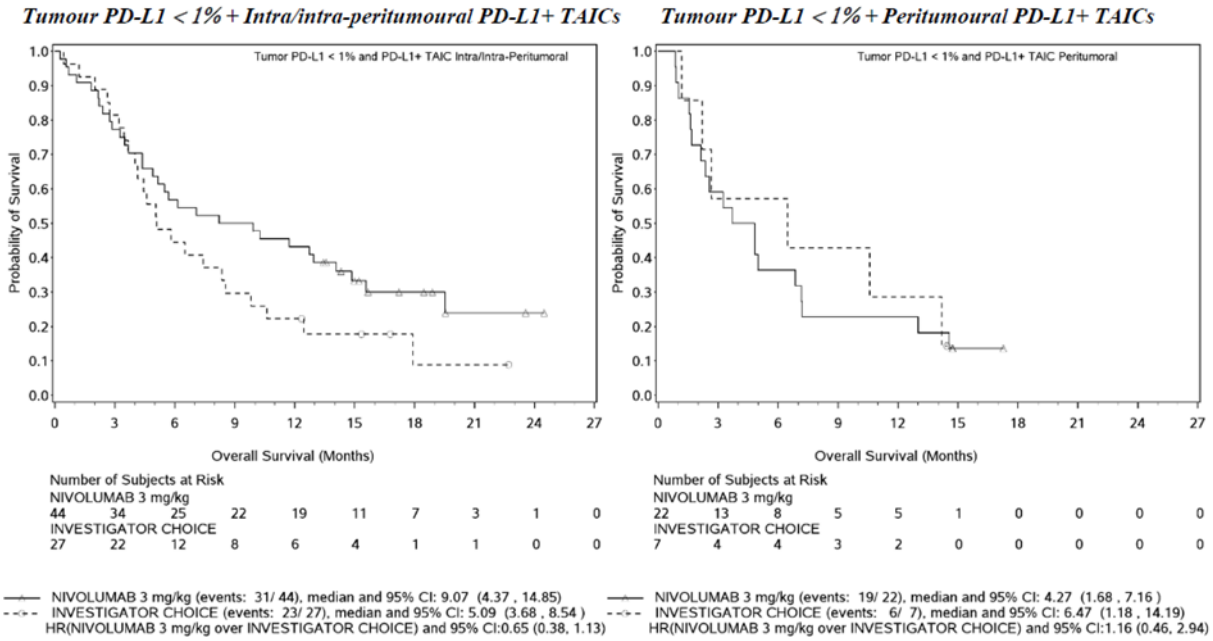
Confidence interval for ORR calculated using the Clopper-Pearson method.

Source: Table AR-RSI24 (ORR, TAIC abundance), Table AR-RSI25 (ORR, TAIC location), Figure AR-RSI20 (OS, TAIC abundance), Figure AR-RSI21 (PFS, TAIC abundance), Figure AR-RSI22 (OS, TAIC location), Figure AR-RSI23 (PFS, TAIC location) are all in Annex 2.



Source: Figure AR-RSI20 (OS, TAIC abundance) in Annex 2

Figure 15: Kaplan-Meier plots of OS in tumour PD-L1 <1 % and PD-L1+ TAIC abundance subset



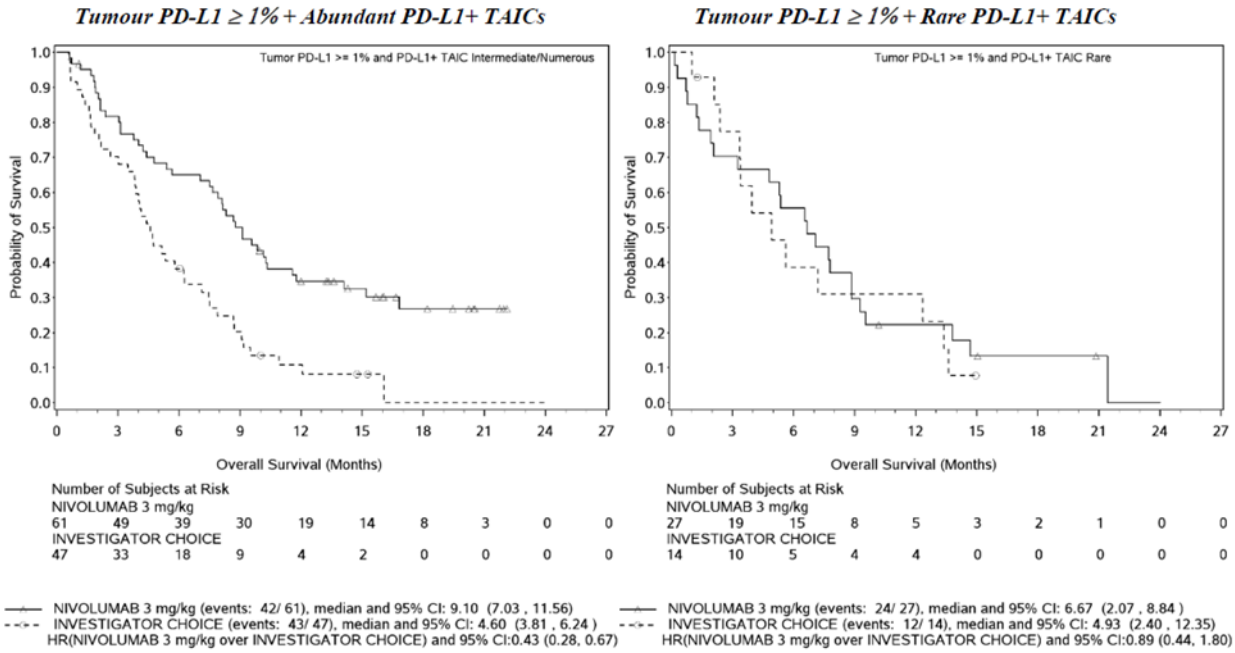
Source: Figure AR-RSI22 (OS, TAIC location) in Annex 2

Figure 16: Kaplan-Meier plots of OS in tumour PD-L1 <1% and PD-L1+ TAIC location subset

Table 26: Efficacy in subjects with ⩾1 % tumour PD-L1 expression by abundance or location of TAICs

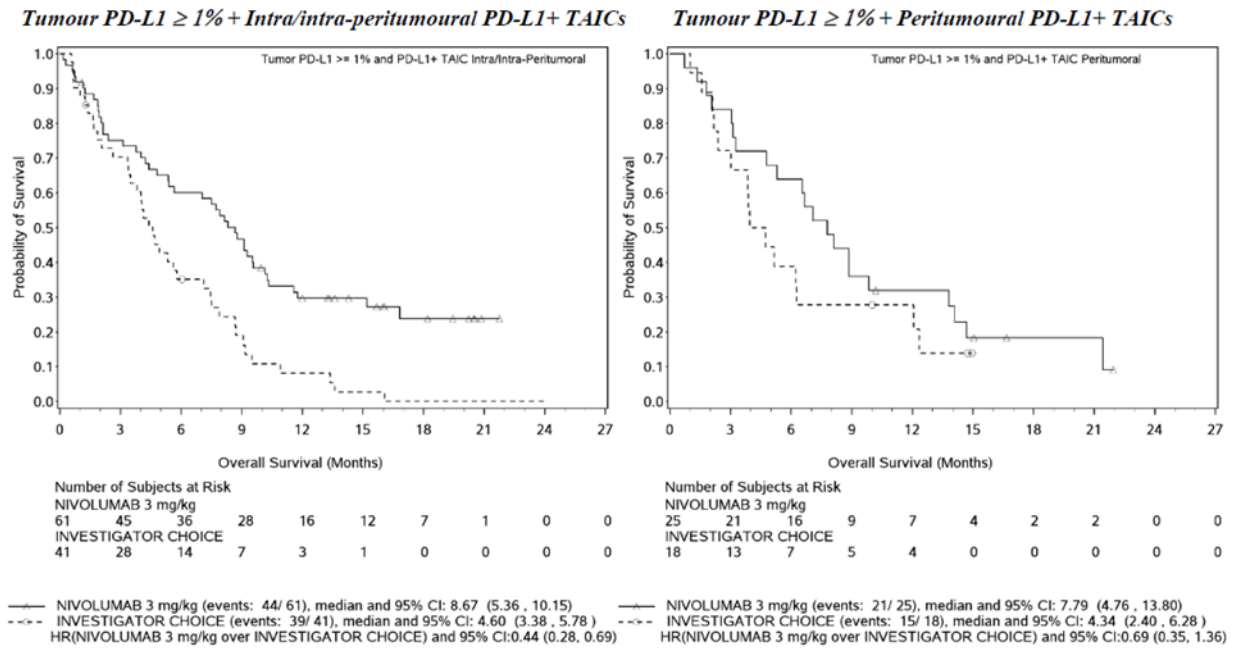
	Median OS, Months HR (95% CI)		Median PFS, Months HR (95% CI)		ORR, % (95% CI)	
	Nivo	IC	Nivo	IC	Nivo	IC
PD-L1≥1%, PD-L1+ TAIC Abundant (61 Nivo, 47 IC)	9.10	4.60	3.19	1.97	19.7	0
	0.43 (0.28, 0.67)		0.48 (0.31, 0.75)		(10.6, 31.8)	(0, 7.5)
PD-L1≥1%, PD-L1+ TAIC Rare (27 Nivo, 14 IC)	6.67	4.93	1.99	2.04	11.1	7.1
	0.89 (0.44, 1.80)		0.93 (0.46, 1.88)		(2.4, 29.2)	(0.2, 33.9)
PD-L1≥1%, Intra/Intra-peritumoural PD-L1+ TAICs (61 Nivo, 41 IC)	8.67	4.60	2.14	2.33	14.8	2.4
	0.44 (0.28, 0.69)		0.64 (0.41, 1.01)		(7.0, 26.2)	(<0.1, 12.9)
PD-L1≥1%, Peritumoural PD-L1 TAICs (25 Nivo, 18 IC)	7.79	4.34	2.09	1.89	16.0	0
	0.69 (0.35, 1.36)		0.45 (0.22, 0.90)		(4.5, 36.1)	(0, 18.5)

OS and PFS were estimated using Kaplan-Meier method.
HR is nivolumab over IC.
Confidence interval for ORR calculated using the Clopper-Pearson method.
Source: Table AR-RSI24 (ORR, TAIC abundance), Table AR-RSI25 (ORR, TAIC location), Figure AR-RSI20 (OS, TAIC abundance), Figure AR-RSI21 (PFS, TAIC abundance), Figure AR-RSI22 (OS, TAIC location), and Figure AR-RSI23 (PFS, TAIC location) are all in Annex 2.



Source: Figure AR-RSI20 (OS, TAIC abundance) in in Annex 2

Figure 17: Kaplan-Meier plots of OS in tumour PD-L1 ⩾1% and PD-L1+ TAIC abundance subset



Source: Figure AR-RSI22 (OS, TAIC location) in Annex 2

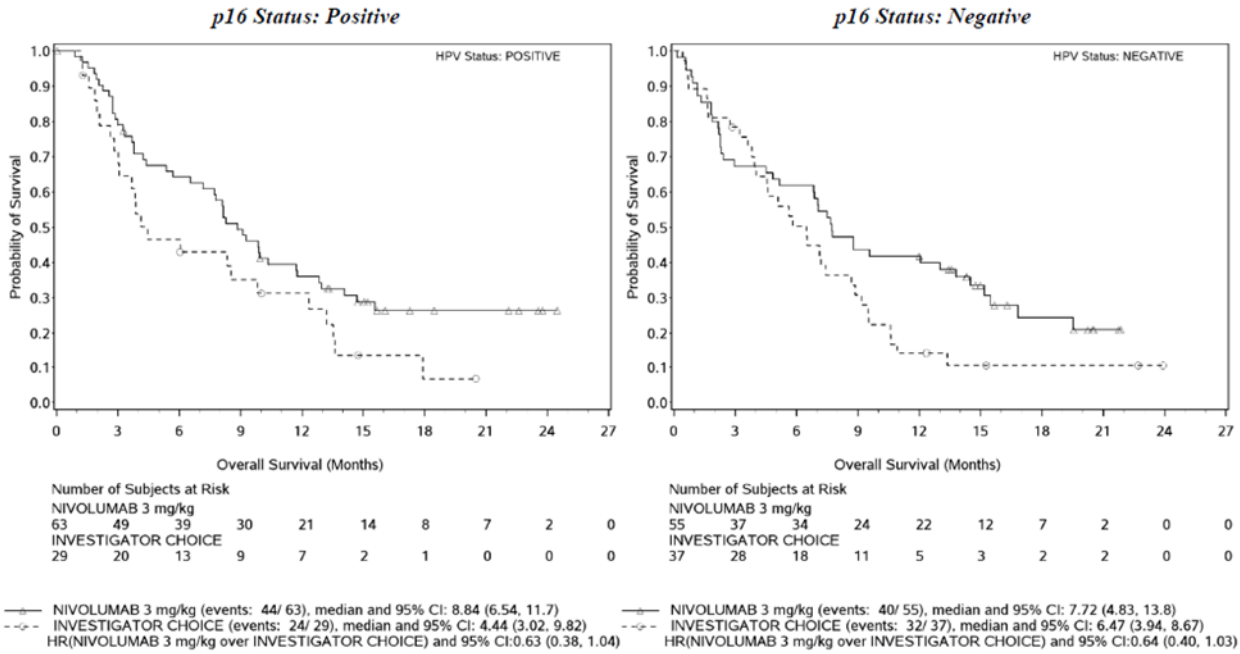
Figure 18: Kaplan-Meier plots of OS in tumour PD-L1 ⩾1% and PD-L1+ TAIC location subset

- HPV Status

HPV testing (determined by p16 immunohistochemistry [IHC]) was only required for subjects with an oropharyngeal (OPSCC) primary location, since HPV does not play a clinically relevant role in non-oropharyngeal SCCHN (non-OPSCC).

The OS HR for nivolumab versus investigator's choice therapy was lower for HPV-positive subjects (0.56 [95% CI: 0.32, 0.99]) than HPV-negative subjects (0.73 [95% CI: 0.42, 1.25). Confidence intervals were wide due to the small sample size. In subjects with HPV-positive status, the OS Kaplan-Meier curves separated early in favour of nivolumab. In subjects with HPV-negative status, OS Kaplan-Meier curves separated after 4 months in favour of nivolumab.

Updated analyses of efficacy by p16 status (p16-positive, p16-negative, or 'unknown' p16 status)
As per protocol guidance, p16 testing by p16 IHC assay was only required for subjects where investigators identified the primary site of the tumour as oropharyngeal. Among all randomized subjects, p16 status was available for 184 (51.0%) subjects (118 nivolumab and 66 investigator's choice [IC]). Of these 184 subjects, 92 were p16-positive (63 nivolumab and 29 IC) and 92 were p16-negative (55 nivolumab and 37 IC).



Symbols represent censored observations.
Hazard ratio is based on unstratified Cox proportional hazard model.
Program Source: /gbs/prod/clin/programs/ca/209/141/csrfa01/rpt/adhoc/20161011_t1 Program Name: rg-ef-os-pfs-hpv-v01.sas

Figure 19: Kaplan-Meier plots of OS by p16 status

- Efficacy by both baseline PD-L1 expression and HPV status

Post hoc exploratory analyses of OS were done by the combination of baseline PD-L1 expression (⩾ 1%, < 1%) and HPV status (positive or negative).

Table 27: Cross Tabulation of Baseline HPV Status (Positive, Negative) by Baseline PD-L1 Status (≥ 1%, < 1%) - All Randomized Subjects with Known HPV Status and Quantifiable PD-L1 Expression

	Number of Subjects (%) (1)		
	Baseline PD-L1		
	>=1%	< 1%	Total
Baseline HPV Status			
POSITIVE	37 (28.5)	34 (26.2)	71 (54.6)
NEGATIVE	33 (25.4)	26 (20.0)	59 (45.4)
Total	70 (53.8)	60 (46.2)	130 (100.0)
Odds ratio and 95% CI for odds ratio (2):	0.86 (0.43, 1.72)		

(1) Percentage in a cell is the number in the cell divided by the grand total
(2) Odds of PD-L1 >= 1% to < 1% in the HPV positive group to odds PD-L1 >=1% to <1% in the HPV negative group

The OS HRs (nivolumab to investigator's choice) in the subgroups suggest that each biomarker is potentially predictive on its own, and are as follows:

- PD-L1 ⩾ 1%, HPV positive: 0.50 (95% CI: 0.21, 1.19)
- PD-L1 ≥ 1%, HPV negative: 0.44 (95% CI: 0.18, 1.10)
- PD-L1 < 1%, HPV positive: 0.55 (95% CI: 0.22, 1.39)
- PD-L1 < 1%, HPV negative: 0.82 (95% CI: 0.31, 2.19)

Updated analysis of efficacy by both baseline PD-L1 expression and p16 status

Table 28: Efficacy by tumour PD-L1 expression and p16 status

	Median OS, Months HR (95% CI)		Median PFS, Months HR (95% CI)		ORR, % (95% CI)	
	Nivo	IC	Nivo	IC	Nivo	IC
PD-L1≥1%, p16+ (23 Nivo, 14 IC)	9.10	3.88	3.29	1.97	17.4	7.1
	0.56 (0.25, 1.25)		0.54 (0.25, 1.19)		(5, 38.8)	(0.2, 33.9)
PD-L1≥1%, p16- (19 Nivo, 16 IC)	9.56	6.37	3.15	3.22	26.3	0
	0.43 (0.20, 0.93)		0.60 (0.28, 1.29)		(9.1, 51.2)	(<0.1, 20.6)
PD-L1≥1%, p16 Unknown (46 Nivo, 31 IC	5.65	4.70	2.10	1.91	13.0	0
	0.59 (0.36, 0.97)		0.56 (0.34, 0.95)		(4.9, 26.3)	(<0.1, 11.2)
PD-L1<1%, p16+ (24 Nivo, 10 IC)	9.10,	6.39	1.94	2.22	16.7	0
	0.55 (0.25, 1.22)		0.84 (0.38, 1.82)		(4.7, 37.4)	(<0.1, 30.8)
PD-L1<1%, p16- (17 Nivo, 13 IC)	13.0	6.47	2.20	3.15	11.8	15.4
	0.53 (0.22, 1.27)		1.29 (0.61, 2.74)		(1.5, 36.4)	(1.9, 45.4)
PD-L1<1%, p16 Unknown (32 Nivo, 15 IC)	4.86	4.60	1.91	2.00	9.4	13.3
	1.43 (0.72, 2.88)		1.48 (0.73, 3.00)		(2, 25)	(1.7, 40.5)

OS and PFS were estimated using Kaplan-Meier method.
HR (unstratified) is nivolumab over IC.
Confidence intervals for ORR were computed using the Clopper and Pearson method.
Source: Figure S.10.105 (OS), Figure Rap Q5.6 (PFS), and Appendix 16 (ORR) in Annex 3

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29: Summary of Efficacy for trial CA209141

Title: An Open Label, Randomised Phase 3 Clinical Trial of Nivolumab vs Therapy of Investigator's choice in Recurrent or Metastatic Platinum-Refractory Squamous Cell Carcinoma of the Head and Neck (HNSCC)		
Study identifier	CA209141	
Design	Phase 3, randomised open-label study Nivolumab versus investigator's choice (cetuximab, methotrexate, or docetaxel) randomised in 2:1 ratio and stratified according to prior cetuximab treatment (yes/no).	
	Duration of main phase:	FPFV: 29-May-2014 LPLV for primary endpoint: 06-Nov-2015
Hypothesis	Superiority	
Treatment groups	**Nivolumab (n=240)**	Nivolumab 3 mg/kg as 60min IV infusion Q2W; no dose increases or reductions were allowed

	Investigator's choice (n=121)		One of following single agents as selected by investigator; dose reductions were allowed – Cetuximab 400 mg/m^2 once, then 250 mg/m^2 weekly (where approved for use as single agent for recurrent HNSCC) – Methotrexate 40 mg/m^2 IV weekly, increased to 60 mg/m^2 if tolerated and as per local practices – Docetaxel 30 mg/m^2 IV weekly, increased to 40 mg/m^2 if tolerated and as per local practices
Endpoints and definitions	**Primary endpoint**	**OS**	Time from randomisation to the date of death from any cause. The survival time for subjects who had not died was censored at the last known date alive. OS was censored at the date of randomisation for subjects who were randomised but had no follow-up.
	Secondary endpoint	**PFS**	Primary definition PFS: Time between date of randomisation and first date of documented progression, as determined by investigator (as per RECIST v1.1 criteria). Secondary definition PFS: Also known as ITT definition, was same as primary definition, except there was no censoring for receipt of subsequent anticancer therapy prior to documented progression.
	Secondary endpoint	**ORR**	Proportion of randomised subjects who achieved best response of CR or PR using RECIST v1.1 criteria as per investigator assessment. To achieve a best response of CR or PR, confirmation was required. BOR was defined as confirmed best response designation, recorded between date of randomisation and date of progression, as assessed by the investigator per RECIST v1.1 or date of subsequent anticancer therapy, whichever occurred first.
	Key exploratory endpoint	**TTR**	Time from randomisation to date of first response (CR or PR), as assessed by investigator. TTR was evaluated for responders only.
	Key exploratory endpoint	**Association baseline PD-L1 expression and efficacy**	PD-L1 expression at baseline was defined based on PD-L1 IHC 28-8 pharmDx assay. Subjects with quantifiable PD-L1 expression at baseline had at least 1 tumour sample collected at baseline and ≥ 100 viable tumour cells. PD-L1 non-quantifiable subjects had no quantifiable PD-L1 expression at baseline (including subjects without available tumour samples). PD-L1 was analysed at predefined expression levels of 1%, 5%, and 10% PD-L1 expression at baseline.
Database lock	18-Dec-2015 clinical database lock (last patient last visit, 06-Nov-2015), 03-Feb-2016 PD-L1 database lock, and 05-May-2016 tumour assessments and subsequent therapies database lock. Data updated based on 20-Sept-2016 database lock.		

Results and analysis			
Analysis population and time point description	All randomised subjects On 18-Dec-2015, the clinical database was locked for the planned formal interim analysis of OS. On 26-Jan-2016, the independent DMC reviewed these interim data, and confirmed the pre-specified boundary for OS had been crossed (nominal significance level p<0.0227).		
Descriptive statistics and estimate variability	Treatment group	**Nivolumab**	**Investigator's choice**
	Number of subjects	240	121
	OS median, months (95% CI) Rate at 6 months %, (95%CI)	7.72 (5.68-8.77) 56.5 (49.9-62.5)	5.06 (4.04-6.24) 43.0 (34.0-51.7)
	PFS prim. median, months (95% CI) Rate at 6 months %, (95%CI)	2.04 (1.91-2.14) 21.0 (15.9-26.6)	2.33 (1.97-3.12) 11.1 (5.9-18.3)
	PFS sec. median, months (95%CI)	2.04 (1.91-2.14)	2.46 (1.97-3.15)
	ORR % responders (95%CI)	13.3 (9.3-18.3)	5.8 (2.4-11.6)
	BOR % CR PR SD PD NA	 2.5 10.8 22.9 41.7 22.1	 0.8 5.0 35.5 34.7 24.0
	TTR median, months (min, max)	2.1 (1.8-7.4)	2.0 (1.9-4.6)
	OS median by PD-L1 expression, months (95%CI) ≥1% <1% Non-quantifiable	 8.1 (n=88) (6.5-9.5) 6.1 (n=73) (4.4-12.7) 7.8 (n=79) (3.8-9.7)	 4.7 (n=61) (3.8-6.2) 5.5 (n=38) (3.7-8.5) 5.8 (n=22) (3.6-8.9)
Effect estimate per comparison	**OS**	**Comparison groups**	**Nivolumab vs. IC**
		HR	0.71
		95%CI	0.55-0.90
		p-value stratified log-rank test	0.0048
	PFS **Primary definition**	**Comparison groups**	**Nivolumab vs. IC**
		HR	0.87
		95%CI	0.69-1.11
		p-value stratified log-rank test	0.2597

	PFS Secondary definition	**Comparison groups**	**Nivolumab vs. IC**
		HR	0.91
		95%CI	0.73-1.15
		p-value stratified log-rank test	0.4208
	ORR	**Comparison groups**	**Nivolumab vs. IC**
		OR estimate	2.49
		95%CI	1.07-5.82
		p-value CMH test	Not available
	OS by PD-L1 expression	**Comparison groups**	**Nivolumab vs. IC**
		Unstratified HR	0.55
		95%CI	0.37-0.77
	≥1%	p-value	Not available
	<1%	Unstratified HR	0.83
		95%CI	0.54-1.29
		p-value	Not available
	Non-quantifiable	Unstratified HR	0.90
		95%CI	0.53-1.52
		p-value	Not available

Clinical studies in special populations

Special populations – Elderly patients

In the pivotal study, 95 patients aged ≥65 – <75 years were included (56 were treated with nivolumab, 93 with IC). In this age group, OS HR was 0.93 [95% CI: 0.56, 1.54]. A very small number of patients aged ≥75 years of age was enrolled, namely 12 in the nivolumab group and 6 in the control group and there were no subjects treated with nivolumab ≥85 years of age.

Special populations – Paediatric patients

The therapeutic indication currently applied for, treatment of oropharyngeal, laryngeal or nasal epithelial carcinoma (excluding nasopharyngeal carcinoma or lymphoepithelioma), is one of the conditions currently listed in the consolidated EMA decision on class waivers, adopted on 19 December 2011 (CW/1/2011). In addition, a PIP for nivolumab in the condition of "treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue)" was approved on 7 March 2014 (EMA Decision P/0064/2014).

Supportive study(ies)

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data to support the proposed indication in SCCHN is based on data derived from 361 randomised subjects (240 nivolumab and 121 investigator's choice) in the single pivotal trial, CA209141. This was an open label, randomised phase 3 clinical trial of nivolumab vs therapy of investigator's choice in the recurrent or metastatic platinum-refractory setting.

The inclusion/exclusion criteria were aimed to recruit patients (mildly symptomatic as ECOG is 0-1) with recurrent or metastatic oropharynx (except salivary gland) SCCHN, who have failed prior platinum therapy

(platinum resistant). This platinum regimen could have been part of induction, adjuvant or metastatic scheme.

SCCHN originating from paranasal sinuses and nasopharynx are usually excluded from trials, which is also applicable here. Nasopharynx carcinoma seems to have the highest likelihood to metastasize to distant size.

In subjects randomised to the investigator's choice group, subjects received one of the following treatments (as selected by the investigator): cetuximab, methotrexate, or docetaxel. Both methotrexate and weekly docetaxel have been used in several studies for recurrent/metastatic head and neck cancer. Cetuximab has also shown some responses in second line. The use of three different options as comparator adds uncertainty to the analysis, however from a clinical perspective, only response rates have been reported with these treatments without increase in survival.

Subjects were randomized 2:1 (nivolumab:investigator's choice) and stratified according to prior cetuximab treatment (yes/no). The 2:1 ratio is accepted given the lack of relevant survival benefit associated to the comparators and the previous results with immunotherapy. The stratification by prior use of cetuximab is agreed however the stratification by HPV status (+ or -) would have been desirable as well.

Given the open-label nature of the study, ORR and PFS data might be biased in view of the investigator-based response assessment.

506 patients were enrolled, 361 randomized (240 nivolumab, 121 investigators' choice), and 347 treated (236 nivolumab, 111 investigator's choice). It should be noted the percentage of subjects not treated in the investigator's choice (8.3%) of them 5% were due to "subject withdrew consent", which probably reflects the open label design of the study.
There are more subjects continuing in the treatment period in the nivolumab arm (17.4% vs 2.7%). Among the main reasons for not continuing in the treatment period, disease progression and toxicity are the most frequent. Both of them higher in the comparator arm, which could imply a better efficacy and tolerability of nivolumab.

Baseline demographic characteristics are evenly balanced between both groups except for patients between 65 and 75 years and < 65. The disease characteristics indicate a mildly symptomatic population (78% ECOG 1), former or current smoker (76%) with stage IV at study entry (90%) and oral cavity or pharynx as primary tumours. Both groups are overall balanced in the sites of lesions, with lung, lymph node and oral cavity as most frequent. All subjects have been previously treated with platinum. Overall, the subjects recruited into the study represent a platinum refractory population in stage IV with prior surgery and radiotherapy.
Patients had a much poorer prognosis (with ~20% of the patients deceased after 2 months), than would be expected from the inclusion criteria (ECOG PS of 0 or 1). Moreover, 40.4% of subjects had disease progression as their best response to their most recent prior platinum-based regimen, indicating that the enrolled patient population had a very poor prognosis. It is therefore plausible, that there was insufficient time for nivolumab to achieve clinical effect in a subset of patients with such poor prognosis. However, an analysis provided by the Applicant demonstrated that, overall, patients with progressive disease within 2 months on their prior treatment regimen do have clinical benefit from treatment with nivolumab compared to treatment with Investigator's Choice Therapy and this is consistent with the OS analysis in the overall study population.

Efficacy data and additional analyses
On 18 December 2015, the clinical database was locked for the planned formal interim analysis of OS as specified in the protocol. On 26 January 2016, with 55.4% of events in the nivolumab arm, there was a gain in the life expectancy of almost 2.5 months (in terms of medians of OS; HR = 0.70 [97.73% CI: 0.51, 0.96]; stratified log-rank test p-value = 0.0101). According to the profile of the curves, the benefit in OS takes approximately 3 months to become apparent. The magnitude of the difference in survival is around 15%

between groups (OS rates at 6, 9 and 12 months). Results from the two sensitivity analyses carried out (unstratified analysis and analysis based on subjects with no relevant deviations) are consistent with the main one. Furthermore, a multivariate analysis adjusted for HPV-p16 status, baseline ECOG PS, and prior chemotherapy for metastatic disease, showed a similar result. When split according to individual investigator's choice therapies, the advantage of nivolumab is retained versus cetuximab (HR 0.54; 95% CI: 0.30, 0.98) and methotrexate (HR 0.60; 95% CI: 0.41, 0.86). However, for docetaxel, even though nivolumab seems superior from the point of 4 months forward, due to likely lack of power to find differences and the crossover of the curves, no statistical conclusion can be drawn (HR 0.84; 95% CI 0.58, 1.23). When focusing on docetaxel comparison, a pattern of higher deaths associated to nivolumab is observed. The curve of nivolumab is clearly below docetaxel's one in the first 4 months. This fact recalls the same effect seen in melanoma and lung. The Applicant performed only univariate analyses to investigate factors that were associated with better 3-months survival for docetaxel instead of nivolumab and which suggest that with PS1, < 3 lines of therapy (especially 2), fast PD (<=4 months), no CR on previous therapy, former/current smokers have a better probability to survive 3 months with docetaxel. Analyses using the updated database (20-Sep-2016 database lock) were conducted to better characterise the subgroup of subjects who died within first 3 months and to explore factors which might be associated with higher risk of early death. During the first 3 months of therapy, there was a higher percentage of patients who died in the nivolumab group vs docetaxel arm (28.3% vs 18.5% of the whole number of nivolumab and docetaxel treated patients respectively). The delay in the onset of action of nivolumab along with some prognostic factors appears the most plausible explanation. Likewise in NSCLC and melanoma, ECOG performance status, fast progressive disease and high tumour burden seem to be an important factor to consider when it comes to starting a nivolumab treatment.

Cross-over from nivolumab to an investigator's choice therapy and from investigator's choice to a regimen with an anti PD-L1 component was limited (20.9 and 7.4%, respectively) and the OS advantage is still in favour of nivolumab, so the impact of cross-over on OS is limited. Subjects in the nivolumab group received more often taxanes, and subjects in the investigator's group were more often treated with an anti-PD-1 targeted agent. The primary endpoint OS is not expected to be impacted to a relevant extent by the use of subsequent anticancer therapies as frequencies were similar in both groups.

In the updated analysis (20-Sep-2016 database lock) nivolumab continued to demonstrate statistically significant and clinically meaningful improvement in OS versus investigator's choice therapy (HR= 0.71 [95% CI: 0.55, 0.90]; stratified log-rank test p-value = 0.0048), with survival rates of 34.0% and 21.5% at 12 and 18 months, respectively. The HR for OS of nivolumab versus individual investigator's choice therapies was 0.49 (95% CI: 0.29, 0.84) for cetuximab, 0.57 (95% CI: 0.41, 0.78) for methotrexate, and 0.92 (95% CI: 0.66, 1.29) for docetaxel.

Regarding the secondary endpoints, no statistically significant difference in terms of PFS was found between nivolumab and control group, even though from the 5th month forward there seem to be some benefit. This lack of positive results in PFS has been previously observed in other clinical developments with nivolumab (renal and non-squamous NSCLC), highlighting the discrepancy between PFS and OS.

ORR results offer better outcomes, with a significant difference in favour of nivolumab (13% vs 6% for the nivolumab and control group respectively) but with only 6 complete responders. Median time to objective response was 2 months.

Results in the various subgroups were not significantly dissimilar to the overall population. In the European population, neither OS (HR 0.91 95%CI 0.62, 1.33) nor ORR (10.1% vs 9.7%) show a clear benefit for nivolumab and even in terms of PFS the control group offers better results (HR 1.27 95%CI 0.90, 1.78). Even though some imbalances in prognostic factors (time from prior platinum to progression, gender and HPV status) could partially explain this absence of benefit, no firm conclusions can be drawn. In a worst-case scenario, nivolumab would offer similar efficacy to docetaxel, though with a priori better safety profile.

Analyses provided by the MAH demonstrate that activity of nivolumab relative to investigator's choice therapy (ICT) is markedly less in patients with low tumour PD-L1 expression (<1%) compared to patients with higher tumour PD-L1 expression (≥1%). However, after several analyses in order to explore the link between PD-L1 expression on tumour cells and tumour-associated immune cells (TAICs) and response to treatment with nivolumab in head and neck squamous cell carcinoma (HNSCC), the subgroup of patients which has intratumoural PD-L1 expressing TAIC appears to have greater benefit from treatment with nivolumab than from treatment with investigator's choice therapy (ICT) while the subgroup of patients with low tumour cell PD-L1 expression (<1%) without intratumoural PD-L1 expressing TAIC appears not to have greater benefit from nivolumab compared to ICT. A less pronounced, but a similar pattern is observed in the group of patients with high tumour cell PD-L1 expression (≥1%), with the number and the localisation of the PD-L1 positive TAIC appearing to be associated with response to nivolumab. It should, however, be acknowledged that the investigated subgroups are small, and in combination with technical challenges, definitive conclusions cannot yet be drawn from this analysis. In order to further investigate the relationship between clinical outcomes to nivolumab and PD-L1 expression in immune cells and other biomarkers (PD-L2, mutational load), a biomarker investigation has been included as post authorisation measure (see Annex II).

In the updated analysis of efficacy by both baseline PD-L1 expression and p16 status, in all subgroups nivolumab treatment had numerically better efficacy than IC treatment, except for PD-L1<1% and p16 unknown (HR 1.41 [95% CI 0.72- 2.88]). Since the confidence interval encompasses 1 and it concerns a small sample size, no conclusion can be drawn on these data. With the addition of 6 p16-negative patients and the updated analyses, the HR for the PD-L1 <1% and p16-negative patients decreased from 0.82 to 0.53, which is reassuring.

Finally, HPV status revealed a different pattern of efficacy in those patients HPV negative (HR 0.73 [95% CI: 0.42, 1.25]) vs HPV positive (HR 0.56 [95% CI: 0.32, 0.99]) with a different profile of the curves. Nevertheless in the updated analysis hazard ratios for OS favour nivolumab treatment compared to investigator's choice for p16-positive, p16-negative, and unknown p16 status, ie. OS benefit was observed regardless of HPV status (HPV-positive: HR = 0.63; 95% CI: 0.38, 1.04, HPV-negative: HR = 0.64; 95% CI: 0.40, 1.03, and HPV-unknown: HR = 0.78; 95% CI: 0.55, 1.10), as reported in the Product Information.

2.4.4. Conclusions on the clinical efficacy

Nivolumab showed an improvement in overall survival compared to the best investigator choice in the overall population in the single pivotal study. However, the overall survival, PFS and ORR data show that this added efficacy versus the standard of care might be limited or even not present in certain subgroups (see section 5.1 of the SmPC).

The CHMP considers the following measures necessary to address issues related to efficacy:

The MAH should further investigate in study CA209141, the association between improved clinical outcomes to nivolumab and the presence of:

- Higher mutational load, and as feasible, PD L1 tumour associated immune cell (TAIC) expression (30 September 2017)
- PD-L2 expression (31 March 2018)
- High inflamed phenotype (30 September 2018)

2.5. Clinical safety

Introduction

Safety was assessed based on the data from Study CA209141 supporting the use of nivolumab (BMS-936558) at the proposed dose and schedule of 3 mg/kg administered as an IV infusion over 1 hour every 2 weeks (Q2W) for the treatment of patients with recurrent or metastatic SCCHN.

Of the 361 subjects randomized (240 to nivolumab, 121 to investigator's choice therapy), 347 (96.1%) were treated (236 with nivolumab, 111 with investigator's choice therapy). Safety analyses were conducted in all treated subjects who received at least one dose of study drug. Safety presentations of AEs, SAEs, AEs leading to discontinuation, select AEs, and laboratory abnormalities are based on all treated subjects using a safety window of 30 days after last dose.

The primary clinical database lock was 18-Dec-2015. The CA209141 Final CSR was updated with safety data following the 20-Sep-2016 database lock. This updated analysis represents a minimum follow-up for survival of 11.4 months. The assessment of longer-term safety was based on frequency of deaths, as well as all-causality and drug-related AEs, SAEs, AEs leading to discontinuation of study drug, and selected AEs.

There were a higher proportion of former/current smokers in the nivolumab group (79.6%) than the in investigator's choice group (71.1%). The only stratification factor in the randomisation was prior cetuximab (yes/no; IVRS source).

In CA209141, the incidence rates of AEs leading to discontinuation, drug-related AEs, and drug-related SAEs, reported within 100 days of last dose were consistent with those reported within 30 days of the last dose.

Patient exposure

As of the clinical database lock date (20-Sep-2016), the majority (82.2%) of treated subjects in the nivolumab group received $\geqslant$ 90% of the planned dose intensity, which was similar to the frequency for cetuximab (84.6%), and higher than for docetaxel (67.3%) and methotrexate (50.0%) (Table 30). The lower proportion of subjects receiving $\geqslant$ 90% of the planned dose intensity in the docetaxel and methotrexate groups is consistent with the protocol, which allowed dose reductions of cetuximab, methotrexate, and docetaxel, but not nivolumab. The median duration of nivolumab therapy was similar to that of the investigator's choice therapy; see Table 30 (by individual investigator's choice agent).

Table 30: Cumulative Dose and Relative Dose Intensity Summary - All Treated Subjects in CA209141 (20-Sep-2016 database lock)

	Nivolumab (N=236)	Investigator's Choice (N=111)		
	Nivolumab 3 mg/kg (N=236)	Cetuximab (N=13)	Methotrexate (N=46)	Docetaxel (N=52)
NUMBER OF DOSES RECEIVED				
MEAN (SD)	9.4 (10.53)	10.5 (7.61)	7.9 (5.22)	11.1 (8.32)
MEDIAN (MIN - MAX)	5.0 (1 - 51)	8.0 (3 - 32)	7.5 (1 - 18)	9.0 (1 - 38)
DURATION OF THERAPY (1)				
MEDIAN	1.9	1.6	1.6	2.0
Q1, Q3	1.0, 4.9	1.6, 2.2	0.5, 3.0	1.4, 3.3
MIN, MAX (2)	0, 24*	0, 7	0, 6	0, 12*
CUMULATIVE DOSE (3)				
MEAN (SD)	28.1 (31.40)	2826.3 (1899.72)	302.7 (195.29)	376.2 (306.95)
MEDIAN (MIN - MAX)	15.0 (3 - 156)	2246.9 (923 - 8232)	272.4 (27 - 725)	279.9 (30 - 1534)
RELATIVE DOSE INTENSITY (%)				
>= 110%	0	1 (7.7)	0	15 (28.8)
90% to < 110%	194 (82.2)	10 (76.9)	23 (50.0)	20 (38.5)
70% to < 90%	35 (14.8)	2 (15.4)	13 (28.3)	10 (19.2)
50% to < 70%	6 (2.5)	0	4 (8.7)	6 (11.5)
< 50%	1 (0.4)	0	5 (10.9)	1 (1.9)
MISSING	0	0	1 (2.2)	0

(1) The first quartile (Q1), the median, and the third quartile (Q3), are computed using a Kaplan-Meier estimate of the duration of treatment. In this analysis, duration of therapy for a subject still on treatment is censored on the date of his or her last dose.
(2) An asterisk will be placed alongside the maximum value if it is associated with a subject who is still on therapy.
(3) Dose units are mg/m2 for investigator's choice of chemotherapeutic agent, and mg/kg for nivolumab.
Source: Table S.4.1

As of the 20-Sep-2016 database lock, 16 (6.8%) subjects in the nivolumab group and 1 (0.9%) subject in investigator's choice group were continuing in the treatment period. Most subjects received all doses of study medication without an infusion interruption, infusion rate reduction, or dose delay. Most of the subjects in the investigator's choice group did not require a dose reduction or escalation; dose reductions or escalations were not permitted with nivolumab treatment. In the investigator's choice group, 0%, 4.3%, and 5.8% of subjects had a dose escalation of cetuximab, methotrexate, or docetaxel, respectively.

Among treated subjects in the nivolumab group, the majority (55.9%; 132/236) were exposed to nivolumab for less than 3 months; 44.1% (104/236) of nivolumab-treated subjects were exposed for 3 or more months, with 25.0% (59/236) and 11.4% (27/236) exposed for ≥ 6 or ≥ 12 months, respectively. The median duration of nivolumab therapy in CA209141 was 1.9 months.

In SCCHN, the mean number of doses received and cumulative dose was lower than RCC, melanoma, and NSCLC; a high proportion of subjects received ≥ 90% of the relative dose intensity, similar to the other tumour types; median duration of therapy was similar to NSCLC and shorter than RCC and melanoma; a similar proportion of subjects were still being treated with nivolumab at the time of database lock compared with RCC and NSCLC; total exposure to nivolumab monotherapy was shorter than in other tumour types.

Table 31: Cumulative Dose and Relative Dose Intensity, Duration of Study Therapy, and Total Exposure to Nivolumab Monotherapy Across Tumour Types - All Treated Subjects

	SCCHN N = 236	RCC N = 406	Melanoma N = 787	NSCLC N = 535
NUMBER OF DOSES RECEIVED				
MEAN (SD)	7.6 (6.71)	19.2 (16.25)	15.4 (10.99)	12.0 (12.49)
MEDIAN (MIN - MAX)	5.0 (1 - 34)	12.0 (1 - 65)	12.0 (1 - 45)	6.0 (1 - 52)
CUMULATIVE DOSE (MG/KG)				
MEAN (SD)	22.8 (20.15)	57.72 (49.025)	46.20 (33.144)	36.05 (37.388)
MEDIAN (MIN - MAX)	15.0 (3 - 102)	36.03 (0.5 - 195.1)	36.00 (3.0 - 135.0)	18.04 (1.4 - 156.0)
RELATIVE DOSE INTENSITY				
>= 110%	0	3 (0.7)	3 (0.4)	0
90% TO < 110%	195 (82.6)	330 (81.3)	681 (86.5)	447 (83.6)
70% TO < 90%	35 (14.8)	64 (15.8)	88 (11.2)	75 (14.0)
50% TO < 70%	5 (2.1)	8 (2.0)	13 (1.7)	11 (2.1)
< 50%	0 (0.4)	1 (0.2)	2 (0.3)	2 (0.4)
DURATION OF THERAPY (MONTHS)				
MIN, MAX (A)	0, 16+	0.03, 29.60+	0.03, 20.30+	0.03, 23.95+
MEDIAN (95% CI) (B)	1.9 (1.6, 2.3)	5.536 (5.060, 6.932)	5.815 (5.092, 6.669)	2.727 (2.300, 3.023)
N OFF TRT/N TREATED (%)	195/236 (82.6)	339/406 (83.5)	499/787 (63.4)	456/535 (85.2)
TOTAL EXPOSURE (P-Y)	79.0	328.3	500.2	277.8

Nivolumab monotherapy treatment groups from the following studies are included in the disease categories: SCCHN: CA209141; RCC: CA209025; Melanoma: CA209037, CA209066, CA209067; NSCLC: CA209063, CA209017, CA209057.
P-Y = person-years of exposure.
(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
Source: refer to Table 6.1-1 and Figure 6.1-1 of the CA209141 Final CSR[2] for SCCHN data.

Adverse events

All-causality AEs

Table 32: Summary of Safety Results Based on 20-Sep-2016 Database lock - All Treated Subjects in CA209141

	Number (%) Subjects	
	Nivolumab 3 mg/kg (N=236)	Investigator's Choice (N=111)
DEATHS	183 (77.5)	96 (86.5)
WITHIN 30 DAYS OF LAST DOSE	52 (22.0)	21 (18.9)
WITHIN 100 DAYS OF LAST DOSE	109 (46.2)	58 (52.3)
DUE TO STUDY DRUG TOXICITY (a)	2 (0.8)	1 (0.9)

	Number (%) Subjects			
	Nivolumab 3 mg/kg (N=236)		Investigator's Choice (N=111)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL-CAUSALITY SAEs	132 (55.9)	80 (33.9)	65 (58.6)	45 (40.5)
DRUG-RELATED SAEs	17 (7.2)	13 (5.5)	17 (15.3)	12 (10.8)
ALL-CAUSALITY AEs LEADING TO DC	55 (23.3)	37 (15.7)	25 (22.5)	13 (11.7)
DRUG-RELATED AEs LEADING TO DC	9 (3.8)	7 (3.0)	10 (9.0)	6 (5.4)
ALL-CAUSALITY AEs	232 (98.3)	113 (47.9)	109 (98.2)	69 (62.2)
Most Frequent AEs (≥ 20% of Any Grade in either treatment group)				
FATIGUE	67 (28.4)	8 (3.4)	37 (33.3)	7 (6.3)
NAUSEA	50 (21.2)	1 (0.4)	34 (30.6)	1 (0.9)
ANAEMIA	48 (20.3)	15 (6.4)	39 (35.1)	10 (9.0)
MALIGNANT NEOPLASM PROGRESSION	46 (19.5)	11 (4.7)	23 (20.7)	10 (9.0)
DIARRHOEA	43 (18.2)	3 (1.3)	26 (23.4)	3 (2.7)
ASTHENIA	25 (10.6)	5 (2.1)	25 (22.5)	5 (4.5)
DRUG-RELATED AEs	146 (61.9)	36 (15.3)	88 (79.3)	40 (36.0)
Most Frequent Drug-related AEs (≥15% of Any Grade in either treatment group)				
FATIGUE	37 (15.7)	5 (2.1)	20 (18.0)	3 (2.7)
NAUSEA	22 (9.3)	0	23 (20.7)	1 (0.9)
ANAEMIA	12 (5.1)	3 (1.3)	19 (17.1)	6 (5.4)
ASTHENIA	10 (4.2)	1 (0.4)	17 (15.3)	2 (1.8)
MUCOSAL INFLAMMATION	4 (1.7)	0	15 (13.5)	2 (1.8)
ALL-CAUSALITY SELECT AES, BY CATEGORY				
ENDOCRINE	29 (12.3)	1 (0.4)	6 (5.4)	0
GASTROINTESTINAL	43 (18.2)	3 (1.3)	26 (23.4)	3 (2.7)
HEPATIC	26 (11.0)	7 (3.0)	12 (10.8)	3 (2.7)
PULMONARY	10 (4.2)	4 (1.7)	2 (1.8)	0
RENAL	9 (3.8)	0	2 (1.8)	1 (0.9)
SKIN	49 (20.8)	0	16 (14.4)	2 (1.8)
HYPERSENSITIVITY/INFUSION REACTIONS	3 (1.3)	0	2 (1.8)	1 (0.9)
DRUG-RELATED SELECT AES, BY CATEGORY				
ENDOCRINE	22 (9.3)	1 (0.4)	1 (0.9)	0
GASTROINTESTINAL	20 (8.5)	1 (0.4)	17 (15.3)	2 (1.8)
HEPATIC	7 (3.0)	2 (0.8)	5 (4.5)	1 (0.9)
PULMONARY	7 (3.0)	2 (0.8)	1 (0.9)	0
RENAL	3 (1.3)	0	2 (1.8)	1 (0.9)
SKIN	40 (16.9)	0	14 (12.6)	2 (1.8)
HYPERSENSITIVITY/INFUSION REACTIONS	3 (1.3)	0	2 (1.8)	1 (0.9)

MedDRA version 19.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

(a) Two deaths in the nivolumab group (Grade 3 pneumonitis and Grade 5 hypercalcaemia) and one death in the investigator's choice group (Grade 5 pneumonia) were assessed as related to study drug.

Source: Table S.6.58 (deaths), Table S.6.62 (all causality SAEs), Table S.6.64 (drug-related SAEs), Table S.6.87 (all causality AEs leading to DC), Table S.6.89 (drug-related AEs leading to DC), Table S.6.3 (all causality AEs), Table S.6.5 (drug-related AEs), Table S.6.12 (all causality select AEs), Table S.6.16 (all causality endocrine select AEs), Table S.6.14 (drug-related select AEs), Table S.6.18 (drug-related endocrine select AEs).

Drug-related AEs

Table 33: Drug-related AEs by Worst CTC Grade Reported in ⩾ 5% of Treated Subjects in CA209141 (20-Sep-2016 database lock)

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	146 (61.9)	36 (15.3)	0	88 (79.3)	40 (36.0)	1 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	61 (25.8)	6 (2.5)	0	50 (45.0)	9 (8.1)	0
FATIGUE	37 (15.7)	5 (2.1)	0	20 (18.0)	3 (2.7)	0
ASTHENIA	10 (4.2)	1 (0.4)	0	17 (15.3)	2 (1.8)	0
MUCOSAL INFLAMMATION	4 (1.7)	0	0	15 (13.5)	2 (1.8)	0
GASTROINTESTINAL DISORDERS	52 (22.0)	4 (1.7)	0	49 (44.1)	6 (5.4)	0
NAUSEA	22 (9.3)	0	0	23 (20.7)	1 (0.9)	0
DIARRHOEA	20 (8.5)	1 (0.4)	0	16 (14.4)	2 (1.8)	0
VOMITING	8 (3.4)	0	0	8 (7.2)	0	0
STOMATITIS	6 (2.5)	1 (0.4)	0	12 (10.8)	3 (2.7)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	46 (19.5)	0	0	32 (28.8)	5 (4.5)	0
PRURITUS	19 (8.1)	0	0	0	0	0
RASH	19 (8.1)	0	0	5 (4.5)	1 (0.9)	0
DRY SKIN	7 (3.0)	0	0	10 (9.0)	0	0
ALOPECIA	0	0	0	14 (12.6)	0	0
METABOLISM AND NUTRITION DISORDERS	37 (15.7)	10 (4.2)	0	19 (17.1)	5 (4.5)	0
DECREASED APPETITE	19 (8.1)	0	0	8 (7.2)	0	0
INVESTIGATIONS	33 (14.0)	10 (4.2)	0	14 (12.6)	4 (3.6)	0
WEIGHT DECREASED	5 (2.1)	1 (0.4)	0	6 (5.4)	0	0
ENDOCRINE DISORDERS	20 (8.5)	1 (0.4)	0	1 (0.9)	0	0
HYPOTHYROIDISM	14 (5.9)	0	0	1 (0.9)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	18 (7.6)	7 (3.0)	0	26 (23.4)	15 (13.5)	0
ANAEMIA	12 (5.1)	3 (1.3)	0	19 (17.1)	6 (5.4)	0
NEUTROPENIA	0	0	0	9 (8.1)	8 (7.2)	0
NERVOUS SYSTEM DISORDERS	9 (3.8)	1 (0.4)	0	17 (15.3)	1 (0.9)	0
NEUROPATHY PERIPHERAL	1 (0.4)	0	0	7 (6.3)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.5

When incidence rates were exposure-adjusted, the AE rate was lower in the nivolumab group than in the investigator's choice group (2101.0 vs. 3783.9 incidence rate per 100 person years).

Adverse Events in CA209141 and Across Pooled Monotherapy Studies

Safety data from nivolumab 3 mg/kg Q2W monotherapy were pooled across tumour types (renal cell carcinoma [RCC, CA209025], melanoma [CA209037, CA209066, and CA209067], non-small cell lung cancer [NSCLC, CA209063, CA209017, and CA209057]), and SCCHN (CA209141).

Exposure-adjusted AE incidence rates (events per 100 person-years of exposure) were 1607.0 in SCCHN and 1648.7, 1747.5, and 1795.6 in RCC, melanoma, and NSCLC, respectively.

No new safety concerns with nivolumab monotherapy treatment were identified in SCCHN (CA209141, 18-Dec-2015 database lock). An update of safety (20-Sep- 2016 database lock) in CA209141 Final CSR confirms that no new safety concerns with nivolumab monotherapy in SCCHN were identified (Table 34).

Table 34: Adverse Events and Reactions with Nivolumab Monotherapy in Clinical Trials using Re-mapped Terms

	SCCHN CA209141 N = 236		All Nivo Mono including CA209141 N = 2227	
Preferred Term (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT (REGARDLESS OF CAUSALITY)	229 (97.0)	97 (41.1)	2163 (97.1)	955 (42.9)
Most Frequent (>20% in any grade in the pool across tumour types)				
FATIGUE	85 (36.0)	13 (5.5)	1076 (48.3)	89 (4.0)
MUSCULOSKELETAL PAIN	44 (18.6)	6 (2.5)	726 (32.6)	74 (3.3)
COUGH	42 (17.8)	1 (0.4)	558 (25.1)	7 (0.3)
NAUSEA	45 (19.1)	1 (0.4)	535 (24.0)	18 (0.8)
RASH	29 (12.3)	0	512 (23.0)	24 (1.1)
DIARRHOEA	35 (14.8)	2 (0.8)	501 (22.5)	36 (1.6)
DYSPNOEA	35 (14.8)	13 (5.5)	458 (20.6)	67 (3.0)
TOTAL SUBJECTS WITH AN EVENT (DRUG-RELATED)	139 (58.9)	31 (13.1)	1617 (72.6)	316 (14.2)
Most Frequent (>10% in any grade in the pool across tumour types)				
FATIGUE	42 (17.8)	6 (2.5)	674 (30.3)	36 (1.6)
RASH	25 (10.6)	0	380 (17.1)	19 (0.9)
NAUSEA	20 (8.5)	0	278 (12.5)	3 (0.1)
PRURITUS	17 (7.2)	0	276 (12.4)	2 (<0.1)
DIARRHOEA	16 (6.8)	0	274 (12.3)	21 (0.9)

MedDRA Version: 18.1, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, and CA20914.
Grade 3-4 by worst CTC grade.
Some preferred terms are re-mapped or deleted based on BMS medical review.

Table 35: Summary of Safety of Nivolumab Monotherapy across tumour types - All Treated Subjects

	SCCHN N = 236	RCC N = 406	Melanoma N = 787	NSCLC N = 535
NUMBER OF SUBJECTS WHO DIED (%)	**132 (55.9)**	**181 (44.6)**	**251 (31.9)**	**339 (63.4)**
WITHIN 30 DAYS	50 (21.2)	19 (4.7)	57 (7.2)	66 (12.3)
WITHIN 100 DAYS	103 (43.6)	56 (13.8)	151 (19.2)	181 (33.8)
STUDY DRUG TOXICITY	2 (0.8)	0	1 (0.1)	2 (0.4)
AEs, all grades	229 (97.0)	**397 (97.8)**	**768 (97.6)**	**524 (97.9)**
AEs, Grade 3-4	97 (41.1)	216 (53.2)	319 (40.5)	244 (45.6)
MOST FREQUENTLY REPORTED AEs (> 20% of subjects, all grades)				
FATIGUE	62 (26.3)	195 (48.0)	328 (41.7)	189 (35.3)
NAUSEA	45 (19.1)	115 (28.3)	213 (27.1)	117 (21.9)
DECREASED APPETITE	44 (18.6)	93 (22.9)	132 (16.8)	156 (29.2)
CONSTIPATION	36 (15.3)	92 (22.7)	155 (19.7)	111 (20.7)
DIARRHOEA	35 (14.8)	96 (23.6)	223 (28.3)	86 (16.1)
COUGH	32 (13.6)	128 (31.5)	148 (18.8)	154 (28.8)
DYSPNOEA	32 (13.6)	94 (23.2)	102 (13.0)	157 (29.3)
PRURITUS	20 (8.5)	75 (18.5)	182 (23.1)	56 (10.5)
RASH	20 (8.5)	64 (15.8)	176 (22.4)	60 (11.2)
BACK PAIN	14 (5.9)	87 (21.4)	104 (13.2)	60 (11.2)
DRUG-RELATED AEs, all grades	**139 (58.9)**	**319 (78.6)**	**609 (77.4)**	**362 (67.7)**
DRUG-RELATED AEs, Grade 3-4	31 (13.1)	76 (18.7)	108 (13.7)	59 (11.0)
MOST FREQUENTLY REPORTED DRUG-RELATED AEs (> 10% of subjects, all grades)				
FATIGUE	33 (14.0)	134 (33.0)	230 (29.2)	105 (19.6)
NAUSEA	20 (8.5)	57 (14.0)	108 (13.7)	64 (12.0)
RASH	18 (7.6)	41 (10.1)	133 (16.9)	45 (8.4)
PRURITUS	17 (7.2)	57 (14.0)	145 (18.4)	34 (6.4)
DECREASED APPETITE	17 (7.2)	48 (11.8)	63 (8.0)	66 (12.3)
DIARRHOEA	16 (6.8)	50 (12.3)	135 (17.2)	44 (8.2)
ASTHENIA	10 (4.2)	18 (4.4)	59 (7.5)	56 (10.5)
ALL SAEs, all grades	**127 (53.8)**	**194 (47.8)**	**319 (40.5)**	**263 (49.2)**
DRUG-RELATED SAEs, all grades	**16 (6.8)**	**47 (11.6)**	**64 (8.1)**	**42 (7.9)**
ALL AEs LEADING TO DC, all grades	**51 (21.6)**	**72 (17.7)**	**91 (11.6)**	**99 (18.5)**
DRUG-RELATED AEs LEADING TO DC, all grades	**9 (3.8)**	**31 (7.6)**	**41 (5.2)**	**32 (6.0)**

MedDRA Version: 18.1 (SCCHN) and 18.0 (RCC, melanoma and NSCLC); CTC version 4.0; Unless stated otherwise, includes events reported between first dose and 30 days after last dose of study therapy.
Nivolumab monotherapy treatment groups from the following studies are included in the disease categories: SCCHN: CA209141; RCC: CA209025; Melanoma: CA209037, CA209066, CA209067; NSCLC: CA209063, CA209017, CA209057.
Source: refer to Table 8.1-1, Table S.6.1, and Table S.6.5 of the CA209141 Final CSR[2] for SCCHN data.

Serious adverse event / deaths / other significant events

Serious Adverse Events (SAEs)

Table 36: Summary of SEAs by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with 1% Cutoff – All Treated Subjects in CA209141 (20-Sep-2016 database lock)

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	132 (55.9)	80 (33.9)	40 (16.9)	65 (58.6)	45 (40.5)	15 (13.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	50 (21.2)	14 (5.9)	36 (15.3)	25 (22.5)	10 (9.0)	13 (11.7)
MALIGNANT NEOPLASM PROGRESSION	46 (19.5)	11 (4.7)	35 (14.8)	23 (20.7)	10 (9.0)	13 (11.7)
TUMOUR PAIN	1 (0.4)	1 (0.4)	0	2 (1.8)	0	0
INFECTIONS AND INFESTATIONS	39 (16.5)	31 (13.1)	0	21 (18.9)	17 (15.3)	1 (0.9)
PNEUMONIA	11 (4.7)	9 (3.8)	0	2 (1.8)	1 (0.9)	1 (0.9)
RESPIRATORY TRACT INFECTION	5 (2.1)	3 (1.3)	0	1 (0.9)	0	0
SEPSIS	5 (2.1)	5 (2.1)	0	3 (2.7)	3 (2.7)	0
LUNG INFECTION	4 (1.7)	3 (1.3)	0	3 (2.7)	3 (2.7)	0
URINARY TRACT INFECTION	4 (1.7)	3 (1.3)	0	0	0	0
LOWER RESPIRATORY TRACT INFECTION	3 (1.3)	1 (0.4)	0	3 (2.7)	3 (2.7)	0
DEVICE RELATED INFECTION	0	0	0	2 (1.8)	1 (0.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	36 (15.3)	33 (14.0)	0	12 (10.8)	11 (9.9)	0
DYSPNOEA	9 (3.8)	9 (3.8)	0	1 (0.9)	1 (0.9)	0
PNEUMONIA ASPIRATION	8 (3.4)	8 (3.4)	0	2 (1.8)	2 (1.8)	0
RESPIRATORY FAILURE	4 (1.7)	4 (1.7)	0	0	0	0
PLEURAL EFFUSION	2 (0.8)	2 (0.8)	0	3 (2.7)	3 (2.7)	0
RESPIRATORY DISTRESS	1 (0.4)	1 (0.4)	0	2 (1.8)	2 (1.8)	0
METABOLISM AND NUTRITION DISORDERS	19 (8.1)	16 (6.8)	0	3 (2.7)	3 (2.7)	0
DECREASED APPETITE	4 (1.7)	2 (0.8)	0	1 (0.9)	1 (0.9)	0
DEHYDRATION	3 (1.3)	3 (1.3)	0	1 (0.9)	1 (0.9)	0
HYPERCALCAEMIA	3 (1.3)	2 (0.8)	0	1 (0.9)	1 (0.9)	0
GASTROINTESTINAL DISORDERS	12 (5.1)	6 (2.5)	0	10 (9.0)	7 (6.3)	0
ABDOMINAL PAIN	2 (0.8)	1 (0.4)	0	2 (1.8)	1 (0.9)	0
DYSPHAGIA	2 (0.8)	2 (0.8)	0	3 (2.7)	3 (2.7)	0
DIARRHOEA	1 (0.4)	0	0	3 (2.7)	2 (1.8)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	11 (4.7)	6 (2.5)	0	12 (10.8)	7 (6.3)	0
PYREXIA	3 (1.3)	1 (0.4)	0	4 (3.6)	3 (2.7)	0
ASTHENIA	1 (0.4)	1 (0.4)	0	2 (1.8)	1 (0.9)	0
MALAISE	0	0	0	2 (1.8)	1 (0.9)	0
NERVOUS SYSTEM DISORDERS	7 (3.0)	5 (2.1)	1 (0.4)	5 (4.5)	4 (3.6)	0
DIZZINESS	0	0	0	2 (1.8)	1 (0.9)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	3 (2.7)	3 (2.7)	0
ANAEMIA	0	0	0	2 (1.8)	2 (1.8)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Data Sources: ADAE, ADSM

Table 37: Drug-related SAEs by Worst CTC Grade Reported in at least 2 subjects - All Treated Subjects- CA209141 (20-Sep-2016 database lock)

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	17 (7.2)	13 (5.5)	0	17 (15.3)	12 (10.8)	1 (0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (2.5)	5 (2.1)	0	1 (0.9)	1 (0.9)	0
PNEUMONITIS	2 (0.8)	2 (0.8)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.4)	0	0	4 (3.6)	3 (2.7)	0
MALAISE	0	0	0	2 (1.8)	1 (0.9)	0
PYREXIA	0	0	0	2 (1.8)	2 (1.8)	0
INFECTIONS AND INFESTATIONS	1 (0.4)	1 (0.4)	0	6 (5.4)	5 (4.5)	1 (0.9)
PNEUMONIA	0	0	0	2 (1.8)	1 (0.9)	1 (0.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	3 (2.7)	3 (2.7)	0
ANAEMIA	0	0	0	2 (1.8)	2 (1.8)	0
GASTROINTESTINAL DISORDERS	0	0	0	4 (3.6)	2 (1.8)	0
DIARRHOEA	0	0	0	2 (1.8)	1 (0.9)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.64

Deaths

Table 38: Summary of Deaths - All Treated Subjects in CA209141 (20-Sep-2016 database lock)

	Nivolumab 3 mg/kg (N=236)	Investigator's Choice (N=111)	Total (N=347)
NUMBER OF SUBJECTS WHO DIED (%)	183 (77.5)	96 (86.5)	279 (80.4)
PRIMARY REASON FOR DEATH (%)			
DISEASE	151 (64.0)	87 (78.4)	238 (68.6)
STUDY DRUG TOXICITY (a)	2 (0.8)	1 (0.9)	3 (0.9)
UNKNOWN	14 (5.9)	2 (1.8)	16 (4.6)
OTHER	16 (6.8)	6 (5.4)	22 (6.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	52 (22.0)	21 (18.9)	73 (21.0)
PRIMARY REASON FOR DEATH (%)			
DISEASE	40 (16.9)	19 (17.1)	59 (17.0)
STUDY DRUG TOXICITY	1 (0.4)	1 (0.9)	2 (0.6)
UNKNOWN	1 (0.4)	0	1 (0.3)
OTHER	10 (4.2)	1 (0.9)	11 (3.2)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	109 (46.2)	58 (52.3)	167 (48.1)
PRIMARY REASON FOR DEATH (%)			
DISEASE	89 (37.7)	53 (47.7)	142 (40.9)
STUDY DRUG TOXICITY	2 (0.8)	1 (0.9)	3 (0.9)
UNKNOWN	3 (1.3)	0	3 (0.9)
OTHER	15 (6.4)	4 (3.6)	19 (5.5)

(a) Two deaths in the nivolumab group (Grade 3 pneumonitis and Grade 5 hypercalcemia) and one death in the investigator's choice group (docetaxel; Grade 5 pneumonia) were assessed as related to study drug.
Source: Table S.6.58

As of the 20-Sep-2016 database lock, two deaths in the nivolumab group (grade 3 pneumonitis and grade 5 hypercalcemia) were assessed as study drug-related, versus one death in the investigator's choice group (docetaxel, grade 5 pneumonia).

Select adverse events / adverse events of special interest

The majority of select AEs reported were Grade 1-2, and most were considered drug-related by the investigator. The most frequently reported any-grade drug-related select AE categories with nivolumab treatment were skin (16.9%), endocrine (9.3%), and gastrointestinal (8.5%).

Endocrine Events

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

Two Grade 3-4 events (hypophysitis and secondary adrenocortical insufficiency) were reported, both in the same subject, and 1 event (hypophysitis) led to permanent discontinuation of nivolumab. This event was ongoing at the time of database lock.

Table 39: Summary of Drug-related Endocrine Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects - CA209141 (20-Sep-2016 database lock)

Subcategory (%) Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	22 (9.3)	1 (0.4)	0	1 (0.9)	0	0
THYROID DISORDER	21 (8.9)	0	0	1 (0.9)	0	0
HYPOTHYROIDISM	14 (5.9)	0	0	1 (0.9)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	3 (1.3)	0	0	0	0	0
HYPERTHYROIDISM	3 (1.3)	0	0	0	0	0
THYROIDITIS	2 (0.8)	0	0	0	0	0
THYROID FUNCTION TEST ABNORMAL	1 (0.4)	0	0	0	0	0
PITUITARY DISORDER	2 (0.8)	1 (0.4)	0	0	0	0
HYPOPHYSITIS	1 (0.4)	1 (0.4)	0	0	0	0
HYPOPITUITARISM	1 (0.4)	0	0	0	0	0
ADRENAL DISORDER	1 (0.4)	1 (0.4)	0	0	0	0
SECONDARY ADRENOCORTICAL INSUFFICIENCY	1 (0.4)	1 (0.4)	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.18

Gastrointestinal Events

As of the 20-Sep-2016 database lock for CA209141, gastrointestinal select AEs (all-causality, any grade) were reported in 43 subjects (18.2%) in the nivolumab group and 26 subjects (23.4%) in the investigator's choice group.

In the nivolumab group, 20 subjects (8.5%) had GI select AEs that were considered to be drug-related by the investigator (Table 40). In the nivolumab group, all drug-related events were diarrhoea and all were Grade 1-2 except for 1 Grade 3 event; 1 Grade 1-2 events led to permanent discontinuation of nivolumab.

Table 40: Summary of Drug-related Gastrointestinal Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects - CA209141 (20-Sep-2016 database lock)

Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	20 (8.5)	1 (0.4)	0	17 (15.3)	2 (1.8)	0
DIARRHOEA	20 (8.5)	1 (0.4)	0	16 (14.4)	2 (1.8)	0
COLITIS	0	0	0	1 (0.9)	0	0

MedDRA Version: 19.0; CTC Version 4.0; Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.14

Hepatic Events

As of the 20-Sep-2016 database lock for CA209141, hepatic select AEs (all-causality, any grade) were reported in 26 subjects (11.0%) in the nivolumab group and 12 subjects (10.8%) in the investigator's choice group.

In the nivolumab group, 7 subjects (3.0%) had hepatic select AEs considered to be drug-related by the investigator (Table 41) most drug-related events were Grade 1-2; two subjects had Grade 3-4 drug-related events. The 2 Grade 3-4 drug-related events led to permanent discontinuation of nivolumab.

Table 41: Summary of Drug-related Hepatic Select Adverse Events Reported Up to 30 days After Last Dose – All Treated Subjects - CA209141 (20-Sep-2016 database lock)

	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	7 (3.0)	2 (0.8)	0	5 (4.5)	1 (0.9)	0
ASPARTATE AMINOTRANSFERASE INCREASED	4 (1.7)	0	0	3 (2.7)	0	0
ALANINE AMINOTRANSFERASE INCREASED	3 (1.3)	1 (0.4)	0	3 (2.7)	1 (0.9)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	3 (1.3)	0	0	0	0	0
TRANSAMINASES INCREASED	2 (0.8)	1 (0.4)	0	0	0	0
BLOOD BILIRUBIN INCREASED	1 (0.4)	0	0	0	0	0
LIVER FUNCTION TEST INCREASED	1 (0.4)	1 (0.4)	0	0	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0	0	0	1 (0.9)	1 (0.9)	0
HEPATIC ENZYME INCREASED	0	0	0	1 (0.9)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.14

Pulmonary Events

As of the 20-Sep-2016 database lock for CA209141, pulmonary select AEs (all-causality, any grade) were reported in 10 subjects (4.2%) in the nivolumab group and 2 subjects (1.8%) in the investigator's choice group.

In the nivolumab group, 7 subjects (3.0%) had pulmonary select AEs considered to be drug-related by the investigator (Table 42). The majority drug-related events were pneumonitis. Two subjects had Grade 3-4 events, 1 of which led to death. Two drug-related pulmonary select AEs led to permanent discontinuation (one of which led to death) of nivolumab (refer to subheading "Deaths" for a narrative of this death).

Table 42: Summary of Drug-related Pulmonary Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects- CA209141 (20-Sep-2016 database lock)

	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	7 (3.0)	2 (0.8)	0	1 (0.9)	0	0
PNEUMONITIS	5 (2.1)	2 (0.8)	0	1 (0.9)	0	0
INTERSTITIAL LUNG DISEASE	1 (0.4)	0	0	0	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
In the nivolumab group, 1 Grade 3 drug-related event of pneumonitis led to death (see Section 7.1).
Source: Table S.6.14

Renal Events

As of the 20-Sep-2016 database lock for CA209141, renal select AEs (all-causality, any grade) were reported in 9 subjects (3.8%) in the nivolumab group and 2 subjects (1.8%) in the investigator's choice group.

In the nivolumab group, 3 (1.3%) subjects had a renal select AE (2 blood creatinine increased and one acute kidney injury) that were considered to be drug-related by the investigator (Table 43). These events were Grade 1-2 and did not lead to permanent discontinuation of nivolumab.

Table 43: Summary of Drug-related Renal Select Adverse Events Reported Up to 30 days After Last Dose - All Treated Subjects- CA209141 (20-Sep-2016 database lock)

	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (1.3)	0	0	2 (1.8)	1 (0.9)	0
BLOOD CREATININE INCREASED	2 (0.8)	0	0	0	0	0
ACUTE KIDNEY INJURY	1 (0.4)	0	0	2 (1.8)	1 (0.9)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
In the nivolumab group, 1 Grade 3 drug-related event of pneumonitis led to death (see Section 7.1).
Source: Table S.6.14

As of the 20-Sep-2016 database lock for CA209141, skin select AEs (all-causality, any grade) were reported in 49 subjects (20.8%) in the nivolumab group and 16 subjects (14.4%) in the investigator's choice group.

In the nivolumab group, 40 subjects (16.9%) had skin select AEs considered to be drug-related by the investigator (Table 44). The most frequently reported drug-related events were rash and pruritus. There was no event of toxic epidermal necrolysis reported. All of the drug-related events were Grade 1-2 and none led to permanent discontinuation of nivolumab.

Table 44: Summary of Drug-related Skin Select Adverse Events Reported Up to 30 days After Last Dose – All Treated Subjects CA209141 (20-Sep-2016 database lock)

	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	40 (16.9)	0	0	14 (12.6)	2 (1.8)	0
PRURITUS	19 (8.1)	0	0	0	0	0
RASH	19 (8.1)	0	0	5 (4.5)	1 (0.9)	0
RASH MACULO-PAPULAR	5 (2.1)	0	0	1 (0.9)	0	0
ECZEMA	2 (0.8)	0	0	0	0	0
ERYTHEMA	2 (0.8)	0	0	4 (3.6)	1 (0.9)	0
SKIN EXFOLIATION	2 (0.8)	0	0	0	0	0
EXFOLIATIVE RASH	1 (0.4)	0	0	0	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1 (0.4)	0	0	2 (1.8)	1 (0.9)	0
RASH MACULAR	1 (0.4)	0	0	1 (0.9)	0	0
URTICARIA	1 (0.4)	0	0	0	0	0
DERMATITIS	0	0	0	2 (1.8)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.14

Hypersensitivity / Infusion Reactions

As of the 20-Sep-2016 database lock for CA209141, hypersensitivity/infusion reactions (all-causality, any grade) were reported in 3 subjects (1.3%) in the nivolumab group and 2 subjects (1.8%) in the investigator's choice group.

All of the infusion reaction events in the nivolumab group were considered to be drug-related by the investigator (Table 45). All drug-related events were infusion-related reactions, all were Grade 1-2, and none led to permanent discontinuation of nivolumab.

Table 45: Summary of Drug-related Hypersensitivity / Infusion Reactions Reported Up to 30 days After Last Dose - All Treated Subjects (20-Sep-2016 database lock)

	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (1.3)	0	0	2 (1.8)	1 (0.9)	0
INFUSION RELATED REACTION	3 (1.3)	0	0	2 (1.8)	1 (0.9)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.14

Safety to Support the Product Information

Safety data to support Section 4.8 of the SmPC were integrated across completed studies in multiple indications using the intended dose and regimen for nivolumab monotherapy. The studies included in the analyses of nivolumab monotherapy (3 mg/kg Q2W) were as follows:

- HNSCC: CA209141
- cHL: CA209205 Cohort A+B+C + CA209039 all cHL
- RCC: CA209025
- Melanoma: CA209037, CA209066, and CA209067 (monotherapy arm)
- NSCLC: CA209057, CA209017, and CA209063

Table 46: Frequencies of Adverse Reactions included in Section 4.8 of the SmPC - Nivolumab Monotherapy Studies

ADR[a,b,c]	No. of Subjects	% of subjects	Designation of frequency
Total no. of nivolumab-monotherapy treated subjects = 2227			
Infections and infestations			
Upper respiratory tract infection	22	(1.0)	Common
Pneumonia	15	(0.7)	Uncommon
Bronchitis	4	(0.2)	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)	1	<0.1	Rare
Blood and lymphatic system disorders			
Eosinophilia	5	(0.2)	Uncommon
Immune system disorders			
Infusion related reaction	77	(3.5)	Common
Anaphylactic reaction	2	<0.1	Rare
Hypersensitivity	35	(1.6)	Common
Endocrine disorders			
Hypothyroidism	134	(6.0)	Common
Hyperthyroidism	41	(1.8)	Common
Hyperglycaemia	25	(1.1)	Common
Adrenal insufficiency	10	(0.4)	Uncommon
Hypopituitarism	5	(0.2)	Uncommon
Hypophysitis	6	(0.3)	Uncommon
Thyroiditis	13	(0.6)	Uncommon
Diabetic ketoacidosis	2	<0.1	Rare
Diabetes mellitus	1	<0.1	Rare
Metabolism and nutrition disorders			
Decreased appetite	202	(9.1)	Common
Dehydration	12	(0.5)	Uncommon
Metabolic acidosis	3	(0.1)	Uncommon
Hepatobiliary disorders			
hepatitis	5	(0.2)	Uncommon
hyperbilirubinemia	3	(0.1)	Uncommon
cholestasis	2	<0.1	Rare

ADR[a,b,c]	No. of Subjects	% of subjects	Designation of frequency
Nervous system disorders			
Peripheral neuropathy	47	(2.1)	Common
Headache	93	(4.2)	Common
Dizziness	45	(2.0)	Common
Polyneuropathy	3	(0.1)	Uncommon
Guillain-Barré syndrome	1	<0.1	Rare
Demyelination	1	<0.1	Rare
Myasthenic syndrome	1	<0.1	Rare
Autoimmune neuropathy (including facial and abducens nerve paresis)	2	<0.1	Rare
Eye disorders			
Vision blurred	18	(0.8)	Uncommon
Dry eye	20	(0.9)	Uncommon
Uveitis	9	(0.4)	Uncommon
Cardiac disorders			
Tachycardia	8	(0.4)	Uncommon
Arrhythmia (including ventricular arrhythmia)	1	<0.1	Rare
Atrial fibrillation	1	<0.1	Rare
Vascular disorders			
Hypertension	27	(1.2)	Common
Vasculitis	2	<0.1	Rare
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	66	(3.0)	Common
Dyspnoea	101	(4.5)	Common
Cough	108	(4.8)	Common
Pleural effusion	6	(0.3)	Uncommon
Lung infiltration	1	<0.1	Rare
Gastrointestinal disorders			
Diarrhoea	274	(12.3)	Very common
Nausea	278	(12.5)	Very common
Colitis	20	(0.9)	Uncommon
Stomatitis	68	(3.1)	Common
Vomiting	122	(5.5)	Common
Abdominal pain	81	(3.6)	Common
Constipation	108	(4.8)	Common
Dry mouth	58	(2.6)	Common
Pancreatitis	7	(0.3)	Uncommon
Gastritis	2	<0.1	Rare
Duodenal ulcer	1	<0.1	Rare
Skin and subcutaneous tissue disorders			
Rash	380	(17.1)	Very common
Pruritus	276	(12.4)	Very common
Vitiligo	69	(3.1)	Common
Dry skin	87	(3.9)	Common
Erythema	38	(1.7)	Common
Alopecia	25	(1.1)	Common
Erythema multiforme	3	(0.1)	Uncommon
Psoriasis	3	(0.1)	Uncommon
Rosacea	3	(0.1)	Uncommon
Urticaria	9	(0.4)	Uncommon
Toxic epidermal necrolysis	2	<0.1	Rare
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	161	(7.2)	Common
Arthralgia	128	(5.7)	Common
Polymyalgia rheumatica	3	(0.1)	Uncommon
Arthritis	21	(0.9)	Uncommon
Myopathy	1	<0.1	Rare
Renal and urinary disorders			
Tubulointerstitial nephritis	4	(0.2)	Uncommon
Renal failure (including acute kidney injury)	15	(0.7)	Uncommon
General disorders and administration site conditions			
Fatigue	674	(30.3)	Very common
Pyrexia	128	(5.7)	Common
Oedema (including peripheral oedema)	67	(3.0)	Common
Pain	18	(0.8)	Uncommon

ADR[a,b,c]	No. of Subjects	% of subjects	Designation of frequency
Chest pain	18	(0.8)	Uncommon
Investigations			
Increased AST	570/2151	(26.5)	Very common
Increased ALT	456/2160	(21.1)	Very common
Increased alkaline phosphatase	520/2148	(24.2)	Very common
Increased lipase	169/871	(19.4)	Very common
Increased amylase	100/752	(13.3)	Very common
Increased creatinine	430/2167	(19.8)	Very common
lymphocyte absolute (lymphopaenia)	881/2155	(40.9)	Very common
leukocyte absolute (leucopenia)	316/2175	(14.5)	Very common
platelet count (thrombocytopenia)	274/2169	(12.6)	Very common
haemoglobin (B) (anemia)	772/2169	(35.6)	Very common
Hypercalcaemia	227/2076	(10.9)	Very common
Hyperkalaemia	396/2112	(18.8)	Very common
Hypokalaemia	223/2112	(10.6)	Very common
Hypomagnesaemia	271/1878	(14.4)	Very common
Hyponatraemia	575/2113	(27.2)	Very common
Increased total bilirubin	177/2157	(8.2)	Common
absolute neutrophil count (neutropenia)	241/2158	(11.2)	Very common
Hypermagnesaemia	82/1878	(4.4)	Common
Hypernatraemia	107/2113	(5.1)	Common
Hypocalcaemia	358/2076	(17.2)	Very common
Weight decreased	49	(2.2)	Common

MedDRA Version: 18.1, CTC Version 4.0

Includes events reported between first dose and 30 days after last dose of study therapy

Unless otherwise noted, some preferred terms are re-mapped or deleted based on BMS medical review.

Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, and CA209141

This event frequency comes from an unmapped output.

This event frequency is based on all causality output.

Includes events autoimmune neuropathy (1/2227), VIth nerve paralysis (1/2227), and VIIth nerve paralysis (0/2227)

Includes events acute kidney injury (9/2227) and renal failure (6/2227)

Laboratory findings

Among all treated subjects, any grade shifts from baseline value were reported within 30 days of last dose for selected laboratory tests including absolute neutrophils, haemoglobin, leukocytes, lymphocytes, platelet count, ALP, total bilirubin, AST, ALT, creatinine, and thyroid stimulating hormone (TSH).

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2 in the nivolumab and investigator's choice groups.

- In the nivolumab group, the only Grade 3-4 haematologic abnormalities reported in ≥5% of treated subjects with on-treatment laboratory results were decreased haemoglobin (8.4% Grade 3 only) and decreased absolute lymphocytes (30% Grade 3; 3.6% Grade 4).
- In the investigator's choice group, the only Grade 3-4 hematologic abnormalities reported in ≥5% of subjects were decreased haemoglobin (11.5% Grade 3 only), decreased leukocytes (6.7% Grade 3 only), decreased lymphocytes (41.3% Grade 3; 8.7% Grade 4), and decreased neutrophil count (5.8% Grade 3; 1.9% Grade 4).

Treated subjects who experienced a ≥2-grade shift from baseline to a Grade 3 or 4 hematologic abnormality are summarized in Table 47.

Table 47: Subjects Who Experienced a ≥ 2-Grade Shift From Baseline to a Grade 3 or 4 Hematologic Abnormality - All Treated Subjects in CA209141

	Nivolumab (N=236)			Investigator's Choice (N=111)		
		Worst Toxicity Grade			Worst Toxicity Grade	
	Baseline	Grade 3	Grade 4	Baseline	Grade 3	Grade 4
Hemoglobin	Grade 0	0	NA	Grade 0	0	NA
	Grade 1	13 (5.5)	NA	Grade 1	7 (6.3)	NA
	Grade 2	--	NA	Grade 2	--	NA
Leucocytes	Grade 0	2 (0.8)	1 (0.4)	Grade 0	7 (6.3)	0
	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Lymphocytes	Grade 0	4 (1.7)	0	Grade 0	0	0
(Absolute)	Grade 1	7 (3.0)	2 (0.8)	Grade 1	11 (9.9)	0
	Grade 2	--	4 (1.7)	Grade 2	--	5 (4.5)
Neutrophils	Grade 0	1 (0.4)	0	Grade 0	6 (5.4)	2 (1.8)
	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Platelet Count	Grade 0	0	0	Grade 0	0	2 (1.8)
	Grade 1	0	1 (0.4)	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0

Percentages in each group are out of all treated subjects (n = 236 nivolumab and n = 111 investigator's choice).
Per anemia criteria in CTC Version 4.0 there is no Grade 4 for hemoglobin.
Source: Refer to Table S.7.3-SI of the CA209141 CSR

Serum Chemistry

Liver parameters

Treated subjects who experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormalities are summarized in Table 48.

Table 48: Subjects Who Experienced a ≥2-Grade Shift From Baseline to a Grade 3 or 4 Liver Test Abnormality - All Treated Subjects in CA209141

	Nivolumab (N=236)			Investigator's Choice (N=111)		
		Worst Toxicity Grade			Worst Toxicity Grade	
	Baseline	Grade 3	Grade 4	Baseline	Grade 3	Grade 4
ALT	Grade 0	2 (0.8)	0	Grade 0	0	0
	Grade 1	0	0	Grade 1	1 (0.9)	0
	Grade 2	--	0	Grade 2	--	0
Alkaline	Grade 0	2 (0.8)	0	Grade 0	0	0
Phosphatase	Grade 1	1 (0.4)	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
AST	Grade 0	1 (0.4)	1 (0.4)	Grade 0	0	0
	Grade 1	2 (0.8)	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Bilirubin	Grade 0	1 (0.4)	0	Grade 0	0	1 (0.9)
(Total)	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0

Percentages in each group are out of all treated subjects (n = 236 nivolumab and n = 111 investigator's choice).
Source: Refer to Table S.7.3-SI of the CA209141 CSR

A summary of on-treatment laboratory abnormalities is provided in Table 49.

Table 49: Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects in CA209141

Lab Test Toxicity Grade	Nivolumab 3 mg/kg (N=236)	Investigator's Choice (N=111)	Total (N=347)
	N = 220	N = 98	N = 318
ALT OR AST > 3XULN	10 (4.5)	5 (5.1)	15 (4.7)
ALT OR AST > 5XULN	4 (1.8)	2 (2.0)	6 (1.9)
ALT OR AST > 10XULN	2 (0.9)	0	2 (0.6)
ALT OR AST > 20XULN	1 (0.5)	0	1 (0.3)
	N = 220	N = 97	N = 317
TOTAL BILIRUBIN > 2XULN	3 (1.4)	2 (2.1)	5 (1.6)
	N = 220	N = 98	N = 318
CONCURRENT (WITHIN ONE DAY) ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN	2 (0.9)	0	2 (0.6)
CONCURRENT (WITHIN 30 DAYS) ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN	2 (0.9)	0	2 (0.6)

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
Percentages in each group are out of all treated subjects (n = 236 nivolumab and n = 111 investigator's choice).

Renal parameters

In the nivolumab and investigator's choice groups, the majority of subjects with at least 1 on treatment measurement had normal creatinine values during the treatment reporting period. In both groups, reported abnormalities in creatinine (increases) were all Grade 1 or 2. No Grade 3 or 4 abnormalities were reported. In both groups, no subjects experienced a ≥2-grade shift from baseline to a Grade 3 or 4 laboratory abnormality in creatinine.

Thyroid function tests

The majority of subjects in both groups had normal TSH levels at baseline and throughout the treatment period (Table 50). The proportion of subjects with TSH increases (> ULN) or decreases (< LLN) from baseline was slightly higher in the nivolumab group than the investigator's choice group.

Table 50: Summary of On-Treatment Laboratory Abnormalities in Specific Thyroid Tests - (SI Units) - Treated Subjects with at Least One On-Treatment TSH in CA209141

	Nivolumab 3 mg/kg (N=236)	Investigator's Choice (N=111)	Total (N=347)
TSH > ULN	107 (45.3)	39 (35.1)	146 (42.1)
TSH > ULN			
WITH TSH <= ULN AT BASELINE	43 (18.2)	14 (12.6)	57 (16.4)
TSH > ULN			
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (a)	67 (28.4)	16 (14.4)	83 (23.9)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (a)	33 (14.0)	16 (14.4)	49 (14.1)
WITH FT3/FT4 TEST MISSING (a) (b)	7 (3.0)	7 (6.3)	14 (4.0)
TSH < LLN	39 (16.5)	13 (11.7)	52 (15.0)
TSH < LLN			
WITH TSH >= LLN AT BASELINE	32 (13.6)	10 (9.0)	42 (12.1)
TSH < LLN			
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (a)	16 (6.8)	3 (2.7)	19 (5.5)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (a)	20 (8.5)	9 (8.1)	29 (8.4)
WITH FT3/FT4 TEST MISSING (a) (b)	3 (1.3)	1 (0.9)	4 (1.2)

Percentages in each group are out of all treated subjects (n = 236 nivolumab and n = 111 investigator's choice).
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(a) Within a 2-week window after the abnormal TSH test date.
(b) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Electrolytes

In the nivolumab and investigator's choice groups, most subjects had normal electrolyte levels during the treatment reporting period. In both groups, abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. In both groups, the only Grade 3-4 abnormality in electrolytes reported in ≥5% of treated subjects with on-treatment laboratory results was hyponatremia (nivolumab: 10.7% Grade 3,0.9% Grade 4; investigator's choice: 14.4% Grade 3, 1.0% Grade 4).

Table 51: Subjects Who Experienced a ≥2-Grade Shift From Baseline to a Grade 3 or 4 Electrolyte Abnormality - All Treated Subjects in CA209141

	Nivolumab (N=236)			Investigator's Choice (N=111)		
		Worst Toxicity Grade			Worst Toxicity Grade	
	Baseline	Grade 3	Grade 4	Baseline	Grade 3	Grade 4
Hypernatremia	Grade 0	0	1 (0.4)	Grade 0	0	0
	Grade 1	0	0	Grade 1	0	1 (0.9)
	Grade 2	--	0	Grade 2	--	0
Hyponatremia	Grade 0	13 (5.5)	0	Grade 0	8 (7.2)	1 (0.9)
	Grade 1	8 (3.4)	2 (0.8)	Grade 1	6 (5.4)	0
	Grade 2	--	0	Grade 2	--	0
Hypermagnesemia	Grade 0	1 (0.4)	0	Grade 0	0	0
	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Hypomagnesemia	Grade 0	0	0	Grade 0	0	0
	Grade 1	1 (0.4)	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Hypercalcemia	Grade 0	2 (0.8)	1 (0.4)	Grade 0	1 (0.9)	0
	Grade 1	1 (0.4)	1 (0.4)	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Hypocalcemia	Grade 0	0	1 (0.4)	Grade 0	0	0
	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Hyperkalemia	Grade 0	1 (0.4)	0	Grade 0	0	0
	Grade 1	0	0	Grade 1	0	0
	Grade 2	--	0	Grade 2	--	0
Hypokalemia	Grade 0	1 (0.4)	1 (0.4)	Grade 0	1 (0.9)	0
	Grade 1	0	0	Grade 1	2 (1.8)	0
	Grade 2	--	0	Grade 2	--	0

Percentages in each group are out of all treated subjects (n = 236 nivolumab and n = 111 investigator's choice).

Safety in special populations

In CA209141, the frequencies of all-causality and drug-related AEs in the nivolumab group for subgroups of gender, race, age, and region were similar to the AE frequencies in the overall treated population. Small numerical differences in frequencies of AEs were observed in nivolumab-treated subjects:

- Any-grade and Grade 3-4 drug-related AEs for male (60.8% and 13.9%) vs female (50.0% and 9.5%).
- No Grade 3-4 AEs were reported in the "other" race group, and all causality and drug-related Grade 3-4 AEs ranged from 30.0% to 43.8% and 10.0% to 14.1%, respectively, in the rest of the race groups.
- A greater frequency of all causality Grade 3-4 AEs were reported in Europe (45.4%) vs. North America (39.8%) or Rest of World (30.0%). The frequency of drug-related (any grade) AEs reported was lower in Europe (51.9%) vs. North America (63.3%) or Rest of World (70.0%).
- Grade 3-4 AEs, all causality and drug-related, reported in subjects < 75 years of age were greater than those > 75 years of age.

  –All causality and drug-related Grade 3-4 AEs in subjects < 65 years: 40.5% and 13.7%

  –All causality and drug-related Grade 3-4 AEs in subjects 65 to < 75 years: 44.6% and 12.5%

  –All causality and drug-related Grade 3-4 AEs in subjects ≥75 years of age: 33.3% and 8.3%

In CA209141, the frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group are presented in Table 52:

Table 52: Summary of Safety Results by Age Group- All Treated Subjects in CA209141

	Number of Subjects (%)			
MedDRA Terms	**Age < 65 years (N = 168)**	**Age 65-74 years (N = 56)**	**Age 75-84 years (N = 12)**	**Age 85+ years (N = 0)**
Total AEs	165 (98.2)	54 (96.4)	10 (83.3)	0
Serious AEs -Total	91 (54.2)	32 (57.1)	4 (33.3)	0
Fatal	38 (22.6)	15 (26.8)	1 (8.3)	0
Hospitalization/prolong existing hospitalization	79 (47.0)	25 (44.6)	4 (33.3)	0
Life-threatening	2 (1.2)	0	0	0
Cancer	0	1 (1.8)	0	0
Disability/incapacity	0	0	0	0
AEs leading to drop-out	34 (20.2)	14 (25.0)	3 (25.0)	0
Psychiatric disorders	31 (18.5)	8 (14.3)	0	0
Nervous system disorders	24 (33.8)	8 (22.2)	1 (25.0)	0
Accidents and Injuries	2 (2.8)	2 (5.6)	0	0
Cardiac disorders	8 (11.3)	4 (11.1)	2 (50.0)	0
Vascular disorders	8 (11.3)	6 (16.7)	1 (25.0)	0
Central nervous system vascular disorders	2 (1.2)	1 (1.8)	2 (16.7)	0
Infections and infestations	61 (36.3)	23 (41.1)	4 (33.3)	0
Anticholinergic syndrome	56 (33.3)	22 (39.3)	5 (41.7)	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	11 (6.5)	2 (3.6)	0	0

MedDRA Version: 18.0; CTC version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Abbreviations: AE: adverse event; HLGT: MedDRA High-Level Group Term; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA Queries; SAE: serious adverse event; SOC: System Organ Class.

Safety by age Across Integrated Monotherapy Studies Including CA209141

Nivolumab monotherapy integrated across indications (SCCHN, cHL, RCC, melanoma, and NSCLC) is presented in Table 53. Frequencies of SAEs, AEs leading to dropout, and postural hypotension increased slightly with increasing age.

Table 53: Summary of On-treatment AEs by Age Group - All Treated Subjects - Nivolumab Monotherapy Data Integrated across Indications including CA209141

	Number of Subjects (%)			
	Monotherapy Data Integrated Across Indications[a]			
MedDRA Terms	Age < 65 years (N = 1469)	Age 65-74 years (N = 560)	Age 75-84 years (N = 177)	Age 85+ years (N = 21)
Total AEs	1425 (97.0)	546 (97.5)	172 (97.2)	21 (100.0)
Serious AEs -Total	592 (40.3)	268 (47.9)	86 (48.6)	12 (57.1)
Fatal	142 (9.7)	60 (10.7)	22 (12.4)	3 (14.3)
Hospitalization/prolong existing hospitalization	524 (35.7)	234 (41.8)	77 (43.5)	8 (38.1)
Life-threatening	22 (1.5)	7 (1.3)	2 (1.1)	0
Cancer	13 (0.9)	12 (2.1)	9 (5.1)	1 (4.8)
Disability/incapacity	1 (<0.1)	1 (0.2)	0	0
AEs leading to drop-out	187 (12.7)	91 (16.3)	41 (23.2)	5 (23.8)
Psychiatric disorders	253 (17.2)	86 (15.4)	26 (14.7)	6 (28.6)
Nervous system disorders	496 (33.8)	189 (33.8)	60 (33.9)	13 (61.9)
Accidents and injuries	95 (6.5)	48 (8.6)	16 (9.0)	3 (14.3)
Cardiac disorders	125 (8.5)	55 (9.8)	14 (7.9)	5 (23.8)
Vascular disorders	215 (14.6)	101 (18.0)	28 (15.8)	9 (42.9)
Central nervous system vascular disorders	19 (1.3)	22 (3.9)	5 (2.8)	1 (4.8)
Infections and infestations	554 (37.7)	240 (42.9)	66 (37.3)	11 (52.4)
Anticholinergic syndrome	496 (33.8)	182 (32.5)	61 (34.5)	9 (42.9)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	139 (9.5)	70 (12.5)	24 (13.6)	4 (19.0)

[a] Includes events reported between first dose and 30 days after last dose of study therapy.
Nivolumab treatment group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037,CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205 and CA209141.

Mental Ability

Nivolumab has minor influence on the ability to drive and use machines. Fatigue is a very common side effect which may also impair the ability to drive and use machines. Patients should be advised not to drive or use machines if they feel tired.

Safety related to drug-drug interactions and other interactions

No new information.

Discontinuation due to adverse events

The overall frequency of AEs (regardless of causality) leading to a *dose delay or reduction* was 29.2% in the nivolumab group and 45.9% in the investigator's choice group.

The overall frequencies of all-causality AEs leading to discontinuation were similar between the treatment groups; however, the frequencies of drug-related AEs leading to discontinuation were lower in the nivolumab group than in the investigator's choice group.

Table 54: Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects - CA209141 (20-Sep-2016 database lock)

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	55 (23.3)	37 (15.7)	14 (5.9)	25 (22.5)	13 (11.7)	4 (3.6)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	20 (8.5)	9 (3.8)	10 (4.2)	5 (4.5)	2 (1.8)	3 (2.7)
MALIGNANT NEOPLASM PROGRESSION	18 (7.6)	7 (3.0)	10 (4.2)	5 (4.5)	2 (1.8)	3 (2.7)
MALIGNANT PLEURAL EFFUSION	1 (0.4)	1 (0.4)	0	0	0	0
TUMOUR HAEMORRHAGE	1 (0.4)	1 (0.4)	0	0	0	0
INFECTIONS AND INFESTATIONS	6 (2.5)	6 (2.5)	0	3 (2.7)	3 (2.7)	0
PNEUMONIA	3 (1.3)	3 (1.3)	0	2 (1.8)	2 (1.8)	0
RESPIRATORY TRACT INFECTION	2 (0.8)	2 (0.8)	0	0	0	0
INFECTION	1 (0.4)	1 (0.4)	0	0	0	0
SEPTIC SHOCK	1 (0.4)	1 (0.4)	0	0	0	0
SEPSIS	0	0	0	1 (0.9)	1 (0.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (2.5)	4 (1.7)	0	5 (4.5)	2 (1.8)	0
PNEUMONIA ASPIRATION	2 (0.8)	2 (0.8)	0	0	0	0
PNEUMONITIS	2 (0.8)	1 (0.4)	0	1 (0.9)	0	0
DYSPNOEA	1 (0.4)	0	0	0	0	0
PULMONARY EMBOLISM	1 (0.4)	1 (0.4)	0	0	0	0
RESPIRATORY DISTRESS	1 (0.4)	1 (0.4)	0	0	0	0
BRONCHOPNEUMOPATHY	0	0	0	1 (0.9)	1 (0.9)	0
LARYNGEAL OEDEMA	0	0	0	1 (0.9)	0	0
PLEURAL EFFUSION	0	0	0	1 (0.9)	1 (0.9)	0
PULMONARY TOXICITY	0	0	0	1 (0.9)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (1.7)	4 (1.7)	0	3 (2.7)	0	0
ASTHENIA	1 (0.4)	1 (0.4)	0	0	0	0

Table 55 Drug-related AEs Leading to Discontinuation by Worst CTC Grade – All Treated Subjects - CA209141 (CA209141 Final CSR, 20-Sep-2016 database lock)

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N=236			Investigator's Choice N=111		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	9 (3.8)	7 (3.0)	0	10 (9.0)	6 (5.4)	0
INVESTIGATIONS	3 (1.3)	3 (1.3)	0	1 (0.9)	0	0
AMYLASE INCREASED	1 (0.4)	1 (0.4)	0	0	0	0
LIPASE INCREASED	1 (0.4)	1 (0.4)	0	0	0	0
LIVER FUNCTION TEST INCREASED	1 (0.4)	1 (0.4)	0	0	0	0
TRANSAMINASES INCREASED	1 (0.4)	1 (0.4)	0	0	0	0
HEPATIC ENZYME INCREASED	0	0	0	1 (0.9)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (0.8)	1 (0.4)	0	3 (2.7)	1 (0.9)	0
PNEUMONITIS	2 (0.8)	1 (0.4)	0	1 (0.9)	0	0
PLEURAL EFFUSION	0	0	0	1 (0.9)	1 (0.9)	0
PULMONARY TOXICITY	0	0	0	1 (0.9)	0	0
ENDOCRINE DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
HYPOPHYSITIS	1 (0.4)	1 (0.4)	0	0	0	0
SECONDARY HYPOTHYROIDISM	1 (0.4)	1 (0.4)	0	0	0	0
GASTROINTESTINAL DISORDERS	1 (0.4)	0	0	0	0	0
DIARRHOEA	1 (0.4)	0	0	0	0	0
IMMUNE SYSTEM DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
ALLERGIC GRANULOMATOUS ANGIITIS	1 (0.4)	1 (0.4)	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	1 (0.4)	1 (0.4)	0	0	0	0
HYPERCALCAEMIA	1 (0.4)	1 (0.4)	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.4)	0	0	2 (1.8)	1 (0.9)	0
SKIN MASS	1 (0.4)	0	0	0	0	0
ONYCHOLYSIS	0	0	0	1 (0.9)	0	0
ONYCHOMADESIS	0	0	0	1 (0.9)	0	0
RASH	0	0	0	1 (0.9)	1 (0.9)	0
SKIN DISORDER	0	0	0	1 (0.9)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	2 (1.8)	2 (1.8)	0
ANAEMIA	0	0	0	1 (0.9)	1 (0.9)	0
LEUKOPENIA	0	0	0	1 (0.9)	1 (0.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0	0	1 (0.9)	0	0
MALAISE	0	0	0	1 (0.9)	0	0
INFECTIONS AND INFESTATIONS	0	0	0	2 (1.8)	2 (1.8)	0
PNEUMONIA	0	0	0	2 (1.8)	2 (1.8)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	0	1 (0.9)	1 (0.9)	0
INFUSION RELATED REACTION	0	0	0	1 (0.9)	1 (0.9)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.89

3.4% of subjects in the nivolumab group had an infusion interruption. Of the subjects who required an infusion interruption, all had only 1 infusion interrupted. Infusion interruptions were more frequent with cetuximab (30.8% of subjects).

1.7% of subjects in the nivolumab group had an infusion rate reduction. Infusion rate reductions were slightly more frequent with methotrexate (6.5% of subjects).

Dose delays of nivolumab were more frequent than cetuximab and less frequent than methotrexate and docetaxel. 36.4%, 23.1%, 50.0%, and 57.7% of subjects had at least one dose delayed of nivolumab, cetuximab, methotrexate, and docetaxel, respectively. Most subjects with dose delay only experienced only 1.

In the investigator's choice group, 7.7%, 28.3%, and 26.9% of subjects required a dose reduction of cetuximab, methotrexate, or docetaxel, respectively.

Immunogenicity

In CA209141, the incidence of nivolumab ADA was low and did not appear to have an effect on the safety of nivolumab. Of the 148 SCCHN subjects who were evaluable for ADA, 13 (8.8%) subjects were ADA positive.

No subjects were persistent positive, and one subject (0.7%) was neutralizing ADA positive. Of all subjects who were evaluable for ADA, none experienced hypersensitivity/infusion reaction category events.

An integrated analysis of immunogenicity assessments was performed with data available from the following studies: CA209037, CA209063, CA209066, CA209017, CA209067 (nivolumab monotherapy arm), CA209025, CA209039, CA209205, and CA209141. No clear association was established between the presence of ADA and hypersensitivity or infusion reactions, suggesting nivolumab ADA does not alter the safety profile of nivolumab (see also section 2.3.3 of this AR).

Post marketing experience

No new significant safety concerns were identified based on the postmarketing reports.

Nivolumab was first approved on 4 July 2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and the EU, and for other indications (e.g. metastatic NSCLC, advanced RCC). Based on pharmacovigilance activities conducted by BMS Global Pharmacovigilance and Epidemiology, review of postmarketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab. The safety profile of nivolumab in the postmarketing setting remains favourable and similar to the profile established during clinical trials. To date, no new significant safety concerns have been identified based on global postmarketing reports. Postmarketing data for nivolumab are subject to continued active pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements, as well as periodically to global health authorities.

2.5.1. Discussion on clinical safety

Study CA209141 is the main safety dataset supporting this application. Safety data in this application support the use of nivolumab at the proposed dose and schedule of 3 mg/kg administered as an IV infusion Q2W for the treatment of patients with recurrent or metastatic SCCHN relapsing or progressing on or within 6 months of the last dose of a platinum-based therapy.

The overall safety profile of nivolumab was consistent with the safety profile of nivolumab monotherapy previously observed in other tumour types, and no new safety concerns were identified in this study.

Any-grade AEs (regardless of causality) were reported in 98.3% of subjects in the nivolumab group and 98.2% of subjects in the investigator's choice group. In the nivolumab group, the most frequently reported AEs were fatigue (28.4%), nausea (21.2%), anaemia (20.3%), decreased appetite (19.5%), malignant neoplasm progression (19.5%), and constipation (15.7%). Grade 3-4 AEs (regardless of causality) were reported in 47.9% of subjects in the nivolumab group and 62.2% of subjects in the investigator's choice group. In the nivolumab group, the most frequently reported Grade 3-4 AEs were anaemia (6.4%), dyspnoea (5.5%), hyponatremia (4.7%), pneumonia (4.7%) and malignant neoplasm progression (4.7%).

The overall frequency of drug-related any-grade AEs was lower in the nivolumab group (61.9%) compared with the investigator's choice group (79.3%). In the nivolumab group, the most frequently reported drug-related AEs were nausea (9.3%), diarrhoea (8.5%), rash (8.1%), pruritus (8.1%), decreased appetite (8.1%), and anaemia (5.1%). Furthermore, grade ≥3 drug-related AEs were reported much less frequently in the nivolumab group than in the investigator's choice group (15.3% vs. 36.9%, respectively). In the nivolumab group, the most frequently reported Grade 3-4 drug-related AEs were fatigue (2.1%) and anaemia (1.3%).

Among 236 nivolumab monotherapy-treated subjects, 2 deaths (pneumonitis and hypercalcaemia) in the nivolumab group were assessed as study-drug associated by the investigator and one death attributed to study drug toxicity (pneumonia) in the investigator's choice group. Pneumonitis is a known adverse event associated with nivolumab treatment. Serious complications due to hypercalcemia have not been associated with nivolumab treatment and are most likely a consequence of tumour progression.

The overall frequencies of all-causality SAEs (any grade) were similar between the treatment groups. In the nivolumab group, the most frequently reported SAEs were malignant neoplasm progression (19.5%), pneumonia (4.7%), dyspnoea (3.8%), and pneumonia aspiration (3.4%).

Drug-related SAEs were reported in 7.2% of subjects in the nivolumab group and 15.3% of subjects in the investigator's choice group. In the nivolumab group, the only drug-related SAE reported in at least 2 subjects was pneumonitis; 2 (0.8%) subjects.

Grade 3-4 drug-related SAEs were reported in 5.5% and 10.8% of subjects in the nivolumab and investigator's choice groups, respectively.

The frequencies of all types of AEs of special interest (endocrine, gastrointestinal, hepatic, pulmonary, renal, and dermatological events) showed that both all-causality and drug-related AEs of any grade were similar in patients treated with nivolumab and in patients treated with investigator's choice. The majority of select AEs reported were Grade 1-2, and most were considered drug-related by the investigator. The most frequently reported any-grade drug-related select AE categories with nivolumab treatment were skin (16.9%), endocrine (9.3%) and gastrointestinal (8.5%). Across select AE categories, the majority of events were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered. All-causality and drug-related AEs of special interest of grade ≥3 were low in frequency and occurred at similar frequencies in both treatment arms. The frequencies of select AEs are consistent with the existing safety data obtained in melanoma, NSCLC, and RCC.

As of the 20 September 2016 database lock, a lower proportion of treated subjects in the nivolumab group had died (183 subjects [77.5%]) compared with the investigator's choice group (96 subjects [86.5%]). Disease progression was the most common cause of death for both groups, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose.

Two (0.8 %) deaths in the nivolumab group and one death in the investigator's choice group were attributed to study drug toxicity by the investigator

In CA209141 (18 December 2015 database lock), the frequencies of all-causality and drug-related AEs in the nivolumab group for subgroups of gender, race, age, and region were similar to the AE frequencies in the overall treated population. Observed small numerical differences in frequencies of AEs are of limited interpretability due to low sample sizes and event rates, and do not alter the overall safety profile of nivolumab in these subgroups.

Interpretation of safety in the elderly is limited by the small number of subjects in the 75 to 84 years of age subgroup (n=12) and the fact that there were no treated subjects ≥ 85 years of age. However, in the already approved indications for nivolumab, there were no indications of worse (or better) safety in the elderly compared to younger patients. The data in patients with SCCHN > 75 years of age has been included as missing information in the RMP.

Abnormalities in haematology laboratory results, liver tests, kidney function tests, and electrolytes in nivolumab subjects were primarily Grade 1 or 2.

The overall frequency of all-causality AEs leading to discontinuation were similar between the treatment groups; however, the frequencies of drug-related AEs leading to discontinuation were lower in the nivolumab group than in the investigator's choice group.

In CA209141, the incidence of nivolumab ADA was low and did not appear to have an effect on the safety of nivolumab. The results regarding immunogenicity are in line with the results obtained in previously authorised indications.

No clear association was established between the presence of ADA and hypersensitivity or infusion reactions, suggesting nivolumab ADA does not alter the safety profile of nivolumab. Overall, immunogenicity is not

clinically meaningful based on low ADA titers, low persistent positive rates, low incidence of neutralising antibodies, minimal impact on nivolumab CL, and no evidence of an altered safety profile.

No meaningful differences in the safety profile were observed based on PD-L1 expression levels as compared to the overall study population, and the safety profile with nivolumab was favourable across PD-L1 expression levels as compared with investigator's choice therapy (data not shown).

2.5.2. Conclusions on clinical safety

In study CA209141, the safety profile of nivolumab compared favourably with that of investigator's choice in terms of the frequency of all-grade and severe (grade $\geqslant$3) drug-related AEs.

The observed safety profile of nivolumab is consistent with the safety profile of nivolumab monotherapy previously observed in other tumour types, and no new safety concerns were identified in study CA209141. No new risks in addition to those identified in previous studies in other indications were identified.

Clinically significant select AEs were manageable using treatment algorithms that recommend nivolumab dose delay or discontinuation and introduction of immune-modulating therapy or other targeted medical intervention (eg, hormone replacement therapy for endocrine events).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 3/07/2017.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 6.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 6.3 with the following content:

Safety concerns

Table 56

Summary of safety concerns	
Important identified risks	Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related skin ARs Other immune-related adverse reactions ~~(ARs)~~ Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Cardiac arrhythmias (previously treated melanoma indication, only) Complications of allogeneic HSCT following nivolumab therapy
Missing information	Pediatric patients <18 years of age Elderly patients with: - cHL ≥ 65 years of age *- SCCHN ≥ 75 years of age* Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab Use in patients who have undergone influenza vaccination

Due to the limited data in SCCHN patients over 75 years of age, the summary of safety concerns for nivolumab has been updated to include 'Elderly patients with SCCHN ≥ 75 years of age' as missing information.

Pharmacovigilance plan

Table 57 Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)	**Objectives**	**Safety concerns addressed**	**Status Planned, started**	**Date for submission of interim or final reports (planned or actual)**
CA209835: A registry study in patients who underwent post-nivolumab allogeneic HSCT Category 3	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	Planned	Final CSR submission: 4Q2022

Activity / Study title (type of activity, study title [if known] category 1-3)	Objectives	Safety concerns addressed	Status Planned, started	Date for submission of interim or final reports (planned or actual)
CA209234: Pattern of Use, Safety, and Effectiveness of Nivolumab in Routine Oncology Practice. Category 3	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 or renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, and myasthenic syndrome, and encephalitis), and infusion reactions Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, ~~and~~ rhabdomyolysis, and encephalitis), and infusion reactions	Started	Final CSR submission: 4Q2024 (interim report annually)

The PRAC Rapporteur, having considered the updated data submitted, was of the opinion that the proposed post-authorisation PhV development plan remains sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 58 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction	The SmPC warns the risks of immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis and renal dysfunction, immune-related	To further raise awareness of HCPs on important risks and their appropriate management, additional risk minimization activity includes a Communication Plan.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs	endocrinopathies, immune-related rash, and other immune-related adverse reactions in Section 4.4 (Special warnings and precautions for use), and provides specific guidance on their monitoring and management, including treatment delay or discontinuation and intervention with corticosteroids in Sections 4.2, 4.4 and 4.8, as appropriate. Further ADRs are included in Section 4.8. In addition, the package leaflet also includes specific warnings and descriptions of the most important safety information in the language suitable for patients.	The Plan comprising 2 tools to be distributed to potential prescribers at launch by BMS: • Adverse Reaction Management Guide • Patient Alert Card
Severe infusion reactions	The SmPC warns the risk of severe infusion reactions in Section 4.4 and ADR in Section 4.8.	None
Important Potential Risks		
Embryofetal Toxicity	SmPC includes Embryofetal Toxicity in Section 4.6 Fertility, pregnancy and lactation, Section 5.3 Preclinical safety data The package leaflet also includes specific description on the safety information in the language suitable for patients.	None
Immunogenicity	SmPC Section 4.8 Immunogenicity	None
Cardiac arrhythmias (previously treated melanoma indication, only)	SmPC Section 4.8 Undesirable effects	None
Complications of allogeneic HSCT following nivolumab therapy	SmPC Section 4.4 recommends case by case considerations, and close monitoring of patients undergoing allogeneic HSCT for hyperacute GVHD, Grade 3-4 acute GVHD, steroid requiring febrile syndrome, hepatic veno-occlusive disease, and other transplant related complications. Related information is found in SmPC Section 4.8 Undesirable effects.	Adverse Reaction Management Guide
Missing Information		
Pediatric patients	SmPC Section 4.2 Posology and method of administration, subsection on Pediatric population	None
Elderly patients with: - cHL ≥ 65 years of age *- SCCHN ≥ 75 years of age*	SmPC Sections 4.*2 Posology and method of administration, 4*.8 Undesirable effects, and 5.1 Pharmacodynamic properties	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe hepatic and/or renal impairment	SmPC Section 4.2 Posology and method of administration: Patients with hepatic or renal impairment; SmPC Section 5.2 Pharmacokinetic properties: Hepatic or renal impairment	None
Patients with autoimmune disease	SmPC Section 4.4 provides warning and cautionary information for patients with a history of autoimmune disease	None
Patients already receiving systemic immunosuppressants before starting nivolumab	SmPC Sections 4.4 Special populations and 4.5 Systemic Immunosuppressants	None
Use in patients who have undergone influenza vaccination	Safety monitoring and signal detection	None

The PRAC Rapporteur, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, a new warning to recommend careful consideration before initiating treatment with nivolumab in patients excluded from the SCCHN clinical trial (patients with a baseline performance score $\geqslant 2$, untreated brain metastasis, active autoimmune disease, medical conditions requiring systemic immunosuppression, or carcinoma of the nasopharynx or salivary gland as the primary tumour sites) has been added to the product information. In addition, physicians are also recommended to consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In head and neck cancer, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were ECOG performance status, fast progressive disease on prior platinum therapy and high tumour burden.

The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable as the changes introduced in the PL as part of this variation application do not have a relevant impact on the readability of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The present application is to extend the indication of nivolumab (Opdivo) in the treatment of recurrent or metastatic squamous cell cancer of the head and neck after platinum-based therapy.

In SCCHN, approximately 50% of the population initially treated with curative intent will either have refractory disease or will eventually develop recurrent disease. For these patients, the 1-year survival rate is 5-33% by various estimates with a median OS (mOS) of 6 to 9 months. Patients whose disease progresses within 6 months of platinum-based therapy (for locally advanced or metastatic disease), have a poor prognosis.

3.1.2. Available therapies and unmet medical need

In this patient population, no OS benefit has ever been demonstrated, and thus the choice of chemotherapy is not well defined. Treatment choice is based on several factors including previous chemotherapy exposure, performance status, and comorbid conditions. In the US and the EU, recommendations include best supportive care, clinical trials, and single agents including paclitaxel, docetaxel, 5-FU, methotrexate, cetuximab, ifosfamide, bleomycin, gemcitabine, capecitabine, and vinorelbine.

3.1.3. Main clinical studies

The results of an open label, randomized phase 3 clinical trial of nivolumab vs therapy of investigator's choice in the recurrent or metastatic platinum-refractory SCCHN have been submitted.

3.2. Favourable effects

Based on a pre-specified interim analysis, with 55.4% of events in the experimental arm, nivolumab showed a gain in median OS of almost 2.5 months (HR = 0.70 [97.73% CI: 0.51, 0.96]; stratified log-rank test p-value = 0.0101).
The magnitude of the difference in survival is around 15% between groups (OS rates at 6, 9 and 12 months). Results from the two sensitivity analyses carried out (unstratified analysis and analysis based on subjects with no relevant deviations) are consistent with the main one. Furthermore, a multivariate analysis adjusted for HPV-p16 status, baseline ECOG PS, and prior chemotherapy for metastatic disease, showed similar result. When the results are analysed by individual investigator’s choice therapy subgroups, the evidence for an advantage of nivolumab in terms of OS was clearer in the cetuximab (HR 0.54; 95% CI: 0.30, 0.98) and methotrexate (HR 0.60; 95% CI: 0.41, 0.86) subgroups compared to the docetaxel subgroup (HR=0.92; 95% CI: 0.66, 1.29).

In the updated analysis (20 September 2016 database lock) nivolumab continued to demonstrate statistically significant and clinically meaningful improvement in OS versus investigator’s choice therapy (HR= 0.71 [95% CI: 0.55, 0.90]; stratified log-rank test p-value = 0.0048), with survival rates of 34.0% and 21.5% at 12 and 18 months, respectively.

ORR results offer better outcomes, with a significant difference in favour of nivolumab (13% vs 6% nivo and control respectively) but with only 6 complete responders. Median time to objective response was 2 months.

3.3. Uncertainty in the knowledge about the beneficial effects

When OS difference is analysed for the various comparators, the benefit vs docetaxel is not as clear as vs cetuximab and methotrexate. Focusing on docetaxel comparison, the same pattern of higher number of deaths soon after the start of treatment with nivolumab that has been previously noted in melanoma and lung cancer studies is observed again. There was a higher percentage of patients who died within the first 3 months in the nivolumab group vs docetaxel arm (28.3% vs 18.5% of the whole number of nivolumab and docetaxel treated patients respectively). The delay in the onset of action of nivolumab along with some prognostic factors appear the most plausible explanations. Similarly to NSCLC and melanoma, ECOG performance status, fast progressive disease and high tumour burden seem to be important factors to consider when starting a nivolumab treatment.

The lack of positive results in PFS has been previously observed in other clinical developments with nivolumab (renal and non-squamous NSCLC), highlighting the discrepancy between PFS and OS. Despite some hypotheses discussed (pseudoprogression, a delay in the onset of effect, etc), there is no explanation to this phenomenon.

In the European patient population, neither OS (HR 0.91, 95%CI: 0.62, 1.33) nor ORR (10.1% vs 9.7%) showed a clear benefit for nivolumab and the control group seem to offer better results in terms of PFS (HR 1.27, 95%CI: 0.90, 1.78). Even though some imbalances in prognostic factors (time from prior platinum to progression, gender and HPV status) could partly explain this absence of benefit, no firm conclusions can be drawn. In a worst-case scenario, nivolumab would offer similar efficacy vs docetaxel, though with a priori better safety profile.

A lower activity of nivolumab vs investigator's choice therapy (ICT) has been observed in patients with low tumour PD-L1 expression (<1%) compared to patients with higher tumour PD-L1 expression (≥1%).

Several exploratory, post-hoc analyses exploring the link between PD-L1 expression on tumour cells and tumour-associated immune cells (TAICs) and response to treatment with nivolumab in HNSCC showed greater benefit of nivolumab in the subgroup of patients with intratumoural PD-L1 expressing TAIC compared to ICT.

The subgroup of patients with low tumour cell PD-L1 expression (<1%) without intratumoural PD-L1 expressing TAIC appears not to show greater benefit from nivolumab treatment compared to ICT. A less pronounced, but a similar pattern is observed in the subgroup of patients with tumour cell PD-L1 expression ≥1%, with the number and the localisation of the PD-L1 positive TAIC appearing to be associated with response to nivolumab. Investigated subgroups are small, and in combination with technical aspects (it was based on qualitative data collected using a non-validated assay) definitive conclusions cannot yet be drawn from this analysis. In order to further investigate the relationship between clinical outcomes to nivolumab and PD-L1 expression in immune cells and other biomarkers (PD-L2, mutational load), a biomarker investigation in SCCNH patients has been included as post authorisation measure (see Annex II).

In the updated analysis of efficacy by both baseline PD-L1 expression and p16 status, nivolumab treatment had numerically better efficacy than ICT in all subgroups, except for PD-L1<1% and p16 unknown (HR 1.41 [CI95 0.72- 2.88]). Since the confidence interval encompasses 1 and it concerns a small sample size, no conclusion can be drawn on these data. With the addition of 6 p16-negative patients and the updated analyses, the HR for the PD-L1 <1% and p16-negative patients decreased from 0.82 to 0.53, which is reassuring.

3.4. Unfavourable effects

The safety of nivolumab in SCCHN was consistent with the overall experience with nivolumab in other tumour types. No new safety concerns have been identified in patients with SCCHN compared to the other indications.

3.5. Uncertainty in the knowledge about the unfavourable effects

As of 20 September 2016 database lock, the number of subject who died within 30 days of last dose were higher in the nivolumab group (22.0%, 52/236 subjects) compared to the ICT group (18.9%, 21/111 subjects) and may be attributed to longer duration of study treatment in the nivolumab group compared to ICT.

Interpretation of safety in the elderly is limited by small numbers of subjects in the 75 to 84 years of age subgroup (n = 12) and the fact that there were no treated subjects ≥ 85 years of age (see missing

information in the RMP). However, in other indications for which nivolumab has already been approved, there were no indications of worse (or better) safety in the elderly relative to younger patients.

Subjects with active, known or suspected autoimmune disease were excluded from the pivotal study and therefore the B/R is uncertain in this population. However, the current SmPC accurately reflects a warning regarding the potential risks associated with patients with active, known or suspected autoimmune disease.

Experience with nivolumab in SCCHN is, from a safety perspective, limited, and long-term safety is not well characterised. There is, however, a relatively large safety dataset of nivolumab monotherapy in other indications.

3.6. Effects Table

Table 59: Effects Table for nivolumab for the treatment of SCCHN (data cut-off: 05-May-2016; tumour assessment; September 2016 safety/efficacy assessment)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
OS	Time from randomization to the date of death from any cause	Median (months)	7.72	5.06	Lower benefit as compared to docetaxel. Higher number of deaths associated to nivo vs docetaxel in the first 3 months Uncertainty in European population	
		HR (95%CI)	0.71 (0.55-0.90)			
PFS	Time from randomization to first date of documented progression, or to death due to any cause.	Median (months)	2.04	2.33	Nivolumab does not show better PFS outcomes than comparators Uncertainty in European population	
		HR (95% CI)	0.87 (0.69-1.11)			
ORR	% of randomized subjects who achieved a best response of CR or PR (RECIST v1.1 investigator).	%	13.3	5.8	Lower benefit as compared to docetaxel Uncertainty in European population	
Unfavourable Effects						
All Grade 3/4 AEs	Drug-related AEs	%	15.3	36.0	No new safety concerns with nivolumab monotherapy treatment were identified in SCCHN	
SAEs	Drug-related SAEs	%	7.2	15.3		
Fatigue	Most frequent drug-related AE	%	15.7	18.0		
Nausea	Most frequent drug-related AE	%	9.3	20.7		
Anaemia	Most frequent drug-related AE	%	5.1	17.1		
Asthenia	Most frequent drug-related AE	%	4.2	15.3		
Mucosal inflammation	Most frequent drug-related AE	%	1.7	13.5		

Abbreviations: AEs (adverse events), AR (assessment report), CR (complete response), HR (hazard ratio), PFS (progression free survival), ORR (objective response rate), OS (overall survival), PR (partial response), SCCHN (squamous cell carcinoma of the head and neck).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefit in survival is considered clinically meaningful. Despite the a priori modest result in the absolute gain in terms of median OS (2.5 months), it is deemed relevant since no other therapies in the platinum refractory setting have been able to achieve such improvement.

The uncertainties related to some subgroup analysed (PD-L1<1% and European population) were further explored. In the European population, where no benefit has been demonstrated, the better safety profile favours a positive B/R profile.

Further analyses have explored the relationship between PD-L1 expression in the tumour/tumour microenvironment and efficacy of nivolumab in HNSCC. While certain patient subgroups benefit less from nivolumab than others, it cannot be concluded at present that certain patient subgroups could benefit significantly less from nivolumab than from ICT. When considered in the context of a more favourable safety profile of nivolumab compared to ICT, it is concluded that the B/R is positive for the overall population.

From a safety point of view, the toxicity and tolerability of nivolumab was consistent with previously submitted pooled data of nivolumab monotherapy in melanoma, NSCLC and RCC. No new safety concerns with nivolumab monotherapy treatment were identified in SCCHN. The safety profile of nivolumab compared favourably with that of ICT in terms of the frequency of all-grade and grade ≥3 drug-related AEs. The safety profile of nivolumab was in line with that of previously authorised indications. Furthermore, comparative safety data from CA209141 demonstrate that nivolumab monotherapy has an acceptable safety profile compared to ICT group, as evidenced by the rates of drug-related AEs and drug-related AEs leading to discontinuation.

3.7.2. Balance of benefits and risks

The efficacy of nivolumab in the overall studied population seems undisputable. The longer survival obtained with this treatment when compared to different alternatives is clinically meaningful. The increase in life expectancy overcomes the risks associated to nivolumab, which are considered tolerable and manageable, with an overall apparently better safety profile than alternatives.

3.7.3. Additional considerations on the benefit-risk balance

The CHMP considers the following measures necessary to address issues related to efficacy:

The MAH should further investigate in study CA209141, the association between improved clinical outcomes to nivolumab and the presence of:

- Higher mutational load, and as feasible, PD L1 tumour associated immune cell (TAIC) expression (30 September 2017)
- PD-L2 expression (31 March 2018)
- High inflamed phenotype (30 September 2018)

4. Recommendations

Outcome

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

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

Extension of Indication to include treatment of squamous cell cancer of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy for OPDIVO as monotherapy.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, of the SmPC are updated in order to add the proposed new indication, add a warning to recommend careful consideration before initiating treatment with nivolumab in patients excluded from the SCCHN clinical trial (patients with a baseline performance score $\geqslant$ 2, untreated brain metastasis, active autoimmune disease, medical conditions requiring systemic immunosuppression, or carcinoma of the nasopharynx or salivary gland as the primary tumour sites) and update the undesirable effect and safety information. Package leaflet is updated in accordance.
Moreover, the updated RMP version 6.3 has been submitted, and agreed during procedure.

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

This CHMP recommendation is subject to the following new condition:

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

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

Description	Due date
6. To further investigate, in CA209141, the association between improved clinical outcomes to nivolumab and the presence of: - Higher mutational load, and as feasible, PD L1 tumour associated immune cell (TAIC) expression - PD-L2 expression - High inflamed phenotype.	- 30th September 2017 - 31st March 2018 - 30th September 2018

These conditions do fully reflect the advice received from the PRAC.