21 April 2017
EMA/CHMP/392346/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0019

Note

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

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Table of contents

List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIRC	blinded independent review committee
BMS	Bristol-Myers Squibb Company
BOR	best overall response
BSC	best supportive care
cHL	classical Hodgkin lymphoma
CI	confidence interval
CR	complete response
CSR	clinical study report
DBL	database lock
DC	discontinuation
DOR	duration of response
E-R	exposure-response
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GC	Gastric carcinoma
GHS	Global Health Status
GI	gastrointestinal
HRQoL	health-related quality of life
IC	immune cell(s)
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMM	immune modulating medication
IND	investigational new drug
IV	intravenous(ly)
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
NA	not applicable, not available
NCCN	National Comprehensive Cancer Network
NR	not reached
NSCLC	non-small cell lung cancer
NSQ	non-squamous
OESI	other event(s) of special interest
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death receptor 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PR	partial response
PT	preferred term

Q2W	every 2 weeks
QLQ-C30	Quality of Life Questionnaire - 30-item core
QoL	quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy
SCLC	small cell lung cancer
SCS	Summary of Clinical Safety
SD	stable disease; standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SQ	squamous
TTR	time to response
UC	urothelial carcinoma
US	United States
VAS	visual analog scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 25 August 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 the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy for Opdivo.
As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed indication, add a warning about the patient populations excluded from the clinical trial, and update the safety information. The Package Leaflet is updated in accordance.
Moreover, the updated RMP version 7.0 has been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

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 were:

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

Timetable	Actual dates
Submission date	25 August 2016
Start of procedure:	17 September 2016
CHMP Co-Rapporteur Assessment Report	16 November 2016
CHMP Rapporteur Assessment Report	21 November 2016
PRAC Rapporteur Assessment Report	18 November 2016
PRAC Outcome	1 December 2016
CHMP members comments	N/A
Request for supplementary information (RSI)	15 December 2016
CHMP Rapporteur Assessment Report on Responses	03 March 2017
CHMP members comments	13 March 2017

Updated CHMP Rapporteur Assessment Report	16 March 2017
2nd Request for supplementary information (RSI)	23 March 2017
Submission of MAH's responses	28 March 2017
Restart of the procedure	30 March 2017
CHMP Rapporteur Assessment Report	7 April 2017
CHMP members comments	10 April 2017
Opinion	21 April 2017

2. Scientific discussion

2.1. Introduction

Nivolumab (Opdivo) is a programmed death receptor 1 (PD-1) blocking antibody that is currently approved in the EU in indications for melanoma (as monotherapy and in combination with ipilimumab), lung cancer, classical Hodgkin's lymphoma and renal cell carcinoma. The CHMP recently gave a positive opinion on an 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. The approved dose and schedule of nivolumab monotherapy for the approved indications is 3 mg/kg administered as an IV infusion over 60 minutes Q2W.

Problem statement

Bladder cancer is the ninth most common cancer in the world, with approximately 430,000 new cases (330,380 in men and 99,413 in women) diagnosed in 2012. It is three times more prevalent in men than in women, resulting in 123,051 deaths in men and 42,033 deaths in women in 2012. In the EU, bladder cancer is the fifth most common cause of cancer, with approximately 124,188 new cases and 40,635 resulting deaths reported in 2012[1].

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is the most common type of bladder cancer, accounting for 90% of cases. Among patients diagnosed with UC, the majority have non-muscle invasive (approximately half) or localised muscle-invasive disease (approximately 1 in 3) at the time of diagnosis, with the remaining patients having metastatic disease. Approximately 50% of patients presenting with muscle-invasive urothelial cancer eventually develop metastatic recurrence after therapy for clinically localised disease. The most important risk factor identified in bladder cancer is smoking, with the presence of visceral or liver metastases, ECOG performance scores greater than 0, and baseline hemoglobin lower than 10 g/dL predicting worse clinical outcomes for patients with advanced or metastatic disease after platinum failure.

For patients with advanced and metastatic UC, standard first-line treatment involves platinum-based combination chemotherapy[2]. Despite responses in 40 - 60% of patients with advanced UC receiving first-line cisplatin-based chemotherapy, disease progression occurs in nearly all patients at a median of about 8 months[3]. In addition, 50% of patients are cisplatin-ineligible due to poor performance status, impaired

[1] GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012
[2] J. Bellmunt et al., Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology 25
[3] Von der Maase H et al. 2005. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Onc. 2005. 23:4602–08.

renal function, or comorbidity[4]. These patients receive carboplatin regimens such as gemcitabine+carboplatin, which offer a response rate of 41% and a median PFS of 5.8 months[5].

Adverse prognostic factors for survival for patients with advanced and metastatic disease failing platinum-based chemotherapy have been defined (PS >0, haemoglobin level <10 g/dl, and the presence of liver metastasis)[6]. In patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy, there is no global standard of care. ESMO guidelines[2] recommend second-line treatment with single-agent vinflunine, taxanes, or enrollment in clinical trials. Standard regimens described in the NCCN Guidelines[7] are taxanes (i.e., paclitaxel or docetaxel), gemcitabine, pemetrexed, and atezolizumab which are only approved in the US.

The MAH applied for the following indication: Opdivo is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

The recommended indication is: Opdivo as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy (see SmPC section 5.1).

The recommended dose of Opdivo in the above indication is 3 mg/kg nivolumab administered intravenously over 60 minutes every 2 weeks which is consistent with existing approved dose and schedule of nivolumab monotherapy in adults (see SmPC section 5.2). Treatment with Opdivo should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

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 ERA studies as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion on 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.

2.2.3. Conclusion on the non-clinical aspects

The lack of non-clinical studies is acceptable given that no changes to the SmPC section 5.3 have been proposed. Nivolumab is not expected to pose a significant risk to the environment.

[4] Galsky MD, Hahn NM, Rosenberg J, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol. 2011;29:2432-8.
[5] 13 De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol.2012;30:191-9.
[6] Bellmunt J, Choueiri TK, Fougeray R et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010; 28:1850–1855.
[7] NCCN Clinical Practices guidelines in Oncology: Bladder Cancer, Version 2.2017

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 1

- 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	CA209275/ Module 5.3.5.2 (clinical study report available)	To estimate ORR based on BIRC assessments (using RECIST 1.1) of nivolumab monotherapy in subjects with tumor expressing PD-L1 and overall treated subjects with metastatic or surgically unresectable UC who have progressed or recurred following treatment with a platinum agent	Phase 2 single arm trial of nivolumab monotherapy	Nivolumab 3 mg/kg IV Q2W	270 (270)	Adult (≥ 18 years) subjects with metastatic or surgically unresectable UC with disease progression or recurrence on or after at least one platinum-based chemotherapy
Efficacy, Safety	CA209032 (**UC mono cohort**) / Module 5.3.5.2 (clinical study report available)	To evaluate the ORR of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors	A Phase 1/2, open-label Study of nivolumab monotherapy or nivolumab combined with ipilimumab	Nivolumab 3 mg/kg IV Q2W	78 (78)	Adult (≥ 18 years) subjects with metastatic or surgically unresectable UC with disease progression or recurrence on or after at least one platinum-based chemotherapy

Abbreviations: BICR: blinded independent review committee; BMS: Bristol-Myers Squibb; IV: intravenous; No: number; ORR: objective response rate; PD-L1: programmed death-ligand 1; Q2W: every 2 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; UC: urothelial cancer

2.3.2. Pharmacokinetics

The clinical pharmacology data in this application support the proposed use of nivolumab as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following a platinum-containing chemotherapy regimen or within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy regimen.

The recommended dose and schedule is 3 mg/kg every 2 weeks (Q2W), which is the same as that approved for melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC).

The PK of nivolumab in subjects with solid tumours and cHL have been previously characterised by PPK analysis. Nivolumab PK in these analyses was described by a stationary model, in which nivolumab CL was constant with respect to time. However, in a subsequent exploratory analysis following guidance from the US FDA, it was found that nivolumab CL tended to decrease with time. A PPK model with time-varying CL was thus used to characterise the nivolumab serum concentration-time profile in subjects with

multiple solid tumours and cHL, including subjects with UC (subjects from a Phase ½ study, Study CA209032 and a Phase 2 single arm trial with nivolumab 3 mg/kg, Study CA209275, were included).

An assessment of the effect of the following covariates on nivolumab PK was also performed: body weight (BW), age, sex, race, hepatic function status, eGFR, baseline performance status (PS) and tumour type.

Pharmacokinetics in UC - Population Pharmacokinetic Analysis

The PPK analysis was performed using data from 3458 subjects with solid tumours or cHL. The analysis population consisted of all subjects enrolled in studies who received nivolumab monotherapy, and for whom nivolumab concentration values were available.

These studies were selected to enable a robust characterisation of nivolumab PK in the following tumour types: NSCLC, melanoma, RCC, SCCHN, UC, gastric carcinoma (GC), and cHL, as well as Phase 1 studies in which there was intense PK sampling.

The PPK model development consisted of: 1) Base Model to re-assess the structural model, in particular time-varying CL, and 2) Full Model to assess the effect of covariates on nivolumab PK, which included an assessment of tumour type (including UC vs NSCLC 2L+) effect on nivolumab CL, and 3) Final model to attain the parsimonious model including significant covariates on nivolumab PK, which was further utilised for model applications.

The Final Model was a two-compartment, zero-order IV infusion with time-varying CL (sigmoidal-Emax function) with a proportional residual error model, random effect on CL, VC, VP and Emax, and correlation of random effects between CL and VC. The final PPK model, contained baseline BWT (BBWT), eGFR, PS, sex, race and tumour type on CL and BBWT and sex on VC and the parameter estimates are described in the table below.

Table 2 Parameter estimates of the final PPK Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e,f]
Fixed Effects				
CL_{REF} [L/h]	θ_1	0.0108	3.11E-04 (2.88)	0.01, 0.011
VC_{REF} [L]	θ_2	4.26	0.0397 (0.932)	4.187, 4.339
Q_{REF} [L/h]	θ_3	0.0334	0.00190 (5.69)	0.03, 0.039
VP_{REF} [L]	θ_4	2.64	0.0899 (3.41)	2.472, 2.796
CL_{BBWT}	θ_7	0.584	0.0326 (5.58)	0.517, 0.645
CL_{GFR}	θ_9	0.137	0.0228 (16.6)	0.09, 0.185
CL_{SEX}	θ_{12}	-0.161	0.0165 (10.2)	-0.197, -0.13
CL_{PS}	θ_{13}	0.172	0.0138 (8.02)	0.144, 0.198
CL_{OTH}	θ_{15}	0.0214	0.0166 (77.6)	-0.017, 0.055
VC_{BBWT}	θ_{17}	0.619	0.0359 (5.80)	0.556, 0.699
VC_{SEX}	θ_{18}	-0.142	0.0181 (12.7)	-0.173, -0.103
CL_{GC}	θ_{21}	0.186	0.0486 (26.1)	0.084, 0.275
CL_{EMAX}	θ_{24}	-0.311	0.0336 (10.8)	-0.384, -0.251
CL_{T50}	θ_{25}	1.40E+03	76.1 (5.44)	1246, 1566
HILL	θ_{26}	2.77	0.530 (19.1)	1.983, 4.274
CL_{RAAA}	θ_{27}	0.0576	0.0406 (70.5)	-0.027, 0.138
CL_{RAAS}	θ_{28}	-0.0769	0.0264 (34.3)	-0.129, -0.025
CL_{CHL}	θ_{30}	-0.320	0.0270 (8.44)	-0.376, -0.268
Random Effects				
ω^2-CL [-]	$\omega_{1,1}$	0.111 (0.333)	0.00575 (5.18)	0.099, 0.122
ω^2-VC [-]	$\omega_{2,2}$	0.127 (0.356)	0.0139 (10.9)	0.1, 0.158
ω^2-VP [-]	$\omega_{3,3}$	0.231 (0.481)	0.0243 (10.5)	0.187, 0.288
ω^2-EMAX [-]	$\omega_{4,4}$	0.0509 (0.226)	0.00914 (18.0)	0.034, 0.071
ω^2-CL: ω^2VC	$\omega_{1,2}$	0.0361 (0.304)	0.00351 (9.72)	0.029, 0.045
Residual Error				
PERR [-]	θ_6	0.206	0.00518 (2.51)	0.197, 0.216

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 (ωi,i or σi,i) and Covariance (Correlation) for off-diagonal elements (ωi,j or σi,j)

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

e Confidence intervals of Random Effects and Residual Error parameters are for Variance or Covariance

f-Confidence Interval values are taken from bootstrap calculations (433 successful out of a total of 500).

g-CL and VC are typical value of CL and VC at the reference values. Covariate effect was estimated relative to reference subject who is a male, weighing 80kg, eGFR of 80 [mL/min/1.73 m2], age of 65 years, NSCLC2L+ tumor type and performance status of 0. The reference value for hepatic impairment is normal, and race is Caucasian or other. The reference values for continuous valued covariates were selected to be approximately the median of the covariate values in the analysis data set. RAAA indicates race (african american) and RAAS indicates (Race Asian)

h- Eta shrinkage: ETA_CL: 14.2, ETA_VC: 21.6, ETA_VP: 45.8, ETA_EMAX: 54.0

Source: /global/pkms/data/CA/209/C16/prd/ppk/final/nm/e-final3-2-line-adj/e-final3-2.-line-adj.rtf

The model estimated Emax (CLEMAX, -0.311, Table 2), indicates that nivolumab CL decreases with time, and that the maximal decrease is approximately 26% [calculated as: 1 −exp(Emax)]. The change in CL is estimated to occur soon after initiation of treatment, with the half-maximal change estimated to occur at approximately 2 months (T50 = 1400 h). The geometric mean CL of 10.8 mL/h after the first dose reaches a steady-state value of 7.91 mL/h.

The results of the PPK analysis indicated that the PK of nivolumab was linear in the dose range of 0.1 to 20 mg/kg.

A summary of the individual PK parameter estimates obtained from the final PPK model is provided in Table 3.

Table 3 Summary Statistics of individual PK parameter Values (N=3458)

PK Parameter[a]	Mean	Geometric Mean	Median (min, max)	SD	CV%
Baseline CL (BCL) [L/h]	0.0115	0.0108	0.0107 (0.00155, 0.0425)	0.00455	39.5
CLSS [L/h]	0.00858	0.00791	0.00783 (0.000597, 0.0884)	0.00394	46
VC [L]	4.08	3.88	3.95 (0.133, 11.9)	1.23	30.1
VP [L]	2.73	2.63	2.63 (0.351, 21.6)	0.911	33.4
VSS [L]	6.81	6.62	6.61 (0.748, 25.3)	1.66	24.4
T-HALFα [h]	31.5	30.6	31 (2.23, 95.2)	6.97	22.1
T-HALFβ [d]	27	25.2	25.4 (3, 525)	14.9	55.4
EMAXP	26	NA	26.7 (-125, 64.4)	8.49	32.6

NA: Not applicable

[a]T1/2β and T1/2α were calculated using formula as below:

KE = CL/VC; K12 = Q/VC; K21 = Q/VP; AA = KE + K12 + k21

$\beta = (\frac{AA - \sqrt{AA^2 - 4 \times KE \times K21}}{2})$, and $t_\beta = (\frac{0.693}{\beta})$

$\alpha = (\frac{AA + \sqrt{AA^2 - 4 \times KE \times K21}}{2})$, and $t_\alpha = (\frac{0.693}{\alpha})$

VSS was calculated using formula: VSS=VC+VP.

EMAXP was a percentage of maximal CL change from baseline and was calculated as (1-exp(EMAX))*100. Individual estimates of Q, T50 and HILL are 0.0336 L/h, 58.3 and 2.76, respectively, as there are no random or covariate effect parameters associated with these parameters in the final PPK model.

Analysis -Directory: /global/pkms/data/CA/209/C16/prd/ppk/final

R-Program Source: Analysis-Directory/R/scripts/exposure-summary.r

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

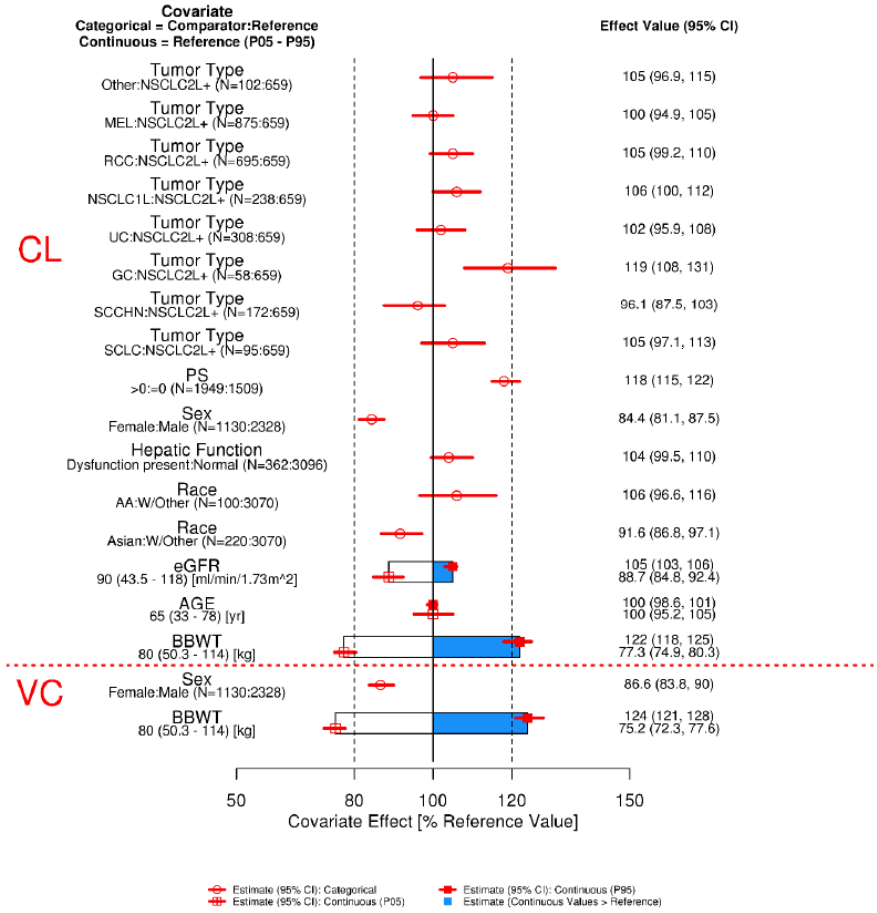
The geometric mean Cavgss in all subjects administered 3 mg/kg Q2W was 86.6 µg/mL.

Analysis of Covariate Effects

Inferences regarding the effect of covariates were based upon the full model parameter estimates, which incorporated all pre-specified covariate parameter relationships of interest into the model.

The effects of categorical (tumour type, race, performance status, hepatic function and sex) and continuous covariates (eGFR, age and body weight) on PK parameters (CL and VC) in the full covariate model are summarized in Figure 1. The assessment for the effect of solid tumors on CL was done by including a separate parameter for each solid tumor type, except for cHL.

The effect of the following covariates were found to be statistically significant on nivolumab CL: baseline body weight (BBWT), performance status (PS), sex, race (Asian), tumor type (GC), eGFR; and the effect of BBWT and sex were found to be significant on nivolumab VC. The magnitude of the effect of covariates on CL, accounting for uncertainty, was within the ± 20% boundaries for all covariates, except baseline body weight. Sex appears to have some level of effect on CL and VC; it was close the ± 20% boundary for CL and VC, where female subjects had lower CL and VC than males.



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

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

Note 3: Reference subject is white/others male age=65 yr, PS=0, eGFR=90 ml/min/1.73m^2 and body weight=80kg, subject with normal hepatic function with NSCLC2L+. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

CI values were taken from bootstrap calculations (289 successful out of a total of 500)

Figure 1 Covariate effects on PK Model Parameters (Full PPK Model excluding cHL patients)

2.3.3. Pharmacodynamics

E-R analyses for safety and efficacy in subjects with UC from study CA209275 and CA209032 (UC arm) were not conducted, as data were available from only one dose level.

The rate of AE-DC/D in studies CA209032 (UC cohort) and CA209275 was similar to that seen in previous studies (see clinical safety).

Immunogenicity

The immunogenicity of nivolumab at 3 mg/kg Q2W monotherapy has been well characterised in the nivolumab development program across multiple tumour types. An updated immunogenicity analysis integrated with data from studies CA209032 and CA209275 was presented.

Study CA209032:

Nine subjects (13.0%) were ADA positive following administration of nivolumab. No subject was considered persistent positive and one subject was neutralising ADA positive. The titer values observed in ADA positive subjects ranged from 1 to 8.

Only 1 ADA positive subject (not neutralising ADA positive) had Grade 1 hypersensitivity/infusion reaction on Day 1 after the first dose of nivolumab. Given that this subject was ADA positive on Days 1 (baseline), 15, 29, and 99 and continued to receive nivolumab treatment for 6 months with no other occurrences of hypersensitivity/infusion reaction, it is unlikely that the Day 1 occurrence was ADA related. Thus, there were no apparent effects of nivolumab immunogenicity on safety in nivolumab monotherapy treated UC subjects in this study.

Among 9 ADA positive subjects, 1 had CR, 1 had PR, 4 had a SD, and 3 (including the neutralising ADA positive subject) had a PD.

Study CA209275:

Fifty-two subjects (23.7%) were ADA positive following administration of nivolumab. No subject was considered persistent positive and four subjects were neutralising ADA positive. In all ADA positive subjects the ADA titres were low, ranging from 1 to 32.

Hypersensitivity/infusion related reactions were not observed in any ADA positive subjects. Thus, the presence of ADA was not associated with the occurrence of hypersensitivity and/or infusion-related reactions in Study CA209275. Of the 52 subjects that were ADA positive, 1 subject had a BOR of CR, 6 subjects had a BOR of PR, and 9 subjects had a BOR of SD. Thus, approximately 30% of the ADA positive subjects had a response of CR, PR, or had SD. This response was consistent to the overall response observed in CA209275, which included the ADA negative subjects.

Table 4 Summary of nivolumab antibody assessments using method ICDIM 140 following nivolumab 3 mg/kg every 2 weeks

	Number of Subjects (%)			
Study Number	Summary of Previous Studies[a] (N=1734)	CA209032 (UC Subjects) (N=69)	CA209275 (N=219)	Pooled Summary (N=2022)
Baseline ADA Positive	92 (5.3)	4 (5.8)	11 (5.0)	107 (5.3)
ADA Positive	170 (9.8)	9 (13.0)	52 (23.7)	231 (11.4)
Persistent Positive[b]	2 (0.1)	0	0	2 (0.1)
Not PP - Last Sample Positive	63 (3.6)	1 (1.4)	24 (11)	88 (4.4)
Other Positive	105 (6.1)	8 (11.6)	28 (12.8)	141 (7.0)
Neutralizing ADA Positive	10 (0.6)	1 (1.4)	4 (1.8)	15 (0.7)
ADA Negative	1564 (90.2)	60 (87.0)	167 (76.3)	1791 (88.6)

Source: See note a and Table 8.13.1-1 of the CA209032 UC CSR[11] and 8.14.1-1 of the CA209275 CSR[12]

[a] Previous studies includes studies CA209-063, -037, -066, -017, -057, -067, -025, -039, -205, -141 summarized in Module 2.7.2 Summary of Clinical Pharmacology for Squamous Cell Carcinoma of the Head and Neck[20]

[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.

To further explore the relationship between immunogenicity and safety, an integrated assessment of the potential impact of nivolumab ADA on immunogenicity-related effects was performed by summarising the

select adverse events in the hypersensitivity/infusion reaction category by ADA 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), CA209141, CA209032 (UC subjects), and CA209275. Of the 2071 subjects evaluable for the presence of ADA and hypersensitivity/infusion reactions, a total of 116 experienced hypersensitivity/infusion reactions. Of the 116 subjects who experienced hypersensitivity/infusion reactions, 5 were positive for nivolumab ADA and 111 were negative for nivolumab ADA. A total of 5/241 (2.07%) ADA 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 mADA were not detectable in subsequent assessments.
- One subject from Study CA209032 had Grade 1 hypersensitivity/infusion reaction on Day 1 after the first dose of nivolumab. Given that this subject was ADA positive on Days 1 (baseline), 15, 29, and 99 and continued to receive nivolumab treatment for 6 months with no other occurrences of hypersensitivity/infusion reaction, it is unlikely that the Day 1 occurrence was ADA related.

2.3.4. Discussion on clinical pharmacology

A new PPK model has been developed for the evaluation of the PK of subjects that received nivolumab for the treatment of solid tumours (including the new urothelial cancer (UC) indication) as well as patients with cHL. Following FDA guidance, the applicant has now characterised nivolumab CL as time-dependent, rather than constant as considered in the previously developed PPK models.

Nivolumab PK was described by a linear 2-compartiment model with time decreasing CL (~26%). 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 monoclonal antibody (CL=0.0108 L/h; VC=4.26 L; VP=2.64 L). The effect of baseline body weight (BBWT) was found to be statistically significant and clinically relevant on both nivolumab CL and VC in line with previous PPK models. The effect of sex, race (Asian), PS, and eGFR are unlikely to be clinically relevant. Sex appears to have some level of effect on CL and VC; it was close the ± 20% boundary for CL and VC, where female subjects had lower CL and VC than males. These results are in alignment with the previous reported analyses, and the magnitude of the effect of PS, body weight and eGFR on CL, and the effect of sex and body weight on VC are comparable to what was previously reported in other solid tumour populations including RCC, NSCLC and melanoma.

Overall, no relevant changes are observed in the estimated PK parameters of the effect of covariables on nivolumab PK compared to previous models. The SmPC has been changed according to the new estimated parameters (see SmPC section 5.2).

Nivolumab has low immunogenic potential. The pooled analysis of all tumour types showed that approximately 11% of subjects who were treated with nivolumab 3 mg/kg every 2 weeks (Q2W) monotherapy tested positive for treatment-emergent anti-nivolumab antibody. There is no apparent effect of ADA on efficacy of nivolumab.

The impact of immunogenicity on nivolumab clearance has been assessed as part of the PPK analyses as a time-varying covariate, and was associated with a 14% increase in nivolumab CL, which was not considered clinically relevant.

Overall immunogenicity results are in line with previous information (see also clinical safety).

The applicant did not conduct E-R analysis in subjects with UC from study CA209275 and CA209032 (UC arm) as data were available from only one dose level which would limit the interpretability of the data. This is considered acceptable.

2.3.5. Conclusions on clinical pharmacology

A new PPK model including time-dependent CL, has been developed for the evaluation of the PK of subjects that received nivolumab for the treatment of solid tumours (including the new urothelial cancer (UC) indication) as well as patients with cHL. No relevant changes are observed in the estimated PK parameters or the effect of covariables on nivolumab PK compared to previous models. The SmPC has been changed according to the new estimated parameters.

The updated immunogenicity data is in line with previous analysis showing that nivolumab has low immunogenic potential.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was submitted. The dose and schedule of nivolumab, 3 mg/kg IV infusion over 60 minutes Q2W was selected for CA209275 and CA209032 based upon the collective experience of nivolumab monotherapy across multiple tumour types i.e. for melanoma, NSCLC, RCC, and classical Hodgkin lymphoma.

2.4.2. Main studies

Study CA209275

This was a Phase 2 Single Arm Clinical Trial of Nivolumab (BMS-936558) in Subjects with Metastatic or Unresectable Urothelial Cancer Who Have Progressed or Recurred Following Treatment with a Platinum Agent.

Methods

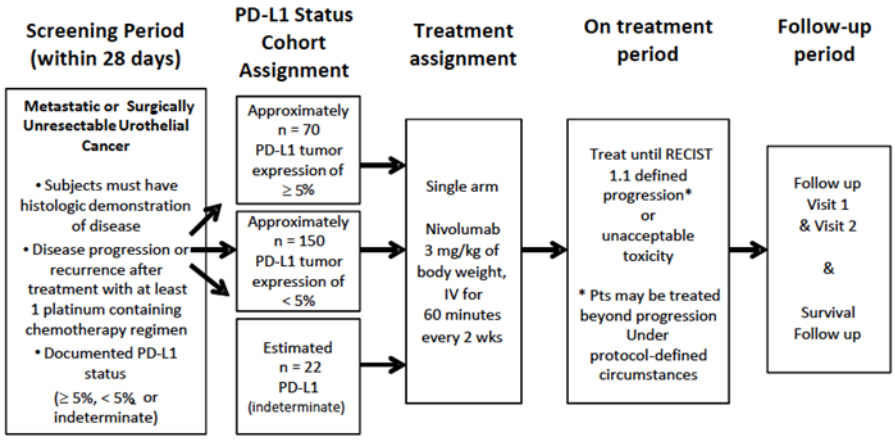


Figure 2 study design scheme (Study CA209275)

Study participants

Main inclusion criteria

- Subjects ≥18 years and older.
- Histological or cytological evidence of metastatic or surgically unresectable UC (bladder, urethra, ureter, or renal pelvis). Minor histologic variants (< 50% overall) were acceptable.
- Metastatic or surgically unresectable (cT4b, or any N+ [N1-3] or any M-1) disease.
- Measurable disease by CT or MRI per RECIST 1.1 criteria.
- Subjects must have progression or recurrence after treatment

  - with at least 1 platinum-containing chemotherapy regimen for metastatic or surgically unresectable locally advanced urothelial cancer, or

  - within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with platinum agent in the setting of cystectomy for localised muscle-invasive urothelial cancer.
- Subjects that have received more than 2 prior lines of chemotherapy must not have liver metastases.
- Evaluable tumour tissue (fresh or archival) for biomarker analysis.
- ECOG PS 0 or 1.
- Serum creatinine ≤ 1.5 x upper limit of normal or creatinine clearance (CrCl) ≥ 30 mL/min (using the Cockcroft-Gault formula).

Main exclusion criteria

- Active brain metastases or leptomeningeal metastases.
- Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enrol.

- Systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, anti-CD137, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
- Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment.

Treatments

Nivolumab 3 mg/kg was administered as a 60 minute IV infusion Q2W. Subjects received treatment with nivolumab on Day 1 of a treatment cycle every 2 weeks (14 days). No pre-medications were recommended on the first cycle.

Dose reductions or escalations were not permitted for nivolumab.

Dose delays were permitted.

Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug administration.

Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient experienced a clinical benefit, did not have rapid disease progression, and was tolerating study drug as determined by the investigator.

Objectives

The primary objective of the CA209275 study was to estimate ORR based on (BIRC) assessments of nivolumab monotherapy in subjects with tumour expressing PD-L1 (membranous staining in ≥ 5% and ≥ 1% tumor cells) and overall treated subjects with metastatic or surgically unresectable UC who have progressed or recurred following treatment with a platinum agent.

The secondary objectives were the following:

- To evaluate progression free survival (PFS) based on BIRC assessments in subjects with tumor expressing PD-L1 (membranous staining in 5% and 1% tumour cells) and overall subjects treated with nivolumab monotherapy.
- To evaluate overall survival (OS) in subjects with tumour expressing PD-L1 (membranous staining in 5% and 1% tumor cells) and overall subjects treated with nivolumab monotherapy.
- To estimate investigator assessed ORR in subjects with tumour expressing PD-L1 (membranous staining in 5% and 1% tumor cells) and overall subjects treated with nivolumab monotherapy

The first tumour assessments were conducted 8 weeks after the start of treatment and continued every 8 weeks thereafter up to 48 weeks, then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Tumour assessments were continued after treatment discontinuation in patients who discontinued treatment for reasons other than progression.

Outcomes / endpoints

Primary and secondary endpoints for Study CA209275

Table 5 Summary of Primary and Secondary Objectives (Study CA209275)

Objective	Endpoint	Endpoint Description
PRIMARY		
To estimate ORR based on BIRC assessments (using RECIST 1.1) of nivolumab monotherapy in subjects with tumor expressing PD-L1 (membranous staining in ≥ 5% and ≥ 1% tumor cells) and overall treated subjects	ORR (per BIRC)	The primary objective will be measured by the primary endpoint of ORR (based on BIRC assessments) among all treated subjects, PD-L1 ≥ 1% subjects and PD-L1 ≥ 5% subjects. It is defined as the number of subjects with a best overall response of confirmed CR or PR divided by the number of all treated subjects, PD-L1 ≥ 1% subjects or PD-L1 ≥ 5% subjects respectively. Best overall response is defined as the best response designation, as determined by BIRC, recorded between the date of first dose and the date of objectively documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.
SECONDARY		
To evaluate PFS based on BIRC assessments (using RECIST 1.1) in subjects with tumor expressing PD-L1 (membranous staining in ≥ 5% and ≥ 1% tumor cells) and overall treated subjects	PFS (per BIRC)	Primary PFS definition will be based on BIRC assessments. It is defined as the time from first dosing date to the date of the first documented tumor progression, based on BIRC assessments (per RECIST 1.1), or death due to any cause. Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the first dosing date. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy
To evaluate overall survival (OS) in subjects with tumor expressing PD-L1 (membranous staining in ≥ 5% and ≥ 1% tumor cells) and overall subjects treated with nivolumab monotherapy	OS	OS is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive
To estimate investigator assessed ORR (using RECIST 1.1) in subjects with tumor expressing PD-L1 (membranous staining in ≥ 5% and ≥ 1% tumor cells) and overall subjects treated with nivolumab monotherapy	ORR (per investigator)	ORR as assessed by investigators is defined similarly as for the primary endpoint ORR.

Objective	Endpoint	Endpoint Description
EXPLORATORY		
To evaluate the safety of nivolumab monotherapy in subjects with metastatic or surgically unresectable urothelial carcinoma	Deaths, AEs, SAEs, AEs leading to DC & dose delay, and specific laboratory abnormalities	Safety was analyzed through the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, select adverse events, immune-mediated adverse events (IMAEs) and specific laboratory abnormalities (worst grade). Select AE analyses included incidence, time-to-onset, and time-to-resolution. AEs and laboratory abnormalities were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. AEs were coded using the MedDRA Version 19.0.
To evaluate investigator assessed PFS (using RECIST 1.1)s.	PFS (per investigator)	PFS based on investigator assessments is defined as the time from first dosing date to the date of the first documented tumor progression, as determined by investigators (per RECIST 1.1), or death due to any cause. Clinical deterioration in the absence of radiographic evidence is not considered progression for the purpose of determining PFS per investigator. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the first dosing date. Subjects who started subsequent therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy.
To characterize the PK of nivolumab monotherapy and to explore exposure-response relationships	Nivolumab concentrations	PK was determined from serum nivolumab concentrations. Samples were collected to characterize pharmacokinetics of nivolumab and to explore exposure-safety and exposure-efficacy relationships
To characterize the immunogenicity of nivolumab monotherapy	Serum ADA and neutralizing ADA response to nivolumab	Human serum samples from nivolumab-treated subjects were evaluated for the presence of ADA at PPD Inc. (Richmond, VA) using a validated immunoassay method (Method ICDIM 140)[2] and neutralizing activity at BMS (Princeton NJ) using a validated functional cell-based assay (Method 15400).[3] See Appendix 8.2 and 8.3 for immunogenicity bioanalytical study reports. Baseline ADA Positive: an ADA-positive sample at baseline. ADA Positive: at least one ADA-positive sample relative to baseline at any time after initiation of treatment. Persistent Positive: ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart. Other Positive: not persistent positive with ADA-negative sample

Objective	Endpoint	Endpoint Description
		in the last sampling time point. Last Sample Positive: Not persistent positive with ADA-positive sample in the last sampling time point. Neutralizing Positive: At least 1 ADA positive sample with neutralizing antibodies detected. ADA Negative: no ADA positive sample after the initiation of treatment
To investigate the association between biomarkers in the tumor tissue, such as PD-L1 expression, with safety and efficacy for subjects treated with nivolumab monotherapy	PD-L1	PD-L1 expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per the validated Dako PD-L1 PharmDx IHC kit assay. This is referred to as quantifiable PD-L1 expression. If the PD-L1 staining could not be quantified, it is further classified as: Indeterminate: Tumor cell membrane staining hampered for reasons attributed to the biology of the tumor tissue sample and not because of improper sample preparation or handling. Not evaluable: Tumor tissue sample was not optimally collected or prepared and PD-L1 expression is neither quantifiable nor indeterminate. Not evaluable can be determined from H&E process before the tumor biopsy specimen is sent for PD-L1 evaluation or from the H&E process during PD-L1 evaluation.
To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organisation for Research and Treatment of Care (EORTC) QLQ-C30	QLQ-C30 responses	The **QLQ-C30** has 30 items divided among 5 functional scales (physical, role, emotional, social, and cognitive), 3 symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and 6 single-item scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Two items measuring overall health status and quality of life are graded on a 7-point Likert scale, while all remaining items are graded on a 4-point scale: 1 (not at all) to 4 (very much).
To assess changes in reported global health outcomes based on the EQ-5D index score	EQ-5D responses	The **EQ-5D** is a standardized instrument used to measure self-reports of general health status. EQ-5D essentially has 2 components: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D descriptive system is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no, moderate problems, and extreme health problems. The EQ-5D VAS recorded the subject's self-rated health state on a 100-point vertical VAS (0 = worst imaginable health state; 100 = best imaginable health state).

DOR and TTR were estimated in subjects with confirmed PR + CR. TTR is defined as the time from first dosing date to the date of the first confirmed response (CR or PR), as assessed by the BIRC. DOR is defined as the time from first confirmed response (CR or PR) to the date of the first documented tumour progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.

Sample size

Assuming ORR is 30%, 70 treated subjects with PD-L1 expression 5% would provide 99.1% power at 5% type 1 error to reject the null hypothesis of a two-sided test that the true ORR was 10% (single agent chemotherapy historical control) a threshold below which was considered not clinical meaningful in this population, and 90% power at 5% type I error to reject the null hypothesis of a two-sided test that the true ORR was 14.7%. Under the assumption of 32% prevalence rate of PD-L1 5% among all PD-L1 evaluable subjects, approximately up to 220 PD-L1 evaluable subjects would be treated. Assuming an additional 10% of treated subjects with PD-L1 indeterminate status, the total sample size was expected to be approximately 242.

Under the assumption of 50% prevalence rate of PD-L1 1% among all PD-L1 evaluable subjects, approximately up to 110 subjects with PD-L1 expression 1% would be treated. This would provide 90% power to reject the null hypothesis of ORR = 10% at a two-sided 5% type 1 error if the true ORR in this population was 20.6%.

For all treated subjects, a sample size of 242 would provide 90% power to reject the null hypothesis of ORR = 10% at a two-sided 5% type I error if the true ORR in this population was 16.9%.

The final analysis of the primary endpoint ORR (based on BIRC assessments) was to be performed six months after approximately 70 subjects with PD-L1 expression of 5% had been treated (i.e., six months after last patient first treatment).

Randomisation

This was a single arm trial.

Blinding (masking)

This was an open-label study. PD-L1 results were blinded to the investigator, subject and BMS study team.

Statistical methods

Unless otherwise noted, discrete variables were tabulated by the frequency and proportion of subjects falling into each category, grouped by cohort (with total). Continuous variables were summarised by cohort (with total) using the mean, standard deviation, median, minimum and maximum values. ORR (both BIRC assessment and investigator-assessed) was summarised by a binomial response rate and its corresponding two-sided 95% exact CIs using the Clopper-Pearson method. BOR was also summarised by response category.

Time to event distributions were estimated using Kaplan Meier techniques. This was done for endpoints progression free survival, overall survival, and duration of response (note that time to response was analysed using summary statistics such as mean, SD, median, min, max). Median survival time along with 95% CI were constructed based on a log-log transformed CI for the survivor function S(t). Rates at fixed time points were derived from the Kaplan Meier estimate and corresponding confidence interval were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t).

Table 6 Censoring Scheme for Primary Definition of PFS (Study CA209275)

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments and no death	First dosing date	Censored
No on study tumor assessments and no death	First dosing date	Censored
New anticancer treatment started without a prior reported progression per RECIST 1.1 or death	Date of last tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Progression per RECIST 1.1 documented at scheduled or unscheduled visit and no new anticancer treatment started before	Date of the first documented tumor progression	Progressed
Subject progression free (per RECIST 1.1) and no new anticancer treatment started	Date of last tumor assessment	Censored
Death without prior progression per RECIST 1.1 and no new anticancer treatment started	Date of death	Progressed

Results

Participant flow

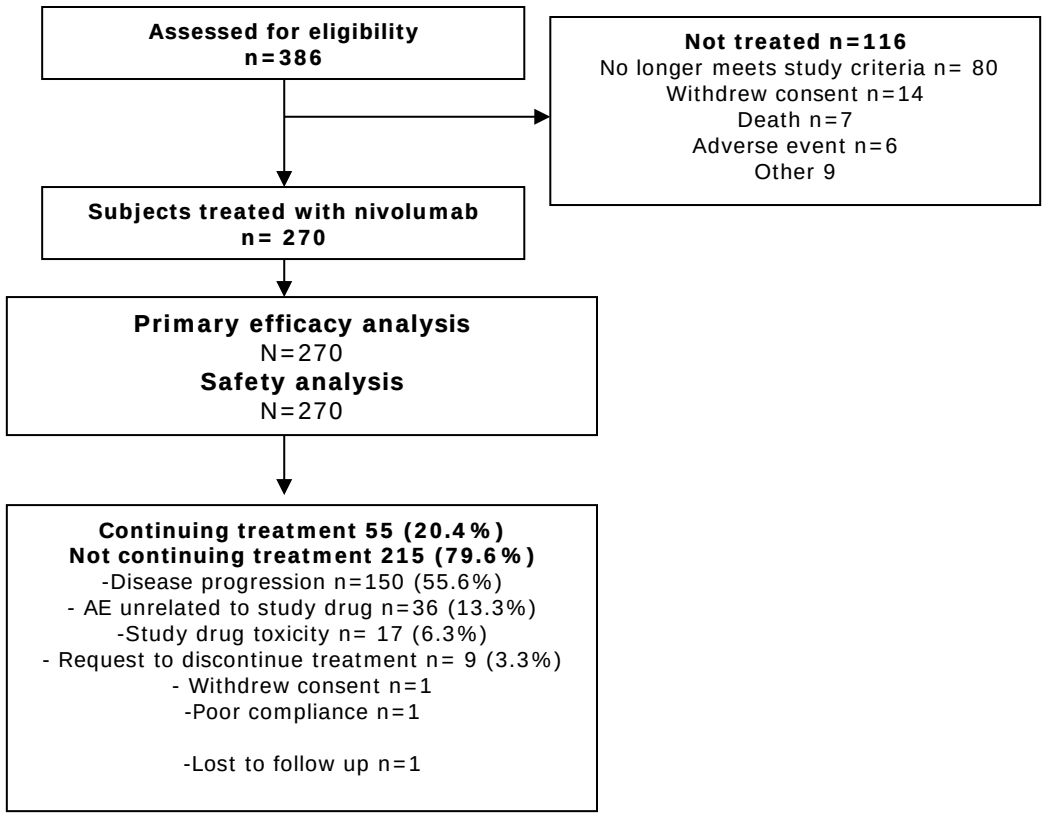


Figure 3 Participant flow (updated efficacy data, Database lock (DBL) 2 Sept 2016)

Table 7 Subject Status Summary - All Enrolled and All Treated Subjects (Study CA209275) (updated efficacy data, DBL 2 Sept 2016)

	Total
SUBJECTS ENROLLED	386
SUBJECTS TREATED (%)	270 (69.9)
SUBJECTS NOT TREATED (%)	116 (30.1)
REASON FOR NOT BEING TREATED (%)	
ADVERSE EVENT	6 (1.6)
SUBJECT WITHDREW CONSENT	14 (3.6)
DEATH	7 (1.8)
POOR/NON-COMPLIANCE	2 (0.5)
SUBJECT NO LONGER MEETS STUDY CRITERIA	80 (20.7)
OTHER	7 (1.8)

End of Treatment Period Subject Status Summary
All Treated Subjects

	PD-L1 <5% N = 187	PD-L1 >=5% N = 83	All Treated Subjects N = 270
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	29 (15.5)	26 (31.3)	55 (20.4)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	158 (84.5)	57 (68.7)	215 (79.6)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)			
DISEASE PROGRESSION	108 (57.8)	42 (50.6)	150 (55.6)
STUDY DRUG TOXICITY	11 (5.9)	6 (7.2)	17 (6.3)
ADVERSE EVENT UNRELATED TO STUDY DRUG	28 (15.0)	8 (9.6)	36 (13.3)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	8 (4.3)	1 (1.2)	9 (3.3)
SUBJECT WITHDREW CONSENT	1 (0.5)	0	1 (0.4)
LOST TO FOLLOW-UP	1 (0.5)	0	1 (0.4)
POOR/NON-COMPLIANCE	1 (0.5)	0	1 (0.4)

Recruitment

The enrolment period lasted approximately 8 months (March 2015 to October 2015). The last patient last visit date (clinical cut-off) for this analysis was 15-Apr-2016, in order to provide pre-specified minimum follow-up of 6 months from the global enrolment last patient first treatment date of 15-Oct-2015. The clinical database lock for this analysis occurred on 30-May-2016. 386 subjects were enrolled at 63 sites in 11 countries. Of the 386 enrolled subjects, 270 (69.9%) were treated with nivolumab; 106 (39.3%) were in the US, 23 (8.5%) were in Japan, 135 (50.0%) in Europe, and 6 (2.2%) in Australia.

Conduct of the study

The original CA209275 protocol was dated 30-Oct-2014. Four global amendments and 4 country-specific amendments were issued for this study. The history of Protocol Amendments is shown in **Error! Reference source not found.**.

Table 8 Summary of Protocol Amendments (Study CA209275)

Document (Sites)	Date	Summary of Change
Amendment 01(DE)	26-Nov-2014	In response to the German Health Authority request, 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 (All)	17-Dec-2014	Table 5.1-1 Screening Procedural Outline, Table 5.1-2 On treatment Period Procedural Outline, and Table 5.1-3 Follow-up Period Procedural Outline; Laboratory tests: Added amylase and lipase. Section 5.3, Safety Assessments: Added amylase and lipase. Table 5.1-2 On treatment Period Procedural Outline; Changed the timing of EORTC QLQ-C30 & EQ-5D to: Assessed following enrollment but prior to dosing on Day 1 and then at every 4th cycle up to 48 weeks, then every 6th cycle until disease progression or treatment is discontinued (whichever occurs later). Synopsis, Secondary Objectives; third bullet: changed to ≥ 1%.
Amendment 03 (Sweden)	26-Feb-2015	In response to the Swedish Medical Products Agency which did not accept the contraception methods listed in Section 3.3.1.3 of the protocol, the following sections were updated: Inclusion Criteria, Age and Reproductive Status Age and Reproductive Status, Highly Effective Methods of Contraption and Less Effective Methods of Contraception
Amendment 04 (All)	19-Mar-2015	Changed the definition of PD-L1 positivity from ≥ 1% to ≥ 5% membranous staining in tumor cells and increased the minimum of PD-L1 positive subjects from 58 to 70. Reduced the Creatinine Clearance (CrCl) threshold in the inclusion criteria from ≥ 40 mL/min to ≥ 30 mL/min. Other updates were made: the medical monitor, SAE reporting timeframes and collection timeframes, statistical considerations regarding sample size, and general protocol clarifications.
Amendment 05 (JP)	29-Apr-2015	Local regulatory requirements for Japanese sites were added.
Amendment 06 (All)	26-Aug-2015	Included an analysis of Objective Response Rate, (ORR), in subjects with tumors expressing PD-L1 at ≥ 1% into the co-primary objective which currently estimates ORR in all treated and subjects with tumors expressing PD-L1 at ≥ 5%. Extended subject enrollment in Japan if the global enrollment in the main study was closed prior to Japan accruing approximately 25 treated subjects (~10% of the global number of treated subjects), or until November 2015, whichever occurred sooner. Enrollment into the main study was to stop once approximately 70 subjects with PD-L1 expression of (≥ 5% membranous staining) are treated. Subjects enrolled from Japan in the main study will be part of the main analysis. Additional analyses will be also conducted on all enrolled Japanese subjects (including Japanese subjects enrolled after the global enrollment) and reported separately. Other updates were made: the medical monitor, statistical considerations regarding the PD-L1 tumor expression and extended enrollment in Japan, and general protocol clarifications.
Amendment 07 (JP)	03-Feb-2016	Added changes to safety reporting requirements for serious adverse events (SAEs) in Japan, along with other minor changes. These changes in the protocol were incorporated into the Amendment 05 prepared for the local regulatory requirements for Japanese sites and apply to all subjects enrolled in Japan.
Amendment 08 (All)	22-Feb-2016	The purpose of this amendment was to clarify the milestone timing and population for the primary analysis. In this amendment, it was clarified that subjects in Japan, who started treatment after last patient first treatment date of subjects who were enrolled before closure of global enrollment, were not be included in the efficacy analysis. Additionally, other items were updated, change to the study's Medical Monitor, new fax number for the Study Director, correction to a footnote in table 5.6.2.6-1.

Relevant Protocol Deviations

Relevant protocol deviations (significant protocol deviations that were programmable and could potentially affect the interpretability of study results) were reported in 3.3% of subjects. The most common relevant protocol deviation at study entry (eligibility deviation) was subjects failing to progress or recur after prior platinum treatment (1.1%). The most common relevant protocol deviation during the treatment period was receipt of concurrent anti-cancer therapy (other than palliative limited field radiation therapy or palliative surgical resection), affecting 1.9% of subjects.

Table 9 Relevant Protocol Deviations - All Treated Subjects (Study CA209275)

	Number of Subjects (%)
	All Treated Subjects N = 270
SUBJECTS WITH AT LEAST ONE DEVIATION	9 (3.3)
AT ENTRANCE	
SUBJECTS WITH BASELINE ECOG PERFORMANCE STATUS > 1 (A)	1 (0.4)
SUBJECTS WITHOUT MEASURABLE DISEASE AT BASELINE	0
SUBJECTS WHO DID NOT RECEIVE PRIOR TREATMENT WITH AT LEAST ONE PLATINUM-BASED CHEMOTHERAPY	0
SUBJECTS WHO DID NOT PROGRESS OR DID NOT RECUR AFTER PRIOR PLATINUM TREATMENT (B) (C)	3 (1.1)
ON-TREATMENT DEVIATIONS	
SUBJECTS RECEIVING ANTI-CANCER THERAPY WHILE ON STUDY THERAPY (D)	5 (1.9)

(A) Subject [redacted] had a PS of 3 at Day 1 (first day of dosing). PS at screening was 1. The subject received only 1 dose of nivolumab before discontinuing due to an unrelated event of respiratory failure.
(B) Includes 1 subject without recurrence after prior platinum therapy and 2 subjects who recurred more than 12 months after prior platinum treatment in neo/adjuvant settings
(C) One subject [redacted] did not have a progression date reported that was associated with a prior platinum regimen, but did progress after a prior regimen within the protocol defined window from last dose of platinum, and is therefore not a deviation.
(D) Subject [redacted] no longer considered a deviation since Fluorouracil was administered as a topical cream. Subject [redacted] no longer considered a deviation because antineoplastic agent was started after last dose of nivolumab, but deviation algorithm is based on investigator-reported date of decision to discontinue nivolumab treatment.

Baseline data

Demographic and baseline disease characteristics are shown in Table 10 and Table 11, respectively.

Table 10 Baseline Demographic Characteristics - All Treated Subjects (Study CA209275)

	All Treated Subjects N = 270
AGE (YEARS)	
N	270
MEAN	65.0
MEDIAN	66.0
MIN , MAX	38 , 90
STANDARD DEVIATION	9.38
AGE CATEGORIZATION (%)	
< 65	122 (45.2)
>= 65 AND < 75	110 (40.7)
>= 75 AND < 85	35 (13.0)
>= 85	3 (1.1)
>= 75	38 (14.1)
>= 65	148 (54.8)
GENDER (%)	
MALE	211 (78.1)
FEMALE	59 (21.9)
RACE (%)	
WHITE	231 (85.6)
BLACK OR AFRICAN AMERICAN	2 (0.7)
ASIAN	30 (11.1)
AMERICAN INDIAN OR ALASKA NATIVE	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0
OTHER	3 (1.1)
NOT REPORTED	4 (1.5)
ETHNICITY (%)	
HISPANIC OR LATINO	2 (0.7)
NOT HISPANIC OR LATINO	156 (57.8)
NOT REPORTED	112 (41.5)
REGION	
US	106 (39.3)
JAPAN	23 (8.5)
ROW	141 (52.2)

Table 11 Baseline Disease Characteristics and Tumour Assessments- All Treated Subjects (Study CA209275)

	All Treated Subjects N = 270
CURRENT (STUDY ENTRY) DIAGNOSIS TUMOR TYPE (%)	
URINARY BLADDER	197 (73.0)
RENAL PELVIS	46 (17.0)
URETER	19 (7.0)
URETHRA	8 (3.0)
CURRENT (STUDY ENTRY) DISEASE SETTING (%)	
METASTATIC	261 (96.7)
LOCALLY UNRESECTABLE/NON-METASTATIC	9 (3.3)
PERFORMANCE STATUS (ECOG) [%]	
0	145 (53.7)
1	124 (45.9)
3	1 (0.4)
BASELINE LIVER METASTASIS (A)	
YES	75 (27.8)
NO	195 (72.2)
BASELINE VISCERAL METASTASIS (A) (B)	
YES	227 (84.1)
NO	43 (15.9)
BASELINE LYMPH NODE ONLY (A)	
YES	43 (15.9)
NO	227 (84.1)
BASELINE CNS METASTASIS (A) (C)	
YES	1 (0.4)
NO	269 (99.6)
BASELINE HEMOGLOBIN	
<10 G/DL	48 (17.8)
>=10 G/DL	222 (82.2)
BASELINE CREATININE CLEARANCE	
<30 ML/MIN	5 (1.9)
30- <60 ML/MIN	102 (37.8)
>=60 ML/MIN	162 (60.0)
NOT REPORTED	1 (0.4)
SMOKING STATUS	
CURRENT/FORMER	194 (71.9)
NEVER SMOKED	67 (24.8)
UNKNOWN	9 (3.3)
NUMBER OF BELLMUNT RISK FACTORS	
0	98 (36.3)
1	111 (41.1)
2	46 (17.0)
3	15 (5.6)

	All Treated Subjects N = 270
SUBJECTS WITH AT LEAST ONE LESION (E) (%)	270 (100.0)
SITE OF LESION (D) (E) (%)	
ABDOMINAL WALL	3 (1.1)
ADRENAL GLAND	28 (10.4)
BLADDER	29 (10.7)
BONE	50 (18.5)
BRAIN	1 (0.4)
CHEST WALL	2 (0.7)
DIAPHRAGM	1 (0.4)
KIDNEY	12 (4.4)
LIVER	75 (27.8)
LUMBAR VERTEBRA	3 (1.1)
LUNG	130 (48.1)
LYMPH NODE	171 (63.3)
MESENTERY	2 (0.7)
MUSCLE	5 (1.9)
OTHER	1 (0.4)
PANCREAS	2 (0.7)
PELVIS	30 (11.1)
PERITONEUM	15 (5.6)
PLEURA	11 (4.1)
PUBIC BONE	6 (2.2)
RECTUM	1 (0.4)
RETROPERITONEUM	10 (3.7)
SKIN	1 (0.4)
SOFT TISSUE	7 (2.6)
SPLEEN	2 (0.7)
URETER	1 (0.4)
NUMBER OF SITES WITH AT LEAST ONE LESION (E) (%)	
1	85 (31.5)
2	94 (34.8)
3	51 (18.9)
4	29 (10.7)
>=5	11 (4.1)
SUBJECTS WITH AT LEAST ONE TARGET LESION (%)	247 (91.5)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)	
MEDIAN (MIN - MAX)	61.0 (12 - 252)

(A) per BIRC assessment
(B) No if subject has lymph node only lesions and/or lesions only located in bladder, ureter, urethra and renal pelvis
(C) per protocol, MRI brain prior to first dose was required for subjects with history of brain metastasis
(D) Subjects may have lesions at more than one site
(E) Includes both target and non-target lesions

Prior cancer therapies of all treated subjects are included in Table 12

Table 12 Prior Cancer Therapy Summary - All Treated Subjects (Study CA209275)

	All Treated Subjects N = 270
SUBJECTS WITH PRIOR REGIMEN IN METASTATIC DISEASE SETTING (%)	193 (71.5)
NUMBER OF PRIOR SYSTEMIC REGIMEN IN METASTATIC SETTING	
0	77 (28.5)
1	114 (42.2)
2	57 (21.1)
>=3	22 (8.1)
SUBJECTS WITH PRIOR REGIMEN IN ADJUVANT THERAPY SETTING (%)	83 (30.7)
SUBJECTS WITH PRIOR REGIMEN IN NEO-ADJUVANT THERAPY SETTING (%)	60 (22.2)
PRIOR PLATINUM CONTAINING REGIMEN IN ANY SETTING	270 (100.0)
PRIOR PLATINUM DRUGS IN METASTATIC SETTING	179 (66.3)
CISPLATIN ONLY	98 (36.3)
CARBOPLATIN ONLY	61 (22.6)
BOTH CISPLATIN AND CARBOPLATIN	20 (7.4)
OTHER	0
SUBJECTS WITH PRIOR PLATINUM CONTAINING REGIMEN ASSOCIATED WITH RECURRENCE/PROGRESSION	269 (99.6)
MOST RECENT PRIOR PLATINUM CONTAINING REGIMEN ASSOCIATED WITH RECURRENCE/PROGRESSION	
RECEIVED IN NEO-ADJUVANT OR ADJUVANT SETTING (A)	92 (34.2)
TIMING OF RECURRENCE/PROGRESSION:	
INDETERMINATE	1 (0.4)
RECURRENCE/PROGRESSION MORE THAN 12 MO OF LAST DOSE	2 (0.7)
RECURRENCE/PROGRESSION WITHIN 12 MO OF LAST DOSE	89 (33.1)
PLATINUM DRUGS:	
BOTH CISPLATIN AND CARBOPLATIN	0
CARBOPLATIN ONLY	18 (6.7)
CISPLATIN ONLY	74 (27.5)
OTHER	0
RECEIVED IN METASTATIC SETTING (A)	177 (65.8)
PLATINUM DRUGS:	
BOTH CISPLATIN AND CARBOPLATIN	1 (0.4)
CARBOPLATIN ONLY	71 (26.4)
CISPLATIN ONLY	105 (39.0)
OTHER	0
TIME BETWEEN LAST DOSE OF MOST RECENT PRIOR PLATINUM CONTAINING REGIMEN TO RECURRENCE/PROGRESSION (MONTHS) (A)	
< 3 MONTHS	158 (58.7)
3 -< 6 MONTHS	57 (21.2)
6 -< 12 MONTHS	39 (14.5)
>= 12 MONTHS	15 (5.6)
PRIOR SURGERY RELATED TO CANCER	
YES	250 (92.6)
NO	20 (7.4)
PRIOR RADIOTHERAPY	
YES	85 (31.5)
NO	185 (68.5)

(A) percentages based on subjects with prior platinum containing regimen associated with recurrence/progression

Table 13 Baseline poor prognostic factors per PD-L1 expression cohort (Study CA209275) (updated efficacy data, DBL 2 Sept 2016)

Baseline poor prognostic factors	PD-L1 < 1% n=146	PD-L1 ≥ 1% n=124	PD-L1 < 5% n=187	PD-L1 ≥ 5% n=81
ECOG PS≥1	74 (50.7)	51 (41.1)	91(48.6)	34 (41.0)
Liver metastasis	44 (30.1)	31 (25.0)	52 (27.8)	23 (27.7)
Hb <10 G/DL	30 (20.5)	18 (14.5)	35 (18.7)	13 (15.7)
Number of Bellmunt risk factors 0 1 2 3	 49 (33.6) 56 (38.4) 31 (21.2) 10 (6.8)	 49 (39.5) 55 (44.5) 15 (12.1) 5 (4.0)	 66 (35.3) 75 (40.1) 35 (18.7) 11 (5.9)	 32 (38.6) 36 (43.4) 11 (13.3) 4 (4.8)

Numbers analysed

The number of subjects included in the population analysis is summarised in Table 10

Table 14 Analysis Populations (Study CA209275)

Population	Number of Subjects
Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS. This is the population for pre-treatment disposition.	386
Treated Subjects: All subjects who received at least one dose of nivolumab. This is the population for baseline demographics and disease characteristics, efficacy, safety, and dosing evaluation.	270
PD-L1 < 1% Subjects : All treated subjects with baseline PD-L1 expression less than 1%	146
PD-L1 ≥ 1% Subjects : All treated subjects with baseline PD-L1 expression greater than or equal to 1%	124
PD-L1 < 5% Subjects: All treated subjects with baseline PD-L1 expression less than 5%	187
PD-L1 ≥ 5% Subjects: All treated subjects with baseline PD-L1 expression greater than or equal to 5%	83

Outcomes and estimation

The efficacy data were provided initially with a minimum follow up of 6 months (Data cutoff 15-Apr-2016; DBL 30-May-2016) and were updated during the procedure with an additional 3 months of follow-up (minimum follow-up of 8.3 months) (Data cutoff 21 July 2016; DBL 2-Sept-2016).

- **Primary endpoint (ORR per BIRC) (DBL 30-May-2016)**

Treatment with nivolumab led to an ORR of 19.6% (95% CI: 15.0, 24.9) in all treated subjects, 23.8% (95% CI: 16.5, 32.3) in PD-L1 ≥1% cohort, and 28.4% (95% CI: 18.9, 39.5) in PDL1 ≥5% cohort (Table 15). Six subjects achieved a CR. The ORR was 16.1% (95% CI: 10.5, 23.1) in PD-L1 <1% cohort and 15.8% (95% CI: 10.8, 21.8) in PD-L1 <5% cohort.

13 additional subjects had unconfirmed responses (1 CR and 12 PRs) per BIRC. Another 3 subjects with confirmed responses of PR had unconfirmed responses of CR.

Table 15 Summary of Efficacy Results All Treated Subjects (study CA209275)

	PD-L1 < 1% N = 143	PD-L1 ≥ 1% N = 122	PD-L1 < 5% N = 184	PD-L1 ≥ 5% N = 81	All Treated Subjects N = 265
Confirmed ORR (CR + PR) per BIRC - Primary Endpoint					
N Responders (%)	23 (16.1)	29 (23.8)	29 (15.8)	23 (28.4)	52 (19.6)
95% CI[a]	(10.5, 23.1)	(16.5, 32.3)	(10.8, 21.8)	(18.9, 39.5)	(15.0, 24.9)
Confirmed ORR (CR + PR) per Investigator - Secondary Endpoint					
N Responders (%)	29 (20.3)	32 (26.2)	35 (19.0)	26 (32.1)	61 (23.0)
95% CI[a]	(14.0, 27.8)	(18.7, 35.0)	(13.6, 25.4)	(22.2, 43.4)	(18.1, 28.6)
DOR per BIRC					
Events/Responders	4/23 (17.4)	6/29 (20.7)	7/29 (24.1)	3/23 (13.0)	10/52 (19.2)
Median (95% CI) Months[b]	N.A. (7.43, N.A.)	N.A. (7.52, N.A.)	7.52 (7.43, N.A.)	N.A.	N.A. (7.43, N.A.)
Min, Max (Months)[c]	1.9+, 9.4+	1.9+, 9.6+	1.9+, 9.4+	1.9+, 9.6+	1.9+, 9.6+
Subjects with Ongoing Response per BIRC, N (%)	19 (82.6)	21 (72.4)	22 (75.9)	18 (78.3)	40 (76.9)
PFS per BIRC - Secondary Endpoint					
N Events (%)	113 (79.0)	88 (72.1)	149 (81.0)	52 (64.2)	201 (75.8)
Median (95% CI) Months[b]	1.87 (1.77, 2.04)	3.55 (1.94, 3.71)	1.87 (1.81, 2.10)	3.71 (1.91, 5.55)	2.00 (1.87, 2.63)
PFS per Investigator - Exploratory Endpoint					
N Events (%)	112 (78.3)	88 (72.1)	146 (79.3)	54 (66.7)	200 (75.5)
Median (95% CI) Months[b]	1.94 (1.81, 2.33)	3.65 (1.94, 5.32)	2.00 (1.87, 2.37)	3.71 (1.87, 5.72)	2.10 (1.87, 2.83)

	PD-L1 < 1% N = 143	PD-L1 ≥ 1% N = 122	PD-L1 < 5% N = 184	PD-L1 ≥ 5% N = 81	All Treated Subjects N = 265
OS - Secondary Endpoint					
N Events (%)	83 (58.0)	52 (42.6)	102 (55.4)	33 (40.7)	135 (50.9)
Median (95% CI) Months[b]	5.95 (4.30, 8.08)	11.30 (8.74, N.A.)	6.24 (5.03, 9.49)	11.30 (9.63, N.A.)	8.74 (6.05, N.A.)
Rate at 6 Months (95% CI)[b]	49.7 (41.2, 57.6)	65.4 (56.2, 73.1)	51.5 (44.0, 58.5)	69.1 (57.8, 78.0)	57.0 (50.7, 62.7)

[a] CR+PR, confidence interval based on the Clopper and Pearson method. RECIST 1.1, confirmation of response required

[b] Kaplan-Meier estimate

[c] Symbol + indicates censored value.

Treated subjects from Japan enrolled after the main enrollment period are excluded.

ORR: objective response rate; CR: complete response; PR: partial response; DOR: duration of response; PFS: progression-free survival; OS: overall survival.

Table 16 Best Overall Response and Objective Response Rate per BIRC Assessment (study CA209275)

	Number or Subjects (%)				
	PD-L1 <1% N = 143	PD-L1 >=1% N = 122	PD-L1 <5% N = 184	PD-L1 >=5% N = 81	All Treated Subjects N =265
BEST OVERALL RESPONSE					
COMPLETE RESPONSE (CR)	1 (0.7)	5 (4.1)	2 (1.1)	4 (4.9)	6 (2.3)
PARTIAL RESPONSE (PR)	22 (15.4)	24 (19.7)	27 (14.7)	19 (23.5)	46 (17.4)
STABLE DISEASE (SD)	25 (17.5)	35 (28.7)	37 (20.1)	23 (28.4)	60 (22.6)
PROGRESSIVE DISEASE (PD)	67 (46.9)	37 (30.3)	83 (45.1)	21 (25.9)	104 (39.2)
UNABLE TO DETERMINE (UTD)	28 (19.6)	21 (17.2)	35 (19.0)	14 (17.3)	49 (18.5)
OBJECTIVE RESPONSE RATE (1) (95% CI)	23/143 (16.1%) (10.5, 23.1)	29/122 (23.8%) (16.5, 32.3)	29/184 (15.8%) (10.8, 21.8)	23/81 (28.4%) (18.9, 39.5)	52/265 (19.6%) (15.0, 24.9)

RECIST 1.1, confirmation of response required
(1) CR+PR, confidence interval based on the Clopper and Pearson method
Treated subjects from Japan enrolled after main enrollment period are excluded

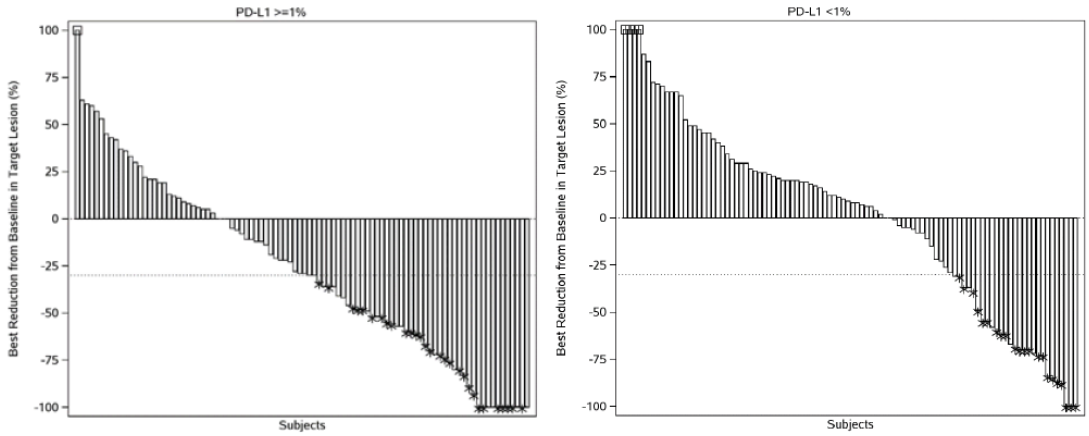


Figure 4 Waterfall Plot of Best Reduction from Baseline in Sum of Diameters of Target Lesions per BIRC Response Evaluable Subjects (study CA209275)

- **Secondary endpoints (DBL 30-May-2016)**

ORR by investigator

Investigator-assessed ORR results are shown in Table 17.

Table 17 Best Overall Response and Objective Response Rate per Investigator - All Treated Subjects (study CA209275)

	Number or Subjects (%)				
	PD-L1 <1% N = 143	PD-L1 >=1% N = 122	PD-L1 <5% N = 184	PD-L1 >=5% N = 81	All Treated Subjects N = 265
BEST OVERALL RESPONSE					
COMPLETE RESPONSE (CR)	2 (1.4)	5 (4.1)	2 (1.1)	5 (6.2)	7 (2.6)
PARTIAL RESPONSE (PR)	27 (18.9)	27 (22.1)	33 (17.9)	21 (25.9)	54 (20.4)
STABLE DISEASE (SD)	24 (16.8)	33 (27.0)	37 (20.1)	20 (24.7)	57 (21.5)
PROGRESSIVE DISEASE (PD)	68 (47.6)	40 (32.8)	83 (45.1)	25 (30.9)	108 (40.8)
UNABLE TO DETERMINE (UTD)	22 (15.4)	17 (13.9)	29 (15.8)	10 (12.3)	39 (14.7)
NEVER TREATED	0	0	0	0	0
WRONG CANCER DIAGNOSIS	0	0	0	0	0
DEATH PRIOR TO DISEASE ASSESSMENT	21 (14.7)	15 (12.3)	26 (14.1)	10 (12.3)	36 (13.6)
EARLY DISCONTINUATION DUE TO TOXICITY	1 (0.7)	1 (0.8)	2 (1.1)	0	2 (0.8)
OTHER	0	1 (0.8)	1 (0.5)	0	1 (0.4)
OBJECTIVE RESPONSE RATE (1) (95% CI)	29/143 (20.3%) (14.0, 27.8)	32/122 (26.2%) (18.7, 35.0)	35/184 (19.0%) (13.6, 25.4)	26/81 (32.1%) (22.2, 43.4)	61/265 (23.0%) (18.1, 28.6)

RECIST 1.1, confirmation of response required
(1) CR+PR, confidence interval based on the Clopper and Pearson method
Treated subjects from Japan enrolled after main enrollment period are excluded
Source: Table 7.2.2-1 of the CA209275 CSR

Progression-free Survival (PFS) per BIRC

The median PFS was 2.00 months in All Treated subjects, 3.55 months in PD-L1 ≥ 1% cohort, and 3.71 months in PD-L1 ≥ 5% cohort. The median PFS was 1.87 months in both PD-L1 < 1% andPD-L1 < 5% cohorts. 64 (24.2%) subjects were censored. 59 (22.3%) subjects had their PFS time censored on the date of last on-study tumour assessment. The most common reason for censoring among these subjects was 'still on treatment'.

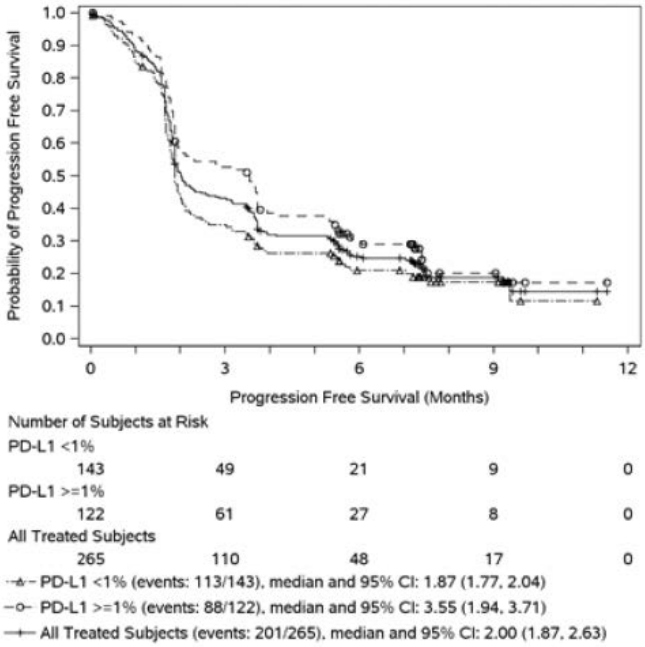


Figure 5 Kaplan-Meier Plot of Progression-free Survival per BIRC – All Treated Subjects (study CA209275)

Overall Survival (OS)

The median OS was 8.74 months (95% CI: 6.05, N.A.) in all treated subjects, 11.30 months (95% CI: 8.74, N.A.) in PD-L1 ≥ 1% cohort, and 11.30 months (95% CI: 9.63, N.A.) inPD-L1 ≥ 5% cohort. The median OS was 5.95 months (95% CI: 4.30, 8.08) in PD L1 < 1% cohort and 6.24 months (95% CI: 5.03, 9.49) in PD L1 < 5% cohort.

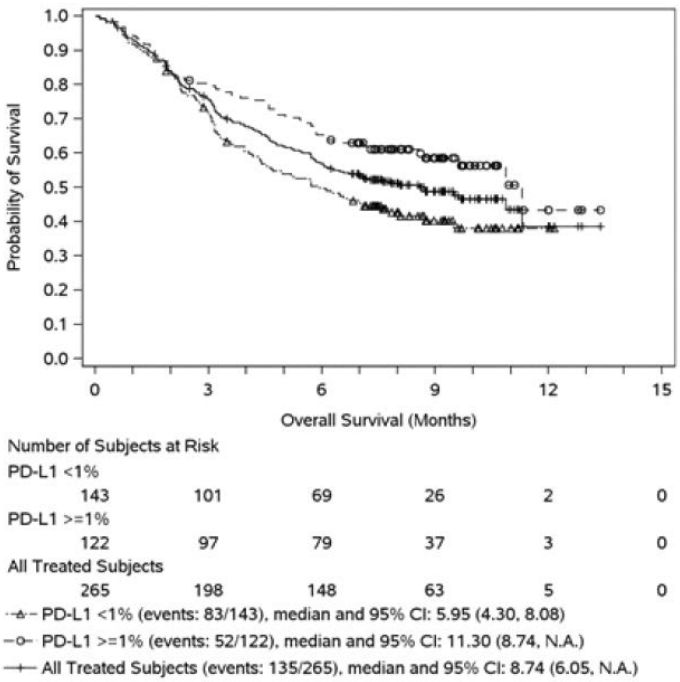


Figure 6 Kaplan-Meier Plot of Overall Survival - All Treated Subjects (study CA209275)

Median follow-up for OS (time between first dose and last known date alive or death) was 7.00 months (range: 0.1 - 13.4 months) among all treated subjects.

Updated data (DBL 2 Sept 2016)

In this updated analysis, all 270 treated subjects were analysed for efficacy, including 5 Japanese subjects excluded from the primary efficacy analysis due to insufficient follow-up. This update of efficacy provides an additional 3 months of follow-up (minimum follow-up of 8.3 months) since the time of the primary analysis for study CA209275.

In the updated analysis, treatment with nivolumab led to an ORR of 20.0% (95% CI: 15.4, 25.3) in all treated subjects, 25.0% (95% CI: 17.7, 33.6) in the PD-L1 ≥1 % cohort, and 30.1% (95% CI: 20.5, 41.2) in the PD-L1 ≥ 5% cohort.

There were 16 additional deaths at the time of this data cut-off. Among all treated subjects, the updated median OS of 8.57 months (95% CI: 6.05, 11.27) was similar to the median OS in the primary analysis (8.74 months [95% CI: 6.05, N.A.]).

More than half (34/54, 63.0%) of the responders had ongoing response at the time of the clinical cut-off for this analysis.

The median DOR was 7.59 months in subjects with PD-L1 expression < 5%, but was not reached in the PD-L1 ≥ 1% or PD-L1 ≥ 5% cohorts.

Table 18 Summary of efficacy results (study CA20275)-updated analysis (DBL 2 Sept 2016)

	PD-L1 < 1% N = 146	PD-L1 ≥ 1% N = 124	PD-L1 < 5% N = 187	PD-L1 ≥ 5% N = 83	All Treated Subjects N = 270
Confirmed ORR (CR + PR) per BIRC - Primary Endpoint					
N Responders (%)	23 (15.8)	31 (25.0)	29 (15.5)	25 (30.1)	54 (20.0)
95% CI[a]	(10.3, 22.7)	(17.7, 33.6)	(10.6, 21.5)	(20.5, 41.2)	(15.4, 25.3)
Confirmed ORR (CR + PR) per Investigator - Secondary Endpoint					
N Responders (%)	28 (19.2)	34 (27.4)	35 (18.7)	27 (32.5)	62 (23.0)
95% CI[a]	(13.1, 26.5)	(19.8, 36.2)	(13.4, 25.1)	(22.6, 43.7)	(18.1, 28.4)
DOR per BIRC					
Events/Responders (%)	10/23 (43.5)	8/31 (25.8)	13/29 (44.8)	5/25 (20.0)	18/54 (33.3)
Median (95% CI) Months[b]	10.35 (7.43, N.A.)	N.A. (7.52, N.A.)	7.59 (7.43, N.A.)	N.A.	10.35 (7.52, N.A.)
Min, Max (Months)[c]	3.7, 12.0+	1.9+, 12.0+	3.7, 12.0+	1.9+, 12.0+	1.9+, 12.0+
Subjects with Ongoing Response per BIRC N (%)	13 (56.5)	21 (67.7)	16 (55.2)	18 (72.0)	34 (63.0)
PFS per BIRC - Secondary Endpoint					
N Events (%)	124 (84.9%)	92 (74.2)	160 (85.6)	56 (67.5)	216 (80.0)
Median (95% CI) Months[b]	1.87 (1.77, 2.04)	3.55 (1.94, 3.71)	1.91 (1.84, 2.10)	3.71 (1.91, 5.55)	2.00 (1.87, 2.63)

	PD-L1 < 1% N = 146	PD-L1 ≥ 1% N = 124	PD-L1 < 5% N = 187	PD-L1 ≥ 5% N = 83	All Treated Subjects N = 270
OS - Secondary Endpoint					
N Events (%)	93 (63.7)	61 (49.2)	114 (61.0)	40 (48.2)	154 (57.0)
Median (95% CI) Months[b]	5.95 (4.37, 8.08)	11.63 (9.10, N.A.)	6.24 (4.96, 8.74)	12.94 (9.63, N.A.)	8.57 (6.05, 11.27)
Rate at 6 months (95% CI)[b]	49.3 (40.9, 57.2)	65.2 (56.1, 72.8)	51.2 (43.7, 58.1)	68.7 (57.5, 77.5)	56.6 (50.5, 62.3)
Rate at 9 months (95% CI)[b]	40.1 (32.1, 48.0)	59.5 (50.3, 67.5)	42.9 (35.6, 49.9)	62.7 (51.3, 72.1)	49.1 (42.9, 54.9)
Rate at 12 months (95% CI)[b]	34.0 (26.1, 42.1)	49.2 (39.6, 58.1)	36.9 (29.7, 44.1)	50.3 (38.3,61.1)	41.0 (34.8, 47.1)

(a) CR+PR, confidence interval based on the Clopper and Pearson method. RECIST 1.1, confirmation of response required
(b) Kaplan-Meier estimate
(c) Symbol + indicates censored value.
ORR: objective response rate; CR: complete response; PR: partial response; DOR: duration of response; PFS: progression free survival; OS: overall survival.

Ancillary analyses

ORR - Sensitivity analysis

In one sensitivity analysis, all time point responses contributed to the BOR, regardless of start of subsequent therapy (palliative/curative radiotherapy, surgery or systemic therapy). In this analysis, the ORR was 20.0% (95% CI: 15.4, 25.3) in all treated subjects, 24.6% (95% CI: 17.2, 33.2) in PD-L1 ≥ 1% cohort, and 29.6% (95% CI: 20.0, 40.8) in PD-L1 ≥ 5% cohort. In the other sensitivity analysis, subjects who progressed within 1 month of start of treatment due to new brain lesion without evidence of baseline brain lesion (most subjects did not get baseline brain MRI as it was only required if there was a history of brain metastases), were excluded. In this analysis, the ORR was 19.9% (95% CI: 15.3, 25.3) in all treated subjects, 23.8% (95% CI: 16.5, 32.3) in PD-L1 ≥ 1% cohort and 28.4% (95% CI: 18.9, 39.5) in PD-L1 ≥ 5% cohort.

PFS - Sensitivity analysis

In one sensitivity analysis, tumour assessments, progression or death that occurred after anti-cancer therapy (palliative/curative radiotherapy, surgery or systemic therapy) were taken into account. In this analysis, the median PFS was 2.00 months in all treated subjects, 3.52 months in PD-L1 ≥ 1% cohort, and 3.71 months in PD-L1 ≥ 5% cohort.

In the other sensitivity analysis, subjects who progressed within 1 month of start of treatment due to new brain lesion, without evidence of baseline brain lesion (most subjects did not get baseline brain MRI as it was only required if there was a history of brain metastases), were excluded. In this analysis, the median PFS was 2.04 months in all treated subjects, 3.55 months in PD-L1 ≥ 1% cohort, and 3.71 months in PD-L1 ≥ 5% cohort

The median PFS per investigator was 2.10 months (95% CI: 1.87, 2.83) in all treated subjects, 3.65 months (95% CI: 1.94, 5.32) in PD-L1 ≥ 1% cohort, and 3.71 months (95% CI: 1.87, 5.72)in PD-L1 ≥ 5% cohort. The median PFS per investigator was 1.94 months (95% CI: 1.81, 2.33) in PD-L1 < 1% cohort, and 2.00 months (95% CI: 1.87, 2.37) in PD-L1 < 5% cohort.

Subjects treated beyond investigator-assessed progression

A total of 26.4% (70/265) of treated subjects received at least one dose after initial RECIST v1.1-defined progression. Treatment beyond progression was defined as a last dosing date after a RECIST v1.1-defined progression date. Of the 70 subjects treated beyond progression, 24 were considered non-conventional benefiters, defined as subjects who had not experienced a BOR of PR/CR prior to initial RECIST v1.1-defined progression.

Time to and Duration of Response (TTR and DOR) per BIRC

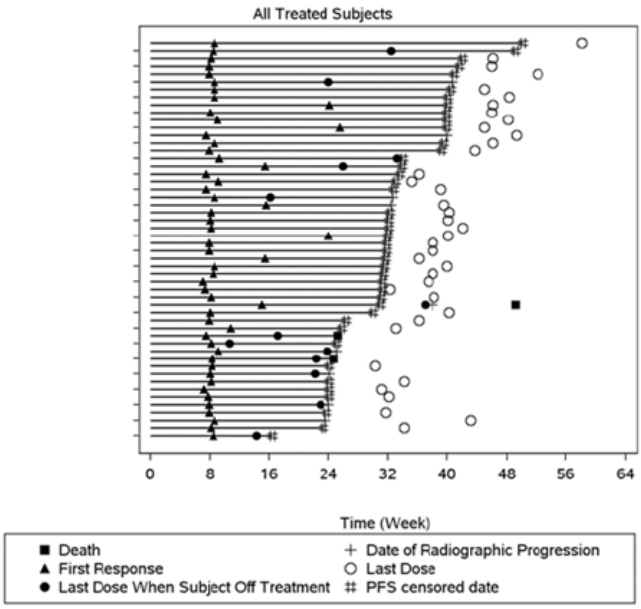
TTR and DOR were estimated in subjects with confirmed PR + CR and shown in Table 19.

The median DOR per BIRC was not reached in all treated subjects; the median DOR was 7.52 months in subjects with PD-L1 expression < 5% but was not reached in the remaining 3 PD-L1 cohorts. Most (40/52, 76.9%) of the responders were still continuing in response at the time of database lock, with nearly all (96.2%) having a DOR of at least 3 months. Ongoing response includes responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excluded responders censored prior to 12 weeks of the clinical data cutoff date.

Table 19 Time to Objective Response and Duration of Response per BIRC - All Treated Subjects (study CA209275) (DBL 30-May-2016)

	PD-L1 <1% N = 23	PD-L1 >=1% N = 29	PD-L1 <5% N = 29	PD-L1 >=5% N = 23	All Treated Subjects N = 52
TIME TO RESPONSE (MONTHS)					
NUMBER OF RESPONDERS	23	29	29	23	52
MEAN	2.32	2.15	2.28	2.16	2.23
MEDIAN	1.94	1.87	1.91	1.87	1.87
MIN, MAX	1.6, 5.9	1.6, 5.6	1.6, 5.9	1.6, 5.6	1.6, 5.9
Q1, Q3	1.81, 2.10	1.81, 1.97	1.81, 2.10	1.81, 1.97	1.81, 1.97
STANDARD DEVIATION	1.133	0.840	1.055	0.881	0.974
DURATION OF RESPONSE (MONTHS)					
MIN, MAX (A)	1.9+, 9.4+	1.9+, 9.6+	1.9+, 9.4+	1.9+, 9.6+	1.9+, 9.6+
MEDIAN (95% CI) (B)	N.A. (7.43, N.A.)	N.A. (7.52, N.A.)	7.52 (7.43, N.A.)	N.A.	N.A. (7.43, N.A.)
N EVENT/N RESP (%)	4/23 (17.4)	6/29 (20.7)	7/29 (24.1)	3/23 (13.0)	10/52 (19.2)
SUBJECTS WITH ONGOING RESPONSE (C)	19 (82.6)	21 (72.4)	22 (75.9)	18 (78.3)	40 (76.9)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)					
3 MONTHS	22 (95.7)	28 (96.6)	28 (96.6)	22 (95.7)	50 (96.2)
6 MONTHS	7 (30.4)	7 (24.1)	10 (34.5)	4 (17.4)	14 (26.9)
12 MONTHS	0	0	0	0	0

(A) Symbol + indicates a censored value
(B) Median computed using Kaplan-Meier method.
(C) Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis, and excludes responders censored prior to 12 weeks of the clinical data cutoff date
Treated subjects from Japan enrolled after main enrollment period are excluded



Bar indicates progression free survival.
Response and progression as assessed per BIRC.
RECIST 1.1 Response Criteria where confirmation of response is required. Horizontal axis origin corresponds to first dose date.
Treated subjects from Japan enrolled after main enrollment period are excluded.

Figure 7 Event Chart for Tumour Response per BIRC - Responders among all treated subjects (study CA209275)

Concordance between BIRC and investigator assessments

The concordance rate of responders between IRRC and investigator assessments was 92.8%. Concordance rates were similar observed for all 4 PD-L1 cohorts (88.9% - 95.8%), as shown in Table 20

Table 20 Concordance rate of responders between IRRC and investigator assessments (study CA209275)

Cohort: All Treated Subjects

	Number of Subjects (%)		
	BIRC ASSESSMENT		
	RESPONDER	NON-RESPONDER	UTD
INVESTIGATOR ASSESSMENT			
RESPONDERS	47 (17.7)	14 (5.3)	0
NON-RESPONDERS	5 (1.9)	146 (55.1)	14 (5.3)
UTD	0	4 (1.5)	35 (13.2)
CONCORDANCE RATE OF RESPONDERS (1):		92.8 %	

Responders: Subjects with confirmed PR/CR. UTD: Unable to Determine
(1) Quantifies the frequency with which INV and IRC agreed on classification of a subject as responder vs. non-responder/UTD as a proportion of the total number of subjects assessed by both the investigator and BIRC
Treated subjects from Japan enrolled after main enrollment period are excluded

Overall Survival and subsequent cancer therapy

Subsequent cancer therapy was received by 19.6% of all treated subjects. Subsequent systemic therapy was received by 9.8% of subjects; the most common was gemcitabine (3.8%), followed by carboplatin, cisplatin, and paclitaxel (1.9% each).

Table 21 Subsequent Cancer Therapy Summary - All Treated Efficacy Subjects (study CA209275) (DBL 30-May-2016)

	Number of Subjects (%)
	All Treated Subjects (Efficacy) N = 265
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	52 (19.6)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	25 (9.4)
CURATIVE	2 (0.8)
PALLIATIVE	23 (8.7)
OTHER	0
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	8 (3.0)
TUMOR RESECTION, CURATIVE	2 (0.8)
TUMOR RESECTION, PALLIATIVE	6 (2.3)
FINE NEEDLE ASPIRATION	0
INCISIONAL BIOPSY	0
EXCISIONAL BIOPSY	0
FLUID ASPIRATION	0
OTHER	0
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	26 (9.8)
IMMUNOTHERAPY (2)	0
OTHER SYSTEMIC CANCER THERAPY - EXPERIMENTAL DRUGS	3 (1.1)
INVESTIGATIONAL ANTINEOPLASTIC	3 (1.1)
OTHER SYSTEMIC CANCER THERAPY - CHEMOTHERAPY	25 (9.4)
CARBOPLATIN	5 (1.9)
CISPLATIN	5 (1.9)
CYCLOPHOSPHAMIDE	1 (0.4)
DOCETAXEL	4 (1.5)
DOXORUBICIN	1 (0.4)
EVEROLIMUS	1 (0.4)
GEMCITABINE	10 (3.8)
METHOTREXATE	2 (0.8)
NIVOLUMAB (3)	2 (0.8)
PACLITAXEL	5 (1.9)
PEMETREXED	2 (0.8)
TRAMETINIB	1 (0.4)
VINBLASTINE	1 (0.4)
VINCRISTINE	1 (0.4)
VINFLUNINE	4 (1.5)

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date.
(2)Two subjects [redacted] and [redacted] received immunotherapy, see Nivolumab listing under chemotherapy category.
(3) Nivolumab treatment should be listed under immunotherapy. These subjects [redacted] and [redacted] also received chemotherapy so the number of subjects receiving chemotherapy remains at 25.
Treated subjects from Japan enrolled after main enrollment period are excluded

Updated analysis (DBL 02-Sep-2016)

As of database lock on 02-Sep-2016, 54 (20%) subjects received subsequent therapy with 28 (10.4%) receiving systemic anticancer therapy, most of which was chemotherapy, and 25 (9.3%) receiving radiation therapy, most of which was palliative. The median time for starting subsequent therapy was 3.98 months (range 0.5, 11.1).

Median overall survival (mOS) in subjects not receiving subsequent therapy (N=216) was 6.47 (95% CI: 4.76, 9.99) months, lower than in the all treated population (mOS 8.57 [95% CI: 6.05, 11.27]). Despite the lower mOS in patients not receiving subsequent therapy in CA209275, the 1-year OS rate of 41% (95% CI: 34.3, 47.6) was similar to the 1-year OS rate in the all treated population of 41% (95% CI: 34.8, 47.1).

Subgroup analysis

- **ORR per BIRC in key subpopulations**

Table 22 Objective Response Rate per BIRC in Key Subpopulations (study CA209275) (DBL 30-May-2016)

	Objective Response Rate (%) (95% CI) (a)	
	All Treated Subjects N = 265	
All Treated Subjects	**52/265 (19.6%)**	**(15.0, 24.9)**
AGE CATEGORIZATION 1		
< 65	16/119 (13.4%)	(7.9, 20.9)
>= 65 AND < 75	24/109 (22.0%)	(14.6, 31.0)
>= 75	12/37 (32.4%)	(18.0, 49.8)
REGION		
US	24/106 (22.6%)	(15.1, 31.8)
JAPAN	3/18 (16.7%)	(3.6, 41.4)
ROW	25/141 (17.7%)	(11.8, 25.1)
GENDER		
MALE	41/207 (19.8%)	(14.6, 25.9)
FEMALE	11/58 (19.0%)	(9.9, 31.4)
BASELINE ECOG PERFORMANCE STATUS		
0	32/141 (22.7%)	(16.1, 30.5)
1	20/123 (16.3%)	(10.2, 24.0)
BASELINE LIVER METASTASES (IRC)		
YES	8/74 (10.8%)	(4.8, 20.2)
NO	44/191 (23.0%)	(17.3, 29.7)
BASELINE VISCERAL METASTASES (IRC)		
YES	35/223 (15.7%)	(11.2, 21.1)
NO	17/42 (40.5%)	(25.6, 56.7)
BASELINE LYMPH NODE ONLY (IRC)		
YES	17/42 (40.5%)	(25.6, 56.7)
NO	35/223 (15.7%)	(11.2, 21.1)
BASELINE HEMOGLOBIN		
<10 G/DL	8/46 (17.4%)	(7.8, 31.4)
>=10 G/DL	44/219 (20.1%)	(15.0, 26.0)

	Objective Response Rate (%) (95% CI) (a)	
	All Treated Subjects N = 265	
NUMBER OF PRIOR REGIMEN IN METASTATIC SETTING		
0	18/77 (23.4%)	(14.5, 34.4)
1	19/112 (17.0%)	(10.5, 25.2)
2	10/54 (18.5%)	(9.3, 31.4)
>=3	5/22 (22.7%)	(7.8, 45.4)
TIME FROM COMPLETION OF MOST RECENT PRIOR REGIMEN TO STUDY TREATMENT		
< 3 MONTHS	18/110 (16.4%)	(10.0, 24.6)
3 -< 6 MONTHS	14/70 (20.0%)	(11.4, 31.3)
>= 6 MONTHS	20/85 (23.5%)	(15.0, 34.0)
NUMBER OF BELLMUNT RISK FACTORS		
0	24/96 (25.0%)	(16.7, 34.9)
1	21/109 (19.3%)	(12.3, 27.9)
2	6/45 (13.3%)	(5.1, 26.8)
3	1/15 (6.7%)	(0.2, 31.9)
BASELINE CREATININE CLEARANCE		
<30 ML/MIN	1/5 (20.0%)	(0.5, 71.6)
30- <60 ML/MIN	20/99 (20.2%)	(12.8, 29.5)
>=60 ML/MIN	30/160 (18.8%)	(13.0, 25.7)
NOT REPORTED	1/1 (100.0%)	(2.5, 100.0)
SUBSET OF INITIAL TUMOR ORIGIN		
URINARY BLADDER	41/190 (21.6%)	(16.0, 28.1)
RENAL PELVIS, URETER	7/65 (10.8%)	(4.4, 20.9)

(a) CR+PR as per RECIST 1.1 criteria confirmation of response required (BIRC Assessment), confidence interval based on the Clopper and Pearson method.
Treated subjects from Japan enrolled after main enrollment period are excluded.
Source: Table 7.2.1.3-1 of the CA209275 CSR

- **Overall Survival in pre-defined subsets**

Table 23: Overall Survival and survival rates in pre-defined subsets - Summary – All treated subjects

	Overall Survival in Pre-Defined Subsets Summary All Treated Subjects	
	PD-L1 <1% N = 146	PD-L1 >=1% N = 124
BASELINE ECOG PERFORMANCE STATUS		
0		
# EVENTS / # SUBJECTS (%)	36/72 (50.0)	30/73 (41.1)
MEDIAN OS (MONTHS) (1) (95% CI)	11.10 (6.57, N.A.)	N.A. (9.69, N.A.)
1		
# EVENTS / # SUBJECTS (%)	56/73 (76.7)	31/51 (60.8)
MEDIAN OS (MONTHS) (1) (95% CI)	3.15 (2.76, 4.17)	9.10 (4.80, 11.63)
BASELINE LIVER METASTASES (IRC)		
YES		
# EVENTS / # SUBJECTS (%)	36/45 (80.0)	21/32 (65.6)
MEDIAN OS (MONTHS) (1) (95% CI)	2.92 (2.23, 3.15)	9.33 (2.04, 12.94)
NO		
# EVENTS / # SUBJECTS (%)	57/101 (56.4)	40/92 (43.5)
MEDIAN OS (MONTHS) (1) (95% CI)	8.74 (6.11, N.A.)	N.A. (9.63, N.A.)

Overall Survival in Pre-Defined Subsets Summary
All Treated Subjects

	PD-L1 <1% N = 146	PD-L1 >=1% N = 124
BASELINE VISCERAL METASTASES (IRC)		
YES		
# EVENTS / # SUBJECTS (%)	84/123 (68.3)	55/101 (54.5)
MEDIAN OS (MONTHS) (1) (95% CI)	4.96 (3.94, 6.74)	10.87 (6.31, N.A.)
NO		
# EVENTS / # SUBJECTS (%)	9/23 (39.1)	6/23 (26.1)
MEDIAN OS (MONTHS) (1) (95% CI)	N.A. (6.47, N.A.)	N.A.
BASELINE LYMPH NODE ONLY (IRC)		
YES		
# EVENTS / # SUBJECTS (%)	9/23 (39.1)	6/23 (26.1)
MEDIAN OS (MONTHS) (1) (95% CI)	N.A. (6.47, N.A.)	N.A.
NO		
# EVENTS / # SUBJECTS (%)	84/123 (68.3)	55/101 (54.5)
MEDIAN OS (MONTHS) (1) (95% CI)	4.96 (3.94, 6.74)	10.87 (6.31, N.A.)

Overall Survival in Pre-Defined Subsets Summary
All Treated Subjects

	PD-L1 <1% N = 146	PD-L1 >=1% N = 124
TIME FROM COMPLETION OF MOST RECENT PRIOR REGIMEN TO STUDY TREATMENT		
< 3 MONTHS		
# EVENTS / # SUBJECTS (%)	40/58 (69.0)	33/54 (61.1)
MEDIAN OS (MONTHS) (1) (95% CI)	4.53 (3.15, 7.85)	6.31 (4.60, 12.94)
3 -< 6 MONTHS		
# EVENTS / # SUBJECTS (%)	31/45 (68.9)	8/28 (28.6)
MEDIAN OS (MONTHS) (1) (95% CI)	4.96 (3.65, 8.08)	N.A. (11.43, N.A.)
>= 6 MONTHS		
# EVENTS / # SUBJECTS (%)	22/43 (51.2)	20/42 (47.6)
MEDIAN OS (MONTHS) (1) (95% CI)	11.10 (4.63, N.A.)	N.A. (5.85, N.A.)

Overall Survival in Pre-Defined Subsets Summary
All Treated Subjects

	PD-L1 <1% N = 146	PD-L1 >=1% N = 124
NUMBER OF HELLMUNT RISK FACTORS		
0		
# EVENTS / # SUBJECTS (%)	19/48 (39.6)	15/49 (30.6)
MEDIAN OS (MONTHS) (1) (95% CI)	N.A. (9.00, N.A.)	N.A.
1		
# EVENTS / # SUBJECTS (%)	39/57 (68.4)	33/54 (61.1)
MEDIAN OS (MONTHS) (1) (95% CI)	5.72 (4.07, 8.57)	9.56 (5.78, 12.94)
2		
# EVENTS / # SUBJECTS (%)	25/31 (80.6)	10/16 (62.5)
MEDIAN OS (MONTHS) (1) (95% CI)	3.15 (2.20, 3.32)	10.20 (1.45, N.A.)
3		
# EVENTS / # SUBJECTS (%)	10/10 (100.0)	3/5 (60.0)
MEDIAN OS (MONTHS) (1) (95% CI)	2.27 (0.30, 3.12)	N.R.

Survival Rate (95% CI)	PD-L1 <1% (N=146)	PD-L1 >=1% (N=124)

BASELINE HEMOGLOBIN		
<10 G/DL		
# EVENTS / # SUBJECTS (%)	26/30 (86.7)	10/18 (55.6)
3-MONTH	66.7 (46.9, 80.5)	61.1 (35.3, 79.2)
6-MONTH	24.6 (10.9, 41.1)	50.0 (25.9, 70.1)
9-MONTH	17.5 (6.4, 33.2)	50.0 (25.9, 70.1)
12-MONTH	9.4 (1.9, 24.1)	37.5 (12.7, 62.8)
>=10 G/DL		
# EVENTS / # SUBJECTS (%)	67/116 (57.8)	51/106 (48.1)
3-MONTH	73.2 (64.1, 80.3)	83.0 (74.4, 88.9)
6-MONTH	55.6 (46.0, 64.1)	67.7 (57.9, 75.8)
9-MONTH	45.8 (36.5, 54.7)	61.1 (51.1, 69.6)
12-MONTH	40.4 (31.1, 49.5)	50.7 (40.4, 60.2)
BASELINE ECOG PERFORMANCE STATUS		
0		
# EVENTS / # SUBJECTS (%)	36/72 (50.0)	30/73 (41.1)
3-MONTH	86.1 (75.7, 92.3)	83.6 (72.9, 90.3)
6-MONTH	67.8 (55.6, 77.3)	69.9 (57.9, 79.0)
9-MONTH	55.1 (42.8, 65.7)	65.8 (53.7, 75.4)
12-MONTH	48.8 (36.6, 59.9)	59.4 (47.0, 69.9)
1		
# EVENTS / # SUBJECTS (%)	56/73 (76.7)	31/51 (60.8)
3-MONTH	58.5 (46.3, 68.9)	74.5 (60.1, 84.3)
6-MONTH	31.4 (21.0, 42.3)	58.4 (43.6, 70.5)
9-MONTH	25.5 (16.1, 36.1)	50.3 (35.9, 63.1)
12-MONTH	19.2 (10.4, 30.0)	36.0 (22.5, 49.8)
BASELINE LIVER METASTASES (IRC)		
YES		
# EVENTS / # SUBJECTS (%)	36/45 (80.0)	21/32 (65.6)
3-MONTH	48.2 (32.9, 61.9)	65.6 (46.6, 79.3)
6-MONTH	22.9 (11.9, 36.1)	56.3 (37.6, 71.3)
9-MONTH	18.4 (8.6, 31.0)	53.1 (34.7, 68.5)
12-MONTH	18.4 (8.6, 31.0)	34.0 (17.3, 51.6)
NO		
# EVENTS / # SUBJECTS (%)	57/101 (56.4)	40/92 (43.5)
3-MONTH	82.2 (73.2, 88.4)	84.8 (75.6, 90.7)
6-MONTH	60.9 (50.6, 69.7)	68.3 (57.6, 76.7)
9-MONTH	49.6 (39.5, 59.0)	61.6 (50.9, 70.7)
12-MONTH	40.7 (30.6, 50.7)	54.6 (43.4, 64.5)
BASELINE VISCERAL METASTASES (IRC)		
YES		
# EVENTS / # SUBJECTS (%)	84/123 (68.3)	55/101 (54.5)
3-MONTH	70.6 (61.7, 77.8)	78.2 (68.8, 85.1)
6-MONTH	44.6 (35.6, 53.2)	62.2 (51.9, 70.8)
9-MONTH	35.3 (26.8, 43.8)	56.1 (45.9, 65.2)
12-MONTH	28.6 (20.4, 37.3)	43.3 (32.8, 53.4)
NO		
# EVENTS / # SUBJECTS (%)	9/23 (39.1)	6/23 (26.1)
3-MONTH	78.3 (55.4, 90.3)	87.0 (64.8, 95.6)
6-MONTH	73.9 (50.9, 87.3)	78.3 (55.4, 90.3)
9-MONTH	65.2 (42.3, 80.8)	73.9 (50.9, 87.3)
12-MONTH	60.9 (38.3, 77.4)	73.9 (50.9, 87.3)
NUMBER OF BELLMONT RISK FACTORS		
0		
# EVENTS / # SUBJECTS (%)	19/48 (39.6)	15/49 (30.6)
3-MONTH	89.6 (76.8, 95.5)	89.8 (77.2, 95.6)
6-MONTH	78.9 (64.3, 88.1)	75.5 (60.9, 85.3)
9-MONTH	66.1 (50.8, 77.7)	71.4 (56.6, 82.0)
12-MONTH	58.8 (43.1, 71.6)	69.4 (54.4, 80.3)
1		
# EVENTS / # SUBJECTS (%)	39/57 (68.4)	33/54 (61.1)
3-MONTH	73.7 (60.2, 83.2)	77.7 (64.1, 86.7)
6-MONTH	47.4 (34.0, 59.6)	60.7 (46.3, 72.3)
9-MONTH	36.6 (24.3, 49.0)	51.2 (37.1, 63.6)
12-MONTH	29.8 (18.0, 42.5)	38.5 (25.2, 51.6)
2		
# EVENTS / # SUBJECTS (%)	25/31 (80.6)	10/16 (62.5)
3-MONTH	53.7 (34.6, 69.5)	68.8 (40.5, 85.6)
6-MONTH	21.5 (8.8, 37.8)	56.3 (29.5, 76.2)
9-MONTH	17.9 (6.6, 33.7)	56.3 (29.5, 76.2)
12-MONTH	13.4 (3.9, 29.0)	25.0 (4.7, 53.3)

- **Subgroup analysis by Bellmunt risk factors (pre-defined subsets)**

Established poor prognostic factors in patients with advanced urothelial carcinoma who have failed platinum-containing regimens include ECOG performance status (PS) more than 0, Hb level < 10 g/dL, and the presence of liver metastasis. A scoring system which groups patients into four categories representing the presence of 0, 1, 2, and 3 of these Bellmunt risk factors has also been established.

Table 24: Efficacy by Bellmunt risk Factors – all treated subjects CA209275 (updated analysis DBL 2 Sept 2016)

Number of Bellmunt Risk Factors	ORR (%) 95% CI N=270	Median PFS (months) 95% CI N=270	Median OS (months) 95% CI N=270
0	26/97 (26.8%) (18.3, 36.8)	3.65 (2.10, 5.32)	NA
1	20/111 (18.0%) (11.4, 26.4)	1.91 (1.81, 2.23)	7.03 (5.42, 9.69)
2	7/47 (14.9%) (6.2, 28.3)	1.87 (1.58, 3.02)	3.22 (2.66, 5.03)
3	1/15 (6.7%) (0.2, 31.9)	1.07 (0.46, 1.81)	2.23 (0.69, 3.12)

Abbreviations: ORR: objective respoonse rate; PFS: progression-free survival; OS: overall survival; CI: confidence interval; NA: not available

Source: Table S.5.13, Table S.5.14, and Table S.5.23 of Addendum 01 of the CA209275 CSR

- **Subgroup analysis for prior regimens in metastatic setting and time from prior regime (pre-defined subset)**

Table 25 Subgroup analyses for prior regimens in metastatic setting and time from prior regime for ORR, PFS and OS (study CA20275)

	ORR	PFS	OS
The influence of time from completion of most recent prior regimen to study treatment.			
< 3 months *(n=110)*	16.4 (CI 10-24.6)	1.87 (CI 1.77-2.04)	5.95 (CI 4.30-8.74)
3-6 months *(n=70)*	20.0 (CI 11.4-31.3)	3.52 (CI 1.81-3.71)	9.49 (CI 6.24- NA)
≥ 6 months *(n=85)*	23.5 (CI 15-34)	2.79 (CI 1.91-3.65)	11.30 (CI 5.85-NA)
Number of prior regimens in metastatic setting			
0 *(n=77)*	23.4 (CI 14.5-34.4)	1.97 (CI 1.77-3.15)	7.62 (CI 4.63-NA)
1 *(n=112)*	17.0 (CI 10.5-25.2)	2.00 (CI 1.87-3.45)	NA (CI 5.68-NA)
2 *(n=54)*	18.5 (CI 9.3-31.4)	1.97 (CI 1.77-3.71)	9.63 (CI 5.03-NA)
≥ 3 *(n=22)*	22.7 (CI 7.8 -45.4)	2.02 (CI 1.64-5.78)	6.47 (CI 4.30 –NA)

- **OS rates (per BIRC) (post-hoc analysis)**

Additional analyses were conducted to further examine survival rates in key subgroups of patients within PD-L1 expression subgroups (02-Sep-2016 database lock).

Table 26: Overall Survival rates – all responders per BIRC

Overall Survival Rates (All Responders per BIRC)					
Survival Rate (95% CI)	PD-L1 < 1% N = 23	PD-L1 ≥ 1% N = 31	PD-L1 < 5% N = 29	PD-L1 ≥ 5% N = 25	All Treated Subjects N = 54
3 month	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
6 month	95.7 (72.9, 99.4)	96.8 (79.2, 99.5)	93.1 (75.1, 98.2)	100.0 (100.0, 100.0)	96.3 (86.0, 99.1)
9 month	95.7 (72.9, 99.4)	96.8 (79.2, 99.5)	93.1 (75.1, 98.2)	100.0 (100.0, 100.0)	96.3 (86.0, 99.1)
12 month	95.7 (72.9, 99.4)	92.6 (73.1, 98.1)	93.1 (75.1, 98.2)	94.7 (68.1, 99.2)	93.9 (82.1, 98.0)

Source: Table S.5.2EUB of Appendix 1

Exploratory Endpoints

- Baseline PD-L1 Expression and Efficacy

The protocol defines two PD-L1 expression cutoffs (1% and 5%).

Ad-hoc exploratory analyses were performed to further explore the effect of baseline PD-L1 expression on confirmed response per BIRC as continuous variable from 0% to 100%. The receiver operating characteristics (ROC) curve based on response showed that there was no optimal cutoff for PD-L1 expression. The logistic regression model with response and PD-L1 expression was consistent with previous observations, i.e. the predicted probability of response was clinically meaningful across the range of PD-L1 expression value.

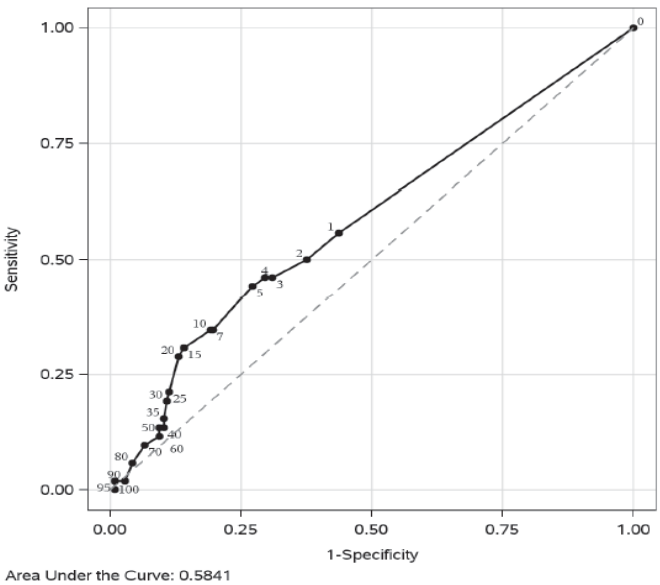


Figure 8 Receiver Operating Characteristic (ROC) Curve Based on Confirmed Response per BIRC - All Treated Subjects (study CA20275)

The association between other biomarker measures and BOR assessed in study CA209275 is presented below.

Table 27 Tumour PD-L1 and Qualitative PD-L1 Immune Cell Staining Scores and ORR-CA209275

PD-L1 expression category	ORR Tumour PD-L1 <1%	ORR Tumour PD-L1 ≥1%	ORR Tumour PD-L1 <5%	ORR Tumour PD-L1 ≥5%
ORR regardless of immune PD-L1 expression, n/N (%)	23/143 (16.1%)	29/122 (23.8%)	29/184 (15.8%)	23/81 (28.4%)
No immune cells or no PD-L1+ immune cells present	0/7 (0%)	0/0 (0%)	0/7 (0%)	0/0 (0%)
Rare PD-L1+ immune cells - responders, n/N (%)	4/50 (8.0%)	6/23 (26.1%)	5/53 (9.4%)	5/20 (25.0%)
Intermediate PD-L1+ immune cells - responders, n/N (%)	15/65 (23.1%)	13/68 (19.1%)	18/92 (19.6%)	10/41 (24.4%)
Numerous PD-L1+ immune cells - responders, n/N (%)	4/21 (19.0%)	10/31 (32.3%)	6/32 (18.8%)	8/20 (40.0%)

RNA/Gene expression was assessed in available pre-treatment tumour tissue by EdgeSeq technology (n = 204 subjects with evaluable gene expression data). A gene signature composed of 25 IFNɣ related genes was tested for association with nivolumab response per BIRC. An IFNɣ signature score for each evaluable sample was calculated as the sum of z-scores for each gene in the signature based on the normalized data generated by EdgeSeq technology (HTG Molecular Diagnostics Inc).

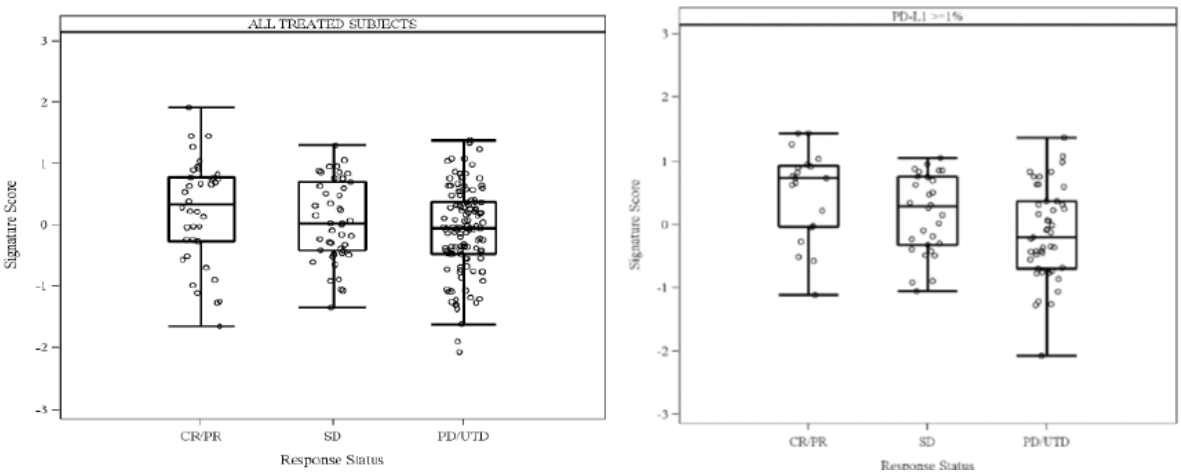


Figure 9 Expression Levels of INFγ Genes and Correlation with Response in all subjects and subjects with tumour PD-L1⩾1%.

In CA209275, the MDSC (% of CD14+ LIN-) abundance in the circulation was measured using freshly collected blood (within 24 h of collection).

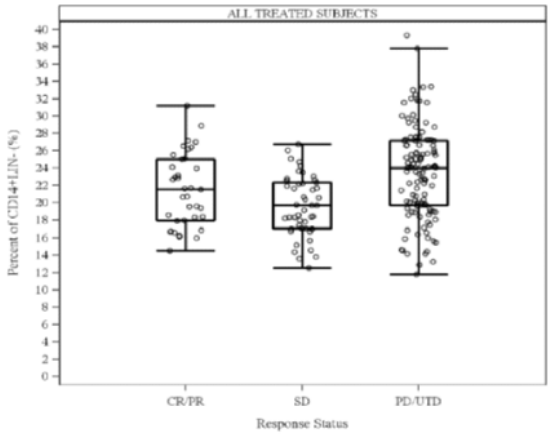


Figure 10 Relative Abundance of MDSCs and Correlation with Response – All Treated Subjects CA209275

Tumour infiltrating lymphocytes have been measured by immunohistochemistry (IHC). The presence of CD8+ and FOXP3+ tumour infiltrating lymphocytes (TILs) was assessed in the pre-treatment tumour samples. CD8+ and FOXP3+ cells were enumerated by digital image analysis in regions of interest within the tumour tissue sections and the percentage of CD8+ and FOXP3+ of total number cells was estimated. Regions of interest were circled by a pathologist around tumour areas that may have included intervening stroma.

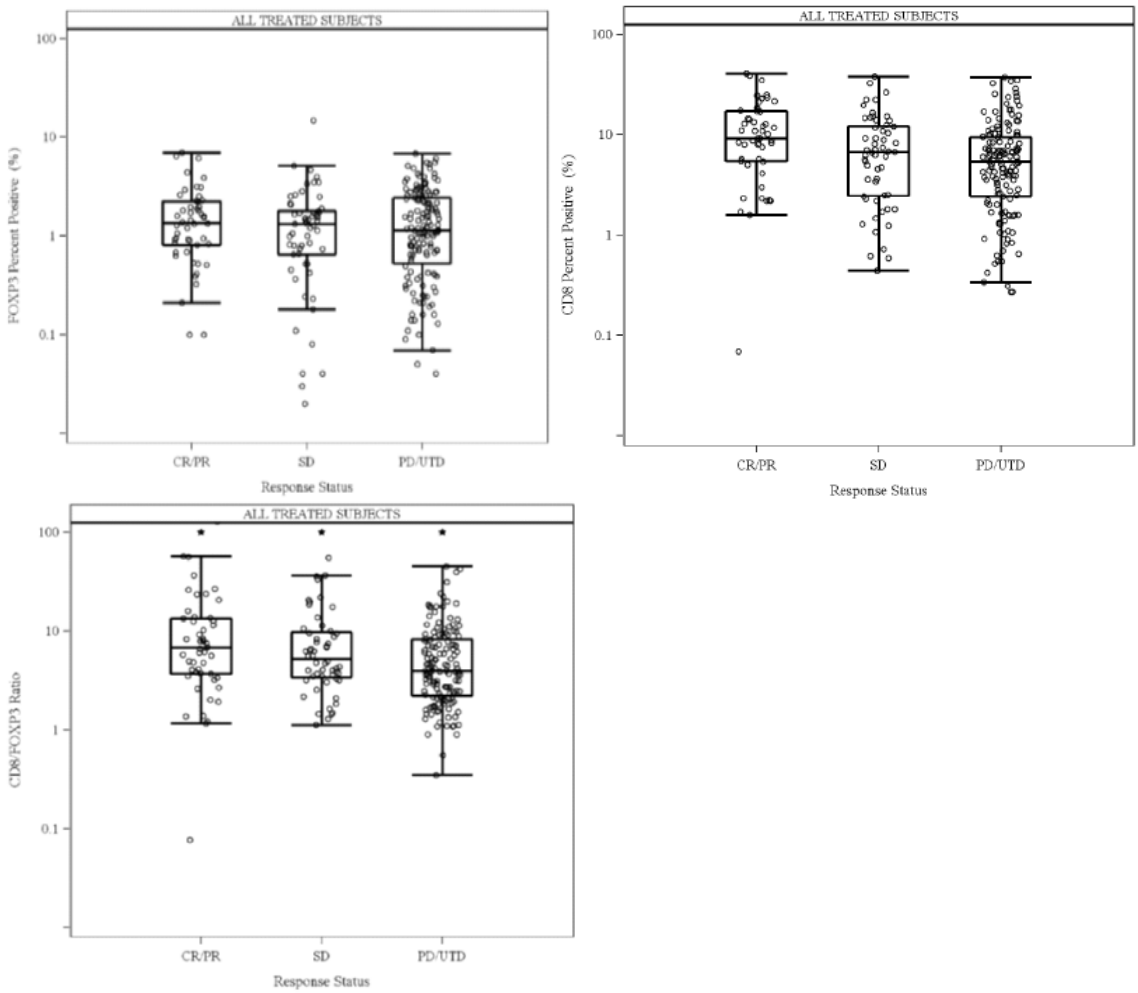


Figure 11 Relative Abundance of FoxP3+ Cells across Response Categories -CA209275; Relative Abundance of CD8+ Cells by Response Category - CA209275; Relative Abundance of the Ratio of CD8+ / FoxP3+ Cells Across Response Categories - CA209275

The expression of PD-L2 in pre-treatment tumour tissue of patients from the CA209275 study was assessed by IHC, using a mouse monoclonal anti-PD-L2 Ab clone.

Table 28 Objective Response Rate per BIRC by PD-L2 Status within PD-L1 expression subgroups - CA209275 (updated analysis, DBL 2 Sept 2016)

	PD-L1 <1% (N=146)	PD-L1 >=1% (N=124)	PD-L1 <5% (N=187)	PD-L1 >=5% (N=83)	ALL TREATED SUBJECTS (N=270)
PD-L2 STATUS (TUMOR CELLS- MEMBRANE) (A)					
PD-L2 POSITIVE	8 (5.5)	10 (8.1)	11 (5.9)	7 (2.6)	18 (6.7)
PD-L2 NEGATIVE	126 (86.3)	101 (81.5)	164 (87.7)	63 (23.3)	227 (84.1)
NOT REPORTED/EVALUABLE	12 (8.2)	13 (10.5)	12 (6.4)	13 (4.8)	25 (9.3)
PD-L2 STATUS (TUMOR CELLS- MEMBRANE or CYTOPLASMIC) (B)					
PD-L2 POSITIVE	17 (11.6)	30 (24.2)	25 (13.4)	22 (8.1)	47 (17.4)
PD-L2 NEGATIVE	117 (80.1)	81 (65.3)	150 (80.2)	48 (17.8)	198 (73.3)
NOT REPORTED/EVALUABLE	12 (8.2)	13 (10.5)	12 (6.4)	13 (4.8)	25 (9.3)

(A) Positive if location is MEMBRANE or CYTOPLASMIC/MEMBRANE and IHC score is 1+, 2+ or 3+
(B) Positive if location is MEMBRANE or CYTOPLASMIC/MEMBRANE and IHC score is 1+, 2+ or 3+ or if location is CYTOPLASMIC and IHC score is 2+ or 3+

Summary of main study

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

Table 29 Summary of Efficacy for trial CA209275

Title: A Phase 2 Single Arm Clinical Trial of Nivolumab (BMS-936558) in Subjects with Metastatic or Unresectable Urothelial Cancer Who Have Progressed or Recurred Following Treatment with a Platinum Agent			
Study identifier	BMS-936558		
Design	Single arm trial		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		On going not applicable not applicable
Hypothesis	The primary objective was to estimate ORR per BIRC		
Treatment groups	Nivolumab		3 mg/kgQ2W.
Endpoints and definitions	Primary endpoint	ORR	ORR based on BIRC assessment in subjects with tumor expressing PD-L1 (membranous staining in ≥ 5% and ≥ 1% tumor cells) and in overall treated subjects
	Secondary endpoint	PFS by BICR	Time from first dosing date to the date of the first documented tumor progression, based on BIRC assessments (per RECIST 1.1), or death due to any cause.
	Secondary endpoint	OS	Time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive
Database lock	02-Sep-2016		
Results and analysis			

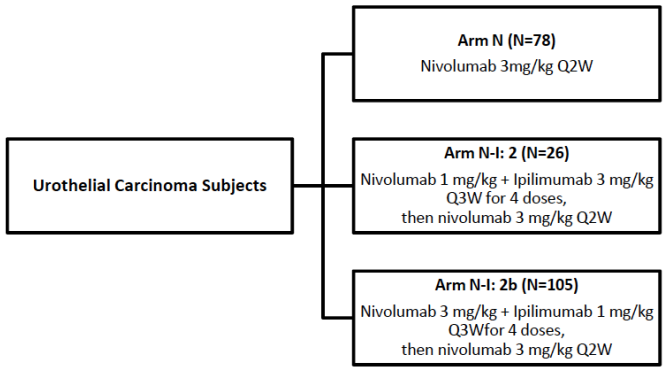
Analysis description	**Primary analysis**	
Analysis population and time point description	All subjects who received at least one dose of nivolumab.	
Descriptive statistics and estimate variability	Treatment group	Nivolumab
	Number of subjects	270
	ORR by BICR (%)	20.0
	CI95%	15.4-25.3
	DOR by BIRC (median)	10.35
	CI 95%	7.52-N.A
	PFS by BICR (median)	2.00 months
	CI 95%	1.87-2.63
	OS (median)	8.57 months
	CI 95%	6.05-11.27

Supportive study

Study CA209032

A Phase 1/2, Open-label Study of Nivolumab Monotherapy or Nivolumab combined with Ipilimumab in Subjects with Advanced or Metastatic Solid Tumors

CA209032 is a multicenter Phase 1/2, open label, randomised study of nivolumab monotherapy or nivolumab combined with ipilimumab designed to evaluate the efficacy and safety of nivolumab as monotherapy or in combination with ipilimumab in subjects with 6 different tumour types including UC. Subjects with UC originating in the renal pelvis, ureter, bladder or urethra with tumour progression or refractory disease and at least 1 platinum-containing chemotherapy regimen unless the subject actively refused chemotherapy were treated with one of following 3 regimens: nivolumab monotherapy 3 mg/kg, nivolumab 3 mg/kg + ipilimumab 1 mg/kg, and nivolumab 1 mg/kg + ipilimumab 3 mg/kg.



Note: The focus of this interim CSR is subjects treated with nivolumab monotherapy (Arm N). The 2 combination arms will be reported separately at a later date.

Figure 12 Design Schematic for Urothelial Carcinoma Cohort (study CA209032)

Treated subjects were evaluated for response according to RECIST v1.1 at baseline and then at 6 weeks after first dose and continuing every 6 weeks for the first 24 weeks, and then every 12 weeks until disease progression (investigator-assessed RECIST v1.1-defined progression) or treatment discontinuation, whichever occurred later. Subjects were treated until progression, unacceptable toxicity, or other protocol-defined reasons. Treatment beyond initial investigator-assessed RECIST v1.1-defined progression was permitted if the subject had an investigator-assessed clinical benefit and was tolerating study drug.

Subjects treated with nivolumab monotherapy who had a confirmed progression were subsequently allowed to cross over to nivolumab 3 mg/kg + ipilimumab 1 mg/kg combination.

The clinical data base lock for this analysis occurred on 24-Mar-2016.

Pre-treatment tumour tissue (archival or fresh biopsy specimen) was systematically collected in order to conduct pre planned analyses of efficacy according to baseline PD-L1 expression status. Subjects were treated, regardless of baseline tumour PD-L1 expression status. Archived tissue could be from prior biopsy of unresectable or metastatic disease or from prior surgical resection. Database lock was 24-Mar-2016.

- Sample Size and Power

An ORR of 10% or less was considered not of clinical value, and an ORR of 25% or greater was considered of strong clinical interest. The sample size 60 - 105 provided 90% to 97% power to reject the null hypothesis of 10% response rate if the true response rate was 25% with a two-sided Type I error rate of 5%.

- Efficacy Endpoints

The primary endpoint for the nivolumab monotherapy treated UC cohort was to assess the investigator-assessed ORR. The ORR was defined as the proportion of treated subjects with a confirmed BOR of CR or PR according to RECIST 1.1.

Additional efficacy assessments included investigator-assessed DOR and PFS according to RECIST v1.1; OS; association between tumour PD-L1 expression and efficacy; HRQoL as assessed by the EQ-5D.

- Baseline characteristics

Table 30 Baseline Disease Characteristics and Tumor Assessments – All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)

	Nivolumab N = 78
PERFORMANCE STATUS (ECOG) [%]	
0	42 (53.8)
1	36 (46.2)
NUMBER OF BELLMUNT RISK FACTORS	
0	27 (34.6)
1	39 (50.0)
2	8 (10.3)
3	4 (5.1)
SMOKING STATUS	
CURRENT/FORMER	48 (61.5)
NEVER SMOKER	29 (37.2)
UNKNOWN	1 (1.3)
BASELINE LIVER METASTASIS	
YES	20 (25.6)
NO	58 (74.4)
BASELINE VISCERAL METASTASIS (A)	
YES	66 (84.6)
NO	12 (15.4)
BASELINE LYMPH NODE ONLY	
YES	11 (14.1)
NO	67 (85.9)
BASELINE HEMOGLOBIN	
<10 G/DL	11 (14.1)
>=10 G/DL	67 (85.9)
BASELINE CREATININE CLEARANCE	
<30 ML/MIN	0
30- <60 ML/MIN	25 (32.1)
>=60 ML/MIN	53 (67.9)
CURRENT (STUDY ENTRY) DISEASE STAGE (%)	
STAGE I	0
STAGE II	0
STAGE III	5 (6.4)
STAGE IIIA	0
STAGE IIIB	1 (1.3)
STAGE IIIC	1 (1.3)
STAGE IV	71 (91.0)

Most (84.6%) subjects received prior systemic cancer treatments in the metastatic setting. Percentages of subjects receiving prior systemic cancer treatments in the neoadjuvant and adjuvant settings were 17.9% and 42.3%, respectively. Nearly all (96.2%) subjects received prior platinum-containing therapy in any setting with the majority (75.6%) receiving the therapy in the metastatic setting. The most frequent prior platinum-containing therapy was cisplatin followed by carboplatin. Prior platinum-containing therapy was associated with recurrence/progression in 92.3% of the subjects. Nearly all subjects progressed within 12 months of their most recent platinum regimen, with nearly two-thirds (59.7%) progressing within 3 months.

- Results

The enrollment period for nivolumab monotherapy UC cohort lasted approximately 11 months (June 2014 to May-2015). The last patient's first treatment date was 08-May-2015, and the last patient last visit date (clinical cut-off) was 11-Feb-2016, providing a minimum follow-up of approximately 9 months. The clinical data base lock occurred on 24-Mar-2016. 86 subjects with advanced or metastatic UC were enrolled in the nivolumab monotherapy treatment arm at 16 sites in 5 countries. Across the 16 sites, 78 (90.7%) of these enrolled subjects were treated with nivolumab monotherapy. Among these treated subjects, 19 (24.4%) were in Europe (Finland, Germany, Spain, and United Kingdom), and 59 (75.6%) were in the US.

76.9% of all treated subjects were no longer continuing in the treatment period (Table 31). The primary reason for treatment discontinuation was disease progression. 18 (23.1%) subjects crossed from nivolumab monotherapy over to nivolumab 3 mg/kg + ipilimumab 1 mg/kg combination regimen, of whom 15 (83.3%) were no longer continuing in the treatment period; the primary reason for treatment discontinuation was disease progression.

Table 31 End of Treatment Subject Status Summary - All Treated Nivolumab Monotherapy Urothelial Carcinoma Subjects (study CA209032)

	Nivolumab
SUBJECTS	78
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	18 (23.1)
SUBJECTS SWITCHING TO CROSSOVER PERIOD (%)	18 (23.1)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	60 (76.9)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)	
DISEASE PROGRESSION	50 (64.1)
STUDY DRUG TOXICITY	2 (2.6)
ADVERSE EVENT UNRELATED TO STUDY DRUG	4 (5.1)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	2 (2.6)
POOR/NON-COMPLIANCE	1 (1.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (1.3)
SUBJECTS CONTINUING TO BE FOLLOWED (%) (A) (B)	53 (67.9)
SUBJECTS NOT CONTINUING TO BE FOLLOWED (%) (B)	7 (9.0)
REASON FOR NOT CONTINUING TO BE FOLLOWED (%)	
SUBJECT WITHDREW CONSENT	2 (2.6)
DEATH	4 (5.1)
OTHER	1 (1.3)

Percentages based on subjects entering period or continuing study
(A) Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period
(B) Subject status at end of treatment; crossover subjects are not counted.

- Outcomes

Table 32 Summary of Efficacy Results - All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)

Endpoint	Nivolumab 3 mg/kg (N = 78)
PRIMARY ENDPOINT	
Confirmed Objective Response Rate (ORR, CR+PR)	
Responders, n (%)	19 (24.4)
95% confidence interval (CI)	(15.3, 35.4)
SECONDARY ENDPOINTS	
Duration of Response (DOR)	
Ongoing responder (as of the last available tumor assessment), n/N (%)	13/19 (68.4)
Median (95% CI), months	NA (9.92, NA)
Min, Max	4.4, 16.6+
Progression-free Survival (PFS)	
Events, n (%)	60 (76.9)
Median (95% CI), months	2.78 (1.45, 5.85)
Rate at 6 months (95% CI), %	38.0 (27.1, 48.7)
Overall Survival (OS)	
Events, n (%)	46 (59.0)
Median (95% CI), months	9.72 (7.26, 16.16)
Rate at 6 months (95% CI), %	69.2 (57.7, 78.2)
Rate at 12 months (95% CI) %	45.6 (34.2, 56.3)
EXPLORATORY ENDPOINTS	
Efficacy by Baseline PD-L1 Expression (1% tumor cell membrane expression)	
Subjects with ≥ 1% PD-L1 Expression (n = 25)	
Confirmed ORR (95% CI)	24.0 (9.4, 45.1)
Median PFS (95% CI), months	5.45 (1.41, 11.17)
Median OS (95% CI), months	16.16 (7.59, NA)
Subjects with < 1% PD-L1 Expression (n = 42)	
Confirmed ORR (95% CI)	26.2 (13.9, 42.0)
Median PFS (95% CI), months	2.76 (1.41, 6.51)
Median OS (95% CI), months	9.89 (7.03, NA)

Best overall response was based on tumor assessment by the investigator using RECIST v1.1.
Confidence interval for confirmed ORR was computed using the Clopper-Pearson method.
Medians and associated 95% CIs for DOR, PFS, and OS were calculated using Kaplan-Meier method.
PFS and OS rates and associated 95% CIs were calculated using Kaplan-Meier method.
Symbol + indicates a censored value.
There were 11 subjects without PD-L1 quantifiable at baseline.

Primary endpoint

Table 33 Best Overall Response per Investigator - All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)

	Number or Subjects (%)
	Nivolumab N = 78
BEST OVERALL RESPONSE (A):	
COMPLETE RESPONSE (CR)	5 (6.4)
PARTIAL RESPONSE (PR)	14 (17.9)
STABLE DISEASE (SD)	22 (28.2)
PROGRESSIVE DISEASE (PD)	30 (38.5)
UNABLE TO DETERMINE (UTD)	7 (9.0)
NEVER TREATED	0
WRONG CANCER DIAGNOSIS	0
DEATH PRIOR TO DISEASE ASSESSMENT	3 (3.8)
EARLY DISCONTINUATION DUE TO TOXICITY	1 (1.3)
OTHER	3 (3.8)
OBJECTIVE RESPONSE RATE (1)	19/78 (24.4%)
(95% CI)	(15.3, 35.4)

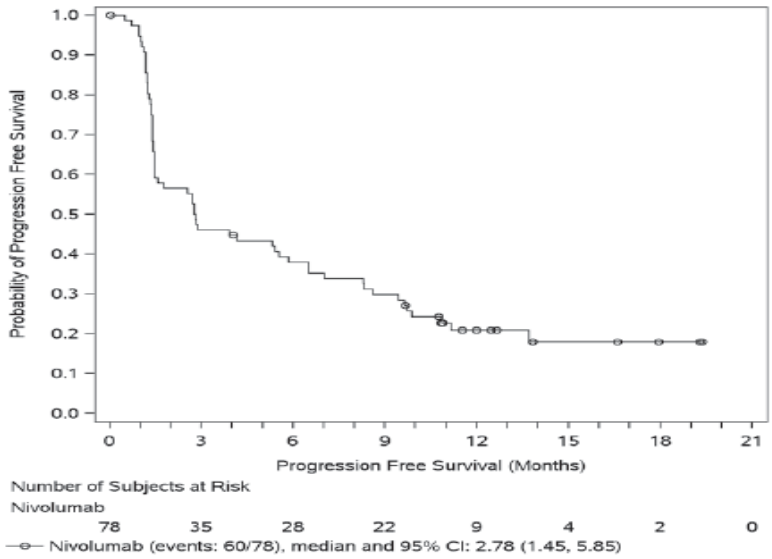
(A) Using RECIST 1.1 criteria.
(1) CR+PR, confidence interval based on the Clopper-Pearson method

Secondary endpoints

Table 34 Time to Response and Duration of Response per Investigator – All Nivolumab Monotherapy Treated Urothelial Carcinoma Responders (study CA209032)

	Nivolumab N = 19
TIME TO RESPONSE (MONTHS)	
NUMBER OF RESPONDERS	19
MEAN	2.92
MEDIAN	1.48
MIN, MAX	1.0, 8.3
Q1, Q3	1.25, 4.14
STANDARD DEVIATION	2.143
DURATION OF RESPONSE (MONTHS)	
MIN, MAX (A)	4.4, 16.6+
MEDIAN (95% CI) (B)	N.A. (9.92, N.A.)
N EVENT/N RESP (%)	6/19 (31.6)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)	
3 MONTHS	19 (100.0)
6 MONTHS	14 (73.7)
12 MONTHS	5 (26.3)
18 MONTHS	0
24 MONTHS	0
NUMBER OF SUBJECTS ACHIEVED PR OR CR (%) (C)	
WITHIN THE FIRST 9 WEEKS	10 (12.8)
WITHIN THE FIRST 4 MONTHS	12 (15.4)
WITHIN THE FIRST 6 MONTHS	18 (23.1)
WITHIN THE FIRST 8 MONTHS	18 (23.1)
WITHIN THE FIRST 12 MONTHS	19 (24.4)
WITHIN THE FIRST 18 MONTHS	19 (24.4)

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
(C) Denominator based on All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects



Symbols represent censored observations.
RECIST 1.1 Response Criteria where confirmation of response is required.

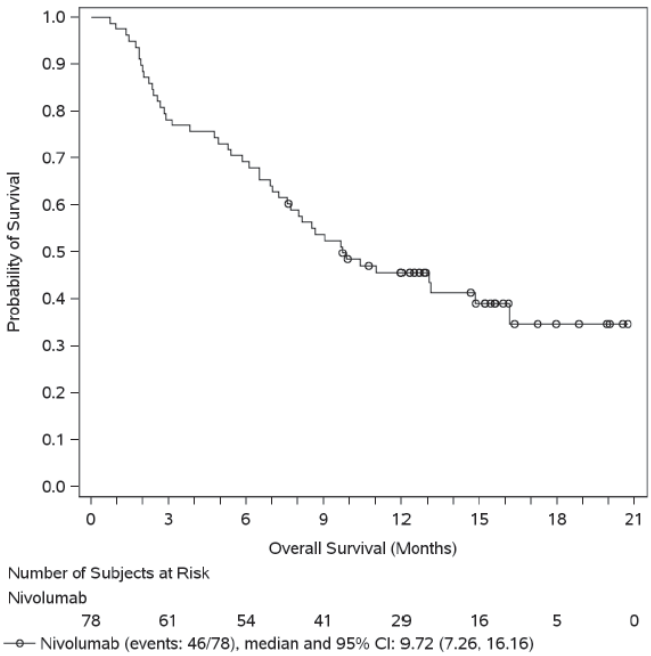
Figure 13 Kaplan-Meier Plot of Progression Free Survival per Investigator – All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)

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. The results of this sensitivity analysis (median PFS: 2.76 [95% CI: 1.45, 5.52] months) were consistent with the PFS analysis using the primary definition.

As highlighted in the Kaplan-Meier plot in

Figure 14, The median OS was 9.72 months and the OS rates (95% CI) were 78.2% (67.3, 85.8) at 3 months, 69.2% (57.7, 78.2) at 6 months, and 45.6% (34.2, 56.3) at 12 months.

Figure 14 Kaplan-Meier Plot of Overall Survival - All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)



Symbols represent censored observations

An ad-hoc sensitivity analysis to assess the impact of planed treatment crossover on OS was conducted using Kaplan-Meier method. The 18 subjects who received planned crossover treatment with nivolumab + ipilimumab combination were separated from the remaining subjects who did not receive planned crossover treatment in the OS analyses. In subjects who did not receive planned crossover treatment, the median OS was 7.89 months (95% CI: 5.29, 16.16); the OS rate (95% CI) was 61.7% (48.2, 72.6) at 6 months and 43.3% (30.6, 55.3) at 12 months.

PD-L1 expression and efficacy results are shown in Table 35

Table 35 Frequency of PD-L1 Expression Status - All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)

	NUMBER OF SUBJECTS (%)
PD-L1 Expression Status	Nivolumab N = 78
SUBJECTS WITH TUMOR TISUUE SAMPLES COLLECTED AT BASELINE	71 (91.0)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (A)	67 (85.9)
>= 1%	25 (37.3)
< 1%	42 (62.7)
>= 5%	14 (20.9)
< 5%	53 (79.1)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE	11 (14.1)
SUBJECTS WITHOUT TUMOR TISSUE SAMPLE (B)	7 (9.0)
SUBJECTS WITH TUMOR TISSUE SAMPLE COLLECTED ON STUDY ONLY (C)	0
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE OR WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (D)	4 (5.1)

(A) 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%
(B)+(C)+(D): Subjects without quantifiable tumor PD-L1 expression at baseline
Source: Table 7.4.1.1-1 of the CA209032 CSR

Table 36 Best Overall Response and Objective Response per Investigator for each PD-L1 Expression Status Group - All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)

PD-L1 Expression Result Group at Baseline	Nivolumab N = 78
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	14 (17.9)
BEST OVERALL RESPONSE (A):	
COMPLETE RESPONSE (CR)	2 (14.3)
PARTIAL RESPONSE (PR)	2 (14.3)
STABLE DISEASE (SD)	6 (42.9)
PROGRESSIVE DISEASE (PD)	3 (21.4)
UNABLE TO DETERMINE (UTD)	1 (7.1)
OBJECTIVE RESPONSE RATE (1)	4/14 (28.6%)
(95% CI)	(8.4, 58.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	53 (67.9)
BEST OVERALL RESPONSE (A):	
COMPLETE RESPONSE (CR)	3 (5.7)
PARTIAL RESPONSE (PR)	10 (18.9)
STABLE DISEASE (SD)	13 (24.5)
PROGRESSIVE DISEASE (PD)	23 (43.4)
UNABLE TO DETERMINE (UTD)	4 (7.5)
OBJECTIVE RESPONSE RATE (1)	13/53 (24.5%)
(95% CI)	(13.8, 38.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	25 (32.1)
BEST OVERALL RESPONSE (A):	
COMPLETE RESPONSE (CR)	4 (16.0)
PARTIAL RESPONSE (PR)	2 (8.0)
STABLE DISEASE (SD)	8 (32.0)
PROGRESSIVE DISEASE (PD)	8 (32.0)
UNABLE TO DETERMINE (UTD)	3 (12.0)
OBJECTIVE RESPONSE RATE (1)	6/25 (24.0%)
(95% CI)	(9.4, 45.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	42 (53.8)
BEST OVERALL RESPONSE (A):	
COMPLETE RESPONSE (CR)	1 (2.4)
PARTIAL RESPONSE (PR)	10 (23.8)
STABLE DISEASE (SD)	11 (26.2)
PROGRESSIVE DISEASE (PD)	18 (42.9)
UNABLE TO DETERMINE (UTD)	2 (4.8)
OBJECTIVE RESPONSE RATE (1)	11/42 (26.2%)
(95% CI)	(13.9, 42.0)
SUBJECTS WITHOUT PD-L1 QUANTIFIABLE AT BASELINE	11 (14.1)
BEST OVERALL RESPONSE (A):	
COMPLETE RESPONSE (CR)	0
PARTIAL RESPONSE (PR)	2 (18.2)
STABLE DISEASE (SD)	3 (27.3)
PROGRESSIVE DISEASE (PD)	4 (36.4)
UNABLE TO DETERMINE (UTD)	2 (18.2)
OBJECTIVE RESPONSE RATE (1)	2/11 (18.2%)
(95% CI)	(2.3, 51.8)

(a) Using RECIST 1.1 criteria.
(1) CR+PR, confidence interval based on the Clopper-Pearson method

Table 37 Time to Response and Duration of Response per Investigator by PD-L1 Status at Baseline – All Nivolumab Monotherapy Treated Urothelial Carcinoma Responders (study CA209032)

	PD-L1 >= 1% N = 6	PD-L1 < 1% N = 11	INDETERMINATE/ NOT EVALUABLE/ MISSING N = 2
TIME TO RESPONSE (MONTHS)			
NUMBER OF RESPONDERS	6	11	2
MEAN	3.87	2.56	2.10
MEDIAN	3.42	1.48	2.10
MIN, MAX	1.0, 8.3	1.2, 5.3	1.3, 2.9
Q1, Q3	1.18, 5.91	1.35, 4.11	1.31, 2.89
STANDARD DEVIATION	3.145	1.544	1.115
DURATION OF RESPONSE (MONTHS)			
MIN, MAX (A)	8.3+, 13.5+	4.4, 16.6+	5.2, 8.0+
MEDIAN (95% CI) (B)	12.48 (9.92, N.A.)	N.A. (5.55, N.A.)	N.A. (5.22, N.A.)
N EVENT/N RESP (%)	2/6 (33.3)	3/11 (27.3)	1/2 (50.0)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)			
3 MONTHS	6 (100.0)	11 (100.0)	2 (100.0)
6 MONTHS	6 (100.0)	7 (63.6)	1 (50.0)
12 MONTHS	2 (33.3)	3 (27.3)	0
18 MONTHS	0	0	0
24 MONTHS	0	0	0
NUMBER OF SUBJECTS ACHIEVED PR OR CR (%) (C)			
WITHIN THE FIRST 9 WEEKS	3 (12.0)	6 (14.3)	1 (9.1)
WITHIN THE FIRST 4 MONTHS	3 (12.0)	7 (16.7)	2 (18.2)
WITHIN THE FIRST 6 MONTHS	5 (20.0)	11 (26.2)	2 (18.2)
WITHIN THE FIRST 8 MONTHS	5 (20.0)	11 (26.2)	2 (18.2)
WITHIN THE FIRST 12 MONTHS	6 (24.0)	11 (26.2)	2 (18.2)
WITHIN THE FIRST 18 MONTHS	6 (24.0)	11 (26.2)	2 (18.2)

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
(C) Denominator based on All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects in Corresponding PD-L1 Subgroup
Subjects who progressed before achieving objective response are excluded from the calculation of time to response.

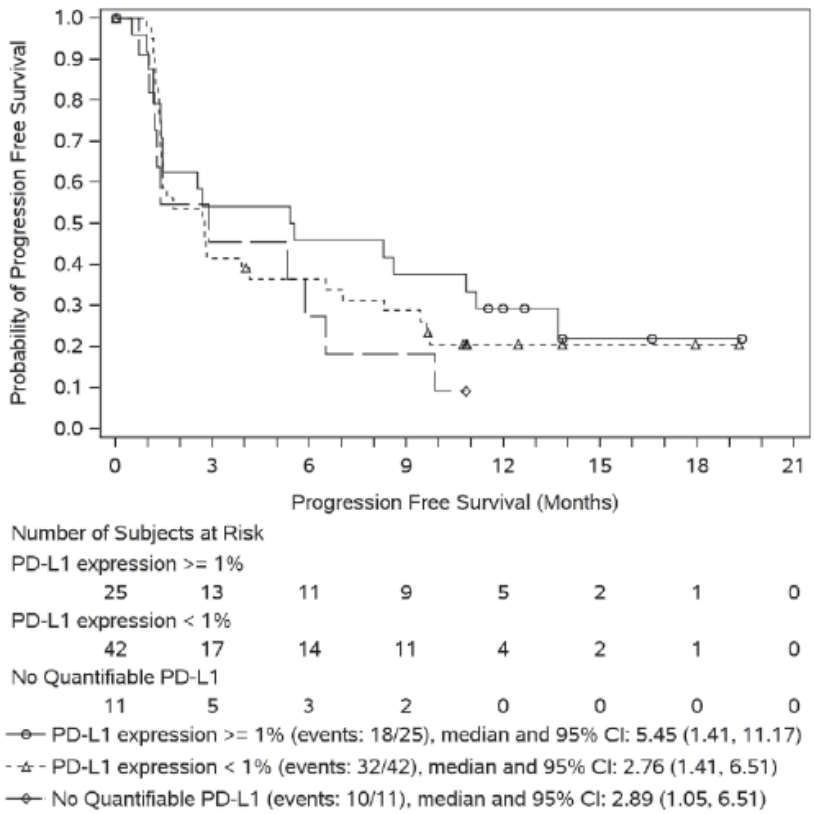


Figure 15 Kaplan-Meier Plot of Progression Free Survival by PD-L1 Status at Baseline (1 Percent Cutoff) - All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)

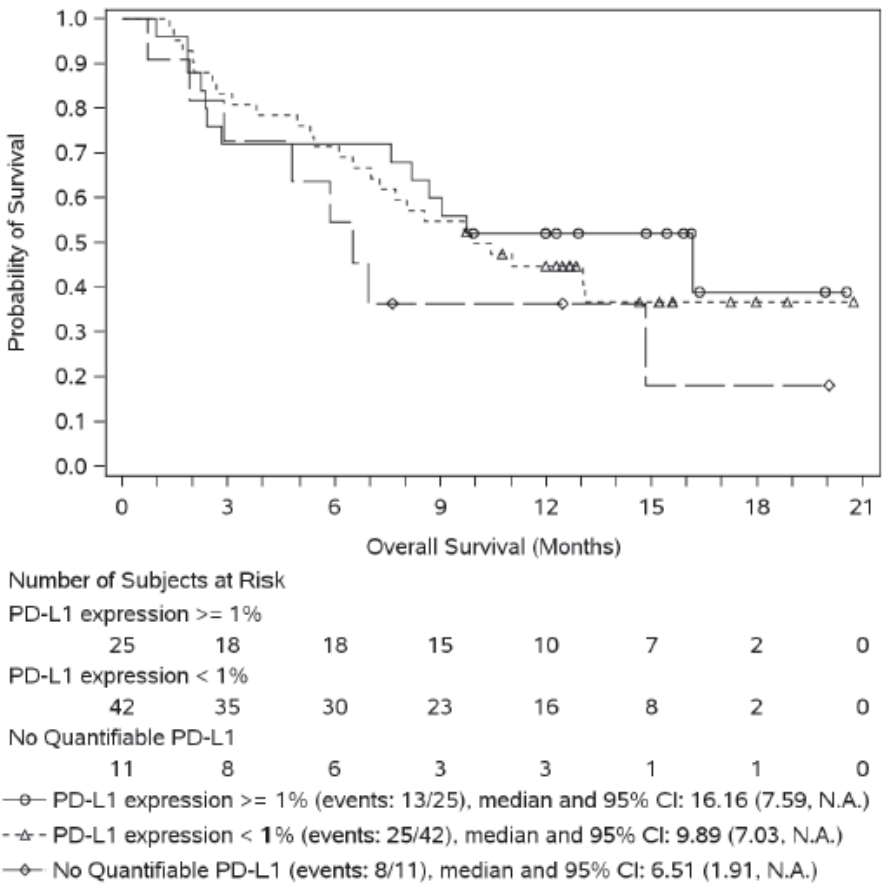


Figure 16 Kaplan-Meier Plot of Overall Survival by PD-L1 Status at Baseline (1 Percent Cutoff) - All Nivolumab Monotherapy Treated Urothelial Carcinoma Subjects (study CA209032)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application in bladder cancer is based on two ongoing clinical studies: one pivotal Phase 2 study in metastatic or unresectable urothelial cancer (CA209275) and one supportive Phase 1/2 study in multiple tumour types, including unresectable locally advanced or metastatic UC (CA209032), both conducted in patients who has progressed on or after to at least 1 platinum-containing chemotherapy regimen.

Both studies are single arm trials hampering any discussion about relative efficacy of nivolumab versus chemotherapy. Previously reported data on therapy for relapse in metastatic and advanced UC are highly variable with results being vastly dependent on patient selection; therefore there is a risk that the outcomes of these two studies are overestimated (see discussion on efficacy data).

Patients intended to be recruited, according to the inclusion/exclusion criteria, were subjects with histological or cytological evidence of metastatic or surgically unresectable urothelial carcinoma originating in the bladder, urethra, ureter, or renal pelvis. They must have progression or recurrence after treatment with at least 1 platinum-containing chemotherapy regimen for metastatic or surgically-unresectable locally advanced urothelial cancer, or within 12 months of peri-operative (neo-adjuvant or adjuvant) treatment with a platinum- containing chemotherapy in the setting of cystectomy for localised muscle- invasive UC. These inclusion criteria can be considered representative of the claimed indication,

i.e. patients with locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum- containing therapy.

The primary endpoint for both studies was confirmed ORR (BICR assessment and investigator assessment in CA209275 and CA209032 respectively). TTR, DoR, PFS and OS were secondary endpoints. The use of ORR as primary endpoint is acceptable for phase I/II studies, although cannot be used on its own to demonstrate the clinical benefit to patients. Long term clinical outcomes like PFS and OS have been provided as secondary endpoints, which are considered appropriate in such trial designs.

Efficacy data and additional analyses

In the Study CA209275, 386 subjects were enrolled at 63 sites in 11 countries. Of them 265 were considered the efficacy population, given the requirement of a minimum follow up of 6 months from the global enrolment last patient first treatment date. The main reason for not treating patients was that subject no longer met the inclusion criteria. Patients included were mainly white (85.6%) and male population (78.1%) with urinary bladder as tumour type (73%). Only 3.3% were locally unresectable. Almost 28% of patients had liver metastasis and 84% with visceral metastases. There were no patients but one with CNS metastases. Regarding the previous treatment received, 71.5% had received previous treatment in the metastatic setting. All patients had received platinum treatment, with almost 66% of patients with the most recent platinum regimen in the metastatic setting. Of note, 59% of patients progressed in less than 3 months from the last platinum treatment. Subjects with ECOG >1 were not included (except for 1 protocol deviation). Results from these patients can not necessarily be extrapolated to patients who have a ECOG performance status of 2 or higher, which comprise almost 40-50% of the advanced and metastatic urothelial carcinoma patients.

Most baseline demographics and disease characteristics were balanced between PD-L1 cohorts, except for the distribution of baseline poor prognostic factors, most apparent when using the 1% cut-off for PD-L1 expression.

Overall, the patients recruited in study CA209275 seem to have a poor prognosis, especially when considering the percentage of patients with visceral metastasis and the treatment free interval. Study CA209032 reveals a similar population in regard to baseline characteristics, though with a smaller number of treated patients (78).

At the time of initial submission, outcomes from the pivotal trial (study CA209275) in terms of ORR by BICR showed a response rate of 19.6% in all treated patients (23% by investigator assessment), with a median of duration of response not reached yet but with the lower bound of 7.43 months (77% of patients were in response at the database lock) and with a time to objective response of around 2 months. This antitumor activity could be translated into a life expectancy of 8-9 months in terms of median, even though the percentage of events was 51%. Two pre-specified sensitivity analyses were performed for BIRC-assessed BOR and the results of these analyses were consistent with those of the primary analysis.

Median PFS was around 2 months with 76% of events. These results are supported by those from the study CA209032, where the ORR were 24% (investigator assessment) and similar PFS and OS results were achieved (median PFS 2.78 months and 9.72 months of OS).

Updated efficacy data submitted during the review, from study CA209275 with a clinical cut-off of 21 July 2016, showed similar results: ORR of 20.0% (95% CI: 15.4, 25.3) in all treated subjects and a median OS of 8.57 months (95% CI: 6.05, 11.27). The median DOR per BIRC was 10.35 months in all treated subjects; however this seemed to be reflective of 1 subject experiencing a late event and which may change with longer follow-up. More than half (34/54, 63.0%) of the responders had ongoing response at the time of the clinical cut-off for this analysis.

Twenty percent of the subject received subsequent cancer therapies in the pivotal trial and 30% of patients in the study CA209032. The MAH was requested to discuss the potential impact of post-progression therapies on OS. The use of subsequent therapies seemed to have an important impact on the OS data. Despite only 54 (20%) subjects received subsequent therapy with 28 (10.4%) receiving systemic anticancer therapy, when these patients were excluded from the analysis, the median OS decreased to 6.47 (95% CI: 4.76, 9.99) months from the 8.57 months in whole population (95% CI: 6.05, 11.27). On the other hand, this decrease in the median did not have a great impact in the long term survival, since the 1-year survival rate appeared to be identical. Similar conclusions were observed in the study CA209032. In any case, the OS data in whole population and especially in PD-L1>1% patients, appeared overall superior to those described with chemotherapy, with higher survival rates at 12 months. However, in the PD-L1<1% subgroup, when only subjects without subsequent anticancer therapy were analysed, the 12-month survival rate decreased to 33.5%, which appeared similar to those described in larger trials with single-agent chemotherapy (25%-30%). The lack of comparator hampered further discussion on this issue.

As expected, results in those subgroups of patients with poorer prognosis (visceral and hepatic metastasis, high ECOG) obtained lower ORR. Of note, the response rate according to the different age groups showed that older subgroups had better results.

In the pivotal study, similar PFS and OS results were observed for subgroups with different numbers of prior regimens in the metastatic setting. Patients with a shorter time from the most recent prior regimen, which could represent those who have experienced rapidly progressing disease, had worse OS and ORR results than patients with longer time since prior treatment, who may have had more indolent disease. The median TTR was 1.87 months. It is possible that patients with rapidly progressing tumours have insufficient time to experience benefit from treatment with nivolumab. Nevertheless, the nivolumab treated group seems to experience a better response than what is expected for chemotherapy and in the subgroup designated as PD-L1<1%, the responses are considered superior to the standard of care. Therefore, while it is possible that patients may experience a delay in the onset of response to nivolumab as observed in other indications, because of the lack of a control arm it is not possible to elucidate whether the survival curve of nivolumab would be below chemotherapy at the beginning of the treatment.

The design of the studies as single arm trials is considered an important drawback as it hampers the interpretation of the results in a heterogeneous patient population. According to the bibliography in metastatic bladder cancer, the therapeutic landscape after a first treatment of platinum (vinflunine, taxanes, gemcitabine and pemetrexed) offers ORRs in monotherapy that range between 10-15% with a median OS of 7-9 months, with the exception of gemcitabine that as single agent has demonstrated ORRs of 11-29%, with median OS that ranged from 5 to 13 months, as second-line therapy in small Phase 2 studies (N<50)[8,9,10,11]. With taxane-based combination chemotherapies, ORRs increase up to 30-70%, with 11-13 months of OS, however these regimens are not frequently used due to their toxicity[12].

In both studies CA209275 and CA209032, in the subset of patients with high tumour PD-L1 expression i.e. >1%, treatment with nivolumab showed consistently higher rates of tumour responses (over 24%) and a trend for higher OS when compared to what has been reported in the literature. These results

[8] Lorusso V, Pollera CF, Antimi M, et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. Eur J Cancer. 1998;34:1208-12.
[9] Gebbia V, Testa A, Borsellino N, et al. Single agent 2',2'-difluorodeoxycytidine in the treatment of metastatic urothelial carcinoma: a phase II study. Clin Ter. 1999;150:11-5.
[10] Albers P, Siener R, Hartlein M, et al. Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma - prognostic factors for response and improvement of quality of life. Onkologie. 2002;25:47-52.
[11] Akaza H, Naito S, Usami M, et al. Efficacy and safety of gemcitabine monotherapy in patients with transitional cell carcinoma after Cisplatin-containing therapy: a Japanese experience. Jpn J Clin Oncol. 2007;37:201-6.
[12] Oing C, Rink M, Oechsle K, Seidel C, von Amsberg G, Bokemeyer C, Second Line Chemotherapy for Advanced and Metastatic Urothelial Carcinoma: Vinflunine and Beyond-A Comprehensive Review of the Current Literature. J Urol. 2016 Feb;195(2):254-63. doi: 10.1016/j.juro.2015.06.115. Epub 2015 Sep 26.

support a trend for a greater benefit in patients that have tumours that express PD-L1. Similar results were provided by the study CA209032. These promising results in patients with high tumour PD-L1 expression are very much in line with those reported for other immunotherapeutic medicinal products with a similar mechanism of action and add further to the biological plausibility to the observed results.

In the pivotal study CA209275, patients with tumour PD-L1 expression≥1% and 5% obtained ORRs of 25% and 30% respectively, while patients with tumour PD-L1 expression<1% had an ORR of 16%. Both PFS and OS were longer for patients with high tumour PD-L1 expression (median OS 11.6 and 12.9 months in PD-L1 ≥1% and PD-L1 ≥5% respectively vs. 6 months in PD-L1 <1% and PD-L1 <5%; median PFS 3.55 months in PD-L1 ≥1% and 3.71 months in PD-L1 ≥5% and 1.9 months in PD-L1 <1% and PD-L1 <5%). The largest baseline differences between the two PD-L1 subgroups (<1% and >1%) encompassed smoking status and Bellmunt Risk Factors. The percentage of never smokers was 10% higher in the PD-L1<1% (29.5 vs 19.4%). On the other hand, there were more patients with 2-3 Bellmunt Risk Factors in the PD-L1<1% than in the >1% subgroup (28% vs. 16.1%). To what extent these imbalances influenced the results is not totally clear. Among the rest of baseline characteristics, the differences were judged as not to have strongly impacted on the survival. It was notable that for patients with tumour PD-L1<1% a shorter median OS was observed in the vast majority of subsets, in particular for patients with poor prognostic factors.

In the supportive study CA209032, ORR did not seem to be affected by tumour PD-L1 expression, with ORR of 24% and 26% for patients with above 1% expression and below 1% expression, respectively. Of importance is that durable responses were observed across all PD-L1 subgroups. The duration of response (DoR) reached with nivolumab appeared better than DoRs described for all other available therapies (including combination-chemotherapy), even in the subgroups with PD-L1 expression below 1%. Therefore, while the response rates achieved with nivolumab in subgroups with PD-L1<1% were not very high, the responses were durable which is considered clinically relevant.

Whilst the median of OS with nivolumab in patients with PD-L1 <1% and with presence of 2 Bellmunt factors was 3.15 months, the OS rates at 1 year was 13.4% (Table 23) which appear to be similar to chemotherapy (i.e. <10%)[13]. The 1 year survival rate in the overall population of patients PD-L1<1% provided similar results to chemotherapy (i.e. 34% reported with nivolumab in study CA209275 (Table 18) versus 31% reported with chemotherapy in study KEYNOTE-45)[14] and the 1-year survival rate in those patients in response, was close to 96%, which is considered clinically meaningful. Therefore, it is considered reasonable to assume that the use of nivolumab, also in patients with PD-L1 <1% for second line treatment of UC, will provide comparable rates of response to chemotherapy. Also, these responses are more durable than achieved with any other therapy, and the survival benefit is very much in line to that reported for chemotherapy.

The SmPC has been updated to reflect that results from post-hoc, exploratory analyses indicate that in patients with low (e.g. <5%) to no tumour PD-L1 expression, other patient characteristics (e.g. liver metastases, visceral metastases, baseline haemoglobin <10g/dL and ECOG performance status = 1) might contribute to the clinical outcome (see SmPC section 5.1).

The ROC curve based on response showed that there was no optimal cut-off for PD-L1 expression. Additional analyses requested by the CHMP showed that some biomarkers analysed were not predictive of response of nivolumab, being Interferon-gamma gene (RNA) expression signature using the provided assay, myeloid-derived suppressor cells (MDSCs; % of CD14+LIN-) abundance, percentage of CD8+ T cells infiltrate in tumour and the ratio of CD8+ T cells to FOXP3+ cells (T regulatory cells). No firm conclusions could be drawn regarding PD-L2 tumour expression, due to the low number of tumour cells expressing PD-L2. The combination of PD-L1 expression on immune cells and PD-L1 on tumour cells

[13] J Clin Oncol. 2010 Apr 10;28(11):1850-5
[14] Bellmunt et al. NEJM 2017

might be helpful in identifying which patients have limited chance of responding to therapy (Table 27). Few responders to nivolumab (RR 7-8%) were observed among patients with both no/rare PD-L1 expression on immune cells and PD-L1<1% or <5% expression on tumour cells, however no quantitative method was used as currently no validated assays and methods exists. Therefore, PD-L1 expression on both immune cells and tumour cells should be assessed in predicting treatment response and survival in a prospective manner and using validated assays and methods where possible. Other biomarkers such as other gene signatures, mutational load, PD-L1 and PD-L2 on mRNA remain to be evaluated, however, tissue inventory limitations have to be taken into account. Annex II has been updated accordingly. In particular the MAH will further explore in UC patients the early identification of those who do/do not respond to treatment with nivolumab, as well as evaluate the association between improved clinical outcomes to nivolumab and the presence of mutational and neoantigen load and of PD -L1 expression on tumour- and tumour associated immune cells using validated approaches as feasible. These biomarker assessments will be exploratory for study CA209275, however they should be prospectively assessed in future UC studies with nivolumab.

Furthermore, in melanoma a high level of LDH seems to be a predictor of low nivolumab benefit. Unfortunately, very few UC patients (3.7%) had a baseline LDH of > 2*ULN, so no firm conclusions can be drawn from the 2*ULN cut-off. Though there are differences observed in efficacy outcomes between those with elevated LDH and those with normal LDH levels, there are still responders among patients with elevated LDH level and thus this cannot be used to exclude patients from treatment. When combined with subgroups stratified for PD-L1 expression, the LDH level provides no additional value for treatment selection.

2.4.4. Conclusions on the clinical efficacy

Nivolumab has shown a clinically meaningful result in terms of ORR and OS in two single arm trials. In patients with PD-L1 expression below 1%, response rates and OS were very much in line to those expected from chemotherapy, also the responses were more durable than achieved with current standard of care.

No useful clinical risk factor or biomarker predictive of treatment response was identified. Based on the above, the CHMP considers the following measures necessary to address issues related to efficacy (Annex II condition):

The value of biomarkers to predict the efficacy of nivolumab therapy should be further explored in patients with urothelial carcinoma:

- To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other genomic-based methods / assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, etc.) as predictive of nivolumab efficacy. This will be provided for urothelial carcinoma studies CA209275 and CA209032: by 30 June 2018
- To further explore in UC patients the early identification of those who do/do not respond to treatment with nivolumab, as well as to evaluate the association between improved clinical outcomes to nivolumab and the presence of:
    - Mutational and neoantigen load, and PD -L1 expression on tumour- and tumour associated immune cells using validated approaches as feasible: by 30 June 2018

2.5. Clinical safety

Introduction

The MAH provided a summary of clinical safety (SCS) that was an integrated view of the safety data from the nivolumab clinical development program supporting the recommended dose schedule for nivolumab monotherapy (3 mg/kg IV Q2W) and the labelling information for an indication in subjects with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following a platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing therapy.

It included safety and tolerability data from 1 Phase 2 study, CA209275: a single arm study of nivolumab (270 treated subjects) in subjects with metastatic or surgically unresectable urothelial carcinoma who have progressed or recurred following treatment with a platinum agent and the 1 supportive Phase 1/2 study, CA209032, an open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in subjects with advanced or metastatic solid tumors (78 treated subjects in nivolumab monotherapy UC cohort). A final CSR for CA209275 based on the 30-May-2016 database lock and an interim CSR for CA209032 based on the 24-Mar-2016 database lock.

Integrated safety data were presented for 348 UC subjects from CA209275 and CA209032 (nivolumab monotherapy UC cohort), hereafter referred to as the 'Integrated UC Population'. Both studies included a nivolumab 3 mg/kg Q2W dosing regimen and the same method of safety data collection. The Integrated UC Population was the population for presentation of safety of nivolumab monotherapy in UC.

Table 38 Summary of Safety Results - All Treated Subjects in CA209275 and Integrated Population

	Number (%) Subjects	
	CA209275 (N = 270)	CA209032 +CA209275 (N = 348)
DEATHS	138 (51.1)	174 (50.0)
WITHIN 30 DAYS OF LAST DOSE	53 (19.6)	60 (17.2)
WITHIN 100 DAYS OF LAST DOSE	121 (44.8)	146 (42.0)
DUE TO STUDY DRUG TOXICITY	3 (1.1) (a)	4 (1.1) (b)

	Number (%) Subjects			
	CA209275 (N = 270)		CA209032 +CA209275 (N = 348)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL CAUSALITY SAEs	147 (54.4)	99 (36.7)	183 (52.6)	122 (35.1)
DRUG-RELATED SAEs	25 (9.3)	18 (6.7)	33 (9.5)	23 (6.6)
ALL CAUSALITY AEs LEADING TO DC	56 (20.7)	42 (15.6)	62 (17.8)	46 (13.2)
DRUG-RELATED AEs LEADING TO DC	13 (4.8)	8 (3.0)	15 (4.3)	10 (2.9)
ALL-CAUSALITY AEs	267 (98.9)	137 (50.7)	345 (99.1)	180 (51.7)
Most Frequent AEs (≥ 20% of Any Grade in either treatment group)				
FATIGUE	87 (32.2)	7 (2.6)	129 (37.1)	10 (2.9)
NAUSEA	60 (22.2)	2 (0.7)	83 (23.9)	3 (0.9)
DECREASED APPETITE	59 (21.9)	6 (2.2)	70 (20.1)	6 (1.7)
DRUG-RELATED AEs	174 (64.4)	48 (17.8)	239 (68.7)	66 (19.0)
Most Frequent Drug-related AEs (≥ 10% of Any Grade in either treatment group)				
FATIGUE	45 (16.7)	5 (1.9)	73 (21.0)	7 (2.0)
PRURITUS	25 (9.3)	0	48 (13.8)	0
ALL CAUSALITY SELECT AES, BY CATEGORY				
ENDOCRINE	43 (15.9)	1 (0.4)	52 (14.9)	1 (0.3)
GASTROINTESTINAL	48 (17.8)	8 (3.0)	64 (18.4)	11 (3.2)
HEPATIC	33 (12.2)	15 (5.6)	45 (12.9)	19 (5.5)
PULMONARY	12 (4.4)	2 (0.7)	14 (4.0)	2 (0.6)
RENAL	28 (10.4)	6 (2.2)	50 (14.4)	11 (3.2)
SKIN	73 (27.0)	4 (1.5)	109 (31.3)	6 (1.7)
HYPERSENSITIVITY/INFUSION REACTION	5 (1.9)	1 (0.4)	8 (2.3)	1 (0.3)
DRUG-RELATED SELECT AES, BY CATEGORY				
ENDOCRINE	39 (14.4)	1 (0.4)	45 (12.9)	1 (0.3)
GASTROINTESTINAL	25 (9.3)	6 (2.2)	33 (9.5)	7 (2.0)
HEPATIC	10 (3.7)	5 (1.9)	14 (4.0)	6 (1.7)
PULMONARY	11 (4.1)	3 (1.1)	13 (3.7)	3 (0.9)
RENAL	3 (1.1)	1 (0.4)	10 (2.9)	2 (0.6)
SKIN	47 (17.4)	4 (1.5)	80 (23.0)	6 (1.7)
HYPERSENSITIVITY/INFUSION REACTION	3 (1.1)	1 (0.4)	5 (1.4)	1 (0.3)

MedDRA Version: 19.0
CTC Version 4.0
Select AEs: Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.

CA209032 crossover subjects are truncated at the first dose date of crossover period.
(a): 3 deaths (Grade 5 cardiovascular failure, Grade 5 pneumonitis, and Grade 5 respiratory failure) were assessed as related to study drug.
(b): For CA209032, 1 death (Subject [redacted] was due to drug-related pneumonitis. One other death (Subject [redacted], not included in the table above, was initially attributed to thrombocytopenia of unknown cause/metastatic urothelial carcinoma, which was subsequently updated to drug-related thrombocytopenia post database lock.

Table 39 Summary of Safety Results (CA209032, CA209275 and Pooled UC)

	CA209032 (N=78) %	CA209275 (N=270) %	Pooled UC CA20925275+CA209032 (N=348) %
All causality AEs, any grade, n (%)	78 (100)	267 (98.9)	345 (99.1)
All causality AEs, Grade 3-4	43 (55.1)	137 (50.7)	180 (51.7)
Drug-related AEs, any grade n (%)	65 (83.3)	174 (64.4)	239 (68.7)
Drug-related AEs, Grade 3-4	18 (23.1)	48 (17.8)	66 (19.0)
Drug-related SAEs, any grade, n (%)	8 (10.3)	25 (9.3)	33 (9.5)
Drug-related SAE, Grade 3-4	5 (6.4)	18 (6.7)	23 (6.6)
Drug-related AEs leading to discontinuation, any grade, n (%)	2 (2.6)	13 (4.8)	15 (4.3)
Drug-related AEs leading to discontinuation, Grade 3-4, n (%)	2 (2.6)	8 (3.0)	10 (2.9)
Drug-related deaths, n (%)	2 (2.6)	3 (1.1)	4 (1.1)

Patient exposure

The nivolumab monotherapy UC safety data from studies CA209275 and CA209032 were pooled for the SCS since both studies used the same dosing schedule and the study populations were comparable. The populations are not comparable enough for pooling of efficacy due to differences in line of therapy. CA209275 and CA209032 are the only studies in which patients with metastatic or surgically unresectable UC have been treated with nivolumab in accordance with International Conference on Harmonisation (ICH) guidance provided in the M4E(R1).

The Study CA209275 is a single arm, open-label Phase 2 trial. Safety analyses were conducted in all 270 subjects with metastatic or surgically unresectable UC who have progressed or recurred following treatment with a platinum agent. At the time of database lock, 270 subjects were treated with nivolumab monotherapy. Safety analyses were conducted in all 270 treated subjects who received at least one dose of study drug. Study CA209032 was a multicenter, open-label, Phase 1/2 study, only data from the nivolumab monotherapy UC cohort is included in the safety analysis. At the time of database lock, 78 subjects were treated with nivolumab monotherapy. Safety analyses were conducted in all 78 treated subjects who received at least one dose of study drug. Both studies included a nivolumab 3 mg/kg Q2W dosing regimen and the same method of safety data collection.

In the Integrated UC Population (Table 40) the majority of subjects (80.2%) received ≥ 90% of the planned nivolumab dose intensity, the median number of nivolumab doses received was 7.0 and the median duration of therapy was 3.25 months with 52.6%, 33.3%, 15.8%, and 5.2% of subjects treated for more than 3, 6, 9, or 12 months, respectively.

Compared with CA209275 and the Integrated UC Population, subjects in CA209032 received a slightly higher median cumulative dose of nivolumab as a higher percentage of subjects were treated for more than 9 and 12 months.

Table 40 Cumulative Dose, Relative Dose Intensity, and Duration of Therapy Summary- All Treated Subjects

	CA209032 N = 78	CA209275 N = 270	CA209032 + CA209275 N = 348
NUMBER OF DOSES RECEIVED			
MEAN (SD)	13.6 (12.24)	9.3 (7.15)	10.2 (8.72)
MEDIAN (MIN - MAX)	8.5 (1 - 46)	7.0 (1 - 30)	7.0 (1 - 46)
CUMULATIVE DOSE (MG/KG)			
MEAN (SD)	40.55 (36.241)	27.82 (21.310)	30.67 (25.918)
MEDIAN (MIN - MAX)	25.88 (3.0 - 138.1)	21.06 (3.0 - 89.0)	21.44 (3.0 - 138.1)
RELATIVE DOSE INTENSITY			
>= 110%	0	0	0
90% TO < 110%	68 (87.2)	211 (78.1)	279 (80.2)
70% TO < 90%	9 (11.5)	51 (18.9)	60 (17.2)
50% TO < 70%	1 (1.3)	5 (1.9)	6 (1.7)
< 50%	0	3 (1.1)	3 (0.9)
DURATION OF THERAPY (MONTHS)			
MIN, MAX (A)	0.0, 20.7+	0.0, 13.4+	0.0, 20.7+
MEDIAN (95% CI) (B)	3.47 (2.33, 5.09)	3.25 (2.33, 3.48)	3.25 (2.73, 3.48)
N OFF TRT/N TREATED (%)	60/78 (76.9)	204/270 (75.6)	264/348 (75.9)
OTHER STATISTICS			
MEAN	6.10	4.13	4.57
STANDARD DEVIATION	5.891	3.437	4.187
> 3 MONTHS (%)	42 (53.8)	141 (52.2)	183 (52.6)
> 6 MONTHS (%)	29 (37.2)	87 (32.2)	116 (33.3)
> 9 MONTHS (%)	23 (29.5)	32 (11.9)	55 (15.8)
> 12 MONTHS (%)	16 (20.5)	2 (0.7)	18 (5.2)

(A) Symbol + indicates a censored value.
(B) Median computed using Kaplan-Meier method.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.
Program Source: Appendix BL.3.1 (cumulative dose and intensity) Appendix BL.3.3 (duration)

Adverse events

Common AEs

In the Integrated UC Population, the frequency, type, and severity of all-causality AEs (any grade and Grade 3-4) reported in subjects treated with nivolumab were consistent with the known safety profile of nivolumab.

In the Integrated UC Population, drug-related AEs consisted mainly of events in the general disorders and administration site conditions, skin and subcutaneous tissue disorders and GI disorders SOCs.

Adverse Events (Regardless of Causality)

In the Integrated UC Population, any-grade AEs (regardless of causality) were reported in 99.1% of subjects treated with nivolumab (Table 41). The most frequently reported AEs were: fatigue (37.1%), nausea (23.9%), anaemia (20.1%), decreased appetite (20.1%), and cough (17.8%).

In the Integrated UC population, Grade 3-4 AEs (regardless of causality) were reported in 51.7% of subjects (Table 41).The most frequently reported Grade 3-4 AEs were anaemia (6.9%), urinary tract infection (5.7%), malignant neoplasm progression (4.3%), dyspnoea (3.7%), asthenia (3.2%), and hyponatremia (3.2%)

Table 41 AEs (All Causality) by Worst CTC Grade Reported within 30 Days of Last Dose in ≥10% of Treated Subjects - CA209275 and Integrated UC Population

System Organ Class (%) Preferred Term (%)	CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	267 (98.9)	137 (50.7)	31 (11.5)	345 (99.1)	180 (51.7)	38 (10.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	177 (65.6)	31 (11.5)	3 (1.1)	231 (66.4)	38 (10.9)	3 (0.9)
FATIGUE	87 (32.2)	7 (2.6)	0	129 (37.1)	10 (2.9)	0
PYREXIA	47 (17.4)	1 (0.4)	0	56 (16.1)	2 (0.6)	0
ASTHENIA	38 (14.1)	11 (4.1)	0	43 (12.4)	11 (3.2)	0
OEDEMA PERIPHERAL	30 (11.1)	0	0	41 (11.8)	0	0
GASTROINTESTINAL DISORDERS	151 (55.9)	30 (11.1)	0	198 (56.9)	39 (11.2)	0
NAUSEA	60 (22.2)	2 (0.7)	0	83 (23.9)	3 (0.9)	0
DIARRHOEA	47 (17.4)	7 (2.6)	0	60 (17.2)	8 (2.3)	0
CONSTIPATION	2 (15.6)	1 (0.4)	0	56 (16.1)	2 (0.6)	0
VOMITING	32 (11.9)	5 (1.9)	0	45 (12.9)	5 (1.4)	0
ABDOMINAL PAIN	29 (10.7)	4 (1.5)	0	43 (12.4)	6 (1.7)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	114 (42.2)	11 (4.1)	0	158 (45.4)	15 (4.3)	0
BACK PAIN	32 (11.9)	3 (1.1)	0	44 (12.6)	4 (1.1)	0
ARTHRALGIA	25 (9.3)	2 (0.7)	0	43 (12.4)	3 (0.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	101 (37.4)	18 (6.7)	3 (1.1)	142 (40.8)	26 (7.5)	4 (1.1)
COUGH	45 (16.7)	0	0	62 (17.8)	0	0
DYSPNOEA	35 (13.0)	9 (3.3)	0	52 (14.9)	13 (3.7)	0
METABOLISM AND NUTRITION DISORDERS	103 (38.1)	25 (9.3)	0	136 (39.1)	32 (9.2)	0
DECREASED APPETITE	59 (21.9)	6 (2.2)	0	70 (20.1)	6 (1.7)	0
INFECTIONS AND INFESTATIONS	103 (38.1)	41 (15.2)	0	133 (38.2)	51 (14.7)	0
URINARY TRACT INFECTION	45 (16.7)	17 (6.3)	0	55 (15.8)	20 (5.7)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	93 (34.4)	6 (2.2)	0	133 (38.2)	9 (2.6)	0
PRURITUS	32 (11.9)	0	0	56 (16.1)	0	0
RASH	28 (10.4)	3 (1.1)	0	33 (9.5)	3 (0.9)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	61 (22.6)	23 (8.5)	0	89 (25.6)	30 (8.6)	0
ANAEMIA	46 (17.0)	18 (6.7)	0	70 (20.1)	24 (6.9)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	57 (21.1)	29 (10.7)	21 (7.8)	67 (19.3)	30 (8.6)	27 (7.8)
MALIGNANT NEOPLASM PROGRESSION	5 (13.0)	14 (5.2)	20 (7.4)	42 (12.1)	15 (4.3)	26 (7.5)

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Frequencies of all-causality AEs (any grade and Grade 3-4) for CA209032 tended to be higher than the Integrated UC Population (Table 42).

Table 42 Summary of Any Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects

System Organ Class (%) Preferred Term (%)	CA209032 N = 78			CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	78 (100.0)	43 (55.1)	7 (9.0)	267 (98.9)	137 (50.7)	31 (11.5)	345 (99.1)	180 (51.7)	38 (10.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	54 (69.2)	7 (9.0)	0	177 (65.6)	31 (11.5)	3 (1.1)	231 (66.4)	38 (10.9)	3 (0.9)
FATIGUE	42 (53.8)	3 (3.8)	0	87 (32.2)	7 (2.6)	0	129 (37.1)	10 (2.9)	0
PYREXIA	9 (11.5)	1 (1.3)	0	47 (17.4)	1 (0.4)	0	56 (16.1)	2 (0.6)	0
ASTHENIA	5 (6.4)	0	0	38 (14.1)	11 (4.1)	0	43 (12.4)	11 (3.2)	0
OEDEMA PERIPHERAL	11 (14.1)	0	0	30 (11.1)	0	0	41 (11.8)	0	0
PAIN	12 (15.4)	0	0	10 (3.7)	4 (1.5)	0	22 (6.3)	4 (1.1)	0
CHILLS	3 (3.8)	0	0	17 (6.3)	0	0	20 (5.7)	0	0
GENERAL PHYSICAL	0	0	0	11 (4.1)	8 (3.0)	2 (0.7)	11 (3.2)	8 (2.3)	2 (0.6)
GASTROINTESTINAL DISORDERS	47 (60.3)	9 (11.5)	0	151 (55.9)	30 (11.1)	0	198 (56.9)	39 (11.2)	0
NAUSEA	23 (29.5)	1 (1.3)	0	60 (22.2)	2 (0.7)	0	83 (23.9)	3 (0.9)	0
DIARRHOEA	13 (16.7)	1 (1.3)	0	47 (17.4)	7 (2.6)	0	60 (17.2)	8 (2.3)	0
CONSTIPATION	14 (17.9)	1 (1.3)	0	42 (15.6)	1 (0.4)	0	56 (16.1)	2 (0.6)	0
VOMITING	13 (16.7)	0	0	32 (11.9)	5 (1.9)	0	45 (12.9)	5 (1.4)	0
ABDOMINAL PAIN	14 (17.9)	2 (2.6)	0	29 (10.7)	4 (1.5)	0	43 (12.4)	6 (1.7)	0
DRY MOUTH	8 (10.3)	0	0	6 (2.2)	0	0	14 (4.0)	0	0
SMALL INTESTINAL OBSTRUCTION	1 (1.3)	1 (1.3)	0	7 (2.6)	5 (1.9)	0	8 (2.3)	6 (1.7)	0
ABDOMINAL DISTENSION	1 (1.3)	0	0	5 (1.9)	0	0	6 (1.7)	0	0
ABDOMINAL PAIN UPPER	4 (5.1)	1 (1.3)	0	2 (0.7)	0	0	6 (1.7)	1 (0.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	44 (56.4)	4 (5.1)	0	114 (42.2)	11 (4.1)	0	158 (45.4)	15 (4.3)	0
BACK PAIN	12 (15.4)	1 (1.3)	0	32 (11.9)	3 (1.1)	0	44 (12.6)	4 (1.1)	0
ARTHRALGIA	18 (23.1)	1 (1.3)	0	25 (9.3)	2 (0.7)	0	43 (12.4)	3 (0.9)	0
MYALGIA	8 (10.3)	0	0	16 (5.9)	1 (0.4)	0	24 (6.9)	1 (0.3)	0
PAIN IN EXTREMITY	7 (9.0)	0	0	17 (6.3)	0	0	24 (6.9)	0	0
MUSCULOSKELETAL PAIN	6 (7.7)	0	0	17 (6.3)	1 (0.4)	0	23 (6.6)	1 (0.3)	0
MUSCULAR WEAKNESS	4 (5.1)	0	0	10 (3.7)	1 (0.4)	0	14 (4.0)	1 (0.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	41 (52.6)	8 (10.3)	1 (1.3)	101 (37.4)	18 (6.7)	3 (1.1)	142 (40.8)	26 (7.5)	4 (1.1)
COUGH	17 (21.8)	0	0	45 (16.7)	0	0	62 (17.8)	0	0
DYSPNOEA	17 (21.8)	4 (5.1)	0	35 (13.0)	9 (3.3)	0	52 (14.9)	13 (3.7)	0
PLEURAL EFFUSION	5 (6.4)	1 (1.3)	0	11 (4.1)	4 (1.5)	0	16 (4.6)	5 (1.4)	0
PNEUMONITIS	2 (2.6)	0	1 (1.3)	11 (4.1)	2 (0.7)	1 (0.4)	13 (3.7)	2 (0.6)	2 (0.6)
NASAL CONGESTION	6 (7.7)	0	0	5 (1.9)	0	0	11 (3.2)	0	0
OROPHARYNGEAL PAIN	3 (3.8)	0	0	6 (2.2)	0	0	9 (2.6)	0	0
RHINORRHOEA	3 (3.8)	0	0	6 (2.2)	0	0	9 (2.6)	0	0
PRODUCTIVE COUGH	5 (6.4)	0	0	3 (1.1)	0	0	8 (2.3)	0	0
METABOLISM AND NUTRITION DISORDERS	33 (42.3)	7 (9.0)	0	103 (38.1)	25 (9.3)	0	136 (39.1)	32 (9.2)	0
DECREASED APPETITE	11 (14.1)	0	0	59 (21.9)	6 (2.2)	0	70 (20.1)	6 (1.7)	0
HYPERGLYCAEMIA	15 (19.2)	4 (5.1)	0	7 (2.6)	3 (1.1)	0	22 (6.3)	7 (2.0)	0
DEHYDRATION	4 (5.1)	0	0	17 (6.3)	2 (0.7)	0	21 (6.0)	2 (0.6)	0
HYPONATRAEMIA	6 (7.7)	3 (3.8)	0	14 (5.2)	8 (3.0)	0	20 (5.7)	11 (3.2)	0
HYPERKALAEMIA	4 (5.1)	0	0	11 (4.1)	4 (1.5)	0	15 (4.3)	4 (1.1)	0
HYPOMAGNESAEMIA	6 (7.7)	0	0	8 (3.0)	0	0	14 (4.0)	0	0
HYPOKALAEMIA	6 (7.7)	0	0	7 (2.6)	1 (0.4)	0	13 (3.7)	1 (0.3)	0
HYPOALBUMINAEMIA	4 (5.1)	0	0	6 (2.2)	0	0	10 (2.9)	0	0
INFECTIONS AND INFESTATIONS	30 (38.5)	10 (12.8)	0	103 (38.1)	41 (15.2)	0	133 (38.2)	51 (14.7)	0
URINARY TRACT INFECTION	10 (12.8)	3 (3.8)	0	45 (16.7)	17 (6.3)	0	55 (15.8)	20 (5.7)	0
UPPER RESPIRATORY TRACT INFECTION	7 (9.0)	0	0	11 (4.1)	0	0	18 (5.2)	0	0
INFECTION	4 (5.1)	3 (3.8)	0	7 (2.6)	4 (1.5)	0	11 (3.2)	7 (2.0)	0
SEPSIS	1 (1.3)	1 (1.3)	0	10 (3.7)	10 (3.7)	0	11 (3.2)	11 (3.2)	0
BRONCHITIS	4 (5.1)	1 (1.3)	0	5 (1.9)	1 (0.4)	0	9 (2.6)	2 (0.6)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	40 (51.3)	3 (3.8)	0	93 (34.4)	6 (2.2)	0	133 (38.2)	9 (2.6)	0
PRURITUS	24 (30.8)	0	0	32 (11.9)	0	0	56 (16.1)	0	0
RASH	5 (6.4)	0	0	28 (10.4)	3 (1.1)	0	33 (9.5)	3 (0.9)	0
RASH MACULO-PAPULAR	16 (20.5)	2 (2.6)	0	5 (1.9)	1 (0.4)	0	21 (6.0)	3 (0.9)	0
DRY SKIN	7 (9.0)	0	0	9 (3.3)	0	0	16 (4.6)	0	0
HYPERHIDROSIS	1 (1.3)	0	0	9 (3.3)	0	0	10 (2.9)	0	0
DERMATITIS ACNEIFORM	4 (5.1)	1 (1.3)	0	1 (0.4)	0	0	5 (1.4)	1 (0.3)	0
ERYTHEMA	1 (1.3)	0	0	4 (1.5)	0	0	5 (1.4)	0	0
ALOPECIA	2 (2.6)	0	0	2 (0.7)	0	0	4 (1.1)	0	0

System Organ Class (%) Preferred Term (%)	CA209032 N = 78			CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
INVESTIGATIONS	38 (48.7)	13 (16.7)	0	94 (34.8)	26 (9.6)	0	132 (37.9)	39 (11.2)	0
BLOOD CREATININE INCREASED	14 (17.9)	0	0	18 (6.7)	2 (0.7)	0	32 (9.2)	2 (0.6)	0
WEIGHT DECREASED	4 (5.1)	0	0	19 (7.0)	0	0	23 (6.6)	0	0
LIPASE INCREASED	11 (14.1)	4 (5.1)	0	7 (2.6)	5 (1.9)	0	18 (5.2)	9 (2.6)	0
ALANINE AMINOTRANSFERASE INCREASED	7 (9.0)	1 (1.3)	0	10 (3.7)	2 (0.7)	0	17 (4.9)	3 (0.9)	0

BLOOD ALKALINE PHOSPHATASE INCREASED	6 (7.7)	1 (1.3)	0	11 (4.1)	4 (1.5)	0	17 (4.9)	5 (1.4)	0			
AMYLASE INCREASED	7 (9.0)	4 (5.1)	0	8 (3.0)	6 (2.2)	0	15 (4.3)	10 (2.9)	0			
ASPARTATE AMINOTRANSFERASE INCREASED	5 (6.4)	1 (1.3)	0	10 (3.7)	6 (2.2)	0	15 (4.3)	7 (2.0)	0			
BLOOD BILIRUBIN INCREASED	1 (1.3)	0	0	10 (3.7)	5 (1.9)	0	11 (3.2)	5 (1.4)	0			
BLOOD THYROID STIMULATING HORMONE INCREASED	1 (1.3)	0	0	10 (3.7)	0	0	11 (3.2)	0	0			
PLATELET COUNT DECREASED	6 (7.7)	0	0	5 (1.9)	3 (1.1)	0	11 (3.2)	3 (0.9)	0			
LYMPHOCYTE COUNT DECREASED	5 (6.4)	2 (2.6)	0	4 (1.5)	3 (1.1)	0	9 (2.6)	5 (1.4)	0			
NEUTROPHIL COUNT DECREASED	3 (3.8)	2 (2.6)	0	4 (1.5)	1 (0.4)	0	7 (2.0)	3 (0.9)	0			
WHITE BLOOD CELL COUNT DECREASED	4 (5.1)	1 (1.3)	0	3 (1.1)	1 (0.4)	0	7 (2.0)	2 (0.6)	0			
BLOOD THYROID STIMULATING HORMONE DECREASED	0	0	0	5 (1.9)	0	0	5 (1.4)	0	0			
BLOOD UREA INCREASED	5 (6.4)	0	0	0	0	0	5 (1.4)	0	0			
NERVOUS SYSTEM DISORDERS	29 (37.2)	2 (2.6)	0	70 (25.9)	8 (3.0)	0	99 (28.4)	10 (2.9)	0			
HEADACHE	10 (12.8)	0	0	17 (6.3)	0	0	27 (7.8)	0	0			
DIZZINESS	4 (5.1)	0	0	13 (4.8)	1 (0.4)	0	17 (4.9)	1 (0.3)	0			
PARAESTHESIA	2 (2.6)	0	0	13 (4.8)	2 (0.7)	0	15 (4.3)	2 (0.6)	0			
DYSGEUSIA	2 (2.6)	0	0	7 (2.6)	0	0	9 (2.6)	0	0			
PERIPHERAL SENSORY NEUROPATHY	8 (10.3)	0	0	0	0	0	8 (2.3)	0	0			
BLOOD AND LYMPHATIC SYSTEM DISORDERS	28 (35.9)	7 (9.0)	0	61 (22.6)	23 (8.5)	0	89 (25.6)	30 (8.6)	0			
ANAEMIA	24 (30.8)	6 (7.7)	0	46 (17.0)	18 (6.7)	0	70 (20.1)	24 (6.9)	0			
THROMBOCYTOPENIA	3 (3.8)	1 (1.3)	0	7 (2.6)	1 (0.4)	0	10 (2.9)	2 (0.6)	0			
LYMPHOPENIA	1 (1.3)	0	0	4 (1.5)	1 (0.4)	0	5 (1.4)	1 (0.3)	0			
NEUTROPENIA	1 (1.3)	0	0	4 (1.5)	2 (0.7)	0	5 (1.4)	2 (0.6)	0			
LEUKOCYTOSIS	1 (1.3)	1 (1.3)	0	3 (1.1)	1 (0.4)	0	4 (1.1)	2 (0.6)	0			
EOSINOPHILIA	1 (1.3)	0	0	1 (0.4)	0	0	2 (0.6)	0	0			
RENAL AND URINARY DISORDERS	29 (37.2)	11 (14.1)	0	51 (18.9)	17 (6.3)	0	80 (23.0)	28 (8.0)	0			
HAEMATURIA	14 (17.9)	4 (5.1)	0	16 (5.9)	4 (1.5)	0	30 (8.6)	8 (2.3)	0			
ACUTE KIDNEY INJURY	8 (10.3)	4 (5.1)	0	6 (2.2)	2 (0.7)	0	14 (4.0)	6 (1.7)	0			
DYSURIA	2 (2.6)	0	0	7 (2.6)	0	0	9 (2.6)	0	0			
HYDRONEPHROSIS	2 (2.6)	1 (1.3)	0	4 (1.5)	2 (0.7)	0	6 (1.7)	3 (0.9)	0			
URINARY INCONTINENCE	2 (2.6)	0	0	4 (1.5)	0	0	6 (1.7)	0	0			
URINARY TRACT OBSTRUCTION	2 (2.6)	1 (1.3)	0	4 (1.5)	4 (1.5)	0	6 (1.7)	5 (1.4)	0			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	10 (12.8)	1 (1.3)	6 (7.7)	57 (21.1)	29 (10.7)	21 (7.8)	67 (19.3)	30 (8.6)	27 (7.8)			
MALIGNANT NEOPLASM PROGRESSION	7 (9.0)	1 (1.3)	6 (7.7)	35 (13.0)	14 (5.2)	20 (7.4)	42 (12.1)	15 (4.3)	26 (7.5)			
PSYCHIATRIC DISORDERS	13 (16.7)	1 (1.3)	0	46 (17.0)	1 (0.4)	0	59 (17.0)	2 (0.6)	0			
INSOMNIA	5 (6.4)	0	0	23 (8.5)	0	0	28 (8.0)	0	0			
ANXIETY	4 (5.1)	0	0	14 (5.2)	1 (0.4)	0	18 (5.2)	1 (0.3)	0			
DEPRESSION	2 (2.6)	0	0	6 (2.2)	0	0	8 (2.3)	0	0			
VASCULAR DISORDERS	13 (16.7)	2 (2.6)	0	43 (15.9)	8 (3.0)	2 (0.7)	56 (16.1)	10 (2.9)	2 (0.6)			
HYPOTENSION	4 (5.1)	0	0	14 (5.2)	2 (0.7)	0	18 (5.2)	2 (0.6)	0			
HYPERTENSION	3 (3.8)	1 (1.3)	0	9 (3.3)	1 (0.4)	0	12 (3.4)	2 (0.6)	0			
DEEP VEIN THROMBOSIS	2 (2.6)	1 (1.3)	0	5 (1.9)	2 (0.7)	0	7 (2.0)	3 (0.9)	0			
ENDOCRINE DISORDERS	9 (11.5)	0	0	35 (13.0)	1 (0.4)	0	44 (12.6)	1 (0.3)	0			
HYPOTHYROIDISM	7 (9.0)	0	0	26 (9.6)	0	0	33 (9.5)	0	0			
HYPERTHYROIDISM	3 (3.8)	0	0	11 (4.1)	0	0	14 (4.0)	0	0			

System Organ Class (%) Preferred Term (%)	CA209032 N = 78			CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
EYE DISORDERS	11 (14.1)	1 (1.3)	0	17 (6.3)	0	0	28 (8.0)	1 (0.3)	0
VISION BLURRED	2 (2.6)	0	0	7 (2.6)	0	0	9 (2.6)	0	0
LACRIMATION INCREASED	2 (2.6)	0	0	2 (0.7)	0	0	4 (1.1)	0	0
CONJUNCTIVAL HAEMORRHAGE	1 (1.3)	0	0	1 (0.4)	0	0	2 (0.6)	0	0
CARDIAC DISORDERS	3 (3.8)	0	0	22 (8.1)	5 (1.9)	2 (0.7)	25 (7.2)	5 (1.4)	2 (0.6)
TACHYCARDIA	0	0	0	10 (3.7)	1 (0.4)	0	10 (2.9)	1 (0.3)	0
ATRIAL FIBRILLATION	0	0	0	3 (1.1)	2 (0.7)	0	3 (0.9)	2 (0.6)	0
SINUS BRADYCARDIA	0	0	0	3 (1.1)	0	0	3 (0.9)	0	0
PALPITATIONS	1 (1.3)	0	0	1 (0.4)	0	0	2 (0.6)	0	0
SINUS TACHYCARDIA	2 (2.6)	0	0	0	0	0	2 (0.6)	0	0
HEPATOBILIARY DISORDERS	1 (1.3)	1 (1.3)	0	13 (4.8)	4 (1.5)	0	14 (4.0)	5 (1.4)	0

Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Frequencies of all-causality AEs (any grade and Grade 3-4) for CA209032 tended to be higher than the Integrated UC Population also in Extended Follow-up (see Table 43 below).

Table 43 Summary of Any Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with Extended Follow-up - All Treated Subjects

System Organ Class (%) Preferred Term (%)	CA209032 N = 78			CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	78 (100.0)	33 (42.3)	24 (30.8)	268 (99.3)	108 (40.0)	88 (32.6)	346 (99.4)	141 (40.5)	112 (32.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	55 (70.5)	9 (11.5)	1 (1.3)	184 (68.1)	39 (14.4)	7 (2.6)	239 (68.7)	48 (13.8)	8 (2.3)
FATIGUE	43 (55.1)	4 (5.1)	0	89 (33.0)	8 (3.0)	0	132 (37.9)	12 (3.4)	0
PYREXIA	9 (11.5)	1 (1.3)	0	48 (17.8)	1 (0.4)	0	57 (16.4)	2 (0.6)	0
ASTHENIA	5 (6.4)	0	0	39 (14.4)	11 (4.1)	0	44 (12.6)	11 (3.2)	0
OEDEMA PERIPHERAL	12 (15.4)	0	0	32 (11.9)	0	0	44 (12.6)	0	0
PAIN	13 (16.7)	1 (1.3)	0	12 (4.4)	6 (2.2)	0	25 (7.2)	7 (2.0)	0
CHILLS	3 (3.8)	0	0	18 (6.7)	0	0	21 (6.0)	0	0
GENERAL PHYSICAL	0	0	0	15 (5.6)	9 (3.3)	5 (1.9)	15 (4.3)	9 (2.6)	5 (1.4)
GASTROINTESTINAL DISORDERS	47 (60.3)	10 (12.8)	0	156 (57.8)	37 (13.7)	1 (0.4)	203 (58.3)	47 (13.5)	1 (0.3)
NAUSEA	23 (29.5)	1 (1.3)	0	64 (23.7)	2 (0.7)	0	87 (25.0)	3 (0.9)	0
DIARRHOEA	13 (16.7)	1 (1.3)	0	50 (18.5)	8 (3.0)	0	63 (18.1)	9 (2.6)	0
CONSTIPATION	15 (19.2)	1 (1.3)	0	45 (16.7)	1 (0.4)	0	60 (17.2)	2 (0.6)	0
VOMITING	13 (16.7)	0	0	35 (13.0)	5 (1.9)	0	48 (13.8)	5 (1.4)	0
ABDOMINAL PAIN	15 (19.2)	3 (3.8)	0	30 (11.1)	4 (1.5)	0	45 (12.9)	7 (2.0)	0
DRY MOUTH	8 (10.3)	0	0	7 (2.6)	0	0	15 (4.3)	0	0
SMALL INTESTINAL OBSTRUCTION	1 (1.3)	1 (1.3)	0	8 (3.0)	6 (2.2)	0	9 (2.6)	7 (2.0)	0
DYSPEPSIA	2 (2.6)	0	0	6 (2.2)	0	0	8 (2.3)	0	0
ABDOMINAL DISTENSION	1 (1.3)	0	0	6 (2.2)	0	0	7 (2.0)	0	0
ABDOMINAL PAIN UPPER	4 (5.1)	1 (1.3)	0	3 (1.1)	0	0	7 (2.0)	1 (0.3)	0
FLATULENCE	4 (5.1)	1 (1.3)	0	3 (1.1)	0	0	7 (2.0)	1 (0.3)	0
STOMATITIS	3 (3.8)	0	0	4 (1.5)	0	0	7 (2.0)	0	0
GASTROOESOPHAGEAL REFLUX DISEASE	1 (1.3)	0	0	5 (1.9)	0	0	6 (1.7)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	44 (56.4)	4 (5.1)	0	117 (43.3)	12 (4.4)	0	161 (46.3)	16 (4.6)	0
BACK PAIN	12 (15.4)	1 (1.3)	0	35 (13.0)	4 (1.5)	0	47 (13.5)	5 (1.4)	0
ARTHRALGIA	18 (23.1)	1 (1.3)	0	27 (10.0)	2 (0.7)	0	45 (12.9)	3 (0.9)	0
MYALGIA	8 (10.3)	0	0	17 (6.3)	1 (0.4)	0	25 (7.2)	1 (0.3)	0
PAIN IN EXTREMITY	7 (9.0)	0	0	18 (6.7)	0	0	25 (7.2)	0	0
MUSCULOSKELETAL PAIN	6 (7.7)	0	0	18 (6.7)	1 (0.4)	0	24 (6.9)	1 (0.3)	0
MUSCULAR WEAKNESS	4 (5.1)	0	0	11 (4.1)	1 (0.4)	0	15 (4.3)	1 (0.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	43 (55.1)	9 (11.5)	1 (1.3)	107 (39.6)	20 (7.4)	3 (1.1)	150 (43.1)	29 (8.3)	4 (1.1)
COUGH	17 (21.8)	0	0	45 (16.7)	0	0	62 (17.8)	0	0
DYSPNOEA	19 (24.4)	5 (6.4)	0	37 (13.7)	10 (3.7)	0	56 (16.1)	15 (4.3)	0
PLEURAL EFFUSION	5 (6.4)	1 (1.3)	0	13 (4.8)	4 (1.5)	0	18 (5.2)	5 (1.4)	0
PNEUMONITIS	2 (2.6)	0	1 (1.3)	11 (4.1)	2 (0.7)	1 (0.4)	13 (3.7)	2 (0.6)	2 (0.6)
NASAL CONGESTION	6 (7.7)	0	0	5 (1.9)	0	0	11 (3.2)	0	0
OROPHARYNGEAL PAIN	3 (3.8)	0	0	6 (2.2)	0	0	9 (2.6)	0	0
RHINORRHOEA	3 (3.8)	0	0	6 (2.2)	0	0	9 (2.6)	0	0
PRODUCTIVE COUGH	5 (6.4)	0	0	3 (1.1)	0	0	8 (2.3)	0	0
DYSPHONIA	2 (2.6)	0	0	5 (1.9)	0	0	7 (2.0)	0	0
RESPIRATORY FAILURE	0	0	0	7 (2.6)	6 (2.2)	1 (0.4)	7 (2.0)	6 (1.7)	1 (0.3)
METABOLISM AND NUTRITION DISORDERS	33 (42.3)	8 (10.3)	0	109 (40.4)	26 (9.6)	0	142 (40.8)	34 (9.8)	0
DECREASED APPETITE	11 (14.1)	0	0	62 (23.0)	6 (2.2)	0	73 (21.0)	6 (1.7)	0
HYPERGLYCAEMIA	15 (19.2)	4 (5.1)	0	8 (3.0)	3 (1.1)	0	23 (6.6)	7 (2.0)	0
HYPONATRAEMIA	6 (7.7)	3 (3.8)	0	16 (5.9)	9 (3.3)	0	22 (6.3)	12 (3.4)	0
DEHYDRATION	4 (5.1)	0	0	17 (6.3)	2 (0.7)	0	21 (6.0)	2 (0.6)	0
HYPOKALAEMIA	6 (7.7)	1 (1.3)	0	10 (3.7)	1 (0.4)	0	16 (4.6)	2 (0.6)	0
HYPOMAGNESAEMIA	8 (10.3)	0	0	8 (3.0)	0	0	16 (4.6)	0	0
HYPERKALAEMIA	4 (5.1)	0	0	11 (4.1)	4 (1.5)	0	15 (4.3)	4 (1.1)	0
HYPOALBUMINAEMIA	6 (7.7)	0	0	6 (2.2)	0	0	12 (3.4)	0	0
INFECTIONS AND INFESTATIONS	30 (38.5)	10 (12.8)	0	108 (40.0)	49 (18.1)	1 (0.4)	138 (39.7)	59 (17.0)	1 (0.3)
URINARY TRACT INFECTION	10 (12.8)	3 (3.8)	0	46 (17.0)	19 (7.0)	0	56 (16.1)	22 (6.3)	0
UPPER RESPIRATORY TRACT INFECTION	7 (9.0)	0	0	11 (4.1)	0	0	18 (5.2)	0	0
SEPSIS	1 (1.3)	1 (1.3)	0	12 (4.4)	12 (4.4)	0	13 (3.7)	13 (3.7)	0
INFECTION	4 (5.1)	3 (3.8)	0	8 (3.0)	4 (1.5)	0	12 (3.4)	7 (2.0)	0
BRONCHITIS	4 (5.1)	1 (1.3)	0	5 (1.9)	1 (0.4)	0	9 (2.6)	2 (0.6)	0

INVESTIGATIONS	40 (51.3)	13 (16.7)	0	98 (36.3)	28 (10.4)	0	138 (39.7)	41 (11.8)	0		
BLOOD CREATININE INCREASED	15 (19.2)	0	0	18 (6.7)	2 (0.7)	0	33 (9.5)	2 (0.6)	0		
WEIGHT DECREASED	5 (6.4)	0	0	20 (7.4)	0	0	25 (7.2)	0	0		
BLOOD ALKALINE PHOSPHATASE INCREASED	7 (9.0)	1 (1.3)	0	11 (4.1)	4 (1.5)	0	18 (5.2)	5 (1.4)	0		
LIPASE INCREASED	11 (14.1)	4 (5.1)	0	7 (2.6)	5 (1.9)	0	18 (5.2)	9 (2.6)	0		
ALANINE AMINOTRANSFERASE INCREASED	7 (9.0)	1 (1.3)	0	10 (3.7)	2 (0.7)	0	17 (4.9)	3 (0.9)	0		
AMYLASE INCREASED	7 (9.0)	4 (5.1)	0	8 (3.0)	6 (2.2)	0	15 (4.3)	10 (2.9)	0		
ASPARTATE AMINOTRANSFERASE INCREASED	5 (6.4)	1 (1.3)	0	10 (3.7)	6 (2.2)	0	15 (4.3)	7 (2.0)	0		
PLATELET COUNT DECREASED	7 (9.0)	0	0	8 (3.0)	5 (1.9)	0	15 (4.3)	5 (1.4)	0		
BLOOD THYROID STIMULATING HORMONE INCREASED	2 (2.6)	0	0	10 (3.7)	0	0	12 (3.4)	0	0		
BLOOD BILIRUBIN INCREASED	1 (1.3)	0	0	10 (3.7)	5 (1.9)	0	11 (3.2)	5 (1.4)	0		
LYMPHOCYTE COUNT DECREASED	6 (7.7)	2 (2.6)	0	4 (1.5)	3 (1.1)	0	10 (2.9)	5 (1.4)	0		
NEUTROPHIL COUNT DECREASED	3 (3.8)	2 (2.6)	0	5 (1.9)	2 (0.7)	0	8 (2.3)	4 (1.1)	0		
WHITE BLOOD CELL COUNT DECREASED	4 (5.1)	1 (1.3)	0	4 (1.5)	2 (0.7)	0	8 (2.3)	3 (0.9)	0		
BLOOD THYROID STIMULATING HORMONE DECREASED	0	0	0	5 (1.9)	0	0	5 (1.4)	0	0		
BLOOD UREA INCREASED	5 (6.4)	0	0	0	0	0	5 (1.4)	0	0		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	40 (51.3)	3 (3.8)	0	98 (36.3)	6 (2.2)	0	138 (39.7)	9 (2.6)	0		
PRURITUS	24 (30.8)	0	0	32 (11.9)	0	0	56 (16.1)	0	0		
RASH	5 (6.4)	0	0	28 (10.4)	3 (1.1)	0	33 (9.5)	3 (0.9)	0		
RASH MACULO-PAPULAR	17 (21.8)	2 (2.6)	0	6 (2.2)	1 (0.4)	0	23 (6.6)	3 (0.9)	0		
DRY SKIN	7 (9.0)	0	0	9 (3.3)	0	0	16 (4.6)	0	0		
HYPERHIDROSIS	1 (1.3)	0	0	10 (3.7)	0	0	11 (3.2)	0	0		
ERYTHEMA	1 (1.3)	0	0	7 (2.6)	0	0	8 (2.3)	0	0		
ALOPECIA	2 (2.6)	0	0	4 (1.5)	0	0	6 (1.7)	0	0		
DERMATITIS ACNEIFORM	4 (5.1)	1 (1.3)	0	1 (0.4)	0	0	5 (1.4)	1 (0.3)	0		
ECZEMA	0	0	0	4 (1.5)	0	0	4 (1.1)	0	0		
NIGHT SWEATS	2 (2.6)	0	0	2 (0.7)	0	0	4 (1.1)	0	0		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	24 (30.8)	1 (1.3)	21 (26.9)	95 (35.2)	19 (7.0)	71 (26.3)	119 (34.2)	20 (5.7)	92 (26.4)		
MALIGNANT NEOPLASM PROGRESSION	22 (28.2)	1 (1.3)	21 (26.9)	78 (28.9)	12 (4.4)	66 (24.4)	100 (28.7)	13 (3.7)	87 (25.0)		
METASTASES TO CENTRAL NERVOUS SYSTEM	0	0	0	6 (2.2)	5 (1.9)	0	6 (1.7)	5 (1.4)	0		
CANCER PAIN	0	0	0	5 (1.9)	3 (1.1)	0	5 (1.4)	3 (0.9)	0		
TUMOUR PAIN	1 (1.3)	0	0	3 (1.1)	2 (0.7)	0	4 (1.1)	2 (0.6)	0		
TRANSITIONAL CELL CARCINOMA	0	0	0	3 (1.1)	0	3 (1.1)	3 (0.9)	0	3 (0.9)		

System Organ Class (%) Preferred Term (%)	CA209032 N = 78			CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
NERVOUS SYSTEM DISORDERS	31 (39.7)	3 (3.8)	0	75 (27.8)	10 (3.7)	1 (0.4)	106 (30.5)	13 (3.7)	1 (0.3)
HEADACHE	11 (14.1)	1 (1.3)	0	17 (6.3)	0	0	28 (8.0)	1 (0.3)	0
DIZZINESS	4 (5.1)	0	0	13 (4.8)	1 (0.4)	0	17 (4.9)	1 (0.3)	0
PARAESTHESIA	2 (2.6)	0	0	14 (5.2)	2 (0.7)	0	16 (4.6)	2 (0.6)	0
DYSGEUSIA	3 (3.8)	0	0	7 (2.6)	0	0	10 (2.9)	0	0
PERIPHERAL SENSORY NEUROPATHY	8 (10.3)	0	0	0	0	0	8 (2.3)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	28 (35.9)	7 (9.0)	1 (1.3)	64 (23.7)	28 (10.4)	0	92 (26.4)	35 (10.1)	1 (0.3)
ANAEMIA	24 (30.8)	6 (7.7)	0	47 (17.4)	20 (7.4)	0	71 (20.4)	26 (7.5)	0
THROMBOCYTOPENIA	3 (3.8)	0	1 (1.3)	8 (3.0)	2 (0.7)	0	11 (3.2)	2 (0.6)	1 (0.3)
LEUKOCYTOSIS	2 (2.6)	2 (2.6)	0	3 (1.1)	1 (0.4)	0	5 (1.4)	3 (0.9)	0
LYMPHOPENIA	1 (1.3)	0	0	4 (1.5)	1 (0.4)	0	5 (1.4)	1 (0.3)	0
NEUTROPENIA	1 (1.3)	0	0	4 (1.5)	2 (0.7)	0	5 (1.4)	2 (0.6)	0
EOSINOPHILIA	1 (1.3)	0	0	1 (0.4)	0	0	2 (0.6)	0	0
RENAL AND URINARY DISORDERS	29 (37.2)	11 (14.1)	0	52 (19.3)	19 (7.0)	0	81 (23.3)	30 (8.6)	0
HAEMATURIA	14 (17.9)	4 (5.1)	0	17 (6.3)	4 (1.5)	0	31 (8.9)	8 (2.3)	0
ACUTE KIDNEY INJURY	8 (10.3)	4 (5.1)	0	7 (2.6)	3 (1.1)	0	15 (4.3)	7 (2.0)	0
DYSURIA	2 (2.6)	0	0	7 (2.6)	0	0	9 (2.6)	0	0
URINARY INCONTINENCE	3 (3.8)	0	0	4 (1.5)	0	0	7 (2.0)	0	0
PSYCHIATRIC DISORDERS	13 (16.7)	1 (1.3)	0	49 (18.1)	2 (0.7)	0	62 (17.8)	3 (0.9)	0
INSOMNIA	5 (6.4)	0	0	24 (8.9)	0	0	29 (8.3)	0	0
ANXIETY	4 (5.1)	0	0	16 (5.9)	2 (0.7)	0	20 (5.7)	2 (0.6)	0
VASCULAR DISORDERS	14 (17.9)	2 (2.6)	0	46 (17.0)	8 (3.0)	2 (0.7)	60 (17.2)	10 (2.9)	2 (0.6)
HYPOTENSION	5 (6.4)	0	0	14 (5.2)	2 (0.7)	0	19 (5.5)	2 (0.6)	0
HYPERTENSION	3 (3.8)	1 (1.3)	0	10 (3.7)	1 (0.4)	0	13 (3.7)	2 (0.6)	0
DEEP VEIN THROMBOSIS	2 (2.6)	1 (1.3)	0	5 (1.9)	2 (0.7)	0	7 (2.0)	3 (0.9)	0
ENDOCRINE DISORDERS	9 (11.5)	0	0	37 (13.7)	1 (0.4)	0	46 (13.2)	1 (0.3)	0
HYPOTHYROIDISM	7 (9.0)	0	0	27 (10.0)	0	0	34 (9.8)	0	0
HYPERTHYROIDISM	3 (3.8)	0	0	12 (4.4)	0	0	15 (4.3)	0	0

EYE DISORDERS	11 (14.1)	1 (1.3)	0	18 (6.7)	0	0	29 (8.3)	1 (0.3)	0
VISION BLURRED	2 (2.6)	0	0	7 (2.6)	0	0	9 (2.6)	0	0
LACRIMATION INCREASED	2 (2.6)	0	0	2 (0.7)	0	0	4 (1.1)	0	0
CONJUNCTIVAL HAEMORRHAGE	1 (1.3)	0	0	1 (0.4)	0	0	2 (0.6)	0	0
EYE PRURITUS	2 (2.6)	0	0	0	0	0	2 (0.6)	0	0
CARDIAC DISORDERS	3 (3.8)	0	0	23 (8.5)	5 (1.9)	2 (0.7)	26 (7.5)	5 (1.4)	2 (0.6)
TACHYCARDIA	0	0	0	10 (3.7)	1 (0.4)	0	10 (2.9)	1 (0.3)	0
ATRIAL FIBRILLATION	0	0	0	3 (1.1)	2 (0.7)	0	3 (0.9)	2 (0.6)	0
SINUS BRADYCARDIA	0	0	0	3 (1.1)	0	0	3 (0.9)	0	0
SINUS TACHYCARDIA	2 (2.6)	0	0	1 (0.4)	0	0	3 (0.9)	0	0
PALPITATIONS	1 (1.3)	0	0	1 (0.4)	0	0	2 (0.6)	0	0

Includes events reported between first dose and 100 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Drug-related AEs

In the Integrated UC Population, any-grade drug-related AEs were reported in 68.7% of subjects (Table 44).The most frequently reported drug-related AEs were fatigue (21.0%), pruritus (13.8%), diarrhoea (8.9%), nausea (8.3%), and decreased appetite (7.8%)

In the Integrated UC Population, Grade 3-4 drug-related AEs were reported in 19.0% of subjects (Table 44).The most frequently reported Grade 3-4 drug-related AEs were lipase increased (2.3%) and fatigue (2.0%).

Table 44 Drug-related AEs by Worst CTC Grade Reported in ≥ 5% of Treated Subjects - CA209275 and Integrated UC Population

System Organ Class (%) Preferred Term (%)	CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade
TOTAL SUBJECTS WITH AN EVENT	174 (64.4)	48 (17.8)	3 (1.1)	239 (68.7)	66 (19.0)	4 (
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	80 (29.6)	10 (3.7)	0	109 (31.3)	12 (3.4)	0
FATIGUE	45 (16.7)	5 (1.9)	0	73 (21.0)	7 (2.0)	0
ASTHENIA	16 (5.9)	4 (1.5)	0	18 (5.2)	4 (1.1)	0
PYREXIA	15 (5.6)	0	0	17 (4.9)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	54 (20.0)	6 (2.2)	0	88 (25.3)	9 (2.6)	0
PRURITUS	25 (9.3)	0	0	48 (13.8)	0	0
RASH	16 (5.9)	3 (1.1)	0	21 (6.0)	3 (0.9)	0
RASH MACULO-PAPULAR	4 (1.5)	1 (0.4)	0	18 (5.2)	3 (0.9)	0
GASTROINTESTINAL DISORDERS	54 (20.0)	7 (2.6)	0	78 (22.4)	9 (2.6)	0
DIARRHOEA	24 (8.9)	5 (1.9)	0	31 (8.9)	5 (1.4)	0
NAUSEA	19 (7.0)	1 (0.4)	0	29 (8.3)	2 (0.6)	0
ENDOCRINE DISORDERS	31 (11.5)	1 (0.4)	0	37 (10.6)	1 (0.3)	0
HYPOTHYROIDISM	21 (7.8)	0	0	25 (7.2)	0	0
METABOLISM AND NUTRITION DISORDERS	27 (10.0)	3 (1.1)	0	37 (10.6)	5 (1.4)	0
DECREASED APPETITE	22 (8.1)	0	0	27 (7.8)	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	20 (7.4)	7 (2.6)	0	31 (8.9)	8 (2.3)	0
ANAEMIA	11 (4.1)	4 (1.5)	0	19 (5.5)	4 (1.1)	0

MedDRA Version: 19.0
CTC Version 4.0

The biggest difference in AE rates between the 2 studies (CA209275 and CA209032), is in the any grade drug-related AEs category: 83.3% any grade drug-related AEs were noted in all treated subjects in CA209032 as compared to 64.4% in CA209275. In all other categories of safety variables assessed, the rates noted were mostly similar between the 2 studies or there was a ≤ 5.5% difference between the 2 studies with no consistent pattern of increase noted specific to CA209032. Drug-related SAEs (any grade and Grade 3-4) were similar between both studies, as were drug-related Grade 3-4 drug-related discontinuation rates.

Study drug-related death rate was higher in CA209032 (2.6%) vs. CA209275 (1.1%). When incidence rates were exposure-adjusted, the AE rates were similar between CA209032, CA209275, and the Integrated UC Population (2355.4, 2184.9, and 2234.2 [respectively] incidence rate per 100 person years) (5% cut-off).

Late-Emergent AEs

Late-emergent drug-related AEs were defined as drug-related AEs with an onset date > 100 days after the last dose of study therapy. No late-emergent drug-related AEs were reported for study CA209032. One subject (0.4%) in CA209275 experienced a Grade 3 late emergent drug-related AE of organizing pneumonia.

AEs in the Integrated UC Population and Across Pooled Monotherapy Studies

A summary of AEs (all causality and drug-related) for nivolumab-treated subjects in the Integrated UC Population is shown side-by-side with the integrated safety data from pooled nivolumab monotherapy studies in other tumor types in Table 45. Anaemia was the only newly reported all-causality PT reported in >20% subjects, which is consistent with haemoglobin being a known prognostic variable in the Integrated UC population. A summary of AEs (all causality and drug-related) for nivolumab treated subjects in individual studies CA209275 and CA209032 is shown side-by-side with the integrated safety data from pooled nivolumab monotherapy studies in other tumour types in Table 46.

Table 45 Adverse Events and Reactions with Nivolumab Monotherapy in Clinical Trials using Re-mapped Terms

	CA209032 + CA209275 N = 348		Nivo Mono in Other Tumor Types N = 2227	
Preferred Term (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
TOTAL SUBJECTS WITH AN EVENT (REGARDLESS OF CAUSALITY)	345 (99.1)	180 (51.7)	2163 (97.1)	955 (42.9)
Most Frequent (>20% in any grade in the Integrated UC Population or the pool of other tumour types)				
FATIGUE	161 (46.3)	21 (6.0)	1076 (48.3)	89 (4.0)
MUSCULOSKELETAL PAIN	112 (32.2)	8 (2.3)	726 (32.6)	74 (3.3)
COUGH	68 (19.5)	0	558 (25.1)	7 (0.3)
NAUSEA	83 (23.9)	3 (0.9)	535 (24.0)	18 (0.8)
RASH	69 (19.8)	7 (2.0)	512 (23.0)	24 (1.1)
DIARRHOEA	60 (17.2)	8 (2.3)	501 (22.5)	36 (1.6)
DYSPNOEA	58 (16.7)	13 (3.7)	458 (20.6)	67 (3.0)
ANAEMIA	72 (20.7)	24 (6.9)	345 (15.5)	82 (3.7)
DECREASED APPETITE	70 (20.1)	6 (1.7)	441 (19.8)	19 (0.9)
TOTAL SUBJECTS WITH AN EVENT (DRUG-RELATED)	239 (68.7)	66 (19.0)	1617 (72.6)	316 (14.2)
Most Frequent (>10% in any grade in the Integrated UC Population or the pool across tumour types)				
FATIGUE	86 (24.7)	11 (3.2)	674 (30.3)	36 (1.6)
RASH	49 (14.1)	7 (2.0)	380 (17.1)	19 (0.9)
NAUSEA	29 (8.3)	2 (0.6)	278 (12.5)	3 (0.1)
PRURITUS	48 (13.8)	0	276 (12.4)	2 (<0.1)
DIARRHOEA	31 (8.9)	5 (1.4)	274 (12.3)	21 (0.9)
DECREASED APPETITE	27 (7.8)	0	202 (9.1)	3 (0.1)

MedDRA Version: 19.0 for Integrated UC Population, 18.1 for Other Tumor Types, 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 CA209141.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.
Grade 3-4 by worst CTC grade.
Some preferred terms are re-mapped or deleted based on BMS medical review.
Source: Appendix BL.6.8a (AEs, remapped) and Appendix BL.6.9a (drug-related AEs, remapped); refer to Appendix HN.438 ((AEs, remapped) and Appendix HN.439 (drug-related AEs, remapped) of the SCCHN SCS for nivolumab monotherapy data in other tumor types.

Serious adverse event / deaths / other significant events

Serious adverse event (SAEs)

SAEs consisted mainly of events in the neoplasms benign, malignant and unspecified (incl cysts and polyps), infections and infestations, and gastrointestinal disorders SOCs in the Integrated UC Population.

Drug-related SAEs consisted mainly of events in the gastrointestinal disorders and respiratory, thoracic and mediastinal disorders SOCs in the Integrated UC Population.

In the Integrated UC Population, SAEs were reported in 52.6% of subjects (Table 46), 54.4% of subjects in Study CA209275 and 46.2% of subjects in Study CA209032. In the Integrated UC Population Grade 3-4 SAEs were reported in 35.1% of subjects and the most frequently reported SAEs were malignant neoplasm progression (11.5%), urinary tract infection (5.2%), general physical health deterioration (2.6%), sepsis (2.3%), and diarrhoea and small intestinal obstruction (2.0%). The most frequently reported SAEs were in Study CA209032 and Study CA209275 respectively: malignant neoplasm (9.0% vs. 12.2%) and urinary tract infection (3.8% vs. 5.6%).

The frequencies of SAEs (any Grade, and Grade 3-4) in treated subjects in the CA209275 and CA209032 populations were similar for Grade 3-4 events to the Integrated UC Population. Grade 5 SAEs occurred at higher frequencies in the CA209275 treated population (11.5%) compared to the Integrated UC Population (10.9%) and CA209032 (9.0%).

In the Integrated UC Population, drug-related SAEs were reported in 9.5% of subjects (Table 47). Grade 3-4 drug-related SAEs were reported in 6.6% of subjects. Drug-related SAEs reported in at least 2 subjects were pneumonitis and diarrhoea, 5 (1.4%) each; fatigue, 3 (0.9%); colitis, nausea, and pemphigoid, 2 (0.6%) subjects each.

The frequencies of drug-related SAEs (any grade, Grade 3-4, and Grade 5) in treated subjects in theCA209275 and CA209032 populations were consistent with the Integrated UC Population.

Table 46 SAEs (All Causality) by Worst CTC Grade Reported in ≥1% of Treated Subjects - CA209275 and Integrated UC Population

System Organ Class (%) Preferred Term (%)	CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	147 (54.4)	99 (36.7)	31 (11.5)	183 (52.6)	122 (35.1)	38 (10.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	46 (17.0)	21 (7.8)	21 (7.8)	53 (15.2)	22 (6.3)	27 (7.8)
MALIGNANT NEOPLASM PROGRESSION	33 (12.2)	12 (4.4)	20 (7.4)	40 (11.5)	13 (3.7)	26 (7.5)
CANCER PAIN	4 (1.5)	2 (0.7)	0	4 (1.1)	2 (0.6)	0
METASTASES TO CENTRAL NERVOUS SYSTEM	4 (1.5)	3 (1.1)	0	4 (1.1)	3 (0.9)	0
INFECTIONS AND INFESTATIONS	36 (13.3)	31 (11.5)	0	47 (13.5)	39 (11.2)	0
URINARY TRACT INFECTION	15 (5.6)	12 (4.4)	0	18 (5.2)	14 (4.0)	0
SEPSIS	8 (3.0)	8 (3.0)	0	8 (2.3)	8 (2.3)	0
INFECTION	2 (0.7)	2 (0.7)	0	5 (1.4)	5 (1.4)	0
UROSEPSIS	2 (0.7)	1 (0.4)	0	4 (1.1)	3 (0.9)	0
GASTROINTESTINAL DISORDERS	24 (8.9)	19 (7.0)	0	32 (9.2)	25 (7.2)	0
DIARRHOEA	6 (2.2)	5 (1.9)	0	7 (2.0)	5 (1.4)	0
SMALL INTESTINAL OBSTRUCTION	6 (2.2)	4 (1.5)	0	7 (2.0)	5 (1.4)	0
ABDOMINAL PAIN	3 (1.1)	2 (0.7)	0	5 (1.4)	4 (1.1)	0
VOMITING	3 (1.1)	3 (1.1)	0	3 (0.9)	3 (0.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	24 (8.9)	17 (6.3)	3 (1.1)	30 (8.6)	21 (6.0)	3 (0.9)
GENERAL PHYSICAL HEALTH DETERIORATION	9 (3.3)	6 (2.2)	2 (0.7)	9 (2.6)	6 (1.7)	2 (0.6)
PYREXIA	3 (1.1)	1 (0.4)	0	5 (1.4)	2 (0.6)	0
PAIN	3 (1.1)	3 (1.1)	0	4 (1.1)	3 (0.9)	0
RENAL AND URINARY DISORDERS	13 (4.8)	11 (4.1)	0	18 (5.2)	16 (4.6)	0
ACUTE KIDNEY INJURY	2 (0.7)	1 (0.4)	0	5 (1.4)	4 (1.1)	0
HAEMATURIA	3 (1.1)	2 (0.7)	0	5 (1.4)	4 (1.1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	15 (5.6)	11 (4.1)	3 (1.1)	18 (5.2)	13 (3.7)	4 (1.1)
DYSPNOEA	4 (1.5)	4 (1.5)	0	5 (1.4)	5 (1.4)	0
PNEUMONITIS	4 (1.5)	2 (0.7)	1 (0.4)	5 (1.4)	2 (0.6)	2 (0.6)
RESPIRATORY FAILURE	5 (1.9)	4 (1.5)	1 (0.4)	5 (1.4)	4 (1.1)	1 (0.3)
CARDIAC DISORDERS	8 (3.0)	4 (1.5)	2 (0.7)	9 (2.6)	4 (1.1)	2 (0.6)
ATRIAL FIBRILLATION	3 (1.1)	2 (0.7)	0	3 (0.9)	2 (0.6)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (1.1)	2 (0.7)	0	6 (1.7)	4 (1.1)	0
ANAEMIA	2 (0.7)	1 (0.4)	0	4 (1.1)	2 (0.6)	0
HEPATOBILIARY DISORDERS	4 (1.5)	4 (1.5)	0	4 (1.1)	4 (1.1)	0
HEPATIC FAILURE	3 (1.1)	3 (1.1)	0	3 (0.9)	3 (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.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Table 47 Drug-Related SAEs by Worst CTC Grade Reported in at Least 2 Treated Subjects - CA209275 and Integrated UC Population

System Organ Class (%) Preferred Term (%)	CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	25 (9.3)	18 (6.7)	3 (1.1)	33 (9.5)	23 (6.6)	4 (1.1)
GASTROINTESTINAL DISORDERS	6 (2.2)	6 (2.2)	0	10 (2.9)	8 (2.3)	0
DIARRHOEA	4 (1.5)	4 (1.5)	0	5 (1.4)	4 (1.1)	0
COLITIS	1 (0.4)	1 (0.4)	0	2 (0.6)	2 (0.6)	0
NAUSEA	1 (0.4)	1 (0.4)	0	2 (0.6)	2 (0.6)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (2.2)	3 (1.1)	2 (0.7)	7 (2.0)	3 (0.9)	3 (0.9)
PNEUMONITIS	4 (1.5)	2 (0.7)	1 (0.4)	5 (1.4)	2 (0.6)	2 (0.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (1.1)	2 (0.7)	0	4 (1.1)	3 (0.9)	0
FATIGUE	2 (0.7)	2 (0.7)	0	3 (0.9)	3 (0.9)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1.1)	3 (1.1)	0	3 (0.9)	3 (0.9)	0
PEMPHIGOID	2 (0.7)	2 (0.7)	0	2 (0.6)	2 (0.6)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Deaths

As of the 30-May-2016 and 24-Mar-2016 database locks for CA209275 and CA209032, respectively, a similar proportion of subjects died in each study (Table 48). Disease progression was the most common cause of death for both studies, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose. A higher proportion of subjects died within 30 days of last dose in CA209275 than in CA209032.

Table 48 Summary of Deaths - All Treated Subjects

	CA209032 N = 78		CA209275 N = 270		CA209032 + CA209275 N = 348	
NUMBER OF SUBJECTS WHO DIED (%)	36 (46.2)		138 (51.1)		174 (50.0)	
PRIMARY REASON FOR DEATH (%)						
DISEASE PROGRESSION	31 (39.7)		121 (44.8)		152 (43.7)	
STUDY DRUG TOXICITY	1 (1.3)	(A)	3 (1.1)	(B)	4 (1.1)	(A,B)
UNKNOWN	3 (3.8)		1 (0.4)		4 (1.1)	
OTHER	1 (1.3)		13 (4.8)	(C)	14 (4.0)	
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	7 (9.0)		53 (19.6)		60 (17.2)	
PRIMARY REASON FOR DEATH (%)						
DISEASE PROGRESSION	6 (7.7)		39 (14.4)		45 (12.9)	
STUDY DRUG TOXICITY	1 (1.3)	(A)	3 (1.1)	(B)	4 (1.1)	(A,B)
UNKNOWN	0		0		0	
OTHER	0		11 (4.1)		11 (3.2)	
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	25 (32.1)		121 (44.8)		146 (42.0)	
PRIMARY REASON FOR DEATH (%)						
DISEASE PROGRESSION	21 (26.9)		104 (38.5)		125 (35.9)	
STUDY DRUG TOXICITY	1 (1.3)	(A)	3 (1.1)	(B)	4 (1.1)	(A,B)
UNKNOWN	2 (2.6)		1 (0.4)		3 (0.9)	
OTHER	1 (1.3)		13 (4.8)		14 (4.0)	

(A) For CA209032, 1 death was due to drug-related pneumonitis. One other death, not included in the table above, was initially attributed to thrombocytopenia of unknown cause/metastatic urothelial carcinoma, which was subsequently updated to drug-related thrombocytopenia post database lock.
(B) Deaths in study CA209275 attributed by the investigator to nivolumab therapy included drug-related cardiovascular failure, drug-related pneumonitis, and drug-related respiratory failure in 1 subject each (see Section 1.2.1).
(C) One subject had cause of death as Other, noted as acute respiratory failure (not related) and also had related Grade 3 pneumonitis ongoing at the time of death.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Deaths Attributed to Study Drug Toxicity

6 (1.7%) deaths assessed by the investigator due to study drug toxicity.

There were 3 deaths in CA209275 due to study drug toxicity as assessed by the investigator (pneumonitis, respiratory failure (preceded by interstitial lung disease)- and cardiovascular failure-). In addition, in one subject, although pneumonitis was considered related to nivolumab, the investigator deemed immediate cause of death to be due to multifactorial acute respiratory failure unrelated to study drug. However, this death was assessed as related by BMS medical surveillance team, due to the consideration that the immunomodulatory nature of nivolumab led to the development of pneumonitis in the first instance, causing acute respiratory failure with fatal outcome.

In study CA209032, one subject died due to pneumonitis. The patient had a metastatic spread of the tumour in the lung at baseline. Although other contributing factors such as lung metastases and concomitant lung infections could not be excluded, a causal association between study therapy and pneumonitis was considered possible. The fatal outcome was likely attributable to multiple factors, including underlying malignancy and the possible lung infection. In addition, 1 subject had a drug-related event post database lock, died due to thrombocytopenia. This subject's death was initially attributed to a reason of 'Other,' verbatim terms for which was reported as 'thrombocytopenia of unknown cause, metastatic bladder cancer'. The cause of subject's death was subsequently updated to drug-related thrombocytopenia. Considering that available information was not suggestive of other alternative aetiologies, a causal association between study therapy and thrombocytopenia was considered possible.

Deaths Attributed to Other Reasons

The following 14 cases were reported: hepatic failure due to disease under study; perforated bowel with subsequent respiratory failure with sepsis likely; cardiac arrest in basic disease; Grade 5 cardiopulmonary arrest; cardiac arrest; hepatic failure; small bowel obstruction (disease progression) resulted in subject death; acute respiratory failure; bowel perforation; brain stroke; sepsis, bradycardia, hypotension; respiratory distress-possible PE; bowel obstruction; liver disorder.

One death was attributed to a reason of 'Other'. The verbatim term for this reason was reported as sepsis that was not considered related to study drug by the investigator. The subject died 59 days after the last dose of nivolumab.

Select adverse events / adverse events of special interest (AESI)

Select AEs were AEs of special clinical interest meeting defined criteria and multiple event terms that were grouped into select AE categories (regardless of treatment with immune modulating medication).

Based on defined guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select AEs. Hypersensitivity/infusion reactions were analyzed along with the select AE categories because multiple event terms may be used to describe such events and pooling of terms was therefore necessary for full characterization. Hypersensitivity/infusion reactions do not otherwise meet criteria to be considered select AEs.

Other events of special interest (OESIs) are events that do not fulfil all criteria to qualify as select AEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow-up(100-day window).OESIs included the following categories: demyelination, encephalitis, Guillain-Barre syndrome, myasthenic syndrome, pancreatitis, and uveitis. Additional events in the categories of myositis, myocarditis, and rhabdomyolysis were recently identified as OESIs but were not included in the programmed outputs.

In the Integrated UC Population, 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 (23.0%) and gastrointestinal (9.5%) (Table 49).

Table 49 Summary of Select AEs Reported Up to 30 Days After Last Dose -All Treated Subjects in CA209275 and Integrated Population

	Number (%) Subjects			
	CA209275 (N = 270)		CA209032 +CA209275 (N = 348)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL CAUSALITY SELECT AES, BY CATEGORY				
ENDOCRINE	43 (15.9)	1 (0.4)	52 (14.9)	1 (0.3)
GASTROINTESTINAL	48 (17.8)	8 (3.0)	64 (18.4)	11 (3.2)
HEPATIC	33 (12.2)	15 (5.6)	45 (12.9)	19 (5.5)
PULMONARY(a)	12 (4.4)	2 (0.7)	14 (4.0)	2 (0.6)
RENAL	28 (10.4)	6 (2.2)	50 (14.4)	11 (3.2)
SKIN	73 (27.0)	4 (1.5)	109 (31.3)	6 (1.7)
HYPERSENSITIVITY/INFUSION REACTION	5 (1.9)	1 (0.4)	8 (2.3)	1 (0.3)
DRUG-RELATED SELECT AES, BY CATEGORY				
ENDOCRINE	39 (14.4)	1 (0.4)	45 (12.9)	1 (0.3)
GASTROINTESTINAL	25 (9.3)	6 (2.2)	33 (9.5)	7 (2.0)
HEPATIC	10 (3.7)	5 (1.9)	14 (4.0)	6 (1.7)
PULMONARY(a)	11 (4.1)	3 (1.1)	13 (3.7)	3 (0.9)
RENAL	3 (1.1)	1 (0.4)	10 (2.9)	2 (0.6)
SKIN	47 (17.4)	4 (1.5)	80 (23.0)	6 (1.7)
HYPERSENSITIVITY/INFUSION REACTION	3 (1.1)	1 (0.4)	5 (1.4)	1 (0.3)

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.
(a) In both CA209275 and CA209032, 1 subject in each study had drug-related Grade 5 pneumonitis assessed by the investigator. See Section 5.5 [Deaths] for further details of study drug toxicities.

Across select AE categories, the majority of events were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered. Some endocrine select AEs, though well-controlled with hormone replacement therapy, were not considered resolved due to the continuing need for hormone replacement therapy.

Endocrine Events

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

In the Integrated UC Population, endocrine select AEs (all-causality, any grade) were reported in 52 (14.9%) subjects treated with nivolumab, 43 (15.9%) in CA209275 and 9 (11.5%) in CA209032.

45 (12.9%) subjects in the Integrated UC Population had endocrine select AEs that were considered to be drug-related by the investigator (Table 50), 39 (14.4%) in CA209275 and 6 (7.7%) in CA209032. The most commonly reported drug-related event was hypothyroidism (7.2%, 7.8% and 5.1%, respectively). With the exception of one Grade 3 event of hypophysitis reported in CA209275, all drug-related endocrine events were Grade 1-2 and none led to discontinuation of nivolumab.

The median time to onset of drug-related endocrine AEs was 8.57 weeks.

Of the 5 subjects who were treated with immune-modulating medication (median duration of 6.14 weeks), 2 resolved with resolution time ranging from 0.6 to 22.1+ weeks. Overall, 16 of the 45 subjects with drug-related endocrine select AEs resolved, with time to resolution ranging from 0.6 to 51.1+ weeks.

Table 50 Summary of Drug-related Endocrine Select Adverse Events by Worst CTC Grade Reported Up to 30 days After Last Dose – All Treated Subjects in CA209275 and Integrated UC Population

Sub Category (%) Preferred Term (%)	CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	39 (14.4)	1 (0.4)	0	45 (12.9)	1 (0.3)	0
THYROID DISORDER	35 (13.0)	0	0	41 (11.8)	0	0
HYPOTHYROIDISM	21 (7.8)	0	0	25 (7.2)	0	0
HYPERTHYROIDISM	11 (4.1)	0	0	14 (4.0)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	10 (3.7)	0	0	11 (3.2)	0	0
BLOOD THYROID STIMULATING HORMONE DECREASED	5 (1.9)	0	0	5 (1.4)	0	0
THYROIDITIS	2 (0.7)	0	0	2 (0.6)	0	0
THYROXINE INCREASED	2 (0.7)	0	0	2 (0.6)	0	0
AUTOIMMUNE THYROIDITIS	1 (0.4)	0	0	1 (0.3)	0	0
THYROXINE DECREASED	1 (0.4)	0	0	1 (0.3)	0	0
THYROXINE FREE INCREASED	1 (0.4)	0	0	1 (0.3)	0	0
ADRENAL DISORDER	2 (0.7)	0	0	2 (0.6)	0	0
ADRENAL INSUFFICIENCY	2 (0.7)	0	0	2 (0.6)	0	0
PITUITARY DISORDER	2 (0.7)	1 (0.4)	0	2 (0.6)	1 (0.3)	0
HYPOPHYSITIS	2 (0.7)	1 (0.4)	0	2 (0.6)	1 (0.3)	0
DIABETES	1 (0.4)	0	0	1 (0.3)	0	0
TYPE 1 DIABETES MELLITUS	1 (0.4)	0	0	1 (0.3)	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.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Gastrointestinal Events

In the Integrated UC Population, gastrointestinal select AEs (all-causality, any grade) were occurring in 64 (18.4%) subjects treated with nivolumab, 48 subjects (17.8%) in CA209275 and 16 subjects (20.5%) in CA209032.

33 (9.5%) subjects had GI select AEs that were considered to be drug-related by the investigator (Table 51). The majority of drug-related diarrhoea events were Grade 1-2; 5 (1.4%) subjects experienced Grade 3-4 diarrhoea events. Two of the 3 colitis events were Grade 3-4. One event (Grade 3 diarrhoea) led to permanent discontinuation of nivolumab.

The median time to onset of drug-related GI select AEs was 6.43 weeks. Of the 9 subjects who were treated with immune modulating medications (high-dose corticosteroids for a median duration of 1.29 weeks), 8 subjects had resolution of their events. Overall, 29 of the 33 subjects with drug-related GI select AEs had resolution of their events, with a median time to resolution of 2.14 weeks.

Table 51 Summary of Drug-related Gastrointestinal Select Adverse Events by Worst CTC Grade Reported Up to 30 days After Last Dose – All Treated Subjects in CA209275 and Integrated UC Population

	CA209275 N = 270			CA209032 + CA209275 N = 348		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	25 (9.3)	6 (2.2)	0	33 (9.5)	7 (2.0)	0
DIARRHOEA	24 (8.9)	5 (1.9)	0	31 (8.9)	5 (1.4)	0
COLITIS	2 (0.7)	1 (0.4)	0	3 (0.9)	2 (0.6)	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Hepatic Events

In the Integrated UC Population, hepatic select AEs (all-causality, any grade) were reported in 45 (12.9%) subjects. 14 (4.0%) subjects had hepatic select AEs considered to be drug-related by the investigator (Table 52). 6 subjects had Grade 3-4 drug-related events. None of the hepatic select AEs led to permanent discontinuation of nivolumab.

The median time to onset of drug-related hepatic events was 5.86 weeks. Four subjects were treated with immune modulating medications for a median duration of 13.71 weeks and none of the subjects had resolution of the event at the time of the database locks. Overall, 7 of the 14 subjects with drug-related hepatic select AEs had resolution of their events; median time to resolution 6.71 weeks.

Table 52 Summary of Drug-related Hepatic Select Adverse Events by Worst CTC Grade Reported Up to 30 days After Last Dose - All Treated Subjects and Integrated UC Population

	CA209275 N = 270			CA209032 + CA209275 N = 348		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	10 (3.7)	5 (1.9)	0	14 (4.0)	6 (1.7)	0
ALANINE AMINOTRANSFERASE INCREASED	8 (3.0)	2 (0.7)	0	11 (3.2)	2 (0.6)	0
ASPARTATE AMINOTRANSFERASE INCREASED	6 (2.2)	3 (1.1)	0	7 (2.0)	4 (1.1)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	3 (1.1)	2 (0.7)	0	4 (1.1)	2 (0.6)	0
BLOOD BILIRUBIN INCREASED	2 (0.7)	1 (0.4)	0	3 (0.9)	1 (0.3)	0
LIVER FUNCTION TEST INCREASED	2 (0.7)	1 (0.4)	0	2 (0.6)	1 (0.3)	0
TRANSAMINASES INCREASED	2 (0.7)	0	0	2 (0.6)	0	0
HYPERBILIRUBINAEMIA	1 (0.4)	0	0	1 (0.3)	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.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.
Program Source: Appendix BL.6.102

Pulmonary Events

In the Integrated UC Population, pulmonary select AEs (all-causality, any grade) were reported in 14 (4.0%) subjects with pneumonitis being the most frequently occurring pulmonary select AE.

13 (3.7%) subjects had pulmonary select AEs considered to be drug-related by the investigator (Table 53). Twelve of these drug-related events were pneumonitis; 2 of the 12 were Grade 3-4. In addition to the pneumonitis events, a Grade 3-4 drug-related event of interstitial lung disease; was reported. Six drug-related pulmonary select AEs, including the event of interstitial lung disease, led to permanent discontinuation of nivolumab.

The median time to onset of drug-related pulmonary events was 15.0 weeks. Eleven subjects were treated with immune modulating medication for a median duration of 2.43 weeks, and 3 subjects had resolution of the event. Overall, 4 of the 13 subjects with drug-related pulmonary select AEs had resolution of their events, with a median time to resolution of 16.14 weeks.

Table 53 Summary of Drug-related Pulmonary Select Adverse Events by Worst CTC Grade Reported Up to 30 days After Last Dose - All Treated Subjects in CA209275 and Integrated UC Population

	CA209275 N = 270			CA209032 + CA209275 N = 348		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	11 (4.1)	3 (1.1)	1 (0.4)	13 (3.7)	3 (0.9)	2 (0.6)
PNEUMONITIS (a)	10 (3.7)	2 (0.7)	1 (0.4)	12 (3.4)	2 (0.6)	2 (0.6)
INTERSTITIAL LUNG DISEASE	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0

MedDRA Version: 19.0
CTC Version 4.0
(a)In both CA209275 and CA209032, 1 subject in each study had drug-related Grade 5 pneumonitis assessed by the investigator. See Section 2.2 [Deaths] for further details of study drug toxicities.
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix EL.6.102

Renal Events

In the Integrated UC Population, renal select AEs (all-causality, any grade) were reported in 50 subjects (14.4%) treated with nivolumab. Renal select AEs were reported more frequently in CA209032 than in CA209275 (28.2% vs. 10.4% for any-grade events); however, the low frequency of events and small sample size limit interpretation.

10 subjects (2.9%) had renal select AEs considered to be drug-related by the investigator (Table 54). The majority of events were Grade 1-2 and no events lead to permanent discontinuation of nivolumab.

The median time to onset was 10.57 weeks. One subject was treated with high dose corticosteroids with resolution of the event. Overall, 5 of the 10 subjects with drug-related renal select AEs had resolution of their events; median time to resolution was 16.29 weeks.

Table 54 Summary of Drug-related Renal Select Adverse Events by Worst CTC Grade Reported Up to 30 days After Last Dose - All Treated Subjects in CA209275 and Integrated UC Population

	CA209275 N = 270			CA209032 + CA209275 N = 348		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (1.1)	1 (0.4)	0	10 (2.9)	2 (0.6)	0
BLOOD CREATININE INCREASED	1 (0.4)	1 (0.4)	0	5 (1.4)	1 (0.3)	0
BLOOD UREA INCREASED	0	0	0	3 (0.9)	0	0
ACUTE KIDNEY INJURY	1 (0.4)	0	0	2 (0.6)	1 (0.3)	0
RENAL FAILURE	1 (0.4)	0	0	1 (0.3)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix BL.6.102

Skin Events

In the Integrated UC Population, skin select AEs (all-causality, any grade) were reported in 109 (31.3%) subjects.

Drug-related skin select AEs were reported in 80 (23.0%) subjects (Table 55). The most frequently reported drug-related events were pruritus (13.8%), rash (6.0%), and rash maculopapular (5.2%). No event of toxic epidermal necrolysis was reported. The majority of drug-related events were Grade 1-2; 6 (1.7%) subjects experienced Grade 3-4 skin events. Two subjects experienced drug-related skin select AEs which led to permanent discontinuation of nivolumab.

The median time to onset of drug-related skin select AEs was 4.0 weeks. 25 subjects were treated with immune modulating medication for a median of 18.29 weeks with resolution of the event in 10 subjects. Overall, 45 of 80 subjects with drug-related skin select AEs had resolution of their events with a median time to resolution of 17.14 weeks.

Table 55 Summary of Drug-related Skin Select Adverse Events by Worst CTC Grade Reported Up to 30 days After Last Dose - All Treated Subjects in CA209275 and Integrated UC Population

	CA209275 N = 270			CA209032 + CA209275 N = 348		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	47 (17.4)	4 (1.5)	0	80 (23.0)	6 (1.7)	0
PRURITUS	25 (9.3)	0	0	48 (13.8)	0	0
RASH	16 (5.9)	3 (1.1)	0	21 (6.0)	3 (0.9)	0
RASH MACULO-PAPULAR	4 (1.5)	1 (0.4)	0	18 (5.2)	3 (0.9)	0
ERYTHEMA	2 (0.7)	0	0	2 (0.6)	0	0
PRURITUS GENERALISED	2 (0.7)	1 (0.4)	0	2 (0.6)	1 (0.3)	0
RASH ERYTHEMATOUS	0	0	0	2 (0.6)	0	0
RASH MACULAR	2 (0.7)	0	0	2 (0.6)	0	0
RASH PRURITIC	2 (0.7)	1 (0.4)	0	2 (0.6)	1 (0.3)	0
BLISTER	1 (0.4)	0	0	1 (0.3)	0	0
DERMATITIS	1 (0.4)	0	0	1 (0.3)	0	0
ECZEMA	1 (0.4)	0	0	1 (0.3)	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	0	0	0	1 (0.3)	0	0
RASH GENERALISED	1 (0.4)	0	0	1 (0.3)	0	0
RASH PAPULAR	0	0	0	1 (0.3)	0	0
SKIN EXFOLIATION	1 (0.4)	0	0	1 (0.3)	0	0
SKIN IRRITATION	0	0	0	1 (0.3)	0	0
URTICARIA	1 (0.4)	0	0	1 (0.3)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.
Source: Appendix BL.6.102

Hypersensitivity / Infusion Reactions

In the Integrated UC Population, hypersensitivity/infusion reactions (all-causality, any grade) were reported in 8 subjects (2.3%). 5 (1.4%) subjects had hypersensitivity/infusion reactions considered to be drug-related by the investigator (Table 56). A Grade 3-4 infusion reaction was reported in 1 subject. No hypersensitivity/infusion reactions led to permanent discontinuation of nivolumab.

The median time to onset of drug-related hypersensitivity/infusion reactions AEs was 2.14 weeks. 2 subjects were treated with immune-modulating medication, both resolved, with median time to resolution of 0.50 weeks.

Table 56 Summary of Drug-related Hypersensitivity / Infusion Reactions Reported Up to 30 days After Last Dose - All Treated Subjects and Integrated UC Population

	CA209275 N = 270			CA209032 + CA209275 N = 348		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (1.1)	1 (0.4)	0	5 (1.4)	1 (0.3)	0
INFUSION RELATED REACTION	2 (0.7)	1 (0.4)	0	3 (0.9)	1 (0.3)	0
HYPERSENSITIVITY	1 (0.4)	0	0	2 (0.6)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Other Events of Special Interest

Other events of special interest (OESIs) are events that do not fulfil all criteria to qualify as select AEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. Analyses of OESIs had extended follow-up (100-day window).

OESIs included the following categories: demyelination, encephalitis, Guillain-Barre syndrome, myasthenic syndrome, pancreatitis, and uveitis.

The only OESI reported in the Integrated UC Population was a Grade 3-4 OESI of pancreatitis reported in CA209032. Time to onset of 46.4 weeks and time to resolution of 3.1 weeks. The event did not lead to treatment discontinuation nor was it treated with immune-modulating medication.

No other OESIs were reported between first dose and 100 days after last dose of study therapy in the Integrated UC Population. No OESIs were considered drug-related or serious AEs by the investigator. No events in the categories of myositis, myocarditis, and rhabdomyolysis were identified.

The total number of subjects in the UC population with at least one immune related adverse reaction was 40.5% (any grade) ad 7.5% (Grade 3-4) (Table 57). These events are defined as any drug-related select adverse event (using 30 days safety windows) from any of the following categories: gastrointestinal, hepatic, pulmonary, renal, skin, endocrine, and hypersensitivity/infusion adverse events.

The rate of any grade event was higher in study CA209032 (51.3%) compared to study CA209275 (37.4%) mainly due to the difference in rates of select adverse events from the skin category (42.3% vs 17.4%, refer to Appendix BL.6.102 of the EU UC SCS). The rate of high grade event from any category (6.4% vs.7.8%) was similar between studies.

Table 57 Summary of Any Drug-Related Select Adverse Event (Any Category) by Worst CTC Grade – All Treated Subjects

	CA209032 N = 78			CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	40 (51.3)	5 (6.4)	1 (1.3)	101 (37.4)	21 (7.8)	1 (0.4)	141 (40.5)	26 (7.5)	2 (0.6)

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.
Program Source: /projects/bms217252/stats/bladder EU SCS/prog/tables/rt-ae-rslaeall.sas 01DEC2016:08:27:09

Adverse drug reactions

Table 58: Frequencies of adverse drug reactions included in the SmPC section 4.8 – Integrated UC population and nivolumab monotherapy population in other tumour types

	Integrated UC Population n = 348 treated subjects				Pooled Nivolumab Monotherapy Population in Other Tumor Types (excluding UC) n = 2227 treated subjects[a]		
ADR[b,c,d]	No. of Subjects	% of subjects	Designation of frequency	Source Appendix	No. of Subjects	% of subjects	Designation of frequency
Total no. of nivolumab-monotherapy							
Infections and infestations							
Upper respiratory tract infection	2	0.6	Uncommon	BL.6.9a	22	1.0	Common
Pneumonia	1	0.3	Uncommon	BL.6.9a	15	0.7	Uncommon
Bronchitis	0	0	-	BL.6.9a	4	0.2	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)							
Histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)	0	0	-	BL.6.9a	1	<0.1	Rare
Blood and lymphatic system disorders							
Eosinophilia	3	0.9	Uncommon	BL.6.9a	5	0.2	Uncommon
Immune system disorders							
Infusion related reaction	3	0.9	Uncommon	BL.6.9a	77	3.5	Common
Anaphylactic reaction[e]	0	0	-	BL.6.3a	2	<0.1	Rare
Hypersensitivity	2	0.6	Uncommon	BL.6.9a	35	1.6	Common
Endocrine disorders							
Hypothyroidism	25	7.2	Common	BL.6.9a	134	6.0	Common
Hyperthyroidism	14	4.0	Common	BL.6.9a	41	1.8	Common

Hyperglycaemia	7	2.0	Common	BL.6.9a	25	1.1	Common
Adrenal insufficiency	2	0.6	Uncommon	BL.6.9a	10	0.4	Uncommon
Hypopituitarism	0	0	-	BL.6.9a	5	0.2	Uncommon
Hypophysitis	2	0.6	Uncommon	BL.6.9a	6	0.3	Uncommon
Thyroiditis	3	0.9	Uncommon	BL.6.9a	13	0.6	Uncommon
Diabetic ketoacidosis	0	0	-	BL.6.9a	2	<0.1	Rare
Diabetes mellitus	1	0.3	Uncommon	BL.6.9a	1	<0.1	Rare
Metabolism and nutrition disorders							
Decreased appetite	27	7.8	Common	BL.6.9a	202	9.1	Common
Dehydration	3	0.9	Uncommon	BL.6.9a	12	0.5	Uncommon
Metabolic acidosis[f]	1	0.3	Uncommon	BL.6.8a	3	0.1	Uncommon
Hepatobiliary disorders							
Hepatitis	0	0	-	BL.6.9a	5	0.2	Uncommon
Hyperbilirubinemia	1	0.3	Uncommon	BL.6.9a	3	0.1	Uncommon
Cholestasis	0	0	-	BL.6.9a	2	<0.1	Rare
Nervous system disorders							
Peripheral neuropathy	3	0.9	Uncommon	BL.6.9a	47	2.1	Common
Headache	6	1.7	Common	BL.6.9a	93	4.2	Common
Dizziness	4	1.1	Common	BL.6.9a	45	2.0	Common
Polyneuropathy	1	0.3	Uncommon	BL.6.9a	3	0.1	Uncommon
Guillain-Barré syndrome	0	0	-	BL.6.9a	1	<0.1	Rare
Demyelination	0	0	-	BL.6.9a	1	<0.1	Rare
Myasthenic syndrome	0	0	-	BL.6.9a	1	<0.1	Rare
Autoimmune neuropathy (including facial and abducens nerve paresis)[g]	0	0	-	BL.6.9a	2	<0.1	Rare
Eye disorders							
Vision blurred	0	0	-	BL.6.9a	18	0.8	Uncommon
Dry eye	1	0.3	Uncommon	BL.6.9a	20	0.9	Uncommon
Uveitis	0	0	-	BL.6.9a	9	0.4	Uncommon
Cardiac disorders							
Tachycardia	0	0	-	BL.6.9a	8	0.4	Uncommon
Arrhythmia (including ventricular arrhythmia)	0	0	-	BL.6.9a	1	<0.1	Rare
Atrial fibrillation	0	0	-	BL.6.9a	1	<0.1	Rare
Vascular disorders							
Hypertension	2	0.6	Uncommon	BL.6.9a	27	1.2	Common
Vasculitis	0	0	-	BL.6.9a	2	<0.1	Rare

Respiratory, thoracic and mediastinal disorders							
Pneumonitis	13	3.7	Common	BL.6.9a	66	3.0	Common
Dyspnoea	16	4.6	Common	BL.6.9a	101	4.5	Common
Cough	7	2.0	Common	BL.6.9a	108	4.8	Common
Pleural effusion	0	0	-	BL.6.9a	6	0.3	Uncommon
Lung infiltration	0	0	-	BL.6.9a	1	<0.1	Rare
Gastrointestinal disorders							
Diarrhoea	31	8.9	Common	BL.6.9a	274	12.3	Very common
Nausea	29	8.3	Common	BL.6.9a	278	12.5	Very common
Colitis	3	0.9	Uncommon	BL.6.9a	20	0.9	Uncommon
Stomatitis	5	1.4	Common	BL.6.9a	68	3.1	Common
Vomiting	9	2.6	Common	BL.6.9a	122	5.5	Common
Abdominal pain	8	2.3	Common	BL.6.9a	81	3.6	Common
Constipation	5	1.4	Common	BL.6.9a	108	4.8	Common
Dry mouth	9	2.6	Common	BL.6.9a	58	2.6	Common
Pancreatitis	0	0	-	BL.6.9a	7	0.3	Uncommon
Gastritis	1	0.3	Uncommon	BL.6.9a	2	<0.1	Rare
Duodenal ulcer	0	0	-	BL.6.9a	1	<0.1	Rare
Skin and subcutaneous tissue disorders							
Rash	49	14.1	Very common	BL.6.9a	380	17.1	Very common
Pruritus	48	13.8	Very common	BL.6.9a	276	12.4	Very common
Vitiligo	0	0	-	BL.6.9a	69	3.1	Common
Dry skin	8	2.3	Common	BL.6.9a	87	3.9	Common
Erythema	2	0.6	Uncommon	BL.6.9a	38	1.7	Common
Alopecia	2	0.6	Uncommon	BL.6.9a	25	1.1	Common
Erythema multiforme	0	0	-	BL.6.9a	3	0.1	Uncommon
Psoriasis	0	0	-	BL.6.9a	3	0.1	Uncommon
Rosacea	0	0	-	BL.6.9a	3	0.1	Uncommon
Urticaria	1	0.3	Uncommon	BL.6.9a	9	0.4	Uncommon
Toxic epidermal necrolysis	0	0	-	BL.6.9a	2	<0.1	Rare
Musculoskeletal and connective tissue disorders							
Musculoskeletal pain	22	6.3	Common	BL.6.9a	161	7.2	Common
Arthralgia	16	4.6	Common	BL.6.9a	128	5.7	Common
Polymyalgia rheumatica	0	0	-	BL.6.9a	3	0.1	Uncommon
Arthritis	1	0.3	Uncommon	BL.6.9a	21	0.9	Uncommon
Myopathy	0	0	-	BL.6.9a	1	<0.1	Rare

Renal and urinary disorders							
Tubulointerstitial nephritis	0	0	-	BL.6.9a	4	0.2	Uncommon
Renal failure (including acute kidney injury)[h]	3	0.9	Uncommon	BL.6.9a	15	0.7	Uncommon
General disorders and administration site conditions							
Fatigue	86	24.7	Very common	BL.6.9a	674	30.3	Very common
Pyrexia	17	4.9	Common	BL.6.9a	128	5.7	Common
Oedema (including peripheral oedema)	5	1.4	Common	BL.6.9a	67	3.0	Common
Pain	3	0.9	Uncommon	BL.6.9a	18	0.8	Uncommon
Chest pain	2	0.6	Uncommon	BL.6.9a	18	0.8	Uncommon
Investigations[i]							
Increased AST	78/330	23.6	Very common	BL.7.11-SI	570/2151	26.5	Very common
Increased ALT	57/329	17.3	Very common	BL.7.11-SI	456/2160	21.1	Very common
Increased alkaline phosphatase	107/330	32.4	Very common	BL.7.11-SI	520/2148	24.2	Very common
Increased lipase	68/325	20.9	Very common	BL.7.27-SI	169/871	19.4	Very common
Increased amylase	54/296	18.2	Very common	BL.7.27-SI	100/752	13.3	Very common
Increased creatinine	125/329	38.0	Very common	BL.7.11-SI	430/2167	19.8	Very common
Lymphocyte absolute (lymphopaenia)	141/330	42.7	Very common	BL.7.11-SI	881/2155	40.9	Very common
Leukocyte absolute (leucopenia)	42/331	12.7	Very common	BL.7.11-SI	316/2175	14.5	Very common
Platelet count (thrombocytopenia)	54/331	16.3	Very common	BL.7.11-SI	274/2169	12.6	Very common
Haemoglobin (B) (anemia)	135/333	40.5	Very common	BL.7.11-SI	772/2169	35.6	Very common
Hypercalcaemia	19/326	5.8	Common	BL.7.11-SI	227/2076	10.9	Very common
Hyperkalaemia	62/328	18.9	Very common	BL.7.11-SI	396/2112	18.8	Very common
Hypokalaemia	26/328	7.9	Common	BL.7.11-SI	223/2112	10.6	Very common
Hypomagnesaemia	59/324	18.2	Very common	BL.7.11-SI	271/1878	14.4	Very common
Hyponatraemia	129/329	39.2	Very common	BL.7.11-SI	575/2113	27.2	Very common
Increased total bilirubin	29/329	8.8	Common	BL.7.11-SI	177/2157	8.2	Common
Absolute neutrophil count (neutropenia)	38/330	11.5	Very common	BL.7.11-SI	241/2158	11.2	Very common
Hypermagnesaemia	15/324	4.6	Common	BL.7.11-SI	82/1878	4.4	Common
Hypernatraemia	10/329	3.0	Common	BL.7.11-SI	107/2113	5.1	Common
Hypocalcaemia	80/326	24.5	Very common	BL.7.11-SI	358/2076	17.2	Very common
Weight decreased	5	1.4	Common	BL.6.9a	49	2.2	Common

a Monotherapy Pooled group consists of nivolumab monotherapy treatment group from studies CA209063, CA209017, CA209057, CA209037, CA209066, CA209067, CA209025, CA209039 (cHL subjects), CA209205, and CA209141.
Source: Refer to Table 2.9.1.4-1 of SCCHN SCS
b MedDRA Version: 19.0 (Integrated UC Population), 18.1 (Pooled Nivolumab Monotherapy Population), CTC Version 4.0
c Includes events reported between first dose and 30 days after last dose of study therapy
d Unless otherwise noted, some preferred terms are re-mapped or deleted based on BMS medical review.
e This event frequency comes from an unmapped output.
f This event frequency is based on all causality output.
g Includes events autoimmune neuropathy, VIth nerve paralysis, and VIIth nerve paralysis
h Includes events acute kidney injury and renal failure
i BMS used the laboratory abnormality change from baseline. This presentation is a conservative approach intended to capture the frequency of all laboratory abnormalities regardless of causality. In doing so, the denominator used to compute frequency is the number of patients for whom laboratory abnormalities data were reported, as opposed to ALL treated patients. Hence, there is variability in the denominator for each individual laboratory abnormality and their respective reported frequencies.

Laboratory findings

Laboratory measurements were recorded regardless of causality and some were correlated with reported laboratory-based AEs. Laboratory results reported after first dose and within 30 days of last dose of study therapy are presented in the sections below.

Haematology

In the Integrated UC Population, abnormalities in haematology tests were primarily Grade 1-2.The majority of subjects did not have on-study worsening in haematology parameters (Table 59). The only hematologic abnormalities that worsened to Grade 3-4 relative to baseline in ≥5% of subjects were decreased absolute lymphocytes (9.7%) and decreased haemoglobin (8.1%).

Table 59 Summary of On-Treatment Worst CTC Grade Haematology Tests that Worsened Relative to Baseline - SI Units - All Treated Subjects in CA209275 and Integrated UC Population

	Number of Subjects (%)					
	CA209275			CA209032 + CA209275		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
HEMOGLOBIN (B)	256	101 (39.5)	18 (7.0)	333	135 (40.5)	27 (8.1)
PLATELET COUNT	254	39 (15.4)	6 (2.4)	331	54 (16.3)	7 (2.1)
LEUKOCYTES	255	27 (10.6)	0	331	42 (12.7)	0
LYMPHOCYTES (ABSOLUTE)	254	106 (41.7)	23 (9.1)	330	141 (42.7)	32 (9.7)
ABSOLUTE NEUTROPHIL COUNT	254	25 (9.8)	1 (0.4)	330	38 (11.5)	3 (0.9)

Toxicity Scale: CTC Version 4.0
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment.
Percentages are based on N as denominator.
(B) Per Anemia criteria in CTC version 4.0 there is no grade 4 for hemoglobin.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032. CA209032 crossover subjects are truncated at the first dose date of crossover period.

Serum Chemistry

Liver Function Tests

In the Integrated UC Population, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2. The majority of subjects did not have on-study worsening in l hepatic parameter (Table 60). No hepatic parameters worsened to Grade 3-4 relative to baseline in ≥5%.

Table 60 Summary of On-Treatment Worst CTC Grade Liver Function Test Results that Worsened Relative to Baseline - SI Units - All Treated Subjects in CA209275 and Integrated UC Population

	Number of Subjects (%)					
	CA209275			CA209032 + CA209275		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
ALKALINE PHOSPHATASE	255	85 (33.3)	14 (5.5)	330	107 (32.4)	16 (4.8)
ASPARTATE AMINOTRANSFERASE	255	62 (24.3)	9 (3.5)	330	78 (23.6)	10 (3.0)
ALANINE AMINOTRANSFERASE	254	45 (17.7)	3 (1.2)	329	57 (17.3)	5 (1.5)
BILIRUBIN, TOTAL	254	24 (9.4)	9 (3.5)	329	29 (8.8)	9 (2.7)

Toxicity Scale: CTC Version 4.0
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment.
Percentages are based on N as denominator.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032. CA209032 crossover subjects are truncated at the first dose date of crossover period.

In the Integrated UC Population, 9 subjects in the nivolumab group (all from CA209275) had concurrent ALT or AST elevation >3 x ULN with total bilirubin > 2 x ULN within 1 day, and 10 subjects in the nivolumab group had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 30 days of last dose of study therapy (Table 61).

There were 9 subjects who met the protocol-specified criteria for drug-induced liver injury (DILI; concurrent [within 1 day] ALT or AST > 3 x ULN and total bilirubin > 2 x ULN within 100 days of the last dose of nivolumab).

Table 61: Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests - (SI Units) - All Treated Subjects in CA209275 and Integrated UC Population

	CA209275 N = 270	CA209032 + CA209275 N = 348
	N = 255	**N = 330**
ALT OR AST > 3XULN	20 (7.8)	24 (7.3)
ALT OR AST > 5XULN	10 (3.9)	13 (3.9)
ALT OR AST > 10XULN	3 (1.2)	3 (0.9)
ALT OR AST > 20XULN	1 (0.4)	1 (0.3)
	N = 254	**N = 329**
TOTAL BILIRUBIN > 2XULN	13 (5.1)	13 (4.0)
	N = 254	**N = 329**
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	9 (3.5)	9 (2.7)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	10 (3.9)	10 (3.0)

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.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Kidney Function Tests

In the Integrated UC Population, the majority of subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period. The majority of subjects did not have on-study worsening in creatinine. Creatinine worsened to Grade 3-4 relative to baseline in 1.8% of subjects.

Thyroid Function Tests

In the Integrated UC Population, the majority of subjects in both groups had normal TSH levels at baseline and throughout the treatment period (Table 62).

Table 62 Summary of On-Treatment Laboratory Abnormalities in Specific Thyroid Tests - (SI Units) - Treated Subjects with at Least One On- Treatment TSH Measurement in CA209275 and Integrated UC Population

	CA209275 N = 251	CA209032 + CA209275 N = 326
TSH > ULN	72 (28.7)	95 (29.1)
TSH > ULN		
WITH TSH <= ULN AT BASELINE	51 (20.3)	68 (20.9)
TSH > ULN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	31 (12.4)	40 (12.3)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	19 (7.6)	32 (9.8)
WITH FT3/FT4 TEST MISSING (A) (B)	22 (8.8)	23 (7.1)
TSH < LLN	60 (23.9)	75 (23.0)
TSH < LLN		
WITH TSH >= LLN AT BASELINE	51 (20.3)	64 (19.6)
TSH < LLN		
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	21 (8.4)	25 (7.7)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	16 (6.4)	25 (7.7)
WITH FT3/FT4 TEST MISSING (A) (B)	23 (9.2)	25 (7.7)

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 with non-abnormal value(s) from only one of the two tests and no value from the other test.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032. CA209032 crossover subjects are truncated at the first dose date of crossover period.

Electrolytes

In the Integrated UC Population, most subjects had normal electrolyte levels at baseline and during the treatment reporting period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. The majority of subjects did not have on-study worsening in electrolyte parameters (Table 63). The only electrolyte abnormality that worsened to Grade 3-4 relative to baseline in ≥5% of subjects was hyponatremia (10.0%); these subjects were mostly from the CA209275 population.

Table 63 Summary of On-Treatment Worst CTC Grade Electrolyte Levels that Worsened Relative to Baseline - SI Units - All Treated Subjects in CA209275 and Integrated UC Population

	Number of Subjects (%)					
	CA209275			CA209032 + CA209275		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
SODIUM						
HYPERNATREMIA	254	5 (2.0)	0	329	10 (3.0)	0
HYPONATREMIA	254	105 (41.3)	28 (11.0)	329	129 (39.2)	33 (10.0)
POTASSIUM						
HYPERKALEMIA	253	49 (19.4)	3 (1.2)	328	62 (18.9)	3 (0.9)
HYPOKALEMIA	253	21 (8.3)	4 (1.6)	328	26 (7.9)	4 (1.2)
CALCIUM						
HYPERCALCEMIA	252	18 (7.1)	1 (0.4)	326	19 (5.8)	1 (0.3)
HYPOCALCEMIA	252	65 (25.8)	2 (0.8)	326	80 (24.5)	2 (0.6)
MAGNESIUM						
HYPERMAGNESEMIA	250	13 (5.2)	1 (0.4)	324	15 (4.6)	1 (0.3)
HYPOMAGNESEMIA	250	43 (17.2)	0	324	59 (18.2)	1 (0.3)

Toxicity Scale: CTC Version 4.0
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment.
Percentages are based on N as denominator.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032. CA209032 crossover subjects are truncated at the first dose date of crossover period.

Glucose Tests

In the Integrated UC Population, abnormalities in fasting glucose values (hyperglycemia) during treatment were primarily Grade 1 to 2 in severity. The majority of subjects did not have on-study

worsening in fasting glucose. Fasting glucose worsened to Grade 3-4 relative to baseline in3.5% of subjects.

Pancreas Function Tests

In the Integrated UC Population, the majority of subjects did not have on-study worsening in amylase or lipase (Table 64). Amylase and lipase worsened to Grade 3-4 relative to baseline in 5.7% and 7.1% of subjects, respectively. There were no discontinuations of study therapy due to reported elevated lipase and/or amylase AEs. Grade 4 amylase or lipase abnormalities not associated with symptoms or clinical manifestation of pancreatitis.

Table 64 Summary of On-Treatment Worst CTC Grade Amylase and Lipase that Worsened Relative to Baseline - All Treated Subjects in CA209275 and Integrated UC Population

	Number of Subjects (%)					
	CA209275			CA209032 + CA209275		
Lab Test Description	N (A)	Grade 1-4	Grade 3-4	N (A)	Grade 1-4	Grade 3-4
AMYLASE, TOTAL	227	40 (17.6)	10 (4.4)	296	54 (18.2)	17 (5.7)
LIPASE, TOTAL	250	51 (20.4)	17 (6.8)	325	68 (20.9)	23 (7.1)

Toxicity Scale: CTC Version 4.0
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment.
Percentages are based on N as denominator.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032. CA209032 crossover subjects are truncated at the first dose date of crossover period.

Safety in special populations

Intrinsic and Extrinsic Factors

In the Integrated UC Population, the frequencies of all-causality and drug-related AEs among all treated subjects for subgroups of gender, race, age, and region were consistent with the AE frequencies in the overall treated population. Small numerical differences in frequencies of AEs were observed in the following subgroups:

- Any-grade and Grade 3-4 drug-related AEs for male (67.5% and 17.0%) vs. female (72.3% and 25.3%). There were 265 male and 83 female treated subjects.
- Slightly higher frequencies of any-grade and Grade 3-4 drug-related AEs were reported in subjects in Japan (73.9% and 17.4%) and US (72.1% and 21.8%) versus Rest of World (64.4% and 16.3%). There were 23, 165, and 160 treated subjects in Japan, US, and Rest of World.

Frequencies of AEs leading to dropout, accident and injuries, cardiac and vascular disorders increased slightly across the age groups (<65; 65-74; 75-84; >=85 years), but were otherwise consistent for all age groups.

Table 65 summary of On-treatment Adverse Events by Age Group All Treated Subjects Pooled UC CA209275 + CA209032

MedDRA Terms (%)	Age Group (Years) < 65 N = 159	65-74 N = 141	75-84 N = 44	>= 85 N = 4	Total N = 348
TOTAL SUBJECTS WITH AN EVENT	158 (99.4)	140 (99.3)	43 (97.7)	4 (100.0)	345 (99.1)
SERIOUS AE - TOTAL	85 (53.5)	74 (52.5)	22 (50.0)	2 (50.0)	183 (52.6)
FATAL	34 (21.4)	29 (20.6)	6 (13.6)	0	69 (19.8)
HOSPITALIZATION/PROLONGATION	74 (46.5)	67 (47.5)	21 (47.7)	2 (50.0)	164 (47.1)
LIFE-THREATENING	4 (2.5)	4 (2.8)	0	0	8 (2.3)
CANCER	7 (4.4)	4 (2.8)	0	1 (25.0)	12 (3.4)
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	6 (3.8)	3 (2.1)	0	0	9 (2.6)
AE LEADING TO DISCONTINUATION	25 (15.7)	27 (19.1)	10 (22.7)	0	62 (17.8)
PSYCHIATRIC DISORDERS	28 (17.6)	23 (16.3)	7 (15.9)	1 (25.0)	59 (17.0)
NERVOUS SYSTEM DISORDERS	49 (30.8)	37 (26.2)	13 (29.5)	0	99 (28.4)
ACCIDENT AND INJURIES	10 (6.3)	10 (7.1)	4 (9.1)	0	24 (6.9)
CARDIAC DISORDERS	10 (6.3)	10 (7.1)	5 (11.4)	0	25 (7.2)
VASCULAR DISORDERS	23 (14.5)	24 (17.0)	8 (18.2)	1 (25.0)	56 (16.1)
CEREBROVASCULAR DISORDERS	3 (1.9)	0	2 (4.5)	0	5 (1.4)
INFECTIONS AND INFESTATIONS	60 (37.7)	56 (39.7)	17 (38.6)	0	133 (38.2)
ANTICHOLINERGIC SYNDROME	46 (28.9)	43 (30.5)	8 (18.2)	2 (50.0)	99 (28.4)
QUALITY OF LIFE DECREASED	1 (0.6)	0	0	0	1 (0.3)
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	16 (10.1)	10 (7.1)	5 (11.4)	0	31 (8.9)

CTC Version 4.0; MedDRA Version: 19.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Crossover subjects from CA209032 are truncated at the first dose date of crossover period.
Program Source: /projects/kms217252/stats/bladder_EU_SCS/prog/tables/rt-ae-eusumage.sas 16NOV2016:01:53:18

By Baseline PD-L1 Expression

In CA209275 and CA209032, no consistent differences were observed in the frequencies of AEs by PD-L1 expression subgroup.

Withdrawal and Rebound

No cases of withdrawal symptoms related to nivolumab were reported during human clinical trials.

Safety related to drug-drug interactions and other interactions

No new information.

Discontinuation due to adverse events

In the Integrated UC Population most subjects received all doses of nivolumab without an infusion interruption, infusion rate reduction, or dose delay. Reasons for infusion interruption, infusion rate reduction, or dose delay are provided in Table 66. Infusion interruptions were reported for 14 (4.0%) of subjects, 6 (18.2%) of infusion interruptions were due to a hypersensitivity reaction. There were no dose interruptions in CA209032. Dose delays were reported in 135 (38.8%) of subjects. Dose delays due to AEs were reported for 66.4% (140/211) of all doses received.

Table 66 Infusion Interruption, Infusion Rate Reduction, and Dose Delays of Study Therapy - All Treated Subjects

	CA209032 N = 78	CA209275 N = 270	CA209032 + CA209275 N = 348
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	0	14 (5.2)	14 (4.0)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT (%)			
0	78 (100.0)	256 (94.8)	334 (96.0)
1	0	10 (3.7)	10 (2.9)
2	0	1 (0.4)	1 (0.3)
3	0	1 (0.4)	1 (0.3)
>= 4	0	2 (0.7)	2 (0.6)
TOTAL NUMBER INFUSIONS INTERRUPTED/ TOTAL NUMBER INFUSIONS RECEIVED	0/1060	33/2505 (1.3)	33/3565 (0.9)
REASON FOR INFUSION INTERRUPTION (A)			
HYPERSENSITIVITY REACTION	0	6 (18.2)	6 (18.2)
INFUSION ADMIN ISSUES	0	22 (66.7)	22 (66.7)
OTHER	0	5 (15.2)	5 (15.2)
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	1 (1.3)	3 (1.1)	4 (1.1)
NUMBER OF INFUSIONS WITH IV RATE REDUCTION PER SUBJECT (%)			
0	77 (98.7)	267 (98.9)	344 (98.9)
1	1 (1.3)	3 (1.1)	4 (1.1)
2	0	0	0
3	0	0	0
>= 4	0	0	0
TOTAL NUMBER IV RATE REDUCED /TOTAL NUMBER DOSE RECEIVED	1/1060 (<0.1)	3/2505 (0.1)	4/3565 (0.1)
REASON FOR IV RATE REDUCTION (B)			
HYPERSENSITIVITY REACTION	0	0	0
INFUSION ADMIN ISSUES	0	2 (66.7)	2 (50.0)
OTHER	1 (100.0)	1 (33.3)	2 (50.0)

	CA209032 N = 78	CA209275 N = 70	CA209032 + CA209275 N = 348
SUBJECTS WITH AT LEAST ONE CYCLE DELAYED (%)	28 (35.9)	107 (39.6)	135 (38.8)
NUMBER OF CYCLES DELAYED PER SUBJECT			
0	50 (64.1)	163 (60.4)	213 (61.2)
1	16 (20.5)	71 (26.3)	87 (25.0)
2	7 (9.0)	25 (9.3)	32 (9.2)
3	3 (3.8)	6 (2.2)	9 (2.6)
>= 4	2 (2.6)	5 (1.9)	7 (2.0)
TOTAL NUMBER CYCLES DELAYED/ TOTAL NUMBER CYCLES RECEIVED (C)	52/ 982 (5.3)	159/2235 (7.1)	211/3217 (6.6)
REASON FOR CYCLE DELAY (D)			
ADVERSE EVENT	34 (65.4)	106 (66.7)	140 (66.4)
OTHER	17 (32.7)	44 (27.7)	61 (28.9)
NOT REPORTED	1 (1.9)	9 (5.7)	10 (4.7)
LENGTH OF DELAY (D)			
4-7 DAYS	20 (38.5)	55 (34.6)	75 (35.5)
8-14 DAYS	22 (42.3)	59 (37.1)	81 (38.4)
15-42 DAYS	10 (19.2)	40 (25.2)	50 (23.7)
> 42 DAYS	0	5 (3.1)	5 (2.4)

A cycle was considered as actually delayed if the delay is exceeding 3 days.
(A) Percentages are computed out of the total number of infusions interrupted.
(B) Percentages are computed out of the total number of INFUSIONS WITH IV RATE REDUCTION.
(C) Total number cycles received is excluding first cycle.
(D) Percentages are computed out of the total number of cycles delayed.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

In the Integrated UC Population, AEs leading to discontinuation were reported in 17.8% of subjects (Table 67). Grade 3-4 AEs leading to discontinuation were reported in 13.2% subjects. The most frequently reported AEs leading to discontinuation were malignant neoplasm progression (3.2%), general physical health deterioration and pneumonitis (1.4% each), and respiratory failure and small intestinal obstruction (0.9% each).

In CA209032, the frequencies of AEs leading to discontinuation were lower (7.7%) than the Integrated UC Population (17.8%), however, this difference may be of limited interpretability due to low sample size. In CA209275, the frequencie of AEs leading to discontinuation was 20.7%.

Grade 3-4 AEs leading to discontinuation were reported in 5.1% and 15.6% subjects in CA209032 and CA209275 respectively.

In the Integrated UC Population, drug-related AEs leading to discontinuation were reported in 4.3% of subjects (

Table 68). Grade 3-4 drug-related AEs leading to discontinuation were reported in 2.9% of subjects. Drug-related AEs leading to discontinuation reported in at least 2 subjects were pneumonitis (1.4%) and pemphigoid (0.6%).

Table 67 AEs Leading to Discontinuation (All Causality) by Worst CTC Grade Reported in at Least 2 Treated Subjects - CA209275 and Integrated UC Population

System Organ Class (%) Preferred Term (%)	CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	56 (20.7)	42 (15.6)	9 (3.3)	62 (17.8)	46 (13.2)	10 (2.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	14 (5.2)	11 (4.1)	3 (1.1)	15 (4.3)	11 (3.2)	4 (1.1)
MALIGNANT NEOPLASM PROGRESSION	10 (3.7)	7 (2.6)	3 (1.1)	11 (3.2)	7 (2.0)	4 (1.1)
METASTASES TO CENTRAL NERVOUS SYSTEM	2 (0.7)	2 (0.7)	0	2 (0.6)	2 (0.6)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	10 (3.7)	7 (2.6)	1 (0.4)	11 (3.2)	8 (2.3)	1 (0.3)
PNEUMONITIS	4 (1.5)	1 (0.4)	1 (0.4)	5 (1.4)	2 (0.6)	1 (0.3)
RESPIRATORY FAILURE	3 (1.1)	3 (1.1)	0	3 (0.9)	3 (0.9)	0
GASTROINTESTINAL DISORDERS	6 (2.2)	5 (1.9)	0	6 (1.7)	5 (1.4)	0
SMALL INTESTINAL OBSTRUCTION	3 (1.1)	2 (0.7)	0	3 (0.9)	2 (0.6)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6 (2.2)	4 (1.5)	1 (0.4)	6 (1.7)	4 (1.1)	1 (0.3)
GENERAL PHYSICAL HEALTH DETERIORATION	5 (1.9)	3 (1.1)	1 (0.4)	5 (1.4)	3 (0.9)	1 (0.3)
INFECTIONS AND INFESTATIONS	4 (1.5)	4 (1.5)	0	5 (1.4)	5 (1.4)	0
SEPSIS	2 (0.7)	2 (0.7)	0	2 (0.6)	2 (0.6)	0
SEPTIC SHOCK	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (1.5)	3 (1.1)	0	4 (1.1)	3 (0.9)	0
PEMPHIGOID	2 (0.7)	2 (0.7)	0	2 (0.6)	2 (0.6)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.4)	1 (0.4)	0	3 (0.9)	3 (0.9)	0
THROMBOCYTOPENIA	1 (0.4)	1 (0.4)	0	2 (0.6)	2 (0.6)	0
HEPATOBILIARY DISORDERS	2 (0.7)	2 (0.7)	0	2 (0.6)	2 (0.6)	0
HEPATIC FAILURE	2 (0.7)	2 (0.7)	0	2 (0.6)	2 (0.6)	0

MedDRA Version: 19.0, CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Table 68 Drug-related AEs Leading to Discontinuation by Worst CTC Grade Reported in All Treated Subjects - CA209275 and Integrated UC Population

System Organ Class (%) Preferred Term (%)	CA209275 N = 270			CA209032 + CA209275 N = 348		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	13 (4.8)	8 (3.0)	2 (0.7)	15 (4.3)	10 (2.9)	2 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (2.2)	3 (1.1)	1 (0.4)	7 (2.0)	4 (1.1)	1 (0.3)
PNEUMONITIS	4 (1.5)	1 (0.4)	1 (0.4)	5 (1.4)	2 (0.6)	1 (0.3)
DYSPNOEA	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0
INTERSTITIAL LUNG DISEASE	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (1.5)	3 (1.1)	0	4 (1.1)	3 (0.9)	0
PEMPHIGOID	2 (0.7)	2 (0.7)	0	2 (0.6)	2 (0.6)	0
RASH MACULO-PAPULAR	1 (0.4)	0	0	1 (0.3)	0	0
RASH PRURITIC	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0
GASTROINTESTINAL DISORDERS	2 (0.7)	2 (0.7)	0	2 (0.6)	2 (0.6)	0
ABDOMINAL PAIN	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0
DIARRHOEA	1 (0.4)	1 (0.4)	0	1 (0.3)	1 (0.3)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	0	0	1 (0.3)	1 (0.3)	0
THROMBOCYTOPENIA	0	0	0	1 (0.3)	1 (0.3)	0
VASCULAR DISORDERS	1 (0.4)	0	1 (0.4)	1 (0.3)	0	1 (0.3)
CIRCULATORY COLLAPSE	1 (0.4)	0	1 (0.4)	1 (0.3)	0	1 (0.3)

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
CA209032 consists of the nivolumab monotherapy urothelial carcinoma (i.e. bladder) cohort of CA209032.
CA209032 crossover subjects are truncated at the first dose date of crossover period.

Immunogenicity

The incidence of immunogenicity and impact on safety in UC is similar to that observed for other tumor types.

CA209275: Of the 219 UC subjects who were evaluable for ADA, 52 (23.7 %) subjects had at least one ADA positive sample relative to baseline at any time after initiation of treatment. No subjects were

persistent positive, and 4 subjects (1.8%) were neutralizing ADA positive. Of all subjects who were evaluable for ADA, no subject that was ADA positive experienced hypersensitivity/infusion reaction category events. Thus, immunogenicity did not appear to have an effect on the safety of nivolumab in the UC subjects.

CA209032: The incidence of nivolumab ADA positive was low (9 subjects [13.0%] had at least one ADA positive sample relative to baseline at any time after initiation of treatment). Only 1 ADA positive subject had Grade 1 hypersensitivity/infusion reaction on Day 1 after the first dose of nivolumab. Given that this subject was ADA positive on Days 1 (baseline), 15, 29, and 99 and continued to receive nivolumab treatment for 6 months with no other occurrences of hypersensitivity/infusion reaction, it is unlikely that the Day 1 occurrence was ADA related.

Integrated analysis: An integrated analysis of immunogenicity assessments was performed with data available from the following studies: CA209037, CA209063, CA209066, CA209017, CA209057, CA209067 (nivolumab monotherapy arm), CA209025, CA209039, CA209205, CA209141, CA209032, and CA209275. These studies included data from NSCLC, melanoma, RCC, cHL, SCCHN, and UC subjects. Overall, the incidence of nivolumab ADA was 11.4%. There was no association established between the presence of ADA and hypersensitivity or infusion reactions.

Post marketing experience

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and in the EU, and for other indications (e.g., metastatic NSCLC, advanced RCC, and cHL [US only]). 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.

2.5.1. Discussion on clinical safety

Integrated safety data were presented for 348 UC subjects from CA209275 (n=270) and CA209032 (n= 78, nivolumab monotherapy UC cohort), hereafter referred to as the ‘Integrated UC Population’.

Any-grade AEs (regardless of causality) were reported in 99.1% of subjects treated with nivolumab. The most frequently reported AEs were: fatigue (37.1%), nausea (23.9%), anaemia (20.1%), decreased appetite (20.1%), and cough (17.8%). Grade 3-4 AEs (regardless of causality) were reported in 51.7% of subjects. The most frequently reported Grade 3-4 AEs were anaemia (6.9%), urinary tract infection (5.7%), malignant neoplasm progression (4.3%), dyspnoea (3.7%), asthenia (3.2%), and hyponatremia (3.2%). Frequencies of all-causality AEs (any grade and Grade 3-4) for CA209032 tended to be higher than the Integrated UC Population, however, this difference may be of limited interpretability due to low sample size.

Any-grade drug-related AEs were reported in 68.7% of subjects. The most frequently reported drug-related AEs were fatigue (21.0%), pruritus (13.8%), diarrhoea (8.9%), nausea (8.3%), and decreased appetite (7.8%). Grade 3-4 drug-related AEs were reported in 19.0% of subjects. The most frequently reported Grade 3-4 drug-related AEs were lipase increased (2.3%) and fatigue (2.0%).

With regards to AE in the integrated UC population and across pooled monotherapy studies, anaemia was the only newly reported all-causality PT reported in >20% subjects for the integrated UC population. Diarrhoea and dyspnoea for study CA209032 tended to be higher than from nivolumab monotherapy studies in other tumor types.

According to the data submitted, the safety profile of nivolumab in UC population has a slight higher rate of AEs Grade 3-4 (regardless of causality and drug-related) and deaths (within 30 and 100 days) than previously submitted pooled data of nivolumab monotherapy in melanoma, NSCLC and RCC.

SAE were reported in 52.6% of subjects. Grade 3-4 SAEs were reported in 35.1% of subjects and the most frequently reported SAEs were malignant neoplasm progression (11.5%), urinary tract infection (5.2%), general physical health deterioration (2.6%), sepsis (2.3%), and diarrhoea and small intestinal obstruction (2.0%).

Drug-related SAE were reported in 9.5% of subjects. Grade 3-4 drug-related SAEs were reported in 6.6% of subjects. Drug-related SAEs reported in at least 2 subjects were pneumonitis and diarrhoea, 5 (1.4%) each; fatigue, 3 (0.9%); colitis, nausea, and pemphigoid, 2 (0.6%) subjects each.

Six (1.7%) deaths assessed by the investigator due to study drug toxicity. There were 4 deaths in CA209275 (pneumonitis, respiratory failure, cardiovascular failure and acute respiratory failure) and two deaths in CA209032 (pneumonitis and thrombocytopenia). Across both studies (CA209275 and CA209032), there were 6 deaths assessed by the investigator as due to study drug toxicity (pneumonitis [2], respiratory failure, acute respiratory failure, thrombocytopenia and cardiovascular failure).

The majority of AESIs 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 (23.0%) and gastrointestinal (9.5%).The majority of events were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered.

In terms of drug-related AESI, endocrine select AE were reported in 12.9% of subjects, the most commonly reported was hypothyroidism (7.2%). With the exception of one Grade 3 event of hypophysitis reported in CA209275. In the gastrointestinal category, AESIs were occurring in 9.5% of subjects, 1.4% subjects experienced Grade 3-4 diarrhoea events. Two of the 3 colitis events were Grade 3-4. Hepatic select AEs were reported in 4.0% of subjects, six subjects had Grade 3-4 drug-related events. Pulmonary select AE were reported in 3.7% of subjects. Pneumonitis being the most frequently occurring pulmonary select AE. Twelve of these drug-related events were pneumonitis; 2 of the 12 were Grade 3-4. In addition to the pneumonitis events, a Grade 3-4 drug-related event of interstitial lung disease; was reported. Renal select AR were reported in 2.9% subjects. Skin select AEs were reported in 23.0%subjects. The most frequently reported drug-related events were pruritus (13.8%), rash (6.0%), and rash maculopapular (5.2%). 1.7% subjects experienced Grade 3-4 skin events.

Hypersensitivity/infusion reactions were reported in 5 (1.4%) subjects. A Grade 3-4 infusion reaction was reported in 1 subject. No hypersensitivity/infusion reactions led to permanent discontinuation of nivolumab.

The only OESI reported in the Integrated UC Population was a Grade 3-4 OESI of pancreatitis reported in CA209032.No events in the categories of myositis, myocarditis, and rhabdomyolysis were identified.

In the Integrated UC Population, the frequencies of all-causality and drug-related AEs among all treated subjects for subgroups of gender, race, age, and region were consistent with the AE frequencies in the overall treated population. No consistent differences were observed in the frequencies of AEs by PD-L1 expression subgroup.

Discontinuation due to AE was reported in 17.8% of subjects. Grade 3-4 AEs leading to discontinuation were reported in 13.2% subjects. The most frequently reported AEs leading to discontinuation were malignant neoplasm progression (3.2%), general physical health deterioration and pneumonitis (1.4% each), and respiratory failure and small intestinal obstruction (0.9% each). Drug-related AEs leading to discontinuation were reported in 4.3% of subjects. Grade 3-4 drug-related AEs leading to discontinuation

were reported in 2.9% of subjects. Drug-related AEs leading to discontinuation reported in at least 2 subjects were pneumonitis (1.4%) and pemphigoid (0.6%).

The rate of antibody positive subjects in trial CA209275, was 2-fold that of the pool of previous trials (23.7%). This finding is not considered clinically relevant taking into account that no patients was persistently positive and only 4 patients (1.8%) tested positively for neutralizing antibodies. Moreover ADA titres in ADA positive subjects were low, ranging from 1 to 32. There was no evidence of loss of efficacy in subjects with neutralizing antibodies and there were no associated adverse events. The rate of antibody positive subjects in the Phase II trial CA209032 was lower (13%). Only one patient in the UC experienced a safety event (grade 1 hypersensitivity/infusion reaction) in the phase II trial.

There was no association established between the presence of ADA and hypersensitivity or infusion reactions, suggesting nivolumab ADA does not alter the safety profile of nivolumab. Immunogenicity did not appear to have an effect on the safety of nivolumab in the UC subjects no evidence of an altered safety profile (refer PK-PD assessment). In the pooled analysis, of the 2022 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 231 patients (11.4%) tested positive for treatment-emergent anti-product-antibodies with fifteen patients (0.7 %) testing positive for neutralising antibodies (see SmPC section 4.8).

The overall safety profile of nivolumab 3 mg/kg in urothelial carcinoma patients (n = 348) was consistent with that established across tumour types for nivolumab monotherapy. Hence, no major SmPC changes to section 4.8 have been made. The integrated UC safety data has been added to the safety pool nivolumab monotherapy (n = 2578) in variation II/32 which is under assessment.

Patients with a baseline performance score ≥2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of urothelial carcinoma (see SmPC sections 4.4., 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit-risk on an individual basis. Patients with brain metastases have been included as missing information in the RMP.

2.5.2. Conclusions on clinical safety

Based on the integrated analyses of safety from CA209275 and CA209032 of nivolumab monotherapy in patients with histologically confirmed UC of the renal pelvis, ureter, bladder or urethra with tumour progression or recurrence on or after at least 1 platinum-based regimen, the safety profile of nivolumab 3 mg/kg Q2W is considered acceptable in the context of the observed clinical activity. The frequency and severity of select AEs were acceptable, with the majority of subjects experiencing resolution when immune-modulating medications were administered. 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 (e.g., hormone replacement therapy for endocrine events).

No new risks in addition to those identified in previous studies in other indications were identified.

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 7.0 is acceptable. The PRAC advice is attached.

Following subsequent list of outstanding issues and responses from the applicant, the CHMP endorsed this advice with the following changes:

Patients with active brain metastases should be included under missing information, as those subjects were excluded from the clinical trials and therefore the benefit risk is unsure in this population.

The CHMP endorsed the Risk Management Plan version 7.1 with the following content:

safety concerns

Summary of safety concerns (changes in bold underlined)

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

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title)	**Objectives**	**Safety concerns addressed**	**Status Planned, started**	**Date for submission of interim or final reports (planned or actual)**
CA209835: Registry study in patients who underwent post-nivolumab allogeneic HSCT Category 3	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	Planned	Final CSR submission: 4Q2022
CA209234: 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 and renal dysfunction, endocrinopathies, rash, and other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, and encephalitis), and infusion reactions	Planned	Final CSR submission: 4Q2024 (interim report annually)

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

Risk minimisation measures

Summary table of Risk Minimisation Measures (changes in bold underlined)

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune related rash Other immune-related ARs	The SmPC warns the risks of immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related nephritis and renal dysfunction, immune-related endocrinopathies, immune-related 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.	To further raise awareness of HCPs on important risks and their appropriate management, additional risk minimization activity includes a Communication Plan. The Plan comprising 2 tools to be distributed to potential prescribers at launch by BMS: • Adverse Reaction Management Guide • Patient Alert Card
Severe infusion reactions	The SmPC warns the risk of severe infusion reactions in Section 4.4 and ADR in Section 4.8.	None
Important Potential Risks		
Embryofetal Toxicity	SmPC includes Embryofetal Toxicity in Section 4.6 Fertility, pregnancy and lactation, Section 5.3 Preclinical safety data The package leaflet also includes specific description on the safety information in the language suitable for patients.	None
Immunogenicity	SmPC Section 4.8 Immunogenicity	None
Cardiac arrhythmias (previously treated melanoma indication, only)	SmPC Section 4.8 Undesirable effects	None
Missing Information		
Pediatric patients	SmPC Section 4.2 Posology and method of administration, subsection on Pediatric population	None
Severe hepatic and/or renal impairment	SmPC Section 4.2 Posology and method of administration: Patients with hepatic or renal	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	impairment; SmPC Section 5.2 Pharmacokinetic properties: Hepatic or renal impairment	
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
Patients with brain metastases: • ***Advanced melanoma, SCCHN, and UC – active brain or leptomeningeal metastases*** • ***NSCLC – active brain metastases*** • ***RCC – any history of or concurrent brain metastases***	***SmPC Section 4.4 provides warning and cautionary information for patients with active brain metastases or leptomeningeal metastases***	***None***

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Annex II has also been revised to reflect the revised conditions.

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 MAH applied for a new indication for nivolumab (Opdivo) in locally advanced unresectable or metastatic urothelial carcinoma (UC) in adults after failure of prior platinum-containing therapy.

In the EU, bladder cancer is the fifth most common cause of cancer, with approximately 124,188 new cases and 40,635 resulting deaths reported in 2012[15]. Urothelial carcinoma, also known as transitional cell carcinoma, is the most common type of bladder cancer, accounting for 90% of cases. Among patients diagnosed with UC, the majority have non-muscle invasive (approximately half) or localized muscle-invasive disease (approximately 1 in 3) at the time of diagnosis, with the remaining patients having

[15] GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

metastatic disease. Approximately 50% of patients presenting with muscle-invasive urothelial cancer eventually develop metastatic recurrence after therapy for clinically localised disease.

3.1.2. Available therapies and unmet medical need

In locally advanced unresectable or metastatic UC after failure of prior platinum-containing therapy, the available monotherapy therapies provide a response rate ranging between 10-15%, which seems to be translated into a median overall survival of around 8-9 months at best[16]. Vinflunine, taxanes, gemcitabine and pemetrexed are the current therapeutic alternatives usually offered to this population in the EU[17]. However, taxanes-combination therapies could offer responses in a higher number of patients (30-70%), leading to an increase in OS, even though the high toxicity associated with these combinations limits their use[18].

3.1.3. Main clinical studies

Two on-going studies are presented in support of the claimed indication, i.e. one Phase 1/2 study in multiple tumour types, including unresectable locally advanced or metastatic UC (CA209032) and one Phase 2 study in metastatic or unresectable urothelial cancer (CA209275).

3.2. Favourable effects

Outcomes from the pivotal trial (study CA209275; clinical cut-off of 21-Jul-2016) in terms of confirmed ORR by BICR (primary endpoint) showed a response rate of 20% (95% CI 15.4, 25.3) in all treated patients (n=270) (23% by investigator assessment; CI 95% 18.1, 28.4), with a median of duration of 10.35 months (more than half [34/54, 63.0%] of the responders had ongoing response at the time of the clinical cut-off) and with a time to objective response of around 2 months. Median OS was 8.57 months, even though the percentage of events was roughly 58%. Median PFS was 2 months.

Consistent results were reported from the supportive study CA209032 (n=78), where the confirmed ORR based on investigator assessment was 24% (CI 95% 15.3, 35.4) and similar PFS and OS results were achieved (median PFS 2.78 months and 9.72 months of OS).

These results were better in those patients with PD-L1 expression >1%, with confirmed ORR (BICR) of 25% (CI 95% 17.7, 33.6), median OS 11.63 months (CI 95% 9,10, NA) and median PFS 3.55 months (CI 95% 1.94, 3.71) in the pivotal Study CA209275. Patients with PD-L1 expression<1% had an ORR of 16%. Median PFS and median OS were 5.95 months (95% CI: 4.37, 8.08 months) and 1.9 months respectively in PD-L1 <1% subgroup.

As expected, results in those subgroups of patients with poorer prognosis (visceral and hepatic metastasis, high ECOG) obtained lower ORR. Of note the response rate was according to the different age groups, where the older subgroups showed the better results.

3.3. Uncertainties and limitations about favourable effects

The main uncertainty in the knowledge about the beneficial effects derives from the study design as single arm trials, where there is no other treatment to compare second line treatment of urothelial carcinoma in this heterogeneous patient population. No phase III trials are ongoing or planned for

[16] Bellmunt J1, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009 Sep 20;27(27):4454-61. doi: 10.1200/JCO.2008.20.5534. Epub 2009 Aug 17.
[17] J. Bellmunt et al., Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology 25
[18] Oing C, et al. Second Line Chemotherapy for Advanced and Metastatic Urothelial Carcinoma: Vinflunine and Beyond-A Comprehensive Review of the Current Literature. J Urol. 2016 Feb;195(2):254-63. doi: 10.1016/j.juro.2015.06.115. Epub 2015 Sep 26.

nivolumab in this setting. Therefore, uncertainties exist on the accuracy of the estimation of the benefit in the absence of an adequately designed randomised controlled trial. Nevertheless results from the two nivolumab studies are consistent with each other and the data supports the benefit observed in terms of ORR.

In the subgroups of patients with low/no tumour PD-L1 expression, results were less outstanding than that observed with patients with tumours with higher tumour PD-L1 expression. Patients with PD-L1 expression <1% had an ORR of 16% compared with 25% in patients with >1% PD-L1 expression. The supportive study CA209032 did not show a difference in ORR based on PD-L1 expression, with an ORR of 24% and 26% for patients with above 1% expression and below 1% expression, respectively. In terms of survival benefit, patients with PD-L1 expression below 1%, showed a shorter median survival than those classified as PD-L1>1%. However, the benefit in terms of survival rate at 1 year in these patients is considered similar to chemotherapy (34% nivolumab vs 31% chemotherapy from Bellmunt et al. NEJM 2017) and the 1-year survival rate in responders was close to 96%. Furthermore, durable responses were observed across all PD-L1 subgroups.

3.4. Unfavourable effects

The safety and tolerability of nivolumab in patients with locally advanced unresectable or metastatic UC was similar to what has been observed in other indications with nivolumab. No new safety concerns were raised and the important safety concerns remain the same.

Any-grade drug-related AEs were reported in 68.7% of subjects treated with nivolumab in Integrated UC Population. The most frequently reported drug-related AEs were fatigue (21.0%), pruritus (13.8%), diarrhoea (8.9%), nausea (8.3%), and decreased appetite (7.8%). Grade 3-4 drug-related AEs were reported in 19.0% of subjects. The most frequently reported Grade 3-4 drug-related AEs were lipase increased (2.3%) and fatigue (2.0%).

The immunogenic potential of nivolumab was found to be low and did not appear to be affect safety profile.

3.5. Uncertainties and limitations about unfavourable effects

The main study as well as the supportive study had a single arm study design. This may have affected adverse event reporting. However, this is not expected to have a large impact on the conclusions drawn for the efficacy and safety of the product.

Subjects with active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of urothelial carcinoma and therefore the B/R is uncertain in this population. However, the current SmPC accurately reflects a warning regarding the potential risks associated with treating patients with active, known or suspected autoimmune disease.

3.6. Effects Table

Table 69: Effects Table for nivolumab for the treatment of UC (Study CA209275, data cut-off: 21-Jul-2016; tumour assessment)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	% of randomized subjects who achieved a best response of CR or PR (RECIST v1.1 BICR).	%	20.0	N/A	Single arm trial PD-L1 >1% 25.0% PD-L1 <1% 15.8% Supported by study CA209032	See discussion on clinical efficacy
DOR	Time from first confirmed response (CR or PR) to the date of the first documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.	Median (Months)	10.4	N/A	PD-L1 >1% 10.4 PD-L1 <1% NR	
OS	Time from randomization to the date of death from any cause	Median (months)	8.6	N/A	Single arm trial PD-L1 >1% 11.6 PD-L1 <1% 6.0 Supported by study CA209032	
PFS	Time from randomization to first date of documented progression, or to death due to any cause.	Median (months)	2.0	N/A	Single arm trial PD-L1 >1% 3.6 PD-L1 <1% 1.9 Supported by study CA209032	
Unfavourable Effects						
All Grade 3/4 AEs	Drug related	%	9.5		No new safety concerns with nivolumab monotherapy treatment were identified in UC	
SAEs	Drug related serious Adverse Events	%	6.6			

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Fatigue	Most frequent drug-related AE	%	21.0			
Pruritus	Most frequent drug-related AE	%	13.8			
Diarrhoea	Most frequent drug-related AE	%	8.9			
Nausea	Most frequent drug-related AE	%	8.3			
Decreased appetite	Most frequent drug-related AE	%	7.8			

Abbreviations: AEs (adverse events), AR (assessment report), BICR (blinded independent review committee); CR (complete response), HR (hazard ratio), PFS (progression free survival), ORR (objective response rate), OS (overall survival), PR (partial response), N/A (not assessed), NR (not reached)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

From a clinical perspective, patients with metastatic urothelial carcinoma after failure of prior platinum-containing therapy, have a poor prognosis. According to the bibliography, the therapeutic landscape based on monotherapies after a first treatment of platinum (vinflunine, taxanes, gemcitabine and pemetrexed) offers ORRs that range between 10-15% with a median OS of 8-9 months; with the exception of gemcitabine that as a single agent has demonstrated ORRs of 11-29%, with median OS that ranged from 5 to 13 months, as second-line therapy in a small Phase 2 study (N<50). On the other hand, efficacy results reported for most taxane-based combinations seem to offer 30-70% ORRs, with longer survival than monotherapies. However, taxane-based combination therapy is accompanied by high toxicity and currently used in a minority of the patients.

Treatment with nivolumab showed consistently higher rates of tumour responses (25%) and a trend for higher OS (12 months) as compared to available monotherapy options in the subset of patients with high PD-L1 expression (i.e. >1%). While the response rates in patients with tumours designated as PD-L1 <1% are lower than for patients with tumours designated as PD-L1 >1%, they seem similar or slightly superior than what is observed for other available options. The responses had a clinically relevant duration across all PD-L1 subgroups, which appear better than DoRs described for all other available therapies (including combination-chemotherapy).

Although patients with PD-L1 expression below 1% showed a shorter median survival than those classified as PD-L1>1% (respectively 6 vs 12 months), the 1 year survival rate provided similar results to chemotherapy in the overall population of patients PD-L1<1% (34% nivolumab versus 31% reported for chemotherapy in Bellmunt et al. NEJM 2017) and the 1-year survival rate in responders was close to 96% which is considered clinically meaningful. Furthermore, in patients with both PD-L1 expression<1% and the presence of poor prognostic factors, the OS rates at 1 year appear similar to those reported with chemotherapy in this population.

The overall safety profile of nivolumab monotherapy in CA209275 and CA209032 has been characterised. No new safety concerns were identified in UC setting.

3.7.2. Balance of benefits and risks

The safety profile of nivolumab compares favourably to chemotherapy and the benefit in those patients considered PD-L1>1% is considered clinically meaningful, both in terms of durable ORR and OS. In patients with low PD-L1 expression (<1%) the use of nivolumab will likely provide both comparable rates of response and similar survival benefit to that reported for chemotherapy, however the responses observed are more durable than achieved with currently available therapy. Considering the observed benefit and safety profile in the overall patient population, the indication is not restricted to patients with tumour expressing PD-L1. Furthermore, no specific PD-L1 expression cut-off that would select patients benefiting most from nivolumab could be identified and further biomarkers assessment is needed (see Annex II).

In conclusion, the benefit/risk balance is positive for nivolumab monotherapy in the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

3.7.3. Additional considerations on the benefit-risk balance

The MAH provided additional analyses for several biomarkers which might predict treatment response. Currently none of the assessed biomarkers could adequately differentiate the responders from the non-responders. Further evaluation on the association between improved clinical outcomes to nivolumab and PD-L1 expression on both immune cells and tumour cells in a quantitative, prospective manner, using validated assays and methods, is lacking at this stage. Other biomarkers such as other gene signatures, mutational and neoantigen load remain to be evaluated.

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

The value of biomarkers to predict the efficacy of nivolumab therapy should be further explored, specifically:

- To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other genomic-based methods / assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, etc.) as predictive of nivolumab efficacy. This will be provided for urothelial carcinoma studies CA209275 and CA209032 (by 30 June 2018)
- To further explore in UC patients, methods to aid in the early identification of those who did not respond to treatment with nivolumab, as well as to evaluate the association between improved clinical outcomes to nivolumab and the presence of:
    - Mutational and neoantigen load, and if feasible, PD-L1 expression on tumour- and tumour associated immune cells using validated approaches (by 30 June 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 and IIIB

Extension of Indication to include the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy for OPDIVO.
As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed indication, add a warning about the patient populations excluded from the clinical trial, and update the safety information. The Package Leaflet is updated in accordance.
Moreover, the updated RMP version 7.2 has been submitted.

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 amended conditions:

Conditions and requirements of the marketing authorisation

Obligation to conduct post-authorisation measures

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

Description	Due date
4. The value of biomarkers to predict the efficacy of nivolumab and/or nivolumab + ipilimumab combination therapy should be further explored, specifically:	
2.To further investigate the value of biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other genomic-based methods / assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, expression of components of antigen-presentation complexes and/or other inhibitory checkpoint receptors/ligands within tumour, etc.) as predictive of nivolumab and/or nivolumab + ipilimumab combination therapy efficacy. This will be provided for all the approved indications:	
- UC: studies CA209275 and CA209032	30th June 2018
7. To further explore in UC patients the early identification of those who do/do not respond to treatment with nivolumab, as well as to evaluate the association between improved clinical outcomes to nivolumab and the presence of:	
- Mutational and neoantigen load, and PD -L1 expression on tumour- and tumour associated immune cells using validated approaches as feasible, by 30 June 2018	30th June 2018