24 February 2022
EMA/155845/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0100

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	bacillus calmette-guerin
CDR	Central Data Review
CI	confidence interval
CIS	carcinoma in situ
CLIA	Clinical Laboratory Improvement Amendments
CPS	combined positive score
CSP	Clinical Safety Program
CSR	clinical study report
CTLA4	cytotoxic T-lymphocyte associated protein 4
DBL	database lock
DFS	disease-free survival
DMC	Data Monitoring Committee
DMFS	distant metastasis-free survival
DSS	disease-specific survival
ECOG	Eastern Cooperative Oncology Group
ECL	electrochemiluminescence
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC QLQ-30	European Organization for the Research and Treatment of Cancer quality of life questionnaire
EuroQoL EQ-5D-3L	EuroQoL 5-dimensional 3-level index
FT3	free triiodothyronine
FT4	free thyroxine
GBDS	Global Biometrics and Data Sciences
GCP	Good Clinical Practice
GDMCM/EDI	Global Data Management & Centralized Monitoring External Data Integration
GI	gastrointestinal
H&E	hematoxylin and eosin
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio

Abbreviation	Definition
HRQoL	health-related quality of life
IA	interim analysis
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IPD	important protocol deviation
IRC	Institutional Review Board
IRT	Interactive Response Technology
ISUP	International Society of Urological Pathology
IV	intravenous
IVRS	Interactive Voice Response System
K-M	Kaplan-Meier
KRI	Key Risk Indicators
LPLV	last patient last visit
LLN	lower limit of normal
LRC	locoregional control
LRDFS	locoregional disease-free survival
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activites
MID	minimal important difference
MIUC	muscle invasive urothelial carcinoma
N.A.	not available
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMIBC	non-muscle invasive bladder cancer
NUTRFS	non-urothelial tract recurrence-free survival
OESI	other event of special interest
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD-1	programmed death receptor 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS2	progression-free survival after the next line of subsequent therapy

Abbreviation	Definition
PK	pharmacokinetics
PP	persistent positive
popPK	population pharmacokinetics
PRO	patient reported outcome
PS	performance status
PSB	potential serious breach
PT	preferred term
Q1, Q3	quartile 1, quartile 3
Q2W	every 2 weeks
RACT	Risk Assessment Categorization Tool
RBM	Risk-Based Monitoring
RC	Radical cystectomy
RCT	Randomised clinical trial
RIRR	Randomization Information Release Request
RNU	radical nefro ureterectomy
RPD	relevant protocol deviation
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCI	Statistics Collaborative Inc.
SD	standard deviation
sDRP	Statistical Data Review Plan
SDV	source data verification
sFTP	secure file transfer
SI	International System of Units
SMP	site monitoring plan
SNP	single nucleotide polymorphism
SOC	system organ class
SOP	standard operating procedure
SUSAR	serious unexpected serious adverse reaction
TAO	trial access online
TSH	thyroid stimulating hormone
TTR	time to recurrence
UC	urothelial cancer
UTUC	upper tract urothelial cancer
UK	United Kingdom
UK TTO	United Kingdom Time Trade-Off

Abbreviation	Definition
ULN	upper limit of normal
USA	United States of America
VAS	visual analogue scale
vs	versus
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 8 March 2021 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 for Opdivo to include adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 23.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision(s) P/0432/2020, P/0433/2020on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0433/2020 was not yet completed as some measures were deferred

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did 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: N/A Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Submission date	8 March 2021

Timetable	Actual dates
Start of procedure:	27 March 2021
CHMP Co-Rapporteur's preliminary assessment report circulated on:	25 May 2021
PRAC Rapporteur's preliminary assessment report circulated on:	28 May 2021
PRAC RMP advice and assessment overview adopted by PRAC on:	10 June 2021
CHMP Co-Rapporteur's updated assessment report circulated on:	18 June 2021
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 June 2021
MAH's responses submitted to the CHMP on:	9 September 2021
CHMP Co-Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 October 2021
CHMP Co-Rapporteur's updated assessment report on the MAH's responses circulated on:	4 November 2021
2nd request for supplementary information and extension of timetable adopted by the CHMP on:	11 November 2021
MAH's responses submitted to the CHMP on:	16 December 2021
CHMP Co-Rapporteur's preliminary assessment report on the MAH's responses circulated on:	31 January 2022
CHMP Co-Rapporteur's updated assessment report on the MAH's responses circulated on:	18 February 2022
CHMP opinion adopted on:	24 February 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Urothelial carcinoma (UC) originates in the urothelial cells (also referred to as transitional cells) that line the bladder, ureter, and renal pelvis. The majority (90%) of UCs originate in the urinary bladder, while up to 10% originate in the upper urinary tract (ureters and/or renal pelvis) (Hepp et al, 2020; Miyazaki & Nishiyama, 2017). Although the majority of patients present with non-invasive disease, 15% to 25% of UCs either present with or eventually progress to muscle invasive or metastatic disease. Once invasive into the muscularis propria, UC of the bladder, commonly referred to as muscle invasive bladder cancer (MIBC), is an aggressive disease that requires multimodal treatment, which includes radical surgery or radiation therapy with or without chemotherapy. Survival depends amongst others on pathological stage; for patients with pT0 a median OS of 11.3 years is reported, for pT2 a median survival of 6.25 years is reported, while for those with pT3/T4 a median OS of 2 years is reported (Supit et al, 2014; Mitra et al, 2011; Barton Grossman et al, 2003).

Despite multimodal treatment, more than 50% of patients with MIBC will eventually develop metastases; upon metastatic relapse, the prognosis is dismal, with a median overall survival (OS) up to 15 months with chemotherapy alone and to up to 21 months when maintenance checkpoint inhibitor is added for patients without disease progression after completing of first line therapy (Von der Maase H et al,2005).

Muscle invasive upper tract urothelial carcinoma (UTUC) is less common. From literature it is not entirely clear whether UTUC is the same or a different disease entity as MIBC. However, as it concerns a different anatomic site and lymphogenic spreading pattern, the course of disease and metastasis pattern might differ. Similar to MIBC, muscle invasive UTUC is an aggressive disease that requires radical surgery with a median disease-free survival (DFS) of 30 months. Cisplatin-based adjuvant chemotherapy has a role in muscle invasive UTUC based on the results of the POUT (Peri-Operative chemotherapy versus surveillance in UTUC) study (Birtle A,2020).

The proposed indication is:

"OPDIVO® as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1)."

Epidemiology

UC of the bladder is among the 10 most common cancers in the world with the highest incidence rates observed in men in Europe (Age-Standardized incidence Rates (ASR) per 100.000 in Southern Europe is 26.5, in Western Europe-ASR is 22.5) and North America (ASR is 19.7).

Aetiology and pathogenesis

Environmental exposures account for most cases of bladder cancer. The surface epithelium (urothelium) that lines the mucosal surfaces of the entire urinary tract is exposed to potential carcinogens that are either excreted in the urine or activated from precursors in the urine by hydrolyzing enzymes. This "field cancerization" effect is one hypothesis to explain the multifocal occurrence that is a characteristic feature of urothelial carcinomas of both the urinary bladder and the upper urinary tract. (Burger M. et al, 2013).
However, in the majority of cases, multifocal urothelial carcinomas are monoclonal. This supports their presumed origin from a single genetically altered cell, which then spreads through the urothelium via intraluminal seeding or intraepithelial migration (monoclonality hypothesis). Although the monoclonality hypothesis appears to conflict with field cancerization, both mechanisms are probably operative in urothelial carcinogenesis, as has been shown with squamous carcinogenesis in the oral cavity.
Chemical carcinogenesis is believed to be responsible for much of the burden of bladder cancer, including the increased risk associated with cigarette smoke as well as various industrial exposures. The relationship of bladder cancer to chemical carcinogens was initially suggested by the high incidence of bladder cancer in workers with particular chemical exposures. (Freedman ND et al, 2011)

Subsequent epidemiologic and laboratory studies have identified a large number of chemical compounds thought to be carcinogenic (EAU Guideline muscle-invasive and metastatic bladder cancer, 2020).

Clinical presentation, diagnosis and stage/prognosis

The most common symptom of bladder cancer is painless haematuria, seen in >80% of patients. Others may also present with irritative symptoms such as dysuria, frequency or urgency.
Pathological diagnosis should be made according to the World Health Organisation (WHO) classification from a biopsy obtained during transurethral resection of the bladder tumour (TURBT). Tumours should be graded as high and low grade according to the latest WHO criteria (2004). MIBC should be staged according to the tumour–node–metastasis (TNM) system.
Complete TURBT is the treatment of choice for any initial bladder tumour, followed by instillations according to risk stratification in NMIBC. In MIBC treatment is far more extensive (see management).

Management

Neoadjuvant chemotherapy
Patients with MIBC, defined as stage T2-T4a, N0, and M0, are at a high risk for developing metastatic disease, even after undergoing radical cystectomy (RC), which represents the standard of care treatment. The administration of neoadjuvant cisplatin-based chemotherapy has consistently demonstrated a survival benefit when given prior to surgery. This was demonstrated in a 2003 meta-analysis of 11 randomised trials that compared cisplatin-based neoadjuvant chemotherapy plus local therapy with local therapy alone (Stadler, 2003). Compared with local therapy alone, neoadjuvant cisplatin-based combination chemotherapy resulted in an improvement in overall survival (five-year overall survival 50 versus 45 percent, hazard ratio (HR) 0.87, 95% CI 0.78-0.98) and a lower risk of recurrence (HR for recurrence 0.81, 95% CI 0.74-0.90). This translated into an absolute disease-free survival (DFS) benefit of 7 percent.

The OS outcome is affected by the pathologic response to the neoadjuvant therapy. For patients that had a residual disease < ypT2N0, the 5-year OS rate is 75%-80%. For patients with post RC stage ≥ ypT2N0, the 5-year OS rate is 20%-45%. The 5-year OS rate for patients who did not receive neoadjuvant cisplatin with high-risk residual disease of pT3–pT4 pN0 or any pT pN+ at RC is reported at 37%-50% (median OS not reported).

For patients with UTUC no randomised clinical trials (RCTs) have been published yet but prospective data from a phase II trial showed that the use of neoadjuvant chemotherapy was associated with a 14% pathological complete response rate for high grade UTUC.

Adjuvant chemotherapy
While there is still insufficient evidence for the routine use of adjuvant chemotherapy in clinical practice for MIBC and UTUC, it is likely that high-risk patients, such as those with extravesical and/or node-positive disease that have not received neoadjuvant chemotherapy, will benefit most from adjuvant chemotherapy (ESMO guideline).
Radical cystectomy (RC) without any neoadjuvant therapy represents the primary treatment choice for patients unfit to receive cisplatin-based chemotherapy (up to 65% of patients) due to poor renal function, advanced age, hearing loss, peripheral neuropathy, or poor performance status and/or New York Heart Association class III heart failure.
Some data indicate that there may be improved outcomes with the addition of adjuvant platinum-based chemotherapy in UTUC.
The POUT trial, an open-label phase III trial that enrolled 261 UTUC patients with either muscle invasive (ie, pT2-4, N any stage) or node positive disease (i.e., T any stage, N1-3) who had undergone nephroureterectomy (Birtle 2020) showed that adjuvant chemotherapy improved DFS compared with

surveillance (at three-year DFS was 71% versus 46 respectively % with an hazard ratio (HR) 0.45, 95% CI 0.30-0.68).
The most extensive data on OS for such approach comes from an observational study (SanjayTanday 2017) from the National Cancer Database of 3253 patients who underwent radical nephroureterectomy between 2004 and 2012 for high-risk urothelial carcinoma of the upper urinary tract. All patients had a T3-T4 primary tumour and/or node positive disease. In this analysis, 762 patients underwent adjuvant chemotherapy, and 2491 were managed with observation. Although selection bias is likely, OS at a median follow-up of 50 months was longer with adjuvant chemotherapy compared with observation (median of 47 versus 36 months, five-year survival rate was 44% versus 36%, HR 0.77, 95% CI 0.68-0.88).
The main limitation of using adjuvant chemotherapy for advanced UTUC remains the limited ability to deliver the full dose cisplatin-based regimen after radical nefro-ureterectomy (RNU), given that this surgical procedure is likely to impact renal function.

Inhibitors of the PD-1/PD-L1 pathway blockade have been approved for the treatment of metastatic UC. Nivolumab (a PD-1 inhibitor) has been approved in patients with locally advanced unresectable or metastatic UC in patients after failure of prior platinum-containing therapy. Pembrolizumab (another PD-1 inhibitor) has been approved for the treatment of locally advanced or metastatic UC in patients who have received prior platinum-containing chemotherapy and in patients who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. Atezolizumab (a PD-L1 inhibitor) has been approved for the treatment of patients with locally advanced or metastatic UC after platinum-containing chemotherapy or in patients who are considered cisplatin eligible and whose tumours have a PD-L1 expression ≥ 5%. Avelumab (a PD-L1 inhibitor) has been approved for first-line maintenance treatment of patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy.

Currently, no agent is approved in the adjuvant treatment for MIUC.

An unmet need exists in patients who have high risk residual disease following RC, regardless of whether they received neo-adjuvant chemotherapy, especially if they are not eligible for cisplatin-based adjuvant chemotherapy.

2.1.2. About the product

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death 1 (PD 1) receptor and blocks its interaction with PD L1 and PD L2. The PD 1 receptor is a negative regulator of T cell activity that has been shown to be involved in the control of T cell immune responses. Engagement of PD 1 with the ligands PD L1 and PD L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T cell proliferation and cytokine secretion. Nivolumab potentiates T cell responses, including anti-tumour responses, through blockade of PD 1 binding to PD L1 and PD L2 ligands. In syngeneic mouse models, blocking PD 1 activity resulted in decreased tumour growth. Nivolumab as monotherapy or combined with other therapeutics is approved for the following indications: (adjuvant or metastatic) melanoma, (metastatic) NSCLC, advanced RCC, classical HL, (recurrent or metastatic) SCCHN, (advanced or metastatic) urothelial cancer, (advanced, recurrent or metastatic) squamous oesophageal cancer.

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

The ongoing clinical development program includes numerous studies evaluating the efficacy and safety of nivolumab as a monotherapy and in combination with other therapeutics across multiple tumour types and lines of therapy.
The current application for adjuvant MIUC is based on data from a pivotal Phase 3 study (CA209274), with a 27-Aug-2020 database lock (DBL).

Paediatric investigation plan

With reference to the Paediatric Investigation Plan (PIP) for nivolumab in the condition treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (EMEA-001407-PIP01-12-M02, latest EMA decision P/0026/2020 dated 9 January 2020), the applicant hereby confirms that no new measures/studies are due for compliance verification since the partial PIP compliance check **EMEA-C2-001407-PIP01-12** conducted by the PDCO.

Also, with reference to the second PIP (PIP02) for nivolumab in the condition of treatment of malignant neoplasms of lymphoid tissue (EMEA-001407-PIP02-15-M03, latest EMA decision P/0027/2020 dated 9 January 2020), the applicant hereby confirms that no new measures/studies are due for compliance verification since the partial PIP compliance check **EMEA-C1-001407-PIP02-15-M01** conducted by the PDCO.

Orphan designation

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

Scientific advice

The MAH did not seek a Scientific Advice for the study related to this procedure.

2.1.4. General comments on compliance with GCP

According to the Applicant, CA209274 was conducted in accordance with the principles of Good Clinical Practice, as defined by the International Council on Harmonisation, and was conducted to meet the ethical requirement of European Directive 2001/20/EC.

Further, the Applicant states that:

- the protocol, amendments, administrative letters, and subject informed consent form received Institutional Review Board/Independent Ethics Committee approval prior to implementation;
- compliance audits were performed as part of implementing quality assurance, and audit certificates were provided as applicable in the study report;
- the quality of data collected and analysed was monitored according to MAH standard operating procedures.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the Committee for Human Medicinal Products (CHMP).

Ecotoxicity/environmental risk assessment

BMS-936558 (nivolumab) is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk. As a protein, nivolumab is exempt from preparation of an Environmental Risk Assessment under the 1 June 2006 "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00). Nivolumab and the product excipients do not pose a significant risk to the environment.

Discussion and conclusion on non-clinical aspects

Not applicable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Marketing Authorization Holder.

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

- Tabular overview of clinical studies

Study/ Phase/ Status	Study Design	Study Population	Primary Efficacy Endpoint	Treatment	Number of Subjects
CA209274/ Phase 3/ Ongoing	Randomized, double-blind, placebo-controlled (adjuvant setting)	Subjects who have undergone radical resection of MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence	DFS in all randomized subjects and randomized subjects with PD-L1≥ 1%	Nivolumab 240 mg IV Q2W until recurrence or discontinuation from study up to 1 year or Placebo with the same dosing schedule and treatment duration as nivolumab	1075 enrolled 709 randomized 699 treated

Abbreviations: BICR-blinded independent central review, DFS-disease free survival, MIUC - muscle invasive urothelial carcinoma, ORR-objective response rate, OS-overall survival, PD-L1-programmed death ligand 1, Q2W-once every 2 weeks, UC-urothelial carcinoma

2.3.2. Pharmacokinetics

The nivolumab clinical pharmacology profile, including single- and multiple-dose pharmacokinetics, drug-drug interaction potential, QT prolongation potential, and dose selection for phase 2/3 studies was well characterized and described in the initial marketing authorization dossier.

Nivolumab pharmacokinetics from study CA209274 were analysed and compared with historical pharmacokinetic monotherapy data including PK data in subjects with locally advanced or metastatic urothelial carcinoma (EMEA/H/C/003985/II/0019). PopPK analyses were performed for nivolumab

adding data from the CA209274 study into the existing popPK models. Exposure-response analyses were conducted to provide a model based bridge from nivolumab 240 mg Q2W (dosing regimen evaluated in study CA209274) to 480 mg Q4W. Nivolumab immunogenicity data are also presented from study CA209274.

Bioanalytical methods

The pharmacokinetic samples from subjects in study CA209274 were analysed by cross-validated electrochemiluminescence assays ICD 416 (previously used) and by 14BASM122. The bioanalytical methods for the assessment of (neutralizing) antibodies against nivolumab were also the same as presented in the previously submitted marketing application for nivolumab.

Population pharmacokinetics

A nivolumab popPK model has been previously developed with data from multiple tumour types, including advanced or metastatic UC (EMEA/H/C/003985/II/0019). The main purpose of the updated popPK analysis was to characterize the PK of nivolumab in subjects with muscle invasive urothelial carcinoma in the adjuvant setting in CA209274 who received nivolumab 240 mg Q2W and to determine the effects of covariates on nivolumab PK. Moreover, the purpose was to compare summary measures of nivolumab exposure in nivolumab 240 mg every 2 weeks (Q2W) and 480 mg every 4 weeks (Q4W), posology which is proposed in adjuvant treatment of subjects with muscle invasive urothelial carcinoma.

In study CA209274 nivolumab pharmacokinetic samples were collected at pre-dose C1, C2, C3, C7 and every 6 cycles after C7 until discontinuation of study treatment and on first 2 follow-up visits, FU1 and 2.

The population pharmacokinetic (popPK) analysis dataset included a total of 5,282 nivolumab concentration values from 1,181 subjects from 7 studies in subjects with non-small cell lung cancer (NSCLC), adjuvant muscle invasive urothelial carcinoma, and advanced UC. These studies included 2 Phase 1 studies (CA209001 and CA209003 (multiple tumour types, only NSCLC included)), 1 Phase 1/2 study (CA209032 (multiple tumour types, only advanced UC included)), 1 Phase 2 study (CA209275 (advanced UC)), and 3 Phase 3 studies (CA209017 (NSCLC), CA029057 (NSCLC), and CA209274 (adjuvant muscle invasive urothelial carcinoma), (N=333)).

Two different full models exploring time-varying versus stationary CL of nivolumab in adjuvant MIUC were evaluated. Nivolumab pharmacokinetics for adjuvant treatment of muscle invasive urothelial carcinoma was best described by a time-varying clearance.

Model development consisted of re-estimating parameters of the previously developed final model (Zhang et al 2019, see also Procedure EMEA/H/C/003985/II/0019) excluding the effect of combination regimen with ipilimumab and tumour type.

The model was a 2-compartment, zero-order infusion model with time-varying total CL described using a sigmoidal Emax function with a proportional residual error model, random effect on CL, intercompartmental clearance (Q), VC, volume of distribution of peripheral compartment (VP), and EMAX and correlation of random effect between CL and VC. The full model was developed from the base model by incorporating additional covariates to assess the impact of tumour type (adjuvant muscle invasive urothelial carcinoma, advanced UC versus NSCLC) on nivolumab CL. The following covariates were already included in the base model: for CL body weight, estimated glomerular filtration rate (eGFR), baseline albumin, performance status, sex, race, covariates for the volume of distribution of the VC were body weight and sex, and covariate for Emax was baseline performance status. Covariate relationships between BBWT and intercompartmental clearance (Q), and BBWT and volume of the peripheral compartment (VP) were assumed identical to the relationships between BBWT and CL, and BBWT and VC, respectively.

The full model with lower Bayesian Information Criteria (BIC) value was chosen for model evaluation, bootstrap, and model application.
Model evaluation was performed for the full model using prediction-corrected visual predictive checks (pcVPC), which provided a graphical assessment of the agreement between the time-course of observed and model-predicted concentrations. In addition, a bootstrap procedure was performed to assess the accuracy of the final parameter estimates in the full model.
Model application for adjuvant muscle invasive urothelial carcinoma and advanced UC consisted of obtaining summary measures of exposures at the nivolumab dose regimens 240 mg Q2W and 480 mg Q4W for each subject in the analysis dataset for whom empirical Bayesian estimates (EBE) of the PK parameters were available. The exposures were summarized by tumour type (adjuvant muscle invasive urothelial carcinoma versus advanced UC) for nivolumab 240 mg Q2W dosing regimen, in adjuvant muscle invasive urothelial carcinoma subjects by nivolumab dosing regimens of 240 mg Q2W versus 480 mg Q4W.

Table 1 presents the structural model parameter estimates from the full model (Full Model 1). The expressions describing the functional form of the time-varying CL and covariate effects are given below the table.

Table 1 *Parameter estimates of the full nivolumab population pharmacokinetic model*

Name [Units]	Symbol	Estimate	Standard Error (%RSE)[a]	95% Confidence Interval (Bootstrap Derived)[b]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	11.3	0.470 (4.16)	10.5 - 12.2
VC_{REF} [L]	θ_2	4.18	0.0719 (1.72)	4.04 - 4.31
Q_{REF} [mL/h]	θ_3	26.4	4.74 (17.9)	18.7 - 37.6
VP_{REF} [L]	θ_4	2.35	0.145 (6.16)	2.09 - 2.60
$EMAX_{REF}$	θ_{13}	-0.318	0.0633 (19.9)	(-0.460) - (-0.217)
T50 [h]	θ_{14}	1380	88.3 (6.40)	1219 - 1596
HILL [-]	θ_{15}	2.49	0.502 (20.1)	1.64 - 3.64

[a] %RSE is the relative standard error (standard error as a percentage of estimate).

[b] Confidence intervals are taken from bootstrap calculations (998 successful out of a total of 1,000 [99.8%]).

Note: The condition number was 236, indicating there was no evidence for ill-conditioning.
Analysis-Directory: bms\nivolumab\010062\
Program Source: d1pk\R\nm-para-table-bms-format.R and d1pk\nm\bootstrap\bs-final-pk-model-bs_results.csv
Source: KIWI Run ID 275712

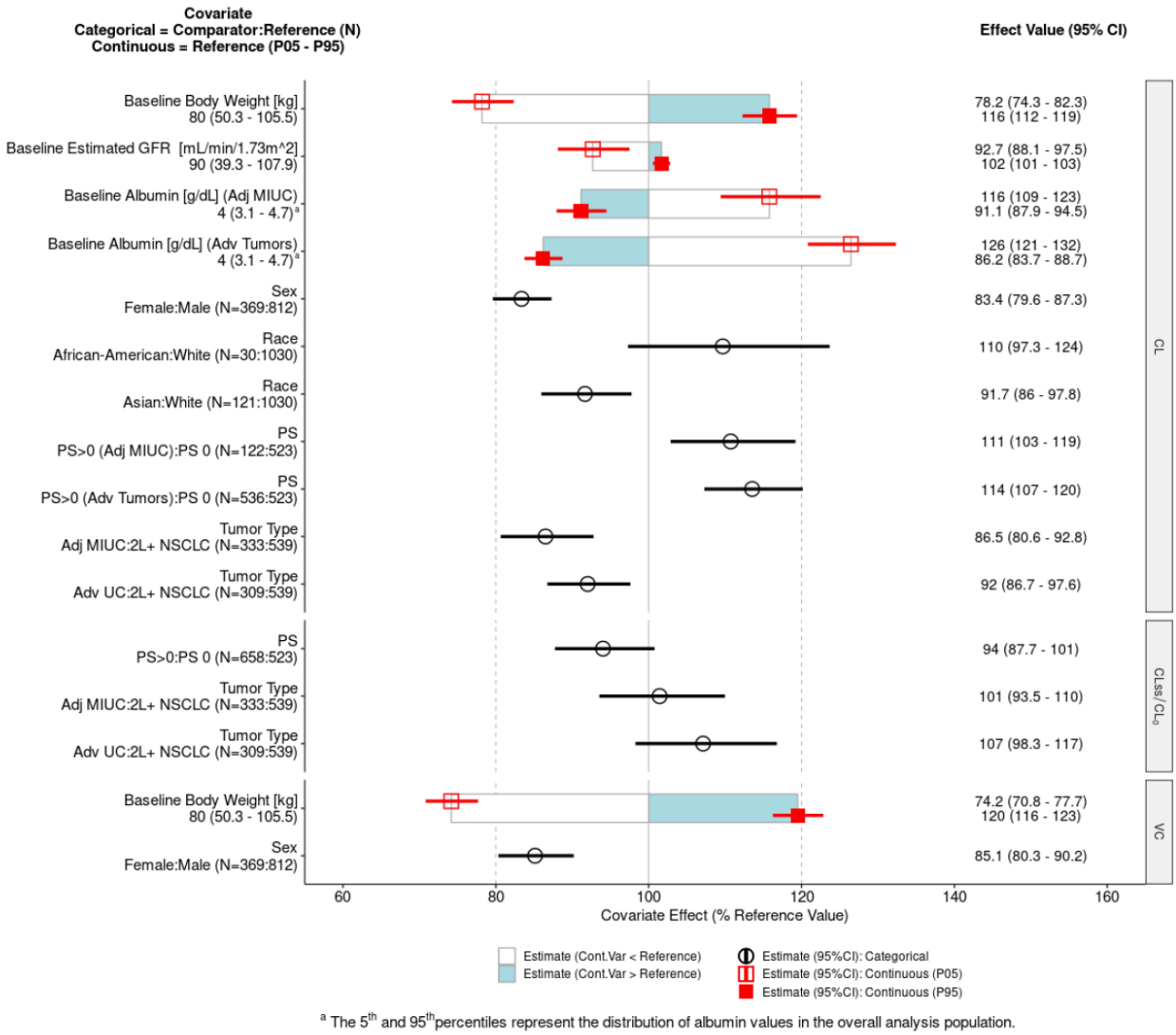
Eta shrinkage on the EMAX parameter was high (45.3%), but < 30% for CL and VC and primary determinants of the empirical Bayesian PK parameter estimates.

Graphical representations of the effects of categorical and continuous covariates on the typical values of the structural model parameters of CL, VC, and clearance at steady state (CLss)/clearance at time 0 (CL0) (exp(EMAX)) are presented in

Figure 1. The estimated covariate effects (and 95% confidence interval (CI)) shown in this figure are relative to CL, VC, and CLss/CL0 at the reference values of the covariates, given in **Table 1**.

Figure **1** shows that the effects of adjuvant muscle invasive urothelial carcinoma and advanced UC on CL were small, corresponding to an approximate 14% and 8% lower CL, respectively, relative to a typical subject with greater than 2L+ NSCLC. The maximal reductions in CL for adjuvant muscle invasive urothelial carcinoma and advanced UC are similar (not statistically significant) relative to the maximal reduction in CL for 2L+ NSCLC, percent changes in CLss/CL0 of 1% and 7% (less reduction), respectively. Based on the estimated time to achieve 50% of the maximum response (T50) of 1,380 hours, the half-maximal change in CL is estimated to occur at approximately 58 days. The estimated effect of eGFR, race (Asian), Performance Status (PS), body weight, albumin, and sex on nivolumab CL were consistent with the previous analyses; the magnitudes of the effects on the parameters (CL and VC) were less than 20% for all other covariates except body weight and albumin.

Figure 1 *Covariate effects on pharmacokinetic model parameters (full nivolumab population pharmacokinetic model)*



Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is male, PS = 0, eGFR = 90 mL/min/1.73 m2, body weight = 80 kg, 2L+ NSCLC tumor type, BALB of 4 g/dL, and race = white, other, unknown, or missing. Parameter estimate in reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.
Note 4: In Race, the reference toWhite includes White, Others, and Missing Race.
Note 5: The reference (P05-P95) value of BALB are summary measures of BALB from all subjects included in the analysis and not by tumor type for comparison purposes.
Abbreviations: 2L = second-line; Adj = adjuvant; Adv = advanced; BALB = baseline albumin; CI = confidence interval; CL = clearance; CLss = clearance at steady state; CL0 = clearance at time 0; Cont. Var = continuous variable; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; MIUC = muscle invasive urothelial carcinoma; NSCLC = non-small cell lung cancer; PS = performance status; UC = urothelial carcinoma; VC = volume of the central compartment.

Nivolumab exposure was higher for all exposure measures in adjuvant muscle invasive urothelial carcinoma compared with advanced UC, but the differences in geometric mean exposure did not exceed 16% for exposures after the first dose or 36% for steady-state exposures

Table 2.

Table 2 *Comparison of predicted nivolumab exposures at 240 mg Q2W for adjuvant muscle invasive urothelial carcinoma and advanced UC*

Summary Exposure	Adjuvant MIUC Geometric Mean (%CV) (n = 333, G1)	Advanced UC Geometric Mean (%CV) (n = 309, G2)	%Diff GM (G1-G2)/G2
Cavg1	33 (21.3)	30.1 (23.5)	9.63
Cmin1	22.6 (23)	19.5 (27.6)	15.9
Cmax1	63.4 (26.7)	60.3 (25.9)	5.14
Cavgss	113 (35)	87.9 (37.4)	28.6
Cminss	91 (40)	67 (43.2)	35.8
Cmaxss	157 (29.9)	129 (32.2)	21.7

Note: The actual clinical dose that was used in Study CA209032 and Study CA209275 that was used to obtain the EBEs was 3 mg/kg Q2W.

Abbreviations: Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgss = time-averaged serum concentration at steady state; Cmax1 = post dose 1 peak serum concentration; Cmaxss = peak serum concentration at steady state; Cmin1 = trough serum concentration after the first nivolumab dose; Cminss = trough serum concentration at steady state; %CV = coefficient of variation expressed as a percent; Diff = difference; GM = geometric mean; MIUC = muscle invasive urothelial carcinoma; n = number of subjects; Q2W = every 2 weeks; UC = urothelial carcinoma.

Nivolumab exposures at 240 mg Q2W versus predicted 480 mg Q4W in adjuvant muscle invasive urothelial carcinoma

A comparison of nivolumab exposures for 240 mg Q2W versus 480 mg Q4W is presented in **Table 3**. For the adjuvant muscle invasive urothelial carcinoma population, the geometric means of nivolumab exposure in the population were higher with 480 mg Q4W dosing relative to 240 mg Q2W dosing for 5 of the 8 summary measures of exposure; namely, Cavg1, Cavgd28, Cmax1, Cmaxss, and Cmin1, whereas the geometric mean exposures matched well between the dosing regimens for Cavgss (difference of 0.885%), and were lower for Cmind28 (23.3%) and Cminss (17.5%). Cmax1 concentrations were twice as high for the 480 mg Q4W dose regimen compared with 240 mg Q2W, the difference in peak nivolumab concentrations was approximately 31% at steady state.

Table 3 *PopPK predicted nivolumab exposures at 240 mg Q2W versus 480 mg Q4W in adjuvant muscle invasive urothelial carcinoma*

Summary Exposure	Nivolumab 240 mg Q2W Geometric Mean (%CV) (n = 333, G2)	Nivolumab 480 mg Q4W Geometric Mean (%CV) (n = 333, G1)	%Diff GM (240 mg) (G1-G2)/G2
Cavgd28	42.2 (21.9)	51.2 (22.4)	21.3
Cmind28	37.3 (24.9)	28.6 (28.5)	-23.3
Cavg1	33 (21.3)	51.2 (22.4)	55.2
Cmin1	22.6 (23)	28.6 (28.5)	26.5
Cmax1	63.4 (26.7)	127 (26.7)	100
Cavgss	113 (35)	114 (35)	0.885
Cminss	91 (40)	75.1 (44.8)	-17.5
Cmaxss	157 (29.9)	206 (27.7)	31.2

Abbreviations: Cavg1 = time-averaged serum concentration over the first dosing interval; Cavgd28 = time-averaged concentration over the first 28 days of treatment; Cavgss = time-averaged serum concentration at steady state; Cmax1 = post dose 1 peak serum concentration; Cmaxss = peak serum concentration at steady state; Cmin1 = trough serum concentration after the first nivolumab dose; Cmind28 = trough concentration at Day 28; Cminss = trough serum concentration at steady state; %CV = coefficient of variation expressed as a percent; Diff = difference; GM = geometric mean; MIUC = muscle invasive urothelial carcinoma; n = number of subjects; Q2W = every 2 weeks; Q4W = every 4 weeks.

Immunogenicity - effect on nivolumab pharmacokinetics

In Study CA209274, serum samples were collected at regular intervals (based on 5 half-lives of nivolumab) for immunogenicity assessment. Of the 305 subjects with evaluable nivolumab Anti Drug Antibody (ADA) in the nivolumab arm, 13 (4.3%) subjects were nivolumab ADA-positive at baseline and 42 (13.8%) subjects were nivolumab ADA-positive after the start of treatment (**Table 4**). For the subjects positive at baseline the titer post-treatment had to increase by 4-fold after start of treatment in order to be categorized as ADA-positive. No subjects were considered persistent positive (ADA-positive sample at 2 or more consecutive time points), and 5 (1.6%) subjects have neutralizing ADA-positive. The highest titer value observed in nivolumab ADA-positive subjects was 128, which occurred in 1 subject. All other titers were low, ranging from 0 to 32.

Table 4 *Immunogenicity. Anti-drug antibody assessments summary - all nivolumab treated subjects with baseline and at least one post-baseline assessment study CA209274*

	Nivolumab
Subject ADA Status (%)	Nivolumab ADA N = 305
BASELINE ADA POSITIVE	13 (4.3)
ADA POSITIVE	42 (13.8)
PERSISTENT POSITIVE (PP)	0
NOT PP - LAST SAMPLE POSITIVE	8 (2.6)
OTHER POSITIVE	34 (11.1)
NEUTRALIZING POSITIVE	5 (1.6)
ADA NEGATIVE	263 (86.2)

Note: Post-baseline assessments are assessments reported after initiation of treatment.

In the popPK analysis, based on the time-varying nature of the ADA data, immunogenicity status was defined as positive when at least one positive ADA result was reported (N=52), negative when none of the samples was positive for ADAs (N=279). Two subjects had no immunogenicity data. Baseline nivolumab clearance in ADA negative subjects was 8.5 mL/h vs. 9.7 mL/h in ADA positive subjects. At steady-state, estimated nivolumab clearance in ADA negative subjects was 6.1 mL/h vs. 7.1 mL/h in ADA positive subjects.

2.3.3. Pharmacodynamics

Mechanism of action

PD-1 is a type I transmembrane protein primarily expressed on activated T-cells, B-cells, myeloid cells, and antigen-presenting cells. Binding of PD-1 to programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2) has been shown to down-regulate T-cell activation in both murine and human systems. Opdivo binds to PD-1 and exhibits its antineoplastic function by upregulating T-cell activation.

Primary and secondary pharmacology

PD-1 is a type I transmembrane protein primarily expressed on activated T-cells, B-cells, myeloid cells, and antigen-presenting cells. Binding of PD-1 to programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2) has been shown to down-regulate T-cell activation in both murine and human systems. Opdivo binds to PD-1 and exhibits its antineoplastic function by upregulating T-cell activation.

No new clinical pharmacology studies were conducted for this application but exposure-response analyses were conducted to provide a model based bridge from nivolumab 240 mg Q2W (dosing regimen evaluated in study CA209274) to 480 mg Q4W.

2.3.4. PK/PD modelling

The objectives of nivolumab exposure-response (E-R) analysis for the adjuvant treatment of muscle invasive urothelial carcinoma were:

- To characterize the relationship between nivolumab exposure (trough concentration at Day 28 (Cmind28)) and efficacy (disease-free survival (DFS)) in subjects with adjuvant muscle invasive urothelial carcinoma (adjuvant muscle invasive urothelial carcinoma).
- To compare predicted efficacy (Disease Free Survival (DFS)) of nivolumab 240 mg every 2 weeks (Q2W) and nivolumab 480 mg every 4 weeks (Q4W) to that of the placebo comparator arm.
- To characterize the relationship between nivolumab exposure (post dose 1 peak serum concentration (Cmax1)) and safety (Grade 2+ immune-mediated adverse events (Gr2+ IMAEs)) in subjects with adjuvant muscle invasive urothelial carcinoma.
- To compare predicted safety (Gr2+ IMAEs) of nivolumab 240 mg Q2W and nivolumab 480 mg Q4W.

DATA:

The exposure-response efficacy (DFS) analysis included data from adjuvant muscle invasive urothelial carcinoma subjects who received nivolumab (N=333) or placebo (N=356) in Study CA209274 and had evaluable PK data. The exposure-response efficacy (DFS) dataset sensoring of the data was 43% for placebo and 52.3% for nivolumab 240 mg Q2W.

Summary statistics of the baseline covariates by treatment and prior neo-adjuvant cisplatin are presented in **Table 5**. A small fraction of subjects was missing covariate information. Continuous covariate values for Baseline Albumin (BALB) were missing for 2.5% of subjects and were imputed at the median value. Categorical covariate values for baseline PS, PD-L1 expression, and pathological status were missing for 0.1%, 1.5%, and 1.7% of subjects, respectively, and were imputed at the mode.

Table 5 *Summary of baseline covariates in exposure-response efficacy analysis dataset, by dosing regimen and neo-adjuvant cisplatin (Study CA209274)*

Subject Characteristic		Placebo/No Cisplatin (n = 203)	Placebo/Cisplatin (n = 153)	Nivolumab 240 mg Q2W/No Cisplatin (n = 195)	Nivolumab 240 mg Q2W / Cisplatin (n = 138)	Overall (n = 689)
Age [years]	Mean (SD)	68.3 (8.4)	62.6 (8.5)	66.9 (10.3)	63.1 (9.6)	65.6 (9.5)
	Median	69.0	64.0	67.0	64.0	67.0
	Min, Max	45, 88	42, 81	30, 92	34, 83	30, 92
Baseline Serum Albumin [g/dL]	Mean (SD)	4.10 (0.47)	4.08 (0.44)	4.07 (0.50)	4.06 (0.47)	4.08 (0.47)
	Median	4.10	4.10	4.10	4.10	4.10
	Min, Max	2.6, 5.0	2.4, 5.0	1.8, 5.3	3.0, 5.3	1.8, 5.3
	Missing n (%)	12 (5.9)	3 (2.0)	2 (1.0)	0 (0.0)	17 (2.5)
Sex, n (%)	Male	160 (78.8)	115 (75.2)	141 (72.3)	108 (78.3)	524 (76.1)
	Female	43 (21.2)	38 (24.8)	54 (27.7)	30 (21.7)	165 (23.9)
Baseline Performance Status, n (%)	0	112 (55.2)	109 (71.2)	123 (63.1)	88 (63.8)	432 (62.7)
	1	81 (39.9)	44 (28.8)	66 (33.8)	50 (36.2)	241 (35.0)
	2	9 (4.4)	0 (0.0)	6 (3.1)	0 (0.0)	15 (2.2)
	Missing n (%)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
PD-L1 Expression (1% Cutoff), n (%)	Negative	117 (57.6)	92 (60.1)	116 (59.5)	82 (59.4)	407 (59.1)
	Positive	84 (41.4)	57 (37.3)	77 (39.5)	54 (39.1)	272 (39.5)
	Missing n (%)	2 (1.0)	4 (2.6)	2 (1.0)	2 (1.4)	10 (1.5)
Nodal Status (IVRS), n (%)	N+	71 (35.0)	80 (52.3)	69 (35.4)	73 (52.9)	293 (42.5)
	N0/x with <10 nodes removed	80 (39.4)	31 (20.3)	78 (40.0)	28 (20.3)	217 (31.5)
	N0/x with ≥10 nodes removed	52 (25.6)	42 (27.5)	48 (24.6)	37 (26.8)	179 (26.0)
Pathological Status, n (%)	pT0-2	25 (12.3)	61 (39.9)	26 (13.3)	48 (34.8)	160 (23.2)
	pT3	139 (68.5)	65 (42.5)	136 (69.7)	61 (44.2)	401 (58.2)
	pT4a	39 (19.2)	23 (15.0)	30 (15.4)	24 (17.4)	116 (16.8)
	Not reported	0 (0.0)	4 (2.6)	3 (1.5)	5 (3.6)	12 (1.7)
Neo-Adjuvant Cisplatin (IVRS), n (%)	Yes	0 (0.0)	153 (100.0)	0 (0.0)	138 (100.0)	291 (42.2)
	No	203 (100.0)	0 (0.0)	195 (100.0)	0 (0.0)	398 (57.8)
Tumor Origin, n (%)	Renal Pelvis	39 (19.2)	13 (8.5)	35 (17.9)	7 (5.1)	94 (13.6)
	Ureter	22 (10.8)	1 (0.7)	24 (12.3)	4 (2.9)	51 (7.4)
	Urinary Bladder	142 (70.0)	139 (90.8)	136 (69.7)	127 (92.0)	544 (79.0)

Abbreviations: E-R = exposure-response; IVRS = interactive voice response system; Max = maximum; Min = minimum; n = number of subjects; N+ = scores are based on the number of nodes with cancer or which nodal groups have cancer; higher values mean a greater extent of the cancer; N0 = score means that no cancer was found in the lymph nodes; PD-L1 = programmed death ligand-1; SD = standard deviation.

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The exposure-response safety (Gr2+ IMAEs) analysis included data (N=1171) from adjuvant muscle invasive urothelial carcinoma subjects who received nivolumab (N=333) in the Study CA209274 and 5 additional studies to characterize exposure-response safety in subjects with adjuvant muscle invasive urothelial carcinoma, advanced urothelial carcinoma (advanced UC), and non-small cell lung cancer (NSCLC) across a broad dose range from 0.3 to 10 mg/kg Q2W. The additional studies included a Phase 1 study (CA209003 (only NSCLC included)), 1 Phase 1/2 study (CA209032 (multiple tumour types, only advanced UC included)), 1 Phase 2 study (CA209275 (advanced UC)), and 3 Phase 3 studies (CA209017 (NSCLC), CA029057 (NSCLC), and CA209274 (adjuvant muscle invasive urothelial carcinoma)).

The analysis dataset was split into a model development cohort and model validation cohort. The summaries of data are presented by the development and validation cohorts.

METHODS:

Exposure-response Analysis of Efficacy for DFS: The exposure-response relationship between time to DFS and nivolumab exposure (Cmind28) was described by a semi-parametric Cox Proportional Hazards (CPH) model and included assessments of the modulatory effect of covariates on this exposure-response relationship. The effect of nivolumab exposure on DFS was calculated relative to the placebo arm. Sensitivity analyses were conducted without the placebo control arm.

The full model characterized the effect of nivolumab exposure on DFS, while taking into account prespecified covariates. Nivolumab Cmind28 was tested as linear and log-linear functions in the full model. Baseline covariates tested for exposure-response relationship of DFS included: baseline albumin, age, performance status (PS), programmed death ligand-1 (PD-L1) status, prior neo-adjuvant cisplatin, sex, pathological status, and nodal status. In addition, interaction between nivolumab Cmind28 and each statistically significant covariate effect in the full model was tested univariately after the functional form of exposure was determined in the full model.

The final model was developed by performing a stepwise backward elimination of the full model to determine a parsimonious model based upon Bayesian information criteria (BIC). The model performance was assessed by visual predictive check (VPC). The CPH model predictions were evaluated by comparing the model-predicted cumulative time-to-event distributions of DFS with the corresponding distribution determined by non-parametric KM analysis. Data used in the model development were used as an internal validation dataset for KM analysis. For external validation, the exposure-response analysis of DFS was performed by 5-fold cross-validation, whereby model prediction was compared with data from subjects who were not included in the estimation of the model.

The final exposure-response model was used to predict the DFS probability at 1 and 2 years and the hazard ratio (HR) by prior neo-adjuvant cisplatin treatment for adjuvant muscle invasive urothelial carcinoma comparing nivolumab 240 mg Q2W and nivolumab 480 mg Q4W to the placebo treatment arm in subjects in Study CA209274.

Exposure-response Analysis of Safety for Grade 2+ IMAEs: The exposure-response relationship between nivolumab exposure (Cmax1) and time to first occurrence of Gr2+ IMAEs was described by a semi-parametric CPH model and included assessments of the modulatory effect of covariates on this exposure-response relationship.

The full model characterized the effect of nivolumab exposure on Gr2+ IMAEs, while taking into account prespecified covariates. Nivolumab Cmax1 was tested as linear and log-linear functions in the full model. Baseline covariates tested for exposure-response relationships of Gr2+ IMAEs included: body weight, age, sex, PS, and tumour type. In addition, interaction between nivolumab Cmax1 and

each statistically significant covariate effect in the full model was tested univariately after the functional form of exposure was determined in the full model.

The final safety model was developed by performing a stepwise backward elimination of the full model to determine a parsimonious model based upon BIC and was used for model evaluation and model application.

The final exposure-response safety model was used to predict the Gr2+ IMAE rate for nivolumab 240 mg Q2W and nivolumab 480 mg Q4W at 6 months and 1 year for adjuvant muscle invasive urothelial carcinoma subjects (Study CA209274) and advanced UC subjects (Studies CA209032 and CA209275).

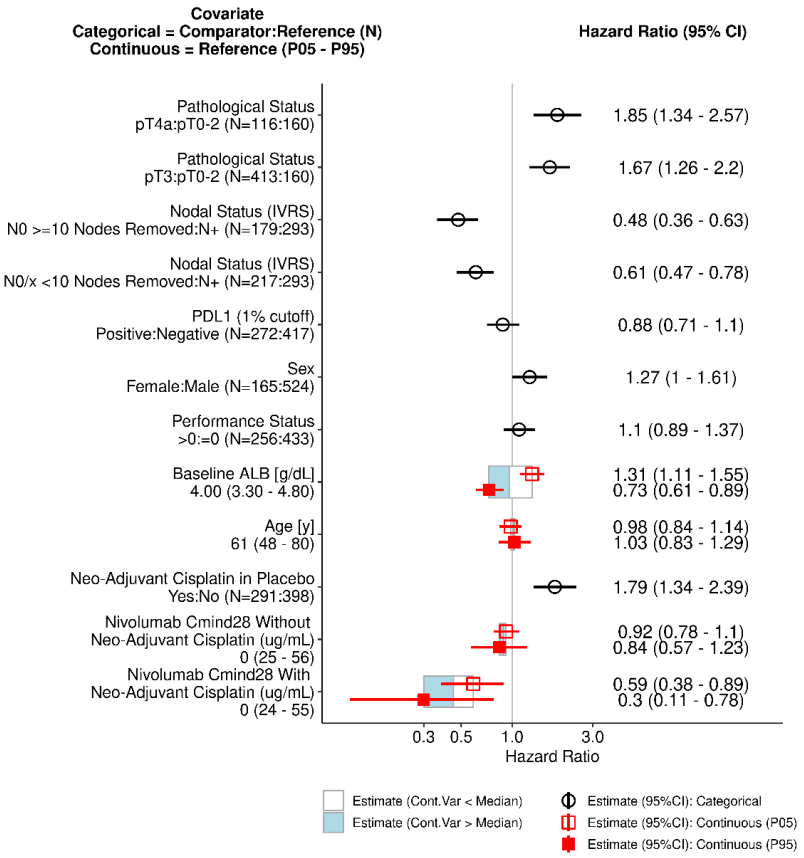
RESULTS:

Exposure-response Analysis of Efficacy for DFS

In the full model assessment, the relationship of nivolumab Cmind28 with DFS was dependent on whether adjuvant muscle invasive urothelial carcinoma subjects received prior neo-adjuvant cisplatin treatment or not (**Figure 2**). In subjects who received prior neo-adjuvant cisplatin, higher nivolumab Cmind28 exposures were associated with significantly (95% CI interval excluded 1) lower risk of disease recurrence or death than the placebo (HR: 0.59 and 0.3 at the 5th and 95th percentile of Cmind28, respectively in reference to placebo). In subjects who did not receive prior neo-adjuvant cisplatin, nivolumab Cmind28 exposures were not significantly associated with risk of disease recurrence or death. Sensitivity analyses excluding placebo or excluding interaction between nivolumab Cmind28 and neo-adjuvant cisplatin treatment were also provided in **Figure 2**.

Prior neo-adjuvant cisplatin treatment, nodal status, pathological status, sex, and baseline albumin (BALB) were also identified as significant predictors of DFS in the full model. The interaction effects between nivolumab Cmind28 and significant covariates were tested and only prior neo-adjuvant cisplatin decreased the BIC and therefore was selected for inclusion in the full model.

Figure 2 *Covariate effects on the Hazard Ratios of disease recurrence or death of adjuvant nivolumab 240 mg Q2W in subjects with muscle invasive urothelial carcinoma (full model with interaction and placebo, study CA209274) (Updated with Reanalysis)*



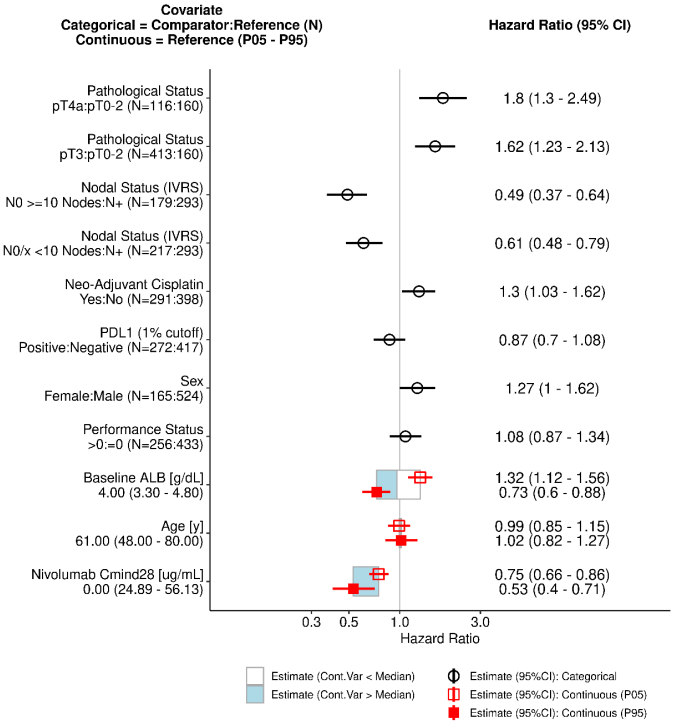
Nivolumab Cmind28 Without Neo-Adjuvant Cisplatin represents the effect of nivolumab exposures in nivolumab-treated subjects who did not receive prior neo-adjuvant cisplatin compared to placebo subjects who did not receive prior neo-adjuvant cisplatin.

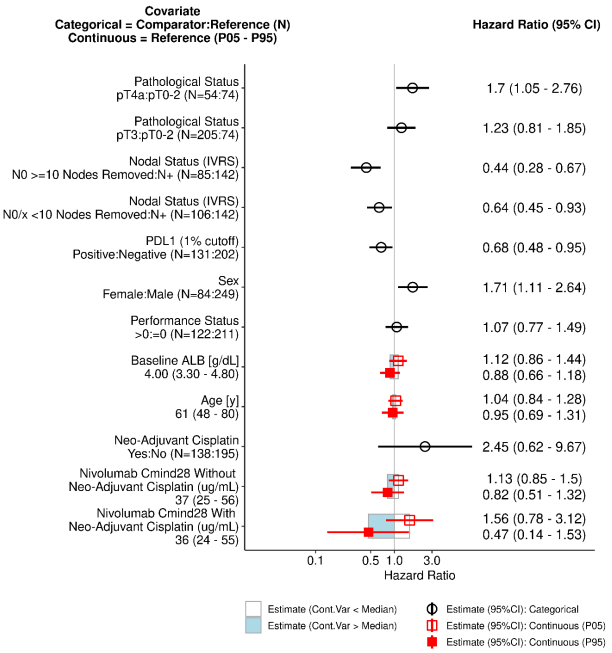
Nivolumab Cmind28 With Neo-Adjuvant Cisplatin represents the effect of nivolumab exposures in nivolumab-treated subjects who received prior neo-adjuvant cisplatin compared to placebo subjects who received prior neo-adjuvant cisplatin.

Abbreviations: Adj = adjuvant; ALB = albumin; CI = confidence interval; Cmind28 = trough concentration at Day 28; Cont. Var = continuous variable; DFS = disease free survival; IVRS = interactive voice response system; MIUC = muscle invasive urothelial carcinoma; N+ = scores are based on the number of nodes with cancer or which nodal groups have cancer; higher values mean a greater extent of the cancer; N0 = score means that no cancer was found in the lymph nodes; Nivo = nivolumab; PDL1 = programmed death ligand-1.

Sensitivity analyses excluding placebo or excluding interaction between nivolumab Cmind28 and neo-adjuvant cisplatin treatment were also provided in **Figure 3**. In comparison to the model with placebo (**Figure 2**), the level of significance of certain covariates changed in the model with nivolumab treated subjects only e.g. for PD-L1 expression and neo-adjuvant cisplatin treatment, however, the direction of effects of exposure and covariates on the risk of DFS events were similar to that of the full model.

Figure 3 *Sensitivity analyses of co-variate analysis on the Hazard Ratios of disease recurrence or death of adjuvant nivolumab 240 mg Q2W in subjects with muscle invasive urothelial carcinoma or full model without interaction including placebo (top) and full model with interaction excluding placebo (bottom) (Updated with Reanalysis)*

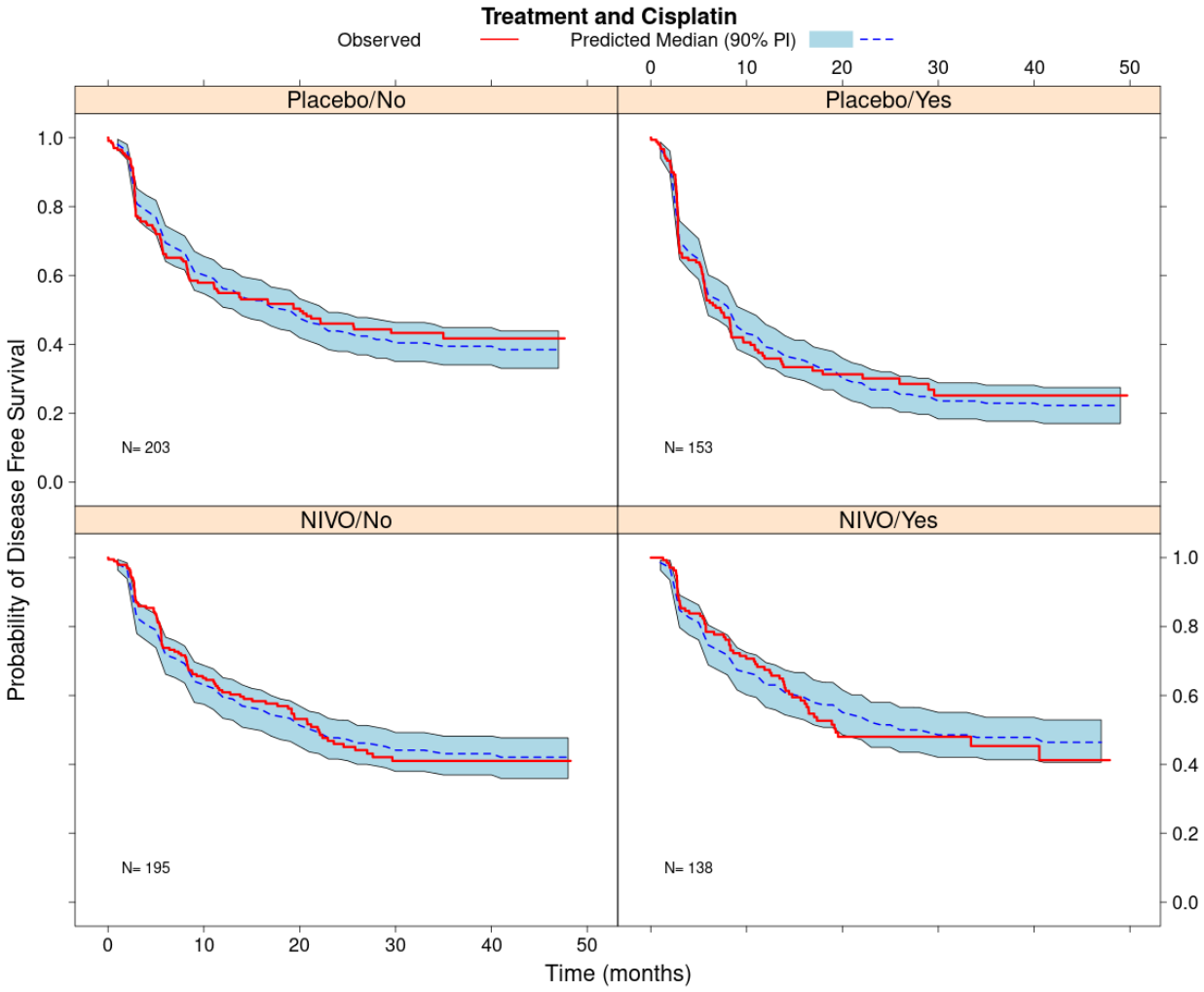




Abbreviations: ALB = albumin; CI = confidence interval; Cmind28 = trough concentration at Day 28; Cont. Var = continuous variable; DFS = disease free survival; IVRS = interactive voice response system; N+ = scores are based on the number of nodes with cancer or which nodal groups have cancer; higher values mean a greater extent of the cancer; N0 = score means that no cancer was found in the lymph nodes; N0/x score means that the lymph nodes can't be assessed; PDL1 = programmed death ligand-1.

Figure 4 shows the model-predicted median (90% PI) of time-to-event of DFS by treatment and prior neo-adjuvant cisplatin treatment compared with the observed KM of DFS in study CA209274.

Figure 4 *Model (including placebo and interaction) evaluation of DFS final model, by treatment and prior neoadjuvant cisplatin treatment (Study CA209274) (Updated with Reanalysis)*



No - No prior neo-adjuvant cisplatin treatment; Yes - Prior neo-adjuvant cisplatin treatment
Abbreviations: DFS = disease free survival; N = number of subjects; NIVO = nivolumab; PI = prediction interval.
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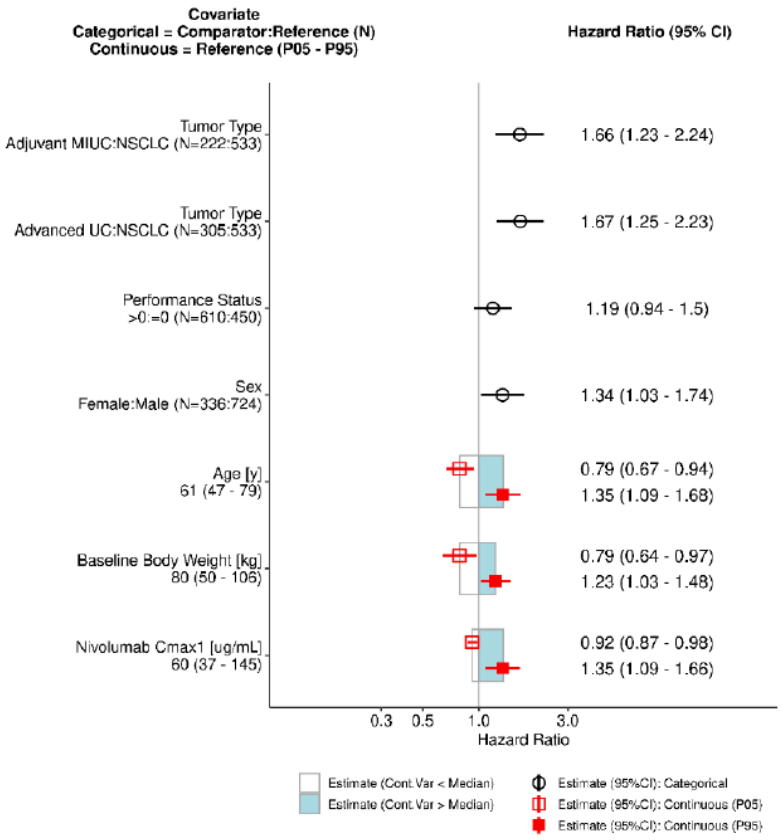
Additional validation of the exposure-response model of DFS was performed by 5-fold cross-validation, whereby model predictions of DFS were compared with data from subjects who were not included in the estimation of the model. Overall, the average bias in the original model (bias overall at 1 year and 2 years was -0.02532 and -0.06158, respectively) was similar to the average bias in the cross-validation models (bias validation at 1 year and 2 years was -0.02665 and -0.06289, respectively).

Exposure-response Analysis of Safety for Grade 2+ IMAEs

In the full model assessment, higher nivolumab Cmax1 was significantly (95% CI for the HR excluded 1) associated with higher risk (HR: 1.35 from median 60 µg/mL to 95th percentile 145 µg/mL) of Gr2+ IMAEs. **Figure 5** presents the estimated effects of exposure and covariates on the HR of Gr2+ IMAEs in the full model. Baseline body weight, age, sex, and tumour type were identified as significant predictors of Gr2+ IMAEs in the full model. The interaction between nivolumab Cmax1 and each

significant covariate was examined and none of the interactions were identified as significant predictors of Gr2+ IMAEs in the full model.

Figure 5 *Covariate effects on the Hazard Ratios of Grade 2+ IMAEs (Full Model)*



Note: The range of Cmax1 includes data from all studies.

Abbreviations: CI = confidence interval; Cmax1 = post dose 1 peak serum concentration; Cont. Var = continuous variable; IMAE = immune-mediated adverse event; MIUC = muscle invasive urothelial carcinoma; NSCLC = non-small cell lung cancer; UC = urothelial carcinoma.

The final model after backward elimination included nivolumab Cmax1 and covariate effects of tumour type and age. The magnitude and directionality effects of exposure and covariates on risk of Gr2+ IMAEs were similar to that of the full model.

Proposed additional dosing regimen of 480 mg Q4W

A summary of nivolumab exposure measures (Cmind28 derived from the popPK analysis) for 240 mg Q2W and simulated 480 mg Q4W in adjuvant muscle invasive urothelial carcinoma by prior neo-adjuvant cisplatin is provided in

Table 6. Nivolumab exposures were comparable in patients with or without neo-adjuvant cisplatin treatment. Approximately a ~23%% decrease in nivolumab median Cmind28 was observed when nivolumab 480 mg Q4W was compared to nivolumab 240 mg Q2W.

Table 6 *Summary of exposure measures in exposure-response efficacy analysis dataset, by dosing regimen and neo-adjuvant cisplatin (study CA209274 and modelling)*

Exposure Measures		Nivolumab 240 mg Q2W (n = 333)		Simulated Nivolumab 480 mg Q4W (n = 333)	
		No Cisplatin	Cisplatin	No Cisplatin	Cisplatin
Nivolumab Cmind28 [µg/mL]	Mean (SD)	39.10 (9.57)	37.48 (9.51)	30.32 (8.59)	29.07 (8.31)
	Median	37.98	35.74	28.55	28.15
	Min, Max	21.0, 71.3	20.2, 69.8	13.4, 61.8	13.2, 58.8

Abbreviations: Cmind28 = trough concentration at Day 28; E-R = exposure-response; Max = maximum; Min = minimum; n = number of subjects; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation.

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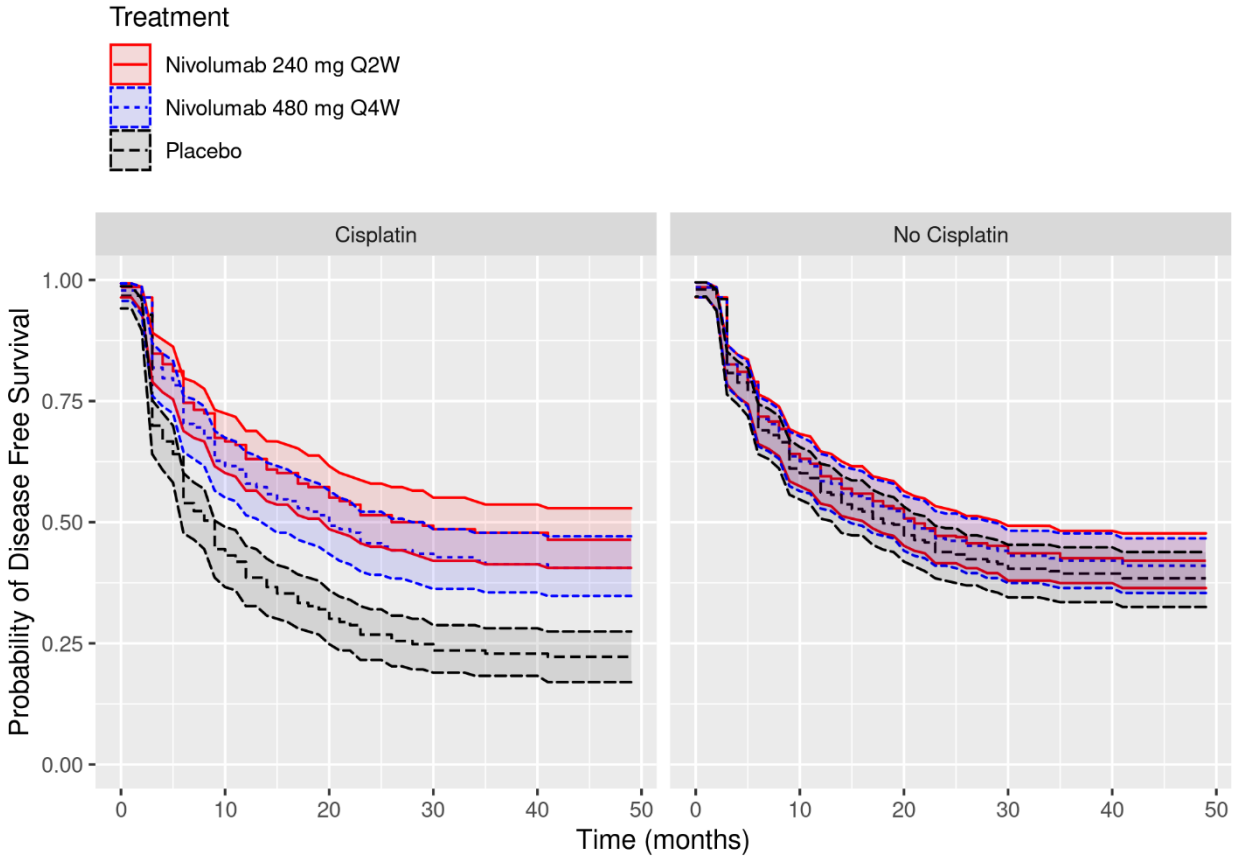
Source: R\export\sumstat-exp-bytxcis.rtf and sumstat-exp-sim480-bytxcis.rtf

For subjects with prior neo-adjuvant cisplatin treatment, the median predicted HRs and associated 90% prediction intervals (PIs) for nivolumab 240 mg Q2W and nivolumab 480 mg Q4W were both below 1, indicating a DFS benefit in these arms compared to the reference placebo group with prior neo-adjuvant cisplatin. While the point estimate of the HR for 480 mg Q4W was slightly higher than the point estimate for 240 mg Q2W, HR=0.59 (0.50-0.70) and HR=0.50 (0.42-0.60), respectively, it overlapped with the 90% PI of the HR for 240 mg Q2W.

For subjects with no prior neo-adjuvant cisplatin treatment, the median predicted HRs for nivolumab 240 mg Q2W and nivolumab 480 mg Q4W were nearly identical, consistent with the lack of an exposure dependence on DFS in this population. The HRs were both below 1, suggesting a DFS benefit over placebo, however, the 90% PIs of the 5th and 95th percentiles of both treatment groups include 1: predicted HR 240 mg Q2W: 0.92 (0.80-1.07) and HR 480 mg Q4W 0.95 (0.82-1.09).

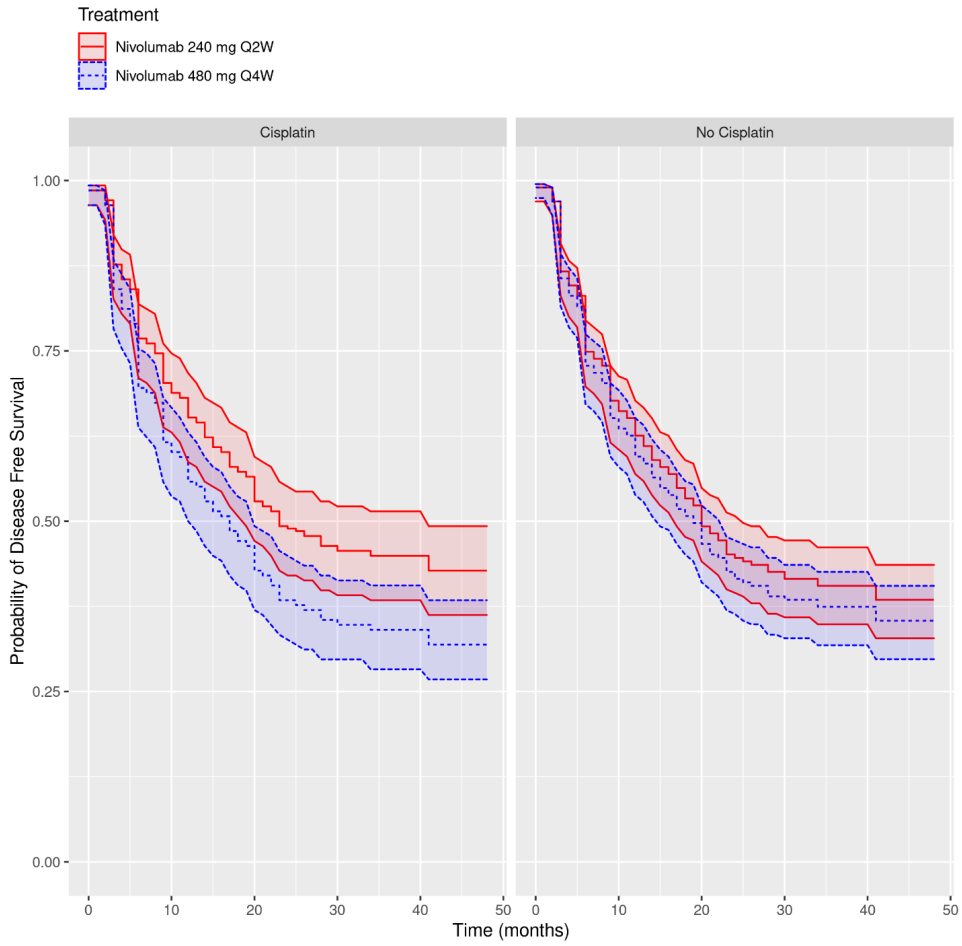
For subjects who received prior neo-adjuvant cisplatin treatment, the model-predicted cumulative probability of DFS for nivolumab 240 mg Q2W and nivolumab 480 mg Q4W was superior to the observed DFS in the placebo comparator arm **(Figure 6a and Figure 6b).** For subjects who did not receive prior neo-adjuvant cisplatin treatment, there was considerable overlap between the 90% PIs for both nivolumab treatments and placebo.

Figure 6a: Predicted Median (90% PI) Probability of DFS Using Cmind28 for Nivolumab 480 mg Q4W and Nivolumab 240 mg Q2W Relative to the Observed Mean DFS from the Placebo Comparator Arm in Study CA209274, by Prior Neo-Adjuvant Cisplatin (Updated with Reanalysis)



Abbreviations: Cmind28 = trough concentration at Day 28; DFS = disease free survival; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure 6b: Predicted Median (90% PI) Probability of DFS Using Cmind28 for Nivolumab 480 mg Q4W and Nivolumab 240 mg Q2W, by Prior Neo-Adjuvant Cisplatin (Full DFS Model *Excluding Placebo*) (Updated with Reanalysis)



Abbreviations: Cmind28 = trough concentration at Day 28; DFS = disease free survival; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Analysis-Directory: bms\nivolumab\010062\d2pkpd-eff

Program Source: R\er-dfs-model-dev-code.Rmd

Using the full DFS model including placebo, the predicted median (90% PI) DFS probability for subjects who received prior neo-adjuvant cisplatin treatment was approximately 5% lower for the nivolumab 480 mg Q4W compared to 240 mg Q2W dosing regimen at 1 year. The median estimates for the 480 mg Q4W fell within the 90% PI for the 240 mg Q2W nivolumab dosing regimen (**Table 7**). At 2 years, the probability of DFS was 5% lower for the nivolumab 480 mg Q4W compared to 240 mg Q2W dosing regimen and the point estimates for 480 mg Q4W fell within the 90% PI for 240 mg Q2W. The DFS probability with prior neo-adjuvant cisplatin was greater with both the nivolumab dosing regimens at both 1 and 2 years compared to the placebo comparator arm in Study CA209274. Predicted median DFS probabilities were similar between 240 mg Q2W and 480 mg Q4W at 1 and 2 years (i.e. 1% and 1% difference between the regimens, respectively) with no prior neo-adjuvant cisplatin treatment (**Table 7**).

The median (90% PI) probabilities of DFS for nivolumab 240 mg Q2W and 480 mg Q4W predicted using the full model with nivolumab treated subjects only **(Table 7)** were similar to those predicted using the final model with placebo arm included: the predicted median (90% PI) DFS probability for

subjects who received prior neo-adjuvant cisplatin treatment was approximately 9% lower for the nivolumab 480 mg Q4W compared to 240 mg Q2W dosing regimen.

Table 7 *Predicted median (90% PI) probability of DFS at select times for nivolumab 480 mg Q4W and nivolumab 240 mg Q2W relative to the observed incidence of DFS from the placebo comparator arm in study CA209274, by prior neo-adjuvant cisplatin (full DFS model including placebo top, excluding placebo bottom) (Updated with Reanalysis)*

Time	Nivolumab 240 mg Q2W		Nivolumab 480 mg Q4W		Percent Difference in Medians (480 mg Q4W - 240 mg Q2W)		Placebo	
	No Cisplatin	Cisplatin	No Cisplatin	Cisplatin	No Cisplatin	Cisplatin	No Cisplatin	Cisplatin
1 Year	0.59 (0.54, 0.65)	0.63 (0.57, 0.69)	0.58 (0.53, 0.64)	0.58 (0.51, 0.64)	-1.00	-5.00	0.56 (0.51, 0.62)	0.39 (0.33, 0.45)
2 Years	0.47 (0.42, 0.53)	0.51 (0.45, 0.58)	0.46 (0.41, 0.52)	0.46 (0.39, 0.52)	-1.00	-5.00	0.44 (0.38, 0.49)	0.27 (0.22, 0.32)

Note: Difference was calculated as median for Nivolumab 480 mg Q4W - median for Nivolumab 240 mg Q2W.
Abbreviations: DFS = disease free survival; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.

Time	Nivolumab 240 mg Q2W		Nivolumab 480 mg Q4W		Percent Difference in Medians (480 mg Q4W - 240 mg Q2W)	
	No Cisplatin	Cisplatin	No Cisplatin	Cisplatin	No Cisplatin	Cisplatin
1 Year	0.63 (0.57, 0.68)	0.65 (0.59, 0.72)	0.59 (0.54, 0.65)	0.56 (0.45, 0.63)	-4.00	-9.00
2 Years	0.45 (0.39, 0.51)	0.49 (0.42, 0.55)	0.42 (0.36, 0.47)	0.38 (0.33, 0.45)	-3.00	-11.00

Abbreviations: DFS = disease free survival; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks.
Analysis-Directory: bms\nivolumab\010062\d2pkpd-eff
Program Source: R\er-dfs-model-dev-code.Rmd
Source: R\export\dfs-model-app-pred-dfs-bytime-tx-active-cispl.csv

Predicted 6 month and 1 year probabilities of **Gr2+ IMAE** for the nivolumab 480 mg Q4W were marginally higher compared to nivolumab 240 mg Q2W for both adjuvant muscle invasive urothelial carcinoma (approximately 6% and 8% at 6 months and 1 year, respectively) and advanced UC (approximately 6% and 8% at 6 months and 1 year, respectively) populations (**Table 8**).

Table 8 *Predicted median (90% PI) probability of Grade 2+ IMAEs at select times for nivolumab 240 mg Q2W and nivolumab 480 mg Q4W, by tumour type*

	Time	Nivolumab 240 mg Q2W	Nivolumab 480 mg Q4W	Percent Difference in Medians (480 mg Q4W - 240 mg Q2W)
Adjuvant MIUC	6 Months	0.32 (0.27, 0.35)	0.38 (0.34, 0.42)	6.00
	1 Year	0.41 (0.37, 0.45)	0.49 (0.44, 0.53)	8.00
Advanced UC	6 Months	0.33 (0.29, 0.37)	0.39 (0.34, 0.44)	6.00
	1 Year	0.42 (0.38, 0.47)	0.50 (0.45, 0.55)	8.00

Note: Difference was calculated as median for Nivolumab 480 mg Q4W - median for Nivolumab 240 mg Q2W.
Abbreviations: IMAE = immune-mediated adverse event; MIUC = muscle invasive urothelial carcinoma; PI = prediction interval; Q2W = every 2 weeks; Q4W = every 4 weeks; UC = urothelial carcinoma.

2.3.5. Discussion on clinical pharmacology

The pharmacology of nivolumab for the applied indication has been supported by pharmacokinetic and exposure-response data. A model based bridge from nivolumab 240 mg Q2W (dosing regimen evaluated in study CA209274) to 480 mg Q4W has been provided. Nivolumab immunogenicity data have also been presented.

Nivolumab pharmacokinetics were analysed by adding data from the CA209274 study into the existing popPK models. Pharmacokinetics of nivolumab for adjuvant treatment of muscle invasive urothelial carcinoma was best described by a time-varying clearance. Nivolumab exposures were 16%-35% higher in adjuvant muscle invasive urothelial carcinoma compared with subjects with locally advanced or metastatic urothelial carcinoma (EMEA/H/C/003985/II/0019).

A modelling approach was used for the alternative dose of 480 mg Q4W while the study was conducted with 240 mg Q2W. In principle, modelling can be used to accept another dosing regimen than has been used in the clinical study provided that there is sufficient knowledge on the exposure-response relationship in the target population. Only one dose 240 mg Q2W was evaluated for adjuvant muscle invasive urothelial carcinoma, which questions the robustness of the exposure-response relationship, in particular considering the confounding effect that patient disease/health status may have on the clearance of nivolumab (Bajaj 2017, Turner 2018). Indeed, as the pharmacokinetics of nivolumab for the adjuvant treatment of subjects who have undergone radical resection of muscle invasive urothelial carcinoma could be best described by a time-varying clearance, this indicates that the confounding effect is likely present in this population. PopPK simulations predict that nivolumab exposures will be lower for Cmind28 (23.3%) and Cminss (17.5%). Cmax1 concentrations will be twice as high for the 480 mg Q4W dose regimen compared with 240 mg Q2W, while the difference in peak nivolumab concentrations was approximately 31% at steady state. This is similar to what was predicted for other populations comparing 480 mg Q4W vs 240 mg Q2W dosing. The potential confounding effect of patient disease on clearance of nivolumab cannot be evaluated because of the high correlation between clearance and Cmin concentrations when only 1 dose has been used and only trough levels have been used to estimate nivolumab exposures.

The reporting and model evaluation of the exposure-effect modelling was well described and in agreement with EMA guidelines (CHMP/EWP/185990/06). The exposure-effect modelling describes the central tendency adequately (**Figure 4**). An interaction between nivolumab exposure (Cmind28) and prior neo-adjuvant cisplatin was included in the model as this reduced the variability of the model. The mechanistic rationale for such interaction is not clear and would imply that there would be a different nivolumab exposure-response for subjects who have received neo-adjuvant cisplatin treatment or not. It is therefore debatable that the exposure-response relationship in the muscle invasive urothelial carcinoma population is well understood. In fact, having a sufficiently large range of exposures (covering the exposures of 480 Q4W) with their associated efficacy and safety data would be needed. In an attempt to use more data, placebo was included in the exposure-response model assuming that the exposure-response relationship was similar over the concentration range 0-lowest Cmin28 for 240 mg Q2W (concentration range not studied) compared to the exposure-response relationship over the lowest to highest Cmin28 nivolumab concentration range observed for nivolumab 240 mg Q2W. As a higher dose of 10 mg/kg Q2W did not improve the ORR and OS in any population tested, the 240 mg Q2W dose is supposedly near or at the flat part of the dose response curve, which does not support such an assumption. Further, by introducing placebo in the model, the weight of placebo to the exposure-response relationship is high for two reasons: i) half of the data then used consists of subjects with placebo have nivolumab = 0 imputed and ii) 0 is an outlier compared the range of nivolumab exposures on 240 mg Q2W, and outliers can substantially affect regression coefficients.

Because of these issues, an exposure-response without placebo included is preferred and these data were provided as sensitivity analyses.

In all exposure-response analyses for DFS, higher nivolumab Cmind28 exposures were associated with a lower risk of disease recurrence or death. Dosing of 480 mg Q4W to 240 mg Q2W will result in average lower Cmind28 exposures. Hence, the exposure-response model predicted a higher point estimate of the HR for 480 mg Q4W than the point estimate for 240 mg Q2W and a higher risk of disease recurrence or death for the 480 mg Q4W compared to the 240 mg Q2W: at 1 year the predicted median (90% PI) DFS probability for subjects who received prior neo-adjuvant cisplatin treatment was approximately 9% lower for the nivolumab 480 mg Q4W compared to 240 mg Q2W dosing regimen i.e. 0.56 (0.50, 0.63) vs 0.65 (0.59, 0.72). For subjects without neo-adjuvant treatment, the predicted median (90% PI) DFS probability was approximately 4% lower for the nivolumab 480 mg Q4W compared to 240 mg Q2W dosing regimen i.e. 0.59 (0.54, 0.65) vs 0.63 (0.57, 0.68). Also a lower plateau was predicted for 480 mg Q4W compared to 240 mg Q2W.

Considering the exposure-safety analysis, an increased probability of Grade 2+ IMAEs for 480 mg Q4W compared to 240 mg Q2W was predicted (**Table 8**): predicted 6 month and 1 year probabilities of **Gr2+ IMAE** for the nivolumab 480 mg Q4W were approximately 6% and 8% at 6 months and 1 year, respectively, higher compared to nivolumab 240 mg Q2W. A similar increase in Grade 2+ IMAEs for 480 mg Q4W compared to 240 mg Q2W has been observed for other indications and was found acceptable for melanoma and RCC indications.

Overall, based on the modelling, it cannot be concluded that the benefit/risk is the same for the 480 mg Q4W and the 240 mg Q2W dosing regimen, and it is considered that the reduction of the burden for the patient with a less frequent dosing regimen does not outweigh the uncertainties concerning the efficacy and safety of the 480 mg Q4W dosing regimen. To ensure minimal loss of efficacy with the 480 mg qw4 dosing regimen, the MAH compared the 5th percentiles of the simulated Cmin, given either dosing (q2w and q4w) regimen. Similar or higher exposures Cmin and Cave (steady-state) of nivolumab are expected in subjects with adjuvant treatment of MIUC with 480 mg Q4W compared to subjects with advanced UC treated with 240 mg Q2W, which is approved in the EU. Since the site of action is the same for the adjuvant treatment of MIUC as for treatment of advanced UC, these comparable nivolumab exposure data from advanced UC are considered supportive for efficacy for the 480 mg Q4W dosing regimen for the adjuvant treatment of MIUC.

For what concern immunogenicity, 42 (13.8%) subjects were nivolumab ADA-positive after the start of treatment and 5 (1.6%) subjects were neutralizing ADA-positive. This is similar to immunogenicity data for nivolumab monotherapy across different indications with an 11% ADA response and 0.7% neutralizing activity. Nivolumab clearance was approximately 15% higher in subjects with ADAs. This is also similar to previous observations.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics and exposure response relationships of nivolumab have been sufficiently investigated to support the 240 mg Q2W dosing for the adjuvant treatment of subjects who have undergone radical resection of muscle invasive urothelial carcinoma.

The additional 480 mg Q4W regimen for the adjuvant treatment of subjects who have undergone radical resection of muscle invasive urothelial carcinoma, is considered acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies were included in this application.

2.4.2. Main study(ies)

Title of Study

CA209274:

A Phase 3 Randomised, Double-blind, Multi-center Study of Adjuvant Nivolumab Versus Placebo in Subjects With High Risk Invasive Urothelial Carcinoma (CheckMate 274: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 274)

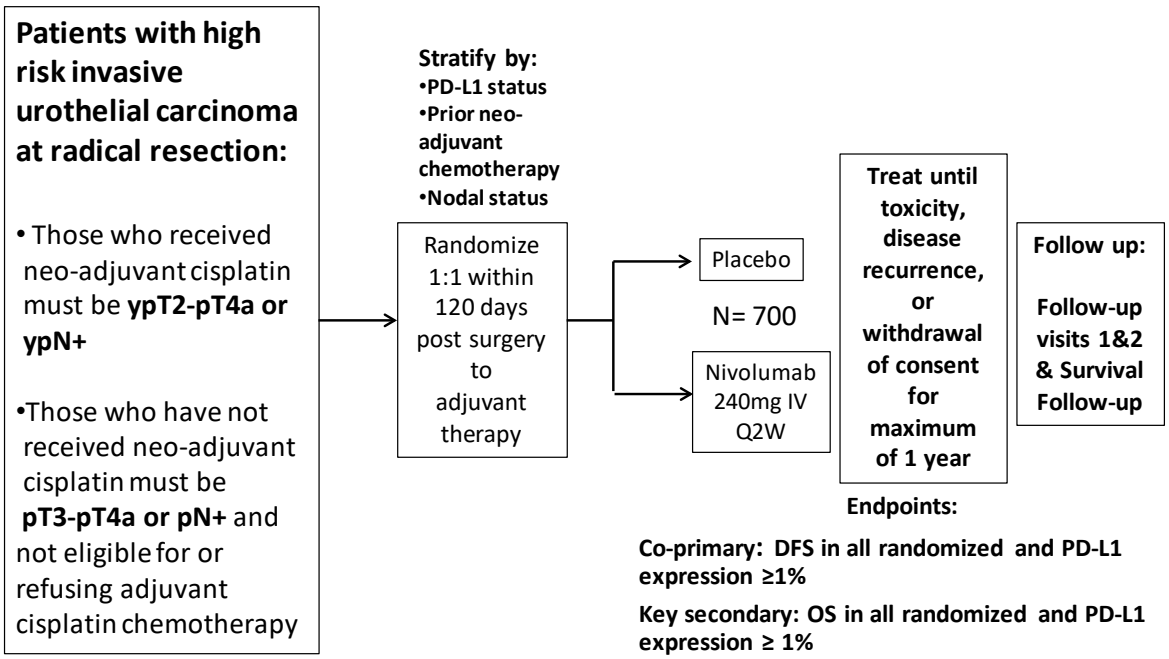
Methods

CA209274 is a Phase 3, randomised, double-blind, placebo-controlled study of nivolumab vs placebo in adult subjects who have undergone radical resection of MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. MIUC pathologic staging criteria for inclusion in this study included:

- Subjects who received neo-adjuvant cisplatin chemotherapy: ypT2-pT4a or ypN+.
- Subjects who have not received neo-adjuvant cisplatin chemotherapy: pT3-pT4a or pN+ and were not eligible for or refused adjuvant cisplatin chemotherapy.

The study schematic is presented in **Figure 6**

Figure 6 *Study CA209274 Objectives and Endpoints Presented in This CSR*



This study consists of 3 phases: screening, treatment, and follow-up. After screening, eligible subjects were randomised in a 1:1 ratio to the nivolumab or placebo treatment arm and stratified by pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs N0 with ≥ 10 nodes removed), tumour cell PD-L1 expression (≥ 1%, < 1%, indeterminate), and use of cisplatin neo adjuvant chemotherapy (yes vs no). In order to be randomised, a subject must have had a tumour cell PD L1 expression level classification (≥ 1%, < 1%, indeterminate) as determined by the central laboratory.

Study participants

The study population included adult male or female subjects who have undergone radical resection of MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence. The number of subjects enrolled with upper tract urothelial carcinoma was capped at 20% due to the lower natural prevalence.

Key Inclusion Criteria:

1. All subjects were required to be in post radical surgical resection (R0) for MIBC performed within 90 days prior to randomization.

2. All subjects must have pathologic evidence of urothelial carcinoma (originating in bladder, ureter, or renal pelvis) at high risk of recurrence as described in one of the two below scenarios (i or ii):

i) Subjects who have not received neo-adjuvant cisplatin chemotherapy: any pT3-pT4a or pT0/x-pT4a/N+ and were not eligible for or refusing adjuvant cisplatin chemotherapy

(1) Subjects ineligible for cisplatin due to any of the following criteria:

a. Creatinine Clearance (using the Cockcroft-Gault formula): < 60 mL/min

b. CTCAE version 4, grade 2 or above audiometric hearing loss

c. CTCAE version 4, grade 2 or above peripheral neuropathy

d. ECOG PS 2

e. New York Heart Association (NYHA) Class III or IV Heart Failure

(2) Subjects eligible for cisplatin could be candidates if they refused available adjuvant chemotherapy, despite being informed by the investigator about the treatment options. The subject's refusal must have been thoroughly documented.

ii) Subjects who received cisplatin based neo-adjuvant chemotherapy: any pT2-pT4a or pT0/x-pT4a/N+

3. Dominant component of histology needed to be urothelial carcinoma or transitional cell carcinoma. Foci of varied histologies (e.g. minor variants) were accepted.

4. All subjects must have had disease-free status (N0M0) defined as no clinical or radiographic evidence of disease documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT of chest and CT or MRI of abdomen and pelvis including primaries who still have bladder intact. Brain imaging (MRI except where contraindicated in which CT scan is acceptable) must be completed within 4 weeks prior to randomization for subjects with clinical suspicion of CNS disease at screening.

5. Tumour tissue from the most recently resected site of disease (preferable) or from the transurethral resection that yielded the initial muscle invasive diagnosis must be provided for biomarker analyses. In order to be randomised, a subject must have a PD-L1 expression level classification (≥ 1%, < 1%, indeterminate) as determined by the central lab. If insufficient tumour tissue content is provided for analysis (e.g. unevaluable), acquisition of additional archived tumour tissue from the most recent resection (preferable) or from the transurethral resection that yielded the initial muscle invasive diagnosis is required.

6. Life expectancy > 6 months

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. Per inclusion 2 i) (1), ECOG PS 2 is listed as part of cisplatin ineligibility criteria. Subjects that have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy, may enter the study with ECOG PS 2.

8. Prior surgery that required general anaesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anaesthesia must be completed at least 72 hours before study drug administration.

Key Exclusion Criteria:

1. Partial cystectomy in the setting of bladder cancer primary tumour or partial nephrectomy in the setting of renal pelvis primary tumour.

2. Adjuvant systemic or radiation therapy for urothelial or prostatic carcinoma following radical surgical resection of urothelial carcinoma.

3. Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may have increased the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

4. Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, prostate cancer with evidence of undetectable Prostate Specific Antigen (PSA) or carcinoma in situ of the prostate, cervix or breast.

5. 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 are permitted to enrol.

6. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

7. Subjects with history of life-threatening toxicity related to prior immune therapy (e.g. anti-CTLA-4 or anti-PD- 1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (e.g. Hormone replacement after adrenal crisis).

8. All toxicities attributed to prior anti-cancer therapy other than nephropathy, neuropathy, hearing loss, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enrol. See protocol inclusion criterion 2) i) (5) for renal function eligibility. Neuropathy must have resolved to Grade 2 (NCI CTCAE version 4).

9. Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment.

Treatments

All subjects were to be treated until recurrence of disease, unacceptable toxicity, or withdrawal of consent with a maximum of 1 year of treatment.

Nivolumab dosing: Subjects randomised to the nivolumab treatment arm received nivolumab 240 mg as a 30 minute intravenous (IV) infusion every 2 weeks (Q2W).

Placebo dosing: Subjects randomised to the placebo arm received placebo as a 30 minute IV infusion Q2W.

Tumour imaging assessments were to be performed every 12 weeks ≤ 1 week from the date of first dose to Week 96, then every 16 weeks < 2 weeks from Week 96 to Week 160, then every 24 weeks until non-urothelial tract recurrence or treatment was discontinued (whichever occurs later) for a maximum of 5 years.

Subjects randomised to the nivolumab treatment arm received nivolumab 240 mg as a 30 minute IV infusion Q2W. Subjects randomised to the placebo arm received placebo as a 30 minute IV infusion Q2W. Placebo for nivolumab was the drug diluent alone, either a normal saline solution or a 5% dextrose solution.

A data monitoring committee (DMC) was established and met regularly during the study to ensure the monitoring of subject safety and to provide oversight regarding safety and efficacy considerations in the protocol.

Selection of Doses Used in the Study

The nivolumab dose of 240 mg Q2W was selected based on clinical data and modelling and simulation approaches using population PK (popPK) and exposure-response analyses of data from studies in multiple tumour types (melanoma, non-small cell lung cancer, colorectal cancer, and renal cell carcinoma) where body weight normalized dosing (mg/kg) has been used.

Objectives

The objectives are as mentioned in ***Table 9***.

Table 9 Study CA209274 Objectives

Objectives	**Endpoints**	**Included in this CSR?**
Primary		
To compare the Disease-Free Survival (DFS) for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects.	DFS	Yes
Secondary:		
To compare the Overall Survival (OS) for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects.	OS	No
To evaluate non-urothelial tract recurrence-free survival (NUTRFS) in each randomised treatment arm (nivolumab versus placebo) in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects.	NUTRFS	Yes
To evaluate Disease-Specific Survival (DSS in each randomised treatment arm (nivolumab versus placebo) in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects.	DSS	No
Exploratory:		
To evaluate overall safety and tolerability of nivolumab and placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	Incidence of AEs, SAEs, select AEs, IMAEs	Yes
To evaluate distant metastasis-free survival (DMFS) for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	DMFS	Yes

Table 9 Study CA209274 Objectives

Objectives	Endpoints	Included in this CSR?
To evaluate time to recurrence (TTR) for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	TTR	Yes
To evaluate locoregional disease-free survival (LRDFS for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	LRDFS	Yes
To evaluate locoregional control (LRC) for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	LRC	Yes
To assess time from randomization to the date of investigator-defined disease progression after the subsequent next-line systemic anti-cancer therapy, or the start of second subsequent next-line systemic anti-cancer therapy, or death due to any cause, whichever comes first (PFS2) for nivolumab vs placebo, as assessed by investigators in subjects with tumour cell PD-L1 expression ≥ 1% and in all randomised subjects.	PFS2	Yes
To explore potential biomarkers associated with clinical efficacy (DFS and OS) and/or incidence of adverse events of nivolumab by analyzing biomarker measures within the tumour microenvironment and periphery (eg, blood, serum, plasma and PBMCs).	Efficacy by PD-L1 tumour cell expression status, PD-L1 CPS, and MDSC	Yes[a]
To assess the effect of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2 and CTLA4 on clinical efficacy and/or incidence of adverse events.	SNPs	No
To characterize pharmacokinetics of nivolumab and to explore exposure response relationships.	PK	No[b]
To characterize the immunogenicity of nivolumab.	Immunogenicity	Yes
To evaluate HRQoL.	EORTC QLQ-C30	Yes
To evaluate patient reported general health status.	EuroQoL EQ-5D-3L	Yes

[a] OS data were immature at the time of the pre-specified interim analysis, therefore potential biomarkers association with clinical efficacy as measured by OS were not included in this CSR.

[b] Nivolumab PK data collected from this study were used for population PK (popPK) modeling and exposure-response analyses, if appropriate.

Abbreviations: AE = adverse events; CPS = combined positive score, CTLA4 = cytotoxic T-lymphocyte-associated protein 4, DFS = disease-free survival, DMFS = distant metastasis-free survival, DSS = disease-specific survival,

EORTC = European Organization for Research and Treatment of Care, EQ-5D-3L = 3-level version of EQ-5D, HRQoL = health-related quality of life, IMAE = immune-mediated adverse event; LRC = locoregional control, LRDFS = locoregional disease-free survival, MDSC = myeloid-derived suppressor cells, NUTRFS = non-urothelial tract recurrence-free survival, OS = overall survival, PBMC = peripheral blood mononuclear cell, PD-1 = programmed death 1 receptor, PD-L1 = programmed death ligand 1; PD-L2 = programmed death-ligand 2, PFS2 = progression-free survival after next line of subsequent therapy; PK = pharmacokinetics; SAE = serious adverse event, SNP = single nucleotide polymorphism, TTR = time to recurrence

Outcomes/endpoints

The objectives and endpoints are defined hereafter in Table 10

Table 10 *Study CA209274 Objectives and Endpoints Presented in the CSR*

Objective	Endpoint(s)	Endpoint Description
PRIMARY		
To compare the DFS for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	DFS	DFS was defined as the time between the date of randomization and the date of the first documented recurrence (local urothelial tract, local non urothelial tract or distant), or death (from any cause), whichever occurred first. Disease recurrence of the local urothelial tract was defined as any high and intermediate risk NMIBC and any new invasive urothelial carcinoma in the lower or upper urothelial tract (defined as T2 or greater), including lesions thought to be a second primary urothelial carcinoma. The primary definition of DFS accounted for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer by censoring at the last evaluable disease assessment on or prior to the date of subsequent therapy/new non-urothelial carcinoma primary cancer. The secondary definition of DFS accounted for disease assessments occurring on or after initiation of subsequent anticancer therapy. The censoring scheme was the same as for the primary DFS definition except that new anticancer therapy censoring was ignored in this sensitivity analysis. The secondary definition of DFS accounted for new non-urothelial carcinoma primary cancer by censoring at the last evaluable disease assessment on or prior to the date of new non-urothelial carcinoma primary cancer.
SECONDARY		
To evaluate NUTRFS in each randomised treatment arm (nivolumab vs placebo) in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour	NUTRFS	NUTRFS was defined as the time between the date of randomization and the date of first documented recurrence (local non-urothelial tract or distant), or death (from any cause), whichever occurred first. The definition of NUTRFS accounted for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer by censoring at the last evaluable disease assessment on or prior to

Objective	Endpoint(s)	Endpoint Description
cells) and all randomised subjects		the date of subsequent therapy/new non-urothelial carcinoma primary cancer.
EXPLORATORY		
To evaluate the overall safety and tolerability of nivolumab and placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	Deaths, AEs, SAEs, AEs leading to discontinuation & dose delay, vital signs, specific laboratory abnormalities	The assessment of safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, select AEs, immune-mediated AEs, other AEs of special interest, and abnormalities in specific clinical laboratory assessments. Analyses were conducted using 30-day and 100-day safety windows from day of last dose received. AEs were coded using the MedDRA version 23.0. AEs and laboratory values were graded for severity according to the NCI CTCAE version 4.0.
To evaluate DMFS for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	DMFS	DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or date of death (from any cause), whichever occurred first. For subjects who remained alive and distant recurrence-free, DMFS was censored on the date of last disease assessment.
To evaluate TTR for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	TTR	TTR was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death due to disease (urothelial cancer), whichever occurred first. For subjects who remained alive and recurrence-free, TTR was censored on the date of last disease assessment. Death not due to disease was considered as a competing risk. Consequently, for subjects who died due to other cause than urothelial cancer, TTR in the analysis of cause-specific hazard analysis were censored on the date of death.
To evaluate LRDFS for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	LRDFS	LRDFS was defined as the time between the date of randomization and the date of first locoregional recurrence (local urothelial or local non-urothelial tract) or date of death from any cause, whichever occurred first. For subjects who remained alive and locoregional recurrence-free, LRDFS was censored on the date of last disease assessment. Distant metastasis was considered as a competing risk. Consequently, for subjects with distant metastasis prior to

Objective	Endpoint(s)	Endpoint Description
		locoregional recurrence, LRDFS in the analysis of cause-specific hazard analysis was censored on the date of distant metastasis.
To evaluate LRC for nivolumab versus placebo in subjects with tumours expressing PD-L1 (≥ 1% membranous staining in tumour cells) and all randomised subjects	LRC	LRC was defined as the time between the date of randomization and the date of first locoregional recurrence (local urothelial or local non-urothelial tract) or date of death due to the disease (urothelial cancer), whichever occurred first. For subjects who remained alive and locoregional recurrence-free, LRC was censored on the date of last disease assessment. Death not due to disease and distant metastasis was considered as a competing risk. Consequently, for subjects with distant metastasis prior to locoregional recurrence, LRC in the analysis of cause-specific hazard analysis was censored on the date of distant metastasis; and for subjects who died due to other cause than urothelial cancer, LRC in the analysis of cause-specific hazard analysis was censored on the date of death.
To assess time from randomization to the date of investigator-defined disease progression after the subsequent next-line systemic anti-cancer therapy, or the start of second subsequent next-line systemic anti-cancer therapy, or death due to any cause, whichever comes first (PFS2) for nivolumab vs placebo, as assessed by investigators in subjects with tumour cell PD-L1 expression ≥ 1% and in all randomised subjects	PFS2	PFS2 was defined as the time from randomization to investigator-defined disease progression after the subsequent next-line systemic anti-cancer therapy, or the start of second subsequent next-line systemic anti-cancer therapy, or to death from any cause, whichever occurred first. Subjects who were alive and without progression after start of the next line of systemic anticancer therapy were censored at last known alive date.
To explore potential biomarkers associated with clinical efficacy (DFS) and/or incidence of adverse events of nivolumab by analyzing biomarker measures within the	DFS by PD-L1 tumour cell expression status, PD-L1 CPS, and MDSC	Biomarkers potentially associated with clinical endpoints were measured by analyzing tumour and blood samples. PD-L1 expression was defined as the percent of tumour cells membrane staining in a minimum of 100 evaluable tumour cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This was referred to as quantifiable PD-L1 expression. If the PD-L1 staining could not be quantified, it was further classified as:

Objective	Endpoint(s)	Endpoint Description
tumour microenvironment and periphery (eg, blood, serum, plasma and PBMCs)		Indeterminate: Tumour cell membrane staining hampered for reasons attributed to the biology of the tumour sample and not because of improper sample preparation of handling. Not evaluable: Tumour tissue sample was not optimally collected or prepared and PD-L1 expression was neither quantifiable nor indeterminate. Not evaluable could be determined from H&E process before the tumour biopsy specimen was sent for PD-L1 evaluation or from the H&E process during PD-L1 evaluation. Subjects with missing tumour cell PD-L1 expression were subjects with no tumour tissue sample available for evaluation. Tumour cell PD-L1 expression was collected in the IRT as well as the clinical database. PD-L1 CPS provides the number of PD-L1 positive tumour and immune cells as a proportion of viable tumour cells in a tissue sample using a single read.
To characterize the immunogenicity of nivolumab	Serum ADA and neutralizing ADA response to nivolumab	Subjects were classified as: **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. ***Not Persistent Positive - Last Sample Positive****:* Not persistent positive with ADA-positive sample at the last sampling time point. ***Other Positive****:* not persistent positive, but with some ADA-positive samples, with the last sample being negative. ***Neutralizing Positive****:* At least 1 ADA positive sample with neutralizing antibodies detected. **ADA Negative:** no ADA positive sample after the initiation of treatment.
To evaluate the HRQoL.	Changes in HRQoL in each treatment arm as assessed by EORTC QLQ-C30 questionnaire	Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL; an increase from baseline indicates improvement in HRQoL compared to baseline. Lower scores for symptom scales indicate better HRQoL; a decline from baseline for symptom scales indicates improvement in symptoms compared to baseline. A difference of 10 points on a 100-point scale between the two treatment arms is considered clinically significant based on the work of Osoba et al. HRQoL was measured by mean score and mean changes from baseline in the EORTC QLQ-C30 global health status/QoL composite scale.

Objective	Endpoint(s)	Endpoint Description
To evaluate patient reported general health status	Changes in global health status in each treatment arm based on EuroQoL's EQ-5D-3L instrument	Responses are converted into 1 of 243 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions (11111) to severe/extreme problems on all 5 dimensions (33333).

Abbreviations: ADA = anti-drug antibodies, AE = adverse event, CPS = combined positive score, DFS = disease-free survival, DMFS = distant metastasis-free survival, EORTC = European Organisation for Research and Treatment of Cancer, EQ-5D-3L = 3-level version of the EQ-5D, H&E = hematoxylin and eosin, HRQoL = Health Related Quality of Life questionnaire, IHC = immunohistochemistry, LRC = locoregional control, LRDFS = locoregional disease-free survival, MDSC = myeloid-derived suppressor cells, MedDRA = medical dictionary for regulatory activities, MID = minimal important difference, NCI CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events, NUTRFS = non-urothelial tract recurrence-free survival, PBMC = peripheral blood mononuclear cell, PD-L1 = programmed death-ligand 1, PFS2 = progression-free survival after the subsequent next-line of systemic anti-cancer therapy, SAE = serious adverse event, SAP = statistical analysis plan, TTR = time to recurrence, UK = United Kingdom, VAS = visual analog scale

Overall Survival (OS)- The key second secondary endpoint of Overall Survival (OS) is defined as the time between the date of randomization and the date of death (of any cause). For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug. This endpoint will be analyzed in two different populations: Subjects with PD-L1 expression level ≥ 1%, and all randomised subjects.

Disease Specific Survival (DSS)- The secondary endpoint DSS is defined as the time between the date of randomization and the date of death due to disease (urothelial cancer). For subjects without documentation of death, DSS will be censored on the last date the subject was known to be alive. DSS will be followed continuously as part of OS follow-up while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug. This endpoint will be analyzed in two different populations: Subjects with PD-L1expression level ≥ 1% and all randomised subjects.

Sample size

DFS in all randomised subjects and DFS in subjects with PD-L1≥1% are dual endpoints, each type I error of 0.025 two-sided. Sample size was based on simulation based on the following assumptions. Under the assumption that PD-L1 is not a prognostic factor, in both control arms the same exponential cure rate distribution $S(t) = p + (1-p)e^{-\alpha t}$ was taken with median 12 months, a 5 year survival rate of 32% based on historical data. In the experimental arm an exponential distribution with 3 months delayed treatment effect was assumed. During the trial the sample size was adapted from 600 to 640 to 700, in response to different assumptions on the prevalence of PD-L1≥1% and a reality check on the assumed effect based on results in other trial. In the end, approximately 410 DFS events in all randomised subjects were estimated to provide around 87% power to detect an average HR of 0.72 with an overall type I error of 2.5% (two-sided) in the all randomised, and approximately 162 DFS events in subjects with PD-L1≥1% (~294 subjects) were estimated for around 80% power to detect an average HR of 0.61 with an overall type I error of 2.5% (two-sided).

Randomisation

After initial eligibility was established and the informed consent was obtained, subjects were enrolled into the study via an Interactive Voice Response System (IVRS). Once enrolled in the IVRS, subjects who met all eligibility criteria were randomised in a 1:1 ratio to the nivolumab or placebo treatment arm, stratified by the following factors; pathologic nodal status (N+ vs. N0/x with < 10 nodes removed vs N0 with ≥ 10 nodes removed), tumour cell PD-L1 expression (≥ 1%, < 1%, indeterminate), and use of cisplatin neo adjuvant chemotherapy (yes vs no). In order to be randomised, a subject must have had a tumour cell PD L1 expression level classification (≥ 1%, < 1%, indeterminate) as determined by the central laboratory.

Blinding (masking)

CA209274 is a randomised, double-blind study.

Statistical methods

Intercurrent events: censoring and competing risks

Several of the secondary and exploratory endpoints have intercurrent events handled via censoring or as competing risk.

Censoring:
DFS was censored in case of start of subsequent therapy (primary definition) and new no-urothelial carcinoma (primary and secondary definition; see ***Table 10*** for definitions and as such handled via hypothetical strategy.
Similarly, NUTFRS was censored for subsequent therapy and new no-urothelial carcinoma.

Competing risks (and treatment policy strategy) was handle as described in ***Table 11***.

Table 11 *Competing events by endpoint*

	Primary	Secondary			Exploratory			
Event	**DFS**	**NUTRFS**	**DSS**	**OS**	**DMFS**	**TTR**	**LRDFS**	**LRC**
Disease at baseline	E	E	I	I	E	E	E	E
Local urothelial tract recurrence	E	I	I	I	I	E	E	E
Local non-urothelial tract recurrence	E	E	I	I	I/C*	E	E	E
Distant recurrence	E	E	I	I	E	E	C	C
Death due to disease	E	E	E	E	E	E	E	E
Death not due to disease	E	E	C	E	E	C	E	C

E: Event, C: Competing risk and I: Ignored in the endpoint definition

* If the rate of subjects with local non-urothelial tract recurrence without distant recurrence exceeds 10% of the population of interest, local non-urothelial tract recurrence will be considered as a competing risk

Notably, DSS and TTR handle death not due to disease as competing risk and LRDFS and LRC handle distant recurrence as competing risk. For interpreting the effect on these endpoints, the effect on the competing risks should be taken into account.

Multiplicity

Only DFS and OS were formally tested. DFS in PD-L1 ≥1% and DFS in all randomised were dual endpoints (both half of the total type I error,0.025 two-sided each). OS was hierarchically tested after DFS in each population, see ***Figure 7*** and

Figure 8. DFS had one interim at approximately 85% of the planned number of events in both populations. OS had two interim analyses. Both endpoints' interim analyses had O'Brien-Fleming type group sequential boundaries based on the actual number of events observed using Lan-DeMets methods.

The timing of the interim analyses is indicated below. In particular, the first interim analysis for OS (T2) takes place at a later time than the first interim for DFS (estimated 15 months later).

Figure 7 *Multiple testing all randomised patients*

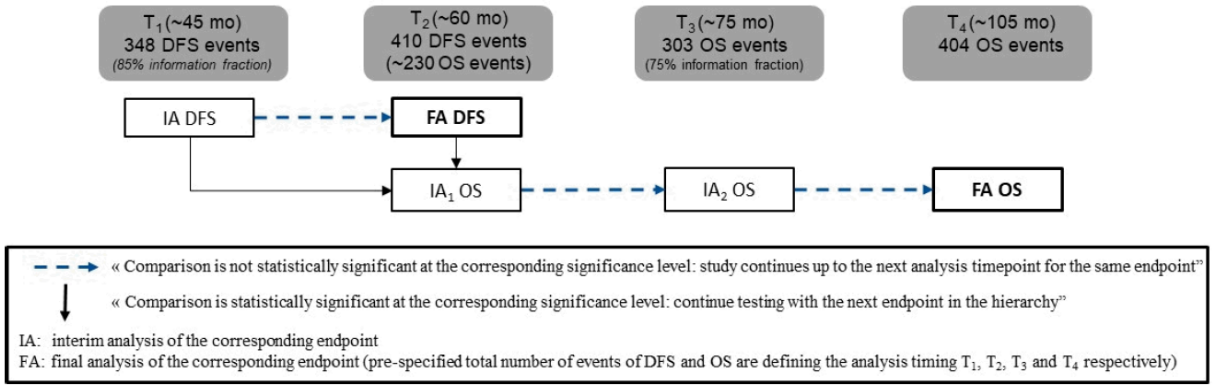
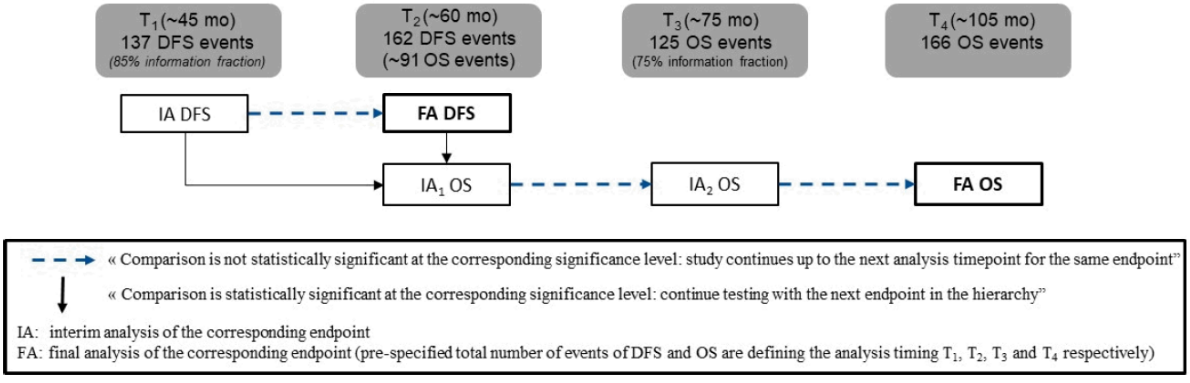


Figure 8 *Multiple testing in PD-L1≥1% patients*



Statistical models and tests

Analyses were stratified on 1) receipt of neo-adjuvant based chemotherapy, 2) N+ vs. N0/x with < 10 nodes removed vs N0 with ≥10 nodes removed, and 3), in the all randomised population, PD-L1 ≥1% vs PD-L1 < 1% or indeterminate.

Time to event endpoints without competing risks were analysed using Kaplan-Meier methodology, stratified log-rank test and Cox-proportional hazard models.
Time to event endpoints with competing risks were analysed using cumulative incidence curves and Cox models for the cause specific hazards (i.e. censoring the competing risks).

Supportive analyses for DFS included an unstratified log-rank test, multivariate Cox models with unbalanced prognostic factors, and analyses investigating the non-proportional hazard: a G(rho=0, gamma=1) Flemington-Harrington test which strongly downweighs early events and upweighs later events, a Cox analysis in the time frame < 6 months and one for > 6 months, and a test on proportional hazards by including a time by treatment interaction.

Results

Participant flow and recruitment

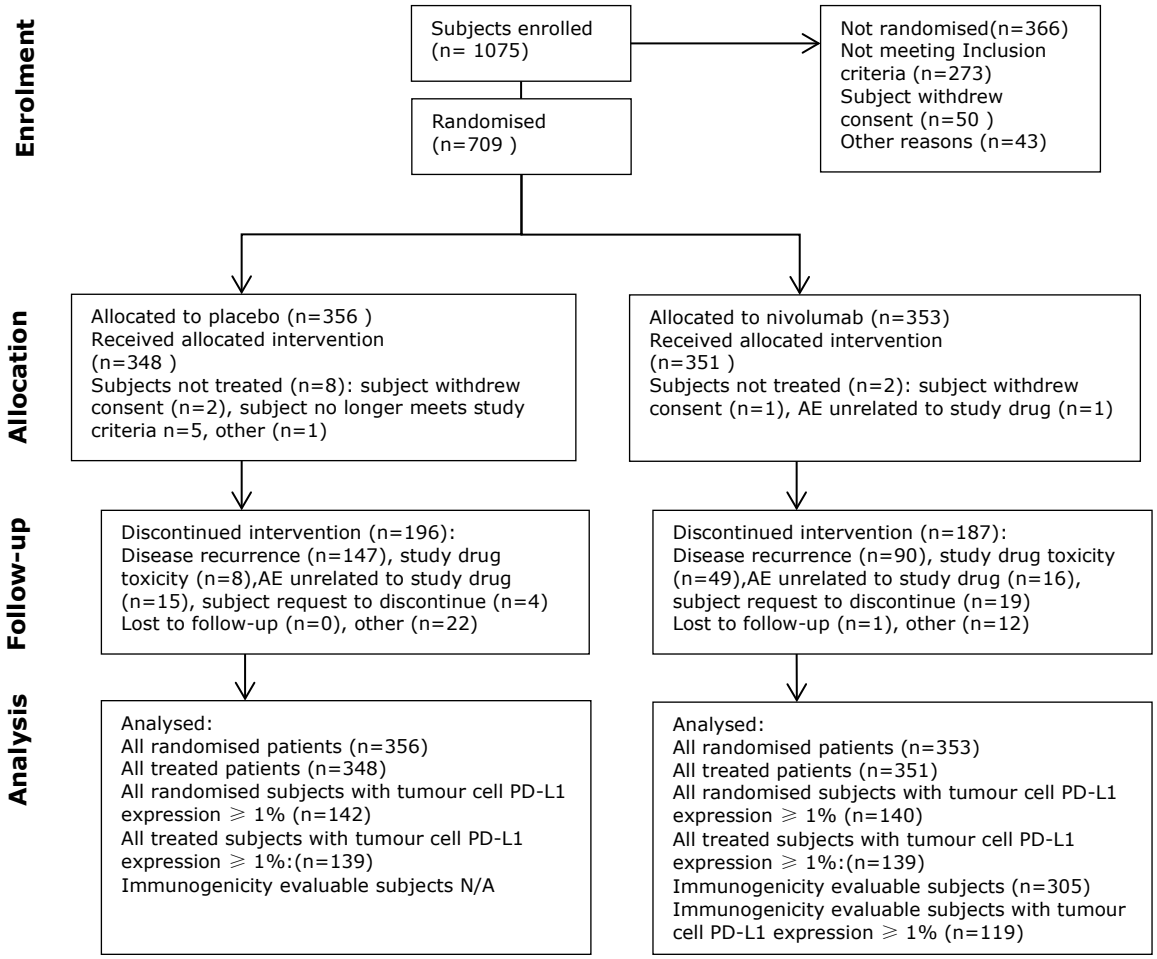
The enrolment period lasted approximately 47 months (Mar-2016 to Jan-2020) and 1,075 subjects were enrolled at 170 sites in 30 countries. In total, 709 subjects were randomised. The last subject was randomised on 20 Jan 2020 in the all-randomised population, and the last patient last visit (LPLV) date (clinical cut-off) for this CSR occurred on 17-Jul-2020, providing a minimum follow-up of 5.9 months. The last subject was randomised on 07-Jan-2020 in the PD-L1 expression level ≥ 1% population, providing a minimum follow-up of 6.3 months.

Of the 709 total subjects randomised in Study CA209274, 353 subjects were randomised to the nivolumab arm and 356 subjects were randomised to the placebo arm. 699 (98.6%) subjects were treated with study drug (351 (99.4%) subjects in the nivolumab arm and 348 (97.8%) subjects in the placebo arm) (***Figure 9***).

At the time of the DBL, 610 (87.3%) subjects were continuing in the study, and 41 (5.9%) subjects were still on study treatment (21 (6.0%) subjects in the nivolumab arm and 20 (5.7%) subjects in the placebo arm). The overall rates of discontinuation during the treatment period were 53.3% and 56.3% in the nivolumab and placebo arms, respectively. The most common reason for discontinuation of study drug in both treatment arms was disease recurrence (90 (25.6%) subjects in the nivolumab arm and 147 (42.2%) subjects in the placebo arm).

Overall, 12 (1.7%) subjects withdrew consent and did not complete the treatment period.

Figure 9 *Participant flow; all enrolled, randomised, treated and analysed patients*



Subject disposition of "All randomised and treated subjects" with tumour PD-L1≥1% showed a similar profile as of 'All randomised and treated patients'.

Conduct of the study

The original protocol for this study was dated 15-Jul-2015. The changes in the protocol as of 17-Jul-2020 (clinical cut-off date) are summarized below.

There were 5 global amendments, 11 country-specific amendments, and 8 administrative letters issued as of the clinical cut-off date. The rationale for key changes, such as changes to enrolled population, changes to statistical assumptions, updated exclusion criteria, and added formal OS interim analyses is provided below.

Revised Protocol 01 (included Amendment 03, dated 21-Oct-2015; number of subjects randomised at time of protocol revision =0):

The subject randomization rate was modified from 2:1 to 1:1, and the sample size of planned treated subjects was increased from 600 to 640 subjects; however, this revised protocol was finalized prior to any subjects being randomised in this study.

Revised Protocol 02 (Amendment 10, dated 18 Aug 2016; number of subjects randomised at time of protocol revision =26):

Extended acceptable period of time between radical resection and randomization from 90 days to 120 days; clarified pathology language for eligibility; clarified recurrence language, updated safety and contraceptive language to be consistent with the nivolumab Investigator Brochure version 15; other minor changes.

Revised Protocol 03 (included Amendment 12, dated 18-Jul-2017; number of subjects randomised at time of protocol revision =252): The rationale for the changed PD-L1 positive percentage from 50% to 46% in accord with recently published data from the CA209275 registrational study, and the 20% cap on the number of pelvis and ureter cancer subjects randomised to the CA209274 study.

At the time the CA209274 protocol was written, the prevalence of urothelial tumour expression PD-L1 at ≥ 1% was approximately 50%, based on preliminary results from the CA209032 and CA209275 clinical trials in second-line urothelial cancer (UC). Given the competitive landscape, which included a similar study that was enrolling only PD-L1 positive subjects, a minimum of 50% PD-L1 positive enrollment was chosen for this study in order to maintain the expected prevalence. Final data from the CA209275 study was published in Lancet Oncology showing that tumours from 122 out of 265 subjects (46%) expressed PD-L1 at levels ≥ 1%. Therefore, the CA209274 protocol was amended to use the 46% PD-L1-positive value as obtained in the CA209275 registrational study as the minimum percentage of PD-L1-expressing subjects to be enrolled in the CA209274 study. The percentage of PD-L1 negative subjects was capped at 54%, and subsequent subjects enrolled in the PD-L1 positive cohort; there was no change in the planned accrual of 640 total randomised subjects. The Statistical Consideration section of the protocol was updated to reflect the change in expected sample size in the PD-L1 ≥ 1% randomised population and the minor change in power of the statistical tests.

The CA209274 protocol was written with the intent that the study population would be representative of the world-wide UC population, to the extent possible. In older cohorts, it was estimated that approximately 90% of urothelial cancers originate in the bladder and the remaining 10% arise in the renal pelvis or ureter (upper tract urothelial cancer (UTUC)). In studies assessing checkpoint inhibitors in the metastatic urothelial carcinoma setting, it is reported that the prevalence of UTUC disease can be as high as 20%. An assessment of the baseline disease characteristics of subjects being enrolled in the CA209274 study indicated that 137 subjects had bladder cancer primaries, and 68 had the primary tumour located in the renal pelvis or ureter. This 33% incidence of UTUC was therefore much higher than the expected value of approximately 10%. It is very likely that a competing study that was enrolling only subjects with bladder cancer was the driving factor for the high number of UTUC subjects enrolled in the CA209274 study.

Little is known about the clinical outcomes of subjects with UTUC treated with checkpoint inhibitors and data suggest that UTUC may have a worse prognostic outlook than bladder cancer. Given that the primary site of disease was not a stratification factor, an overrepresentation of UTUC may lead to a disproportionate impact on treatment and reduced relevance for clinical practice, given the considerable deviation from the expected prevalence of this subset of subjects. Because of these considerations, this amendment capped the number of UTUC subjects enrolled in the CA209274 study at 20% of the planned 640 subjects. The 20% value, chosen to reflect the natural prevalence of UTUC diagnosis as supported by the studies mentioned above, provides a reasonable target, established in a large cohort of patients enrolled in these three international studies. Therefore, once approximately 128 subjects with UTUC were enrolled, only subjects with bladder cancer were to be screened to complete the planned 640 subject enrollment in the CA209274 study.

Revised Protocol 04 (included Amendment 15, dated 19-Dec-2018; number of subjects randomised at time of protocol revision =531): Revisions to exclusion criteria, rationale for removal of the cap on PD-L1 negative subjects, changes to statistical assumptions.

Two exclusion criteria were added to the protocol. These additions were instituted in all nivolumab protocols in the global development program:

- Restriction for participants receiving a live/attenuated vaccine within 30 days of randomization (e.g. varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR));
- Treatment with botanical preparations (e.g. herbal supplements or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment added;
- Removal of the cap on PD-L1 negative subjects:
- The previous study design was based on an estimated prevalence of PD-L1 positive subjects of 46%, and accordingly capped the number of PD-L1 negative subjects allowed into the study at 54%. During the execution of the study, the prevalence of PD-L1 positive subjects has been demonstrated to be 42%. Revised protocol 04 removed the cap on PD-L1 negative subjects to ensure the population recruited was representative of the clinical population (i.e. with PD-L1 positive of 42%), and ensured the study results were broadly applicable.

Changes to statistical assumptions and analysis plan were made:

- A number of events in the adjuvant therapy landscape led to a reassessment of the CA209274 statistical assumptions and analysis plan. Data from the publicly available CA209238 adjuvant melanoma study supported a greater clinical benefit of adjuvant nivolumab treatment in PD-L1 positive population. IMvigor 010 is a randomised Phase 3 study assessing adjuvant atezolizumab (a PD-L1 inhibitor) in a patient population similar to that of the CA209274 study. Upon accrual completion of IMvigor010 in Jun-2018, public information implied that this study had a more conservative target HR than the 0.69 target HR in CA209274. An internal assessment triggered by this understanding concluded that the initial protocol statistical assumptions were aggressive; consequently, a potential scenario could be the adjuvant nivolumab treatment resulting in clinically meaningful activity without reaching the level of significance, due to the rather aggressive initial statistical assumptions. In order to optimize the study design, reducing the chances of an active adjuvant treatment being dismissed on the basis of aggressive statistical assumptions a number of protocol assumptions were reviewed.
- To address the concern that the initial study target HRs were overly aggressive compared to the IMvigor 010 study, more conservative HRs were targeted: 0.72 (all randomised subjects) and 0.61 (PD-L1 positive subjects), while maintaining adequate power for both primary endpoints. This resulted in a sample size increase from 640 to 700 subjects.
- The statistical model included a 3-month delayed treatment effect, based on observations on the pattern of clinical efficacy of nivolumab seen in other clinical settings (eg, CA209238 – adjuvant melanoma). Only the DFS nivolumab arm assumptions were changed by adding the 3-month delayed treatment effect, but the cure rate model parameter remained the same.
- The planned DFS IA (for PD-L1 all-comers only) was planned for 65% events which was projected to occur in Jan-2019. If this DFS IA was positive, enrollment would close and the study would not complete accrual. In this scenario, the secondary endpoint readouts (e.g. NUTRFS, DSS, and OS) would likely be delayed and the power decreased due to lower total number of subjects.
- To mitigate the risk of the IA occurring before the enrollment was completed, the timing of the DFS IA was changed from an information fraction of 65% to 85%. With this change, expected number of DFS events for PD-L1 positive subjects would be enough to trigger an IA in this subgroup as well, and was formally added to the statistical design. Given the importance of OS

to support the DFS primary endpoint, NUTRFS and DSS were removed from the testing hierarchy, but remained as important secondary endpoints. OS was made a key secondary endpoint and was tested following the hierarchical procedure after DFS.

Revised Protocol 05 (dated 18-Oct-2019; number of subjects randomised at time of protocol revision =668): Rationale for the added formal interim OS analyses at the time of final DFS analysis for each of the 2 populations specified in the primary objective in order to provide an earlier assessment of OS.

Following FDA interaction the MAH added a formal interim OS analysis at the time of the final DFS analysis for each of the 2 populations specified in the primary objectives. If DFS achieved the pre-specified boundary for statistical significance at the DFS IA, the first interim OS analysis was to occur when 230 OS events in all randomised subjects and 91 OS events in subjects with PD-L1 expression ≥ 1% was observed. If DFS achieved the pre-specified boundary for statistical significance at the final DFS analysis (410 DFS events in all randomised subjects and 162 events in subjects with PD-L1 expression ≥ 1%), the first interim OS analysis was to occur at the same time (i.e. approximately 230 OS events in all randomised subjects and 91 OS events in subjects with PD-L1 expression ≥ 1% were to be expected).

A summary of relevant protocol deviations is provided in

Table 12 and **Table 13**.

Table 12 *Relevant Protocol Deviations - All Randomised Subjects*

	Number of Subjects (%)		
	Placebo N = 356	Nivolumab N = 353	Total N = 709
SUBJECTS WITH AT LEAST ONE DEVIATION	18 (5.1)	12 (3.4)	30 (4.2)
AT ENTRANCE			
SUBJECTS WITH PRESENCE OF DISEASE AT BASELINE	3 (0.8)	1 (0.3)	4 (0.6)
SUBJECTS WITH INELIGIBLE BASELINE ECOG STATUS	1 (0.3)	1 (0.3)	2 (0.3)
SUBJECTS RANDOMIZED MORE THAN 120 DAYS AFTER IUC SURGERY	11 (3.1)	4 (1.1)	15 (2.1)
SUBJECTS WITH INELIGIBLE PATHOLOGIC STAGE AT RESECTION	3 (0.8)	3 (0.8)	6 (0.8)
ON-STUDY			
SUBJECTS RECEIVING ANTI-CANCER THERAPY (A) WHILE ON STUDY THERAPY AND/OR BEFORE DISEASE RECURRENCE	1 (0.3)	3 (0.8)	4 (0.6)
SUBJECTS TREATED DIFFERENTLY THAN AS RANDOMIZED	0	0	0

(A) Anti-cancer therapy includes chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents, radiotherapy or surgery for treatment of cancer but does not include single dose of BCG or other chemotherapy given via intravesical route.

Abbreviations: BCG = bacillus calmette-guerin, ECOG = Eastern Cooperative Oncology Group, IUC = invasive urothelial carcinoma

Table 13 *Relevant Protocol Deviations - All Randomised Subjects with Tumor PD-L1 ≥ 1%*

	Number of Subjects (%)		
	Placebo N = 142	Nivolumab N = 140	Total N = 282
SUBJECTS WITH AT LEAST ONE DEVIATION AT ENTRANCE	8 (5.6)	4 (2.9)	12 (4.3)
SUBJECTS WITH PRESENCE OF DISEASE AT BASELINE	0	0	0
SUBJECTS WITH INELIGIBLE BASELINE ECOG STATUS	0	0	0
SUBJECTS RANDOMIZED MORE THAN 120 DAYS AFTER IUC SURGERY	7 (4.9)	1 (0.7)	8 (2.8)
SUBJECTS WITH INELIGIBLE PATHOLOGIC STAGE AT RESECTION	1 (0.7)	0	1 (0.4)
ON-STUDY			
SUBJECTS RECEIVING ANTI-CANCER THERAPY (A) WHILE ON STUDY THERAPY AND/OR BEFORE DISEASE RECURRENCE	0	3 (2.1)	3 (1.1)
SUBJECTS TREATED DIFFERENTLY THAN AS RANDOMIZED	0	0	0

(A) Anti-cancer therapy includes chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents, radiotherapy or surgery for treatment of cancer but does not include single dose of BCG or other chemotherapy given via intravesical route.

Abbreviations: BCG = bacillus calmette-guerin, ECOG = Eastern Cooperative Oncology Group, IUC = invasive urothelial carcinoma

Baseline data

Overall, the median age of all randomised subjects was 67.0 years. Most subjects were white (75.6%), male (76.2%) and had an ECOG PS (based on case report form (CRF)) of 0 (62.8%). The predominant tumour type was urinary bladder (79.0% of subjects). Per case report form (CRF), 0.7%, 1.7%, 1.0%, 3.8%, 17.9%, 57.8%, and 16.8% of all randomised subjects had Stage pTX, pT0, pTIS, pT1, pT2, pT3, and pT4A disease (tumour stage) at the time of resection, respectively.

Baseline demographic and disease characteristics in randomised subjects with tumour cell PD-L1 expression level ≥ 1% were consistent with that in all randomised subjects. Among subjects with tumour cell PD-L1 expression level ≥ 1%, demographic and disease characteristics were balanced between the two treatment arms (**Table 14**).

Table 14: ***Key Baseline Demographic and Disease Characteristics in All Randomised Subjects and Randomised Subjects with Tumour Cell PD-L1 Expression ≥ 1%***

	All Randomised			**All Randomised PD-L1 ≥ 1%**		
	Placebo (N = 356)	**Nivolumab (N = 353)**	**Total (N = 709)**	**Placebo (N = 142)**	**Nivolumab (N = 140)**	**Total (N = 282)**
Median age (range)	67.0 (42, 88)	66.0 (30, 92)	67.0 (30, 92)	66.0 (45, 84)	66.0 (34, 92)	66.0 (34, 92)
Male [Sex], n (%)	275 (77.2)	265 (75.1)	540 (76.2)	112 (78.9)	101 (72.1)	213 (75.5)
White [Race], n (%)	272 (76.4)	264 (74.8)	536 (75.6)	109 (76.8)	104 (74.3)	213 (75.5)
Country by Geographic Region, n (%)						
United States	53 (14.9)	49 (13.9)	102 (14.4)	24 (16.9)	17 (12.1)	41 (14.5)
Europe	171 (48.0)	170 (48.2)	341 (48.1)	70 (49.3)	73 (52.1)	143 (50.7)
Asia	74 (20.8)	80 (22.7)	154 (21.7)	28 (19.7)	33 (23.6)	61 (21.6)
ROW	58 (16.3)	54 (15.3)	112 (15.8)	20 (14.1)	17 (12.1)	37 (13.1)
Baseline ECOG PS						
0	221 (62.1)	224 (63.5)	445 (62.8)	85 (59.9)	86 (61.4)	171 (60.6)

	All Randomised			All Randomised PD-L1 ≥ 1%		
	Placebo (N = 356)	**Nivolumab (N = 353)**	**Total (N = 709)**	**Placebo (N = 142)**	**Nivolumab (N = 140)**	**Total (N = 282)**
1	125 (35.1)	122 (34.6)	247 (34.8)	53 (37.3)	51 (36.4)	104 (36.9)
2	9 (2.5)	7 (2.0)	16 (2.3)	4 (2.8)	3 (2.1)	7 (2.5)
Tumour type						
Urinary bladder	281 (78.9)	279 (79.0)	560 (79.0)	117 (82.4)	113 (80.7)	230 (81.6)
Renal Pelvis	52 (14.6)	44 (12.5)	96 (13.5)	14 (9.9)	19 (13.6)	33 (11.7)
Ureter	23 (6.5)	30 (8.5)	53 (7.5)	11 (7.7)	8 (5.7)	19 (6.7)
Receipt of neo-adjuvant cisplatin based chemotherapy (based on clinical database)						
Yes	155 (43.5)	153 (43.3)	308 (43.4)	61 (43.0)	57 (40.7)	118 (41.8)
No	201 (56.5)	200 (56.7)	401 (56.6)	81 (57.0)	83 (59.3)	164 (58.2)
Pathologic stage at resection in patients with neo-adjuvant cisplatin-based chemotherapy						
Tumour Stage						
PTX	0	3 (0.8)	3 (0.4)	0	2 (1.4)	2 (0.7)
PT0	5 (1.4)	5 (1.4)	10 (1.4)	2 (1.4)	3 (2.1)	5 (1.8)
PTIS	3 (0.8)	4 (1.1)	7 (1.0)	0	0	0
PT1	3 (0.8)	3 (0.8)	6 (0.8)	0	2 (1.4)	2 (0.7)
PT2	52 (14.6)	46 (13.0)	98 (13.8)	20 (14.1)	16 (11.4)	36 (12.8)
PT3	68 (19.1)	68 (19.3)	136 (19.2)	29 (20.4)	26 (18.6)	55 (19.5)
PT4A	23 (6.5)	24 (6.8)	47 (6.6)	9 (6.3)	8 (5.7)	17 (6.0)
Nodes stage with node density						
N0/x with < 10 nodes removed	26 (7.3)	27 (7.6)	53 (7.5)	11 (7.7)	10 (7.1)	21 (7.4)
N0 with ≥ 10 nodes removed	42 (11.8)	41 (11.6)	83 (11.7)	19 (13.4)	20 (14.3)	39 (13.8)
N1	34 (9.6)	34 (9.6)	68 (9.6)	14 (9.9)	13 (9.3)	27 (9.6)
N2	39 (11.0)	43 (12.2)	82 (11.6)	14 (9.9)	13 (9.3)	27 (9.6)
N3	13 (3.7)	8 (2.3)	21 (3.0)	3 (2.1)	1 (0.7)	4 (1.4)
Pathologic stage at resection in patients without neo-adjuvant cisplatin-based chemotherapy						
Tumour Stage						
PTX	0	2 (0.6)	2 (0.3)	0	2 (1.4)	2 (0.7)
PT0	2 (0.6)	0	2 (0.3)	1 (0.7)	0	1 (0.4)
PTIS	0	0	0	0	0	0
PT1	11 (3.1)	10 (2.8)	21 (3.0)	2 (1.4)	2 (1.4)	4 (1.4)
PT2	13 (3.7)	16 (4.5)	29 (4.1)	6 (4.2)	3 (2.1)	9 (3.2)
PT3	136 (38.2)	138 (39.1)	274 (38.6)	54 (38.0)	61 (43.6)	115 (40.8)
PT4A	39 (11.0)	33 (9.3)	72 (10.2)	18 (12.7)	15 (10.7)	33 (11.7)
Nodes stage with node density						
N0/x with < 10 nodes removed	73 (20.5)	67 (19.0)	140 (19.7)	27 (19.0)	28 (20.0)	55 (19.5)
N0 with ≥ 10 nodes removed	46 (12.9)	50 (14.2)	96 (13.5)	19 (13.4)	22 (15.7)	41 (14.5)
N1	38 (10.7)	37 (10.5)	75 (10.6)	19 (13.4)	16 (11.4)	35 (12.4)
N2	37 (10.4)	41 (11.6)	78 (11.0)	12 (8.5)	15 (10.7)	27 (9.6)
N3	7 (2.0)	4 (1.1)	11 (1.6)	4 (2.8)	2 (1.4)	6 (2.1)

Prior cancer therapy summary is provided in ***Table 15***.

Table 15 *Prior Cancer Therapy Summary - All Randomised Subjects*

	Number of Subjects (%)		
	Placebo N = 356	Nivolumab N = 353	Total N = 709
SUBJECTS WITH PRIOR SYSTEMIC THERAPY			
TYPE OF PRIOR SYSTEMIC THERAPY RECEIVED (A)			
ANTI-PD1	1 (0.3)	1 (0.3)	2 (0.3)
PLATINUM-BASED CHEMOTHERAPY	158 (44.4)	156 (44.2)	314 (44.3)
UNASSIGNED (B)	149 (41.9)	153 (43.3)	302 (42.6)
PRIOR SYSTEMIC THERAPY REGIMEN SETTING			
NEO-ADJUVANT THERAPY	159 (44.7)	160 (45.3)	319 (45.0)
NUMBER OF PRIOR SYSTEMIC REGIMEN IN NEO-ADJUVANT SETTING			
0	197 (55.3)	193 (54.7)	390 (55.0)
1	159 (44.7)	160 (45.3)	319 (45.0)
TIME FROM COMPLETION OF PRIOR ADJUVANT/NEOADJUVANT THERAPY TO RANDOMIZATION (C)			
0-30 DAYS	0	1 (0.6)	1 (0.3)
>30-60 DAYS	1 (0.6)	0	1 (0.3)
>60-90 DAYS	20 (12.6)	18 (11.3)	38 (11.9)
>90-120 DAYS	54 (34.0)	51 (31.9)	105 (32.9)
>120 DAYS	83 (52.2)	90 (56.3)	173 (54.2)
NOT REPORTED	1 (0.6)	0	1 (0.3)
PRIOR CISPLATIN THERAPY			
YES	155 (43.5)	153 (43.3)	308 (43.4)
NO	201 (56.5)	200 (56.7)	401 (56.6)
REASON NOT TREATED WITH CISPLATIN:			
UNWILLING TO TAKE	108 (30.3)	123 (34.8)	231 (32.6)
INELIGIBLE, RENAL FUNCTION	53 (14.9)	53 (15.0)	106 (15.0)
INELIGIBLE, NEUROPATHY	1 (0.3)	2 (0.6)	3 (0.4)
INELIGIBLE, AUDIOMETRIC LOSS	15 (4.2)	4 (1.1)	19 (2.7)
INELIGIBLE, PERFORMANCE STATUS	12 (3.4)	7 (2.0)	19 (2.7)
INELIGIBLE, HEART FUNCTION	4 (1.1)	4 (1.1)	8 (1.1)
OTHER	6 (1.7)	6 (1.7)	12 (1.7)
NOT REPORTED	2 (0.6)	1 (0.3)	3 (0.4)
SURGERY FOR INVASIVE UROTHELIAL CARCINOMA			
YES	356 (100.0)	353 (100.0)	709 (100.0)
NO	0	0	0
TYPE OF SURGERY (A)			
RADICAL CYSTECTOMY	93 (26.1)	88 (24.9)	181 (25.5)
RADICAL CYSTOPROSTATECTOMY	186 (52.2)	192 (54.4)	378 (53.3)
RADICAL NEPHROURETERECTOMY	73 (20.5)	71 (20.1)	144 (20.3)
RADICAL URETERECTOMY	2 (0.6)	2 (0.6)	4 (0.6)
OTHER	3 (0.8)	1 (0.3)	4 (0.6)
TIME FROM IUC SURGERY TO RANDOMIZATION			
0-30 DAYS	3 (0.8)	2 (0.6)	5 (0.7)
>30-60 DAYS	70 (19.7)	79 (22.4)	149 (21.0)
>60-90 DAYS	177 (49.7)	165 (46.7)	342 (48.2)
>90-120 DAYS	95 (26.7)	103 (29.2)	198 (27.9)
>120 DAYS	11 (3.1)	4 (1.1)	15 (2.1)
PRIOR RADIOTHERAPY			
YES	11 (3.1)	8 (2.3)	19 (2.7)
NO	345 (96.9)	345 (97.7)	690 (97.3)
TIME FROM COMPLETION OF MOST RECENT RADIOTHERAPY TO RANDOMIZATION			
0-30 DAYS	0	0	0
>30-60 DAYS	0	0	0
>60-90 DAYS	0	0	0
>90-120 DAYS	0	0	0
>120 DAYS	7 (2.0)	3 (0.8)	10 (1.4)

NOT REPORTED	4 (1.1)	5 (1.4)	9 (1.3)
PRIOR LOCAL/INTRAVESICAL ANTI-CANCER AGENT RECEIVED (A)			
BCG	6 (1.7)	7 (2.0)	13 (1.8)
MITOMYCIN	1 (0.3)	1 (0.3)	2 (0.3)
OTHER INTRAVESICAL CHEMOTHERAPY	2 (0.6)	5 (1.4)	7 (1.0)

(A) Some subjects may have been treated with more than 1 type of therapy.
(B) The unassigned category are regarding subjects who received gemcitabine-cisplatin as neo-adjuvant therapy.
(C) Percentages are based on subjects with neoadjuvant therapy.
Abbreviations: BCG = bacillus calmette-guerin, PD-1 = programmed death receptor 1

Numbers analysed

The all-randomised and all-randomised with tumour cell PD-L1 expression level ≥ 1% populations were the primary populations used for efficacy analyses. Unless otherwise specified, efficacy analyses were performed based on the treatment arm "as randomised" (ie, using the intent-to-treat principle). Unless otherwise specified, the safety analyses were analyzed in all treated subjects and in all treated subjects with tumour cell PD-L1 expression ≥1% populations (refer also to ***Figure 9***).

Outcomes and estimation

Efficacy data presented are based on the clinical DBL on 27-Aug-2020 for the planned IA of DFS as specified in the protocol.

At the time of the DBL, the median follow-up time was 20.90 months and 19.48 months for all randomised subjects in the nivolumab and placebo arms, respectively. In all randomised subjects with tumour cell PD L1 expression ≥ 1%, the median follow-up was 22.11 months for the nivolumab arm and 18.69 months for the placebo arm. The minimum follow up time was 5.9 months for all randomised subjects and 6.3 months for all randomised subjects with tumour cell PD-L1 expression ≥ 1%.

The efficacy data was re-analysed and updated data were presented in a CSR Erratum based on a 13-Apr-2021 DBL with data cut on the 27-Aug-2020 (reference is made below to "*Updated with Reanalysis")*. At the time of the 27-Aug-2020 DBL, the actual number of DFS events among all randomised subjects was 374 (91.2% of total DFS events). An IA for DFS was performed and the boundary for statistical significance for DFS (observed p-value = 0.0008) was crossed (adjusted alpha = 0.01784). The actual number of DFS events among all randomised subjects with tumour cell PD-L1 expression level ≥ 1% was 136 (84.0% of total DFS events). An IA for DFS was performed and the boundary for statistical significance for DFS (observed p-value = 0.0005) was crossed (adjusted alpha = 0.01282). **See *Table 16*.**

An Updated analysis with DBL 19-May-2021 with data cut on 01-Feb-2021 were presented during the procedure and is included in this section. This analysis is referred to as Updated analysis.

Table 16: Summary of Key Efficacy Results

	All Randomised		All Randomised PD-L1 ≥ 1%	
Efficacy Parameter	**Placebo (N = 356)**	**Nivolumab (N = 353)**	**Placebo (N = 142)**	**Nivolumab (N = 140)**
PRIMARY ENDPOINTS				
DFS Primary Definition				
Events, n (%)	204 (57.3)	170 (48.2)	81 (57.0)	55 (39.3)
Median DFS (95% CI), mo.[a]	10.84 (8.25, 13.86)	20.76 (16.49, 27.63)	8.41 (5.59, 21.19)	N.A. (21.19, N.A.)
HR[b] (% CI)	0.70 (98.22% CI: 0.55, 0.90)		0.55 (98.72% CI: 0.35, 0.85)	
Stratified log-rank p-value[c]	0.0008[d]		0.0005[e]	
Rate at 6 months (95% CI), %[a]	60.3 (54.9, 65.3)	74.9 (69.9, 79.2)	55.7 (46.8, 63.6)	74.5 (66.2, 81.1)
DFS Secondary Definition				
Events, n (%)	205 (57.6)	170 (48.2)	81 (57.0)	55 (39.3)
Median DFS (95% CI), mo.[a]	10.84 (8.25, 13.86)	20.80 (17.05, 27.63)	8.41 (5.59, 21.19)	N.A. (22.01, N.A.)
HR[b] (% CI)	0.70 (98.22% CI: 0.55, 0.90)		0.54 (98.72% CI: 0.35, 0.84)	
Stratified log-rank p-value[c]	0.0006[d]		0.0005[e]	
Rate at 6 months (95% CI), %[a]	60.3 (54.9, 65.3)	75.0 (70.0, 79.2)	55.7 (46.8, 63.6)	74.6 (66.4, 81.2)
SECONDARY ENDPOINTS				
NUTRFS				
Events, n (%)	190 (53.4)	162 (45.9)	78 (54.9)	54 (38.6)
Median NUTRFS (95% CI), mo.[a]	13.70 (8.41, 20.34)	22.93 (19.15, 33.41)	10.84 (5.65, 22.14)	N.A. (24.57, N.A.)
HR (95% CI)[b]	0.72 (0.59, 0.89)		0.55 (0.39, 0.79)	
Rate at 6 months (95% CI), %[a]	62.7 (57.3, 67.6)	77.0 (72.1, 81.1)	56.7 (47.8, 64.6)	75.3 (67.0, 81.7)

Table 16: Summary of Key Efficacy Results

Efficacy Parameter	All Randomised		All Randomised PD-L1 ≥ 1%	
	Placebo (N = 356)	Nivolumab (N = 353)	Placebo (N = 142)	Nivolumab (N = 140)
EXPLORATORY ENDPOINTS				
DMFS				
Events, n (%)	152 (42.7)	132 (37.4)	61 (43.0)	47 (33.6)
Median DMFS (95% CI), mo.[a]	29.54 (16.69, N.A.)	40.54 (22.37, N.A.)	21.19 (10.55, N.A.)	N.A. (25.79, N.A.)
HR (95% CI)[b]	0.75 (0.59, 0.94)		0.61 (0.42, 0.90)	
Rate at 6 months (95% CI), %[a]	69.8 (64.5, 74.4)	82.5 (78.0, 86.2)	65.7 (56.8, 73.3)	78.7 (70.7, 84.8)
TTR				
Events, n (%)	193 (54.2)	153 (43.3)	75 (52.8)	47 (33.6)
Median TTR (95% CI), mo.[f]	11.37 (20.04, 8.38)	27.04 (N.A., 19.45)	11.37 (29.57, 6.54)	N.A. (N.A., 29.67)
HR[g] (95% CI)	0.67 (0.54, 0.83)		0.51 (0.35, 0.73)	
Recurrence rate at 6 months (95% CI), %[f]	37.0 (31.9, 42.2)	23.0 (18.7, 27.6)	41.4 (32.9, 49.6)	23.3 (16.5, 30.7)
LRDFS				
Events, n (%)	98 (27.5)	76 (21.5)	40 (28.2)	19 (13.6)
Median LRDFS (95% CI), mo.[f]	N.A.	N.A.	N.A.	N.A.
HR (95% CI)[g]	0.68 (0.50, 0.91)		0.41 (0.24, 0.70)	
LRD rate at 6 months (95% CI), %[f]	18.8 (14.8, 23.1)	11.2 (8.1, 14.8)	21.1 (14.6, 28.4)	7.5 (3.8, 12.8)
LRC				
Events, n (%)	88 (24.7)	63 (17.8)	35 (24.6)	14 (10.0)
Median LRC (95% CI), mo.[f]	N.A.	N.A.	N.A.	N.A.
HR (95% CI)[g]	0.61 (0.44, 0.85)		0.33 (0.18, 0.62)	
Locoregional recurrence rate at 6 months (95% CI), %[f]	17.0 (13.2, 21.2)	9.7 (6.9, 13.2)	18.8 (12.7, 25.9)	5.3 (2.3, 10.0)
PFS2				
Events, n (%)	125 (35.1)	108 (30.6)	54 (38.0)	36 (25.7)
Median PFS2 (95% CI), mo.[a]	40.67 (29.57, N.A.)	44.02 (37.98, N.A.)	39.43 (25.20, N.A.)	N.A. (37.13, N.A.)
HR (95% CI)[b]	0.79 (0.61, 1.02)		0.60 (0.39, 0.91)	
Rate at 6 months (95% CI), %[a]	88.7 (84.8, 91.6)	95.1 (92.2, 96.9)	86.5 (79.4, 91.3)	94.1 (88.5, 97.0)

As of the 27-Aug-2020 DBL, the median follow-up time was 20.90 months and 19.48 months for all randomised subjects in the nivolumab and placebo arms, respectively. In all randomised subjects with tumour cell PD-L1 expression ≥ 1%, the median follow-up was 22.11 months for the nivolumab arm and 18.69 months for the placebo arm.

[a] Based on Kaplan-Meier Estimates

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

[c] 2 sided p values from stratified regular log-rank test

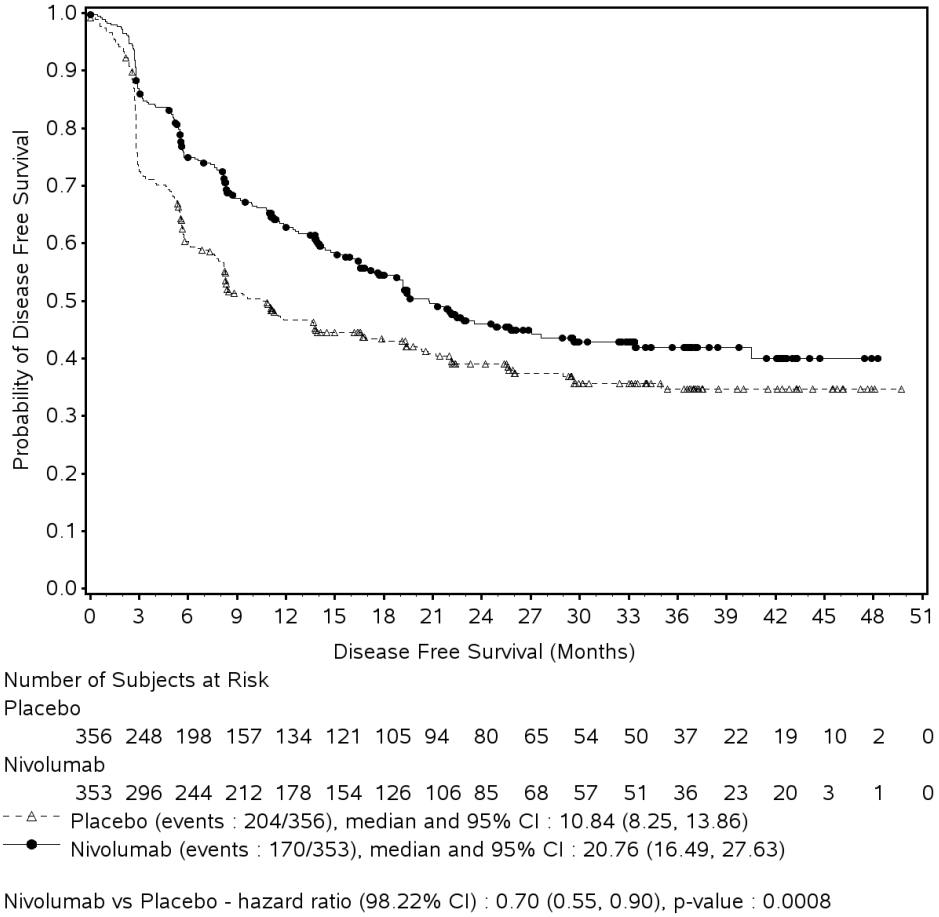
[d] Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, PD-L1 status (>=1% versus <1%/indeterminate) as entered in the IRT
[e] Log-rank test stratified by prior neo-adjuvant cisplatin, pathological nodal status, as entered in the IRT
[f] Based on Cumulative Incidence Estimates
[g] Stratified Cause-specific hazard model
Note: The primary definition of DFS accounted for subsequent anticancer therapy and new non-urothelial carcinoma primary cancer. The secondary definition of DFS accounted for disease assessments occurring on or after initiation of subsequent anticancer therapy

Primary endpoint

Disease-free Survival in <u>All Randomised Subjects</u> - Primary Definition

Nivolumab treatment resulted in a statistically significant benefit in DFS compared to placebo in all randomised subjects.

Figure 10*: Kaplan-Meier Plot of Disease-free Survival (Primary Definition) - All Randomised Subjects (Updated with Reanalysis)*



The type of recurrences are described in ***Table 17***.

At the time of the DBL, 183 (51.8%) subjects in the nivolumab arm and 152 (42.7%) subjects in the placebo arm were censored. Among those censored, most were in follow-up (131 [37.1%] in the nivolumab arm and 109 [30.6%] in the placebo arm).

Table 17 *Type of recurrence and reason for censoring - All randomised patients*

Protocol: CA209274

Reason for Censoring, Disease Free Survival (Primary definition)
All Randomized Subjects

	Placebo N = 356	Nivolumab N = 353
NUMBER OF EVENTS (%)	204 (57.3)	170 (48.2)
TYPE OF EVENTS (%)		
DISEASE AT BASELINE	3 (0.8)	1 (0.3)
RECURRENCE	191 (53.7)	155 (43.9)
DISTANT RECURRENCE	127 (35.7)	108 (30.6)
LOCAL NON-UROTHELIAL TRACT	44 (12.4)	34 (9.6)
LOCAL UROTHELIAL TRACT INVASIVE	7 (2.0)	1 (0.3)
LOCAL UROTHELIAL TRACT NON-INVASIVE	13 (3.7)	12 (3.4)
DEATH	10 (2.8)	14 (4.0)
NUMBER OF SUBJECTS CENSORED (%)	152 (42.7)	183 (51.8)
CENSORED ON DATE OF RANDOMIZATION	13 (3.7)	11 (3.1)
NO BASELINE DISEASE ASSESSMENT (1)	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY DISEASE ASSESSMENT AND NO DEATH (1)	13 (3.7)	11 (3.1)
NEVER TREATED	6 (1.7)	2 (0.6)
NEW NON-UROTHELIAL CARCINOMA PRIMARY CANCER	0	1 (0.3)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY	0	1 (0.3)
OFF STUDY	6 (1.7)	7 (2.0)
OTHER	1 (0.3)	0
CENSORED ON DATE OF LAST DISEASE ASSESSMENT ON-STUDY	139 (39.0)	172 (48.7)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (2)	1 (0.3)	1 (0.3)
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	1 (0.3)	1 (0.3)
RECEIVED SUBSEQUENT RADIOTHERAPY	0	0
RECEIVED SUBSEQUENT SURGERY	0	0
NEW NON-UROTHELIAL CARCINOMA PRIMARY CANCER (2)	3 (0.8)	6 (1.7)
STILL ON-TREATMENT	19 (5.3)	21 (5.9)
IN FOLLOW-UP	109 (30.6)	131 (37.1)
OFF STUDY	7 (2.0)	13 (3.7)
LOST TO FOLLOW-UP	4 (1.1)	2 (0.6)
SUBJECT WITHDREW CONSENT	3 (0.8)	9 (2.5)
OTHER	0	2 (0.6)

Table 18 **:** Disease-Free Survival (Primary Definition) Sensitivity Analyses - All *Randomised Subjects (Updated with Reanalysis)*

SENSITIVITY ANALYSIS	Placebo EVENTS/SUBJECTS	Nivolumab EVENTS/SUBJECTS	HR (1) 95% CI	p-value (2)
UNSTRATIFIED ANALYSIS	204 / 356	170 / 353	0.71 (0.58, 0.87)	0.0011
STRATIFIED WEIGHTED ANALYSIS (A)				0.2605
< 6 MONTHS	135 / 158	85 / 109	0.55 (0.42, 0.73)	
>= 6 MONTHS	69 / 198	85 / 244	0.98 (0.71, 1.36)	
ANALYSIS USING STRATIFICATION FACTORS AS DETERMINED AT BASELINE (CRF SOURCE) (B)	204 / 356	170 / 353	0.71 (0.58, 0.88)	0.0013

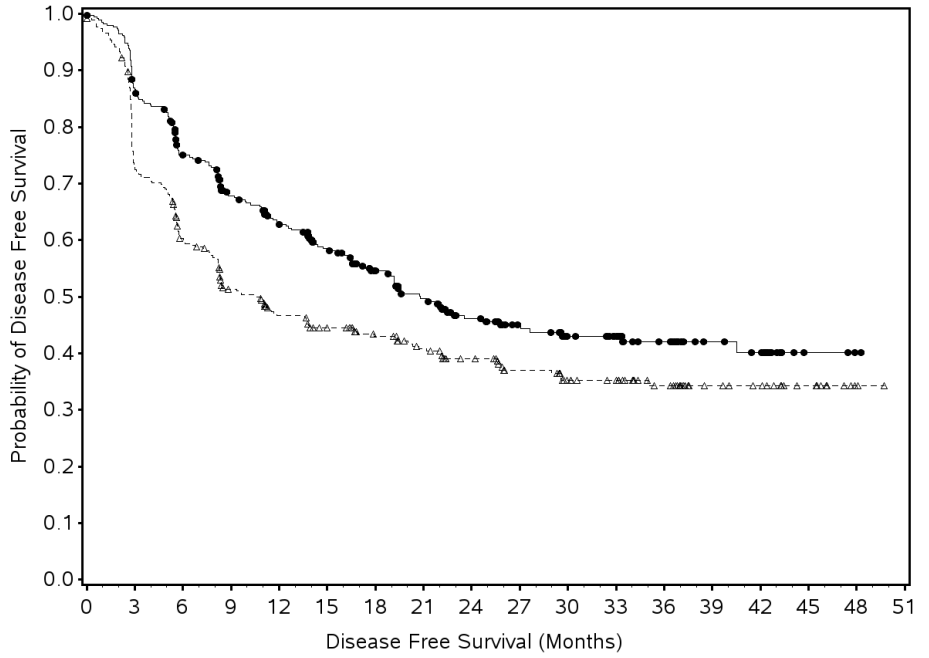
(1) Stratified/unstratified Cox proportional hazards model.
(2) P-value from stratified Log-rank test. For sensitivity analyses, p-values are for descriptive purpose only
(A) Weighted log-rank test is using G (rho = 0, gamma = 1) weights, in the terminology of Fleming and Harrington.
DFS hazard ratios from the periods before and following 6 months were derived using a stratified time-dependent Cox model.
(B) Stratified by prior neo-adjuvant cisplatin, pathological nodal status, PD-L1 status (>=1% versus <1%/indeterminate) as determined at baseline (CRF / clinical database source).
Abbreviations: CI = confidence interval, CRF = case report form, DFS = disease-free survival, HR = hazard ratio

The stratified weighted analysis was the Fleming-Harrington G(rho=0, gamma=1) log rank-test which strongly downweighs early events and upweights later events.

- **Disease-free Survival in All Randomised Subjects - Secondary Definition**

DFS results using the secondary DFS definition (accounts for disease assessments occurring on or after initiation of subsequent anticancer therapy), were consistent with the analysis for the primary DFS definition (HR = 0.70 [98.22% CI: 0.55, 0.90]; p = 0.0006) (***Figure 11***).

Figure 11: *Kaplan-Meier Plot of Disease-Free Survival (Secondary Definition) – All Randomised Subjects (Updated with Reanalysis)*



Number of Subjects at Risk

Placebo	356	248	198	157	134	122	106	95	81	65	54	50	37	22	19	10	2	0
Nivolumab	353	297	244	212	179	155	127	107	86	68	57	51	36	23	20	3	1	0

Placebo (events : 205/356), median and 95% CI : 10.84 (8.25, 13.86)

Nivolumab (events : 170/353), median and 95% CI : 20.80 (17.05, 27.63)

Nivolumab vs Placebo - hazard ratio (98.22% CI) : 0.70 (0.55, 0.90), p-value : 0.0006

DFS by Subgroups

In a subgroup analysis for all randomised subjects, DFS HRs for most subgroups favoured (HR < 1) nivolumab vs placebo **(Figure 12**). The boundary of the treatment effect of nivolumab compared with placebo in the renal pelvis and ureter location (upper urothelial tract) subcategories of initial tumour origin crossed the HR of 1:

- Use of prior neoadjuvant cisplatin therapy (based on clinical database):

Yes: HR = 0.52 (95% CI:0.38, 0.71)

No: HR = 0.92 (95% CI: 0.69, 1.21)

- Tumour cell PD-L1 status (based on clinical database):

≥ 1%: HR = 0.56 (95% CI: 0.40, 0.80)

< 1%: HR = 0.82 (95% CI: 0.63, 1.06)

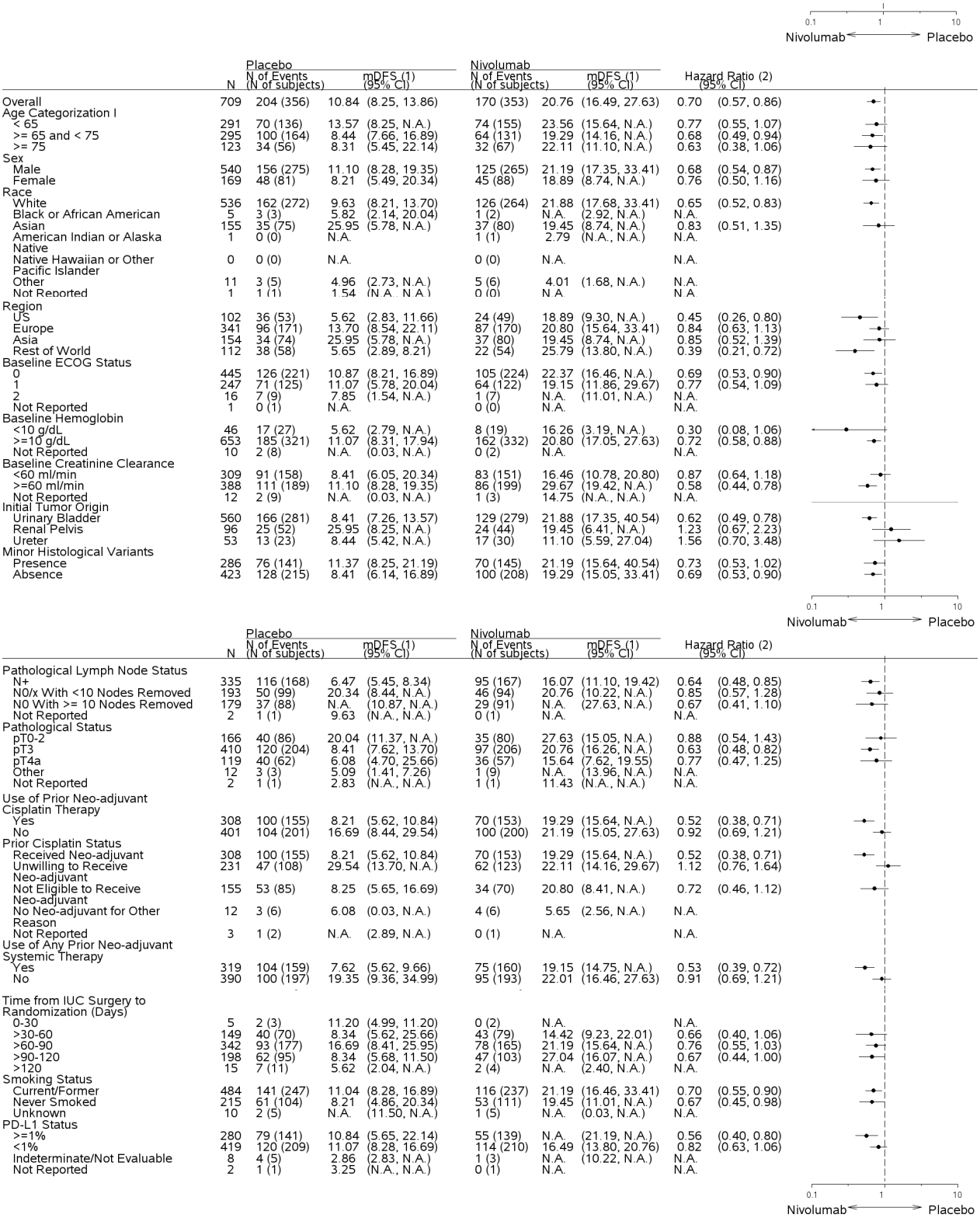
- Initial tumour origin:

Urinary bladder: HR = 0.62 (95% CI: 0.49, 0.78)

Renal pelvis: HR = 1.23 (95% CI: 0.67, 2.23)

Ureter: HR = 1.56 (95% CI: 0.70, 3.48)

Figure 12: Forest Plot of Treatment Effect on Disease-free Survival (Primary Definition) in Pre-Defined Subsets - All Randomised Subjects (Updated with Reanalysis)



	N	Placebo N of Events (N of subjects)	mDFS (1) (95% CI)		Nivolumab N of Events (N of subjects)	mDFS (1) (95% CI)		Hazard Ratio (2) (95% CI)	
Overall	709	204 (356)	10.84	(8.25, 13.86)	170 (353)	20.76	(16.49, 27.63)	0.70	(0.57, 0.86)
Age Categorization I									
< 65	291	70 (136)	13.57	(8.25, N.A.)	74 (155)	23.56	(15.64, N.A.)	0.77	(0.55, 1.07)
>= 65 and < 75	295	100 (164)	8.44	(7.66, 16.89)	64 (131)	19.29	(14.16, N.A.)	0.68	(0.49, 0.94)
>= 75	123	34 (56)	8.31	(5.45, 22.14)	32 (67)	22.11	(11.10, N.A.)	0.63	(0.38, 1.06)
Sex									
Male	540	156 (275)	11.10	(8.28, 19.35)	125 (265)	21.19	(17.35, 33.41)	0.68	(0.54, 0.87)
Female	169	48 (81)	8.21	(5.49, 20.34)	45 (88)	18.89	(8.74, N.A.)	0.76	(0.50, 1.16)
Race									
White	536	162 (272)	9.63	(8.21, 13.70)	126 (264)	21.88	(17.68, 33.41)	0.65	(0.52, 0.83)
Black or African American	5	3 (3)	5.82	(2.14, 20.04)	1 (2)	N.A.	(2.92, N.A.)	N.A.	
Asian	155	35 (75)	25.95	(5.78, N.A.)	37 (80)	19.45	(8.74, N.A.)	0.83	(0.51, 1.35)
American Indian or Alaska Native	1	0 (0)	N.A.		1 (1)	2.79	(N.A., N.A.)	N.A.	
Native Hawaiian or Other Pacific Islander	0	0 (0)	N.A.		0 (0)	N.A.		N.A.	
Other	11	3 (5)	4.96	(2.73, N.A.)	5 (6)	4.01	(1.68, N.A.)	N.A.	
Not Reported	1	1 (1)	1.54	(N.A., N.A.)	0 (0)	N.A.		N.A.	
Region									
US	102	36 (53)	5.62	(2.83, 11.66)	24 (49)	18.89	(9.30, N.A.)	0.45	(0.26, 0.80)
Europe	341	96 (171)	13.70	(8.54, 22.11)	87 (170)	20.80	(15.64, 33.41)	0.84	(0.63, 1.13)
Asia	154	34 (74)	25.95	(5.78, N.A.)	37 (80)	19.45	(8.74, N.A.)	0.85	(0.52, 1.39)
Rest of World	112	38 (58)	5.65	(2.89, 8.21)	22 (54)	25.79	(13.80, N.A.)	0.39	(0.21, 0.72)
Baseline ECOG Status									
0	445	126 (221)	10.87	(8.21, 16.89)	105 (224)	22.37	(16.46, N.A.)	0.69	(0.53, 0.90)
1	247	71 (125)	11.07	(5.78, 20.04)	64 (122)	19.15	(11.86, 29.67)	0.77	(0.54, 1.09)
2	16	7 (9)	7.85	(1.54, N.A.)	1 (7)	N.A.	(11.01, N.A.)	N.A.	
Not Reported	1	0 (1)	N.A.		0 (0)	N.A.		N.A.	
Baseline Hemoglobin									
<10 g/dL	46	17 (27)	5.62	(2.79, N.A.)	8 (19)	16.26	(3.19, N.A.)	0.30	(0.08, 1.06)
>=10 g/dL	653	185 (321)	11.07	(8.31, 17.94)	162 (332)	20.80	(17.05, 27.63)	0.72	(0.58, 0.88)
Not Reported	10	2 (8)	N.A.	(0.03, N.A.)	0 (2)	N.A.		N.A.	
Baseline Creatinine Clearance									
<60 ml/min	309	91 (158)	8.41	(6.05, 20.34)	83 (151)	16.46	(10.78, 20.80)	0.87	(0.64, 1.18)
>=60 ml/min	388	111 (189)	11.10	(8.28, 19.35)	86 (199)	29.67	(19.42, N.A.)	0.58	(0.44, 0.78)
Not Reported	12	2 (9)	N.A.	(0.03, N.A.)	1 (3)	14.75	(N.A., N.A.)	N.A.	
Initial Tumor Origin									
Urinary Bladder	560	166 (281)	8.41	(7.26, 13.57)	129 (279)	21.88	(17.35, 40.54)	0.62	(0.49, 0.78)
Renal Pelvis	96	25 (52)	25.95	(8.25, N.A.)	24 (44)	19.45	(6.41, N.A.)	1.23	(0.67, 2.23)
Ureter	53	13 (23)	8.44	(5.42, N.A.)	17 (30)	11.10	(5.59, 27.04)	1.56	(0.70, 3.48)
Minor Histological Variants									
Presence	286	76 (141)	11.37	(8.25, 21.19)	70 (145)	21.19	(15.64, 40.54)	0.73	(0.53, 1.02)
Absence	423	128 (215)	8.41	(6.14, 16.89)	100 (208)	19.29	(15.05, 33.41)	0.69	(0.53, 0.90)

0.1
1
10
Nivolumab
Placebo

	N	Placebo N of Events (N of subjects)	mDFS (1) (95% CI)		Nivolumab N of Events (N of subjects)	mDFS (1) (95% CI)		Hazard Ratio (2) (95% CI)	
Pathological Lymph Node Status									
N+	335	116 (168)	6.47	(5.45, 8.34)	95 (167)	16.07	(11.10, 19.42)	0.64	(0.48, 0.85)
N0/x With <10 Nodes Removed	193	50 (99)	20.34	(8.44, N.A.)	46 (94)	20.76	(10.22, N.A.)	0.85	(0.57, 1.28)
N0 With >= 10 Nodes Removed	179	37 (88)	N.A.	(10.87, N.A.)	29 (91)	N.A.	(27.63, N.A.)	0.67	(0.41, 1.10)
Not Reported	2	1 (1)	9.63	(N.A., N.A.)	0 (1)	N.A.		N.A.	
Pathological Status									
pT0-2	166	40 (86)	20.04	(11.37, N.A.)	35 (80)	27.63	(15.05, N.A.)	0.88	(0.54, 1.43)
pT3	410	120 (204)	8.41	(7.62, 13.70)	97 (206)	20.76	(16.26, N.A.)	0.63	(0.48, 0.82)
pT4a	119	40 (62)	6.08	(4.70, 25.66)	36 (57)	15.64	(7.62, 19.55)	0.77	(0.47, 1.25)
Other	12	3 (3)	5.09	(1.41, 7.26)	1 (9)	N.A.	(13.96, N.A.)	N.A.	
Not Reported	2	1 (1)	2.83	(N.A., N.A.)	1 (1)	11.43	(N.A., N.A.)	N.A.	
Use of Prior Neo-adjuvant Cisplatin Therapy									
Yes	308	100 (155)	8.21	(5.62, 10.84)	70 (153)	19.29	(15.64, N.A.)	0.52	(0.38, 0.71)
No	401	104 (201)	16.69	(8.44, 29.54)	100 (200)	21.19	(15.05, 27.63)	0.92	(0.69, 1.21)
Prior Cisplatin Status									
Received Neo-adjuvant	308	100 (155)	8.21	(5.62, 10.84)	70 (153)	19.29	(15.64, N.A.)	0.52	(0.38, 0.71)
Unwilling to Receive Neo-adjuvant	231	47 (108)	29.54	(13.70, N.A.)	62 (123)	22.11	(14.16, 29.67)	1.12	(0.76, 1.64)
Not Eligible to Receive Neo-adjuvant	155	53 (85)	8.25	(5.65, 16.69)	34 (70)	20.80	(8.41, N.A.)	0.72	(0.46, 1.12)
No Neo-adjuvant for Other Reason	12	3 (6)	6.08	(0.03, N.A.)	4 (6)	5.65	(2.56, N.A.)	N.A.	
Not Reported	3	1 (2)	N.A.	(2.89, N.A.)	0 (1)	N.A.		N.A.	
Use of Any Prior Neo-adjuvant Systemic Therapy									
Yes	319	104 (159)	7.62	(5.62, 9.66)	75 (160)	19.15	(14.75, N.A.)	0.53	(0.39, 0.72)
No	390	100 (197)	19.35	(9.36, 34.99)	95 (193)	22.01	(16.46, 27.63)	0.91	(0.69, 1.21)
Time from IUC Surgery to Randomization (Days)									
0-30	5	2 (3)	11.20	(4.99, 11.20)	0 (2)	N.A.		N.A.	
>30-60	149	40 (70)	8.34	(5.62, 25.66)	43 (79)	14.42	(9.23, 22.01)	0.66	(0.40, 1.06)
>60-90	342	93 (177)	16.69	(8.41, 25.95)	78 (165)	21.19	(15.64, N.A.)	0.76	(0.55, 1.03)
>90-120	198	62 (95)	8.34	(5.68, 11.50)	47 (103)	27.04	(16.07, N.A.)	0.67	(0.44, 1.00)
>120	15	7 (11)	5.62	(2.04, N.A.)	2 (4)	N.A.	(2.40, N.A.)	N.A.	
Smoking Status									
Current/Former	484	141 (247)	11.04	(8.28, 16.89)	116 (237)	21.19	(16.46, 33.41)	0.70	(0.55, 0.90)
Never Smoked	215	61 (104)	8.21	(4.86, 20.34)	53 (111)	19.45	(11.01, N.A.)	0.67	(0.45, 0.98)
Unknown	10	2 (5)	N.A.	(11.50, N.A.)	1 (5)	N.A.	(0.03, N.A.)	N.A.	
PD-L1 Status									
>=1%	280	79 (141)	10.84	(5.65, 22.14)	55 (139)	N.A.	(21.19, N.A.)	0.56	(0.40, 0.80)
<1%	419	120 (209)	11.07	(8.28, 16.69)	114 (210)	16.49	(13.80, 20.76)	0.82	(0.63, 1.06)
Indeterminate/Not Evaluable	8	4 (5)	2.86	(2.83, N.A.)	1 (3)	N.A.	(10.22, N.A.)	N.A.	
Not Reported	2	1 (1)	3.25	(N.A., N.A.)	0 (1)	N.A.		N.A.	

0.1
1
10
Nivolumab
Placebo

Updated DFS analysis (primary definition) in the all randomized population (DBL 19-May-2021 with data cut on 01-Feb-2021) provided during the procedure.

Figure 13 *Kaplan-Meier Plot of Updated Disease-free Survival (Primary Definition) - All Randomized Subjects (DBL 19-May-2021)*

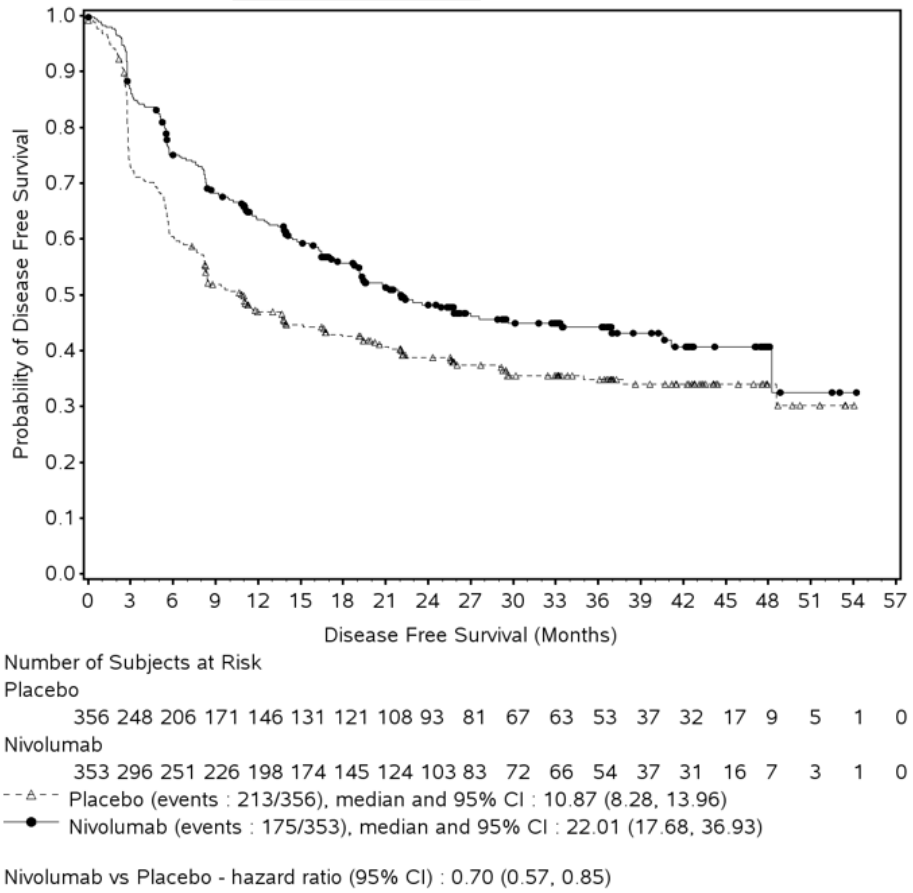


Table 19 *DFS (primary definition) rates- all randomized subjects (DBL 19-May-2021)*

Disease Free Survival Rate (95% CI)	Placebo N = 356	Nivolumab N = 353
3-MONTH	72.8 (67.7, 77.2)	86.8 (82.8, 90.0)
6-MONTH	60.5 (55.1, 65.4)	75.0 (70.1, 79.3)
9-MONTH	51.9 (46.4, 57.0)	68.2 (62.9, 72.8)
12-MONTH (A)	46.9 (41.5, 52.1)	63.5 (58.1, 68.4)
18-MONTH (B)	42.5 (37.2, 47.8)	55.6 (50.0, 60.8)
24-MONTH (C)	38.7 (33.4, 44.1)	48.2 (42.4, 53.7)
30-MONTH (D)	35.5 (30.1, 40.9)	44.9 (39.0, 50.7)

Based on Kaplan-Meier Estimates
(A) 32 patients in nivolumab arm and 30 patients in placebo arm were censored prior or at 12-months
(B) 62 patients in nivolumab arm and 42 patients in placebo arm were censored prior or at 18-months
(C) 86 patients in nivolumab arm and 60 patients in placebo arm were censored prior or at 24-months
(D) 111 patients in nivolumab arm and 79 patients in placebo arm were censored prior or at 30-months

Disease-free Survival in All Randomised Subjects with Tumour Cell PD-L1 Expression Level ⩾ 1% - Primary Definition

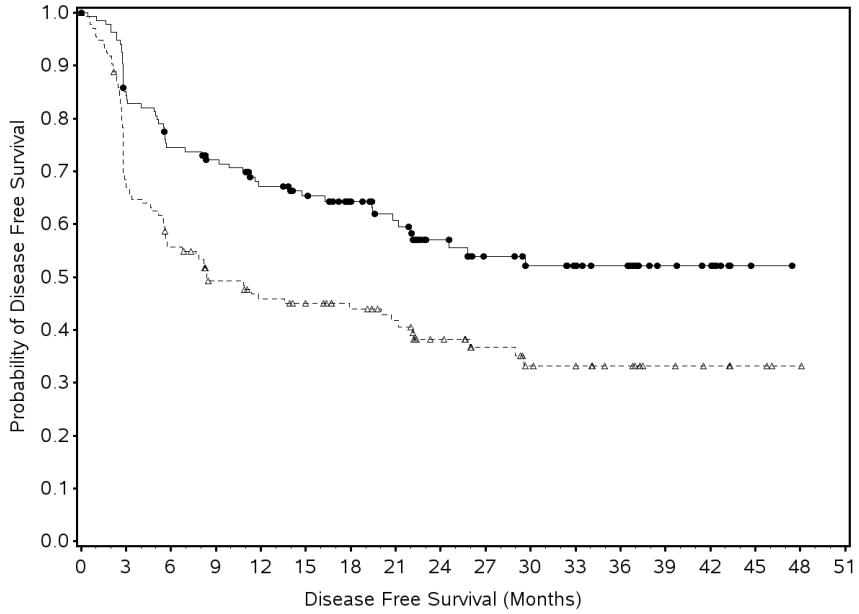
Nivolumab treatment resulted in a statistically significant improvement in DFS compared with placebo in subjects with tumour cell PD-L1 expression ≥ 1% (**Figure 14**).

Results of sensitivity analyses were consistent with the primary DFS analysis and confirm the robustness of the primary analysis results.

For a PD-L1 cut-off of ≥ 1% median DFS was as follows:

- Nivolumab group (events 114/210) 16.49 months (13.80-20.76)
- Placebo group (events 120/209) 11.07 months (8.28-16.69)

Figure 14 *Kaplan-Meier Plot of Disease-free Survival (Primary Definition) - All Randomised Subjects with Tumour PD-L1 expression ≥ 1% (Updated with Reanalysis)*



The type of recurrence is described in **Table *20***.

At the time of the DBL, 85 (60.7%) subjects in the nivolumab arm and 61 (43.0%) subjects in the placebo arm were censored. Among those censored, most were in follow-up (65 [46.4%] in the nivolumab arm and 43 [30.3%] in the placebo arm).

Table 20 Type of recurrence and reason for censoring in PD-L1 ≥ 1% patients (Updated with Reanalysis)

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Reason for Censoring, Disease Free Survival (Primary definition)
All Randomized Subjects with PD-L1 expression >= 1%

	Placebo N = 142	Nivolumab N = 140
NUMBER OF EVENTS (%)	81 (57.0)	55 (39.3)
TYPE OF EVENTS (%)		
DISEASE AT BASELINE	0	0
RECURRENCE	76 (53.5)	50 (35.7)
DISTANT RECURRENCE	52 (36.6)	40 (28.6)
LOCAL NON-UROTHELIAL TRACT	19 (13.4)	7 (5.0)
LOCAL UROTHELIAL TRACT INVASIVE	3 (2.1)	1 (0.7)
LOCAL UROTHELIAL TRACT NON-INVASIVE	2 (1.4)	2 (1.4)
DEATH	5 (3.5)	5 (3.6)
NUMBER OF SUBJECTS CENSORED (%)	61 (43.0)	85 (60.7)
CENSORED ON DATE OF RANDOMIZATION	8 (5.6)	6 (4.3)
NO BASELINE DISEASE ASSESSMENT (1)	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY DISEASE ASSESSMENT AND NO DEATH (1)	8 (5.6)	6 (4.3)
NEVER TREATED	3 (2.1)	1 (0.7)
NEW NON-UROTHELIAL CARCINOMA PRIMARY CANCER	0	1 (0.7)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY	0	1 (0.7)
OFF STUDY	4 (2.8)	3 (2.1)
OTHER	1 (0.7)	0

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Reason for Censoring, Disease Free Survival (Primary definition)
All Randomized Subjects with PD-L1 expression >= 1%

	Placebo N = 142	Nivolumab N = 140
CENSORED ON DATE OF LAST DISEASE ASSESSMENT ON-STUDY	53 (37.3)	79 (56.4)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (2)	0	0
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	0	0
RECEIVED SUBSEQUENT RADIOTHERAPY	0	0
RECEIVED SUBSEQUENT SURGERY	0	0
NEW NON-UROTHELIAL CARCINOMA PRIMARY CANCER (2)	2 (1.4)	1 (0.7)
STILL ON-TREATMENT	4 (2.8)	8 (5.7)
IN FOLLOW-UP	43 (30.3)	65 (46.4)
OFF STUDY	4 (2.8)	5 (3.6)
LOST TO FOLLOW-UP	3 (2.1)	2 (1.4)
SUBJECT WITHDREW CONSENT	1 (0.7)	2 (1.4)
OTHER	0	1 (0.7)

(1) Disease assessments and death if any, occurring after start of subsequent anti-cancer therapy or after new non-urothelial carcinoma primary cancer are not considered.
(2) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy or experienced new non-urothelial primary cancer without a prior reported DFSP event. Those subjects were censored at the last evaluable disease assessment prior to/on start date of subsequent anti-cancer therapy or new non-urothelial primary cancer.
Program Source: /opt/zfs002/prd/kms237954/stats/fa01relock/prog/tables/rt-ef-reascens.sas 22APR2021:11:16:03

Table 21: *Disease-Free Survival (Primary Definition) Sensitivity Analyses - All Randomised Subjects with PD-L1 Expression ≥ 1% (Updated with Reanalysis)*

SENSITIVITY ANALYSIS	Placebo EVENTS/SUBJECTS	Nivolumab EVENTS/SUBJECTS	HR (1) 95% CI	p-value (2)
UNSTRATIFIED ANALYSIS	81 / 142	55 / 140	0.55 (0.39, 0.77)	0.0004
STRATIFIED WEIGHTED ANALYSIS (A)				0.0460
< 6 MONTHS	59 / 69	34 / 42	0.49 (0.32, 0.74)	
>= 6 MONTHS	22 / 73	21 / 98	0.70 (0.38, 1.29)	
ANALYSIS USING STRATIFICATION FACTORS AS DETERMINED AT BASELINE (CRF SOURCE) (B)	81 / 142	55 / 140	0.58 (0.41, 0.82)	0.0019

(1) Stratified/unstratified Cox proportional hazards model.

(2) P-value from stratified Log-rank test. For sensitivity analyses, p-values are for descriptive purpose only
(A) Weighted log-rank test is using G (rho = 0, gamma = 1) weights, in the terminology of Fleming and Harrington. DFS hazard ratios from the periods before and following 6 months were derived using a stratified time-dependent Cox model.
(B) Stratified by prior neo-adjuvant cisplatin, pathological nodal status, as determined at baseline (CRF / clinical database source).
Abbreviations: CI = confidence interval, CRF = case report form, DFS = disease-free survival, HR = hazard ratio

- **Disease-free Survival in All Randomised Subjects with Tumour Cell PD-L1 Expression Level ≥ 1% (Primary Endpoint) - Secondary Definition**

DFS results using the secondary DFS definition (accounted for disease assessments occurring on or after initiation of subsequent anticancer therapy) were consistent with the analysis for the primary DFS definition (HR = 0.54 [98.72% CI: 0.35, 0.84]; p = 0.0005).

Figure 15: *Kaplan-Meier Plot of Disease-Free Survival (Secondary Definition) - All Randomised Subjects with PD-L1 Expression ≥ 1% (Updated with Reanalysis)*

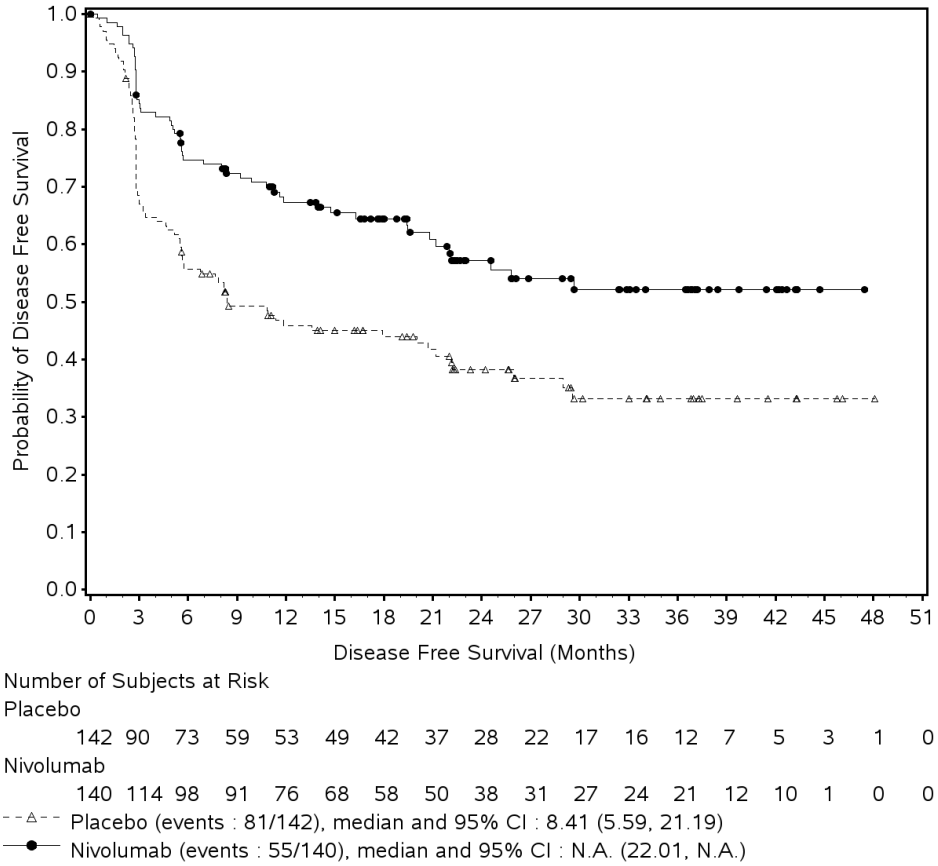
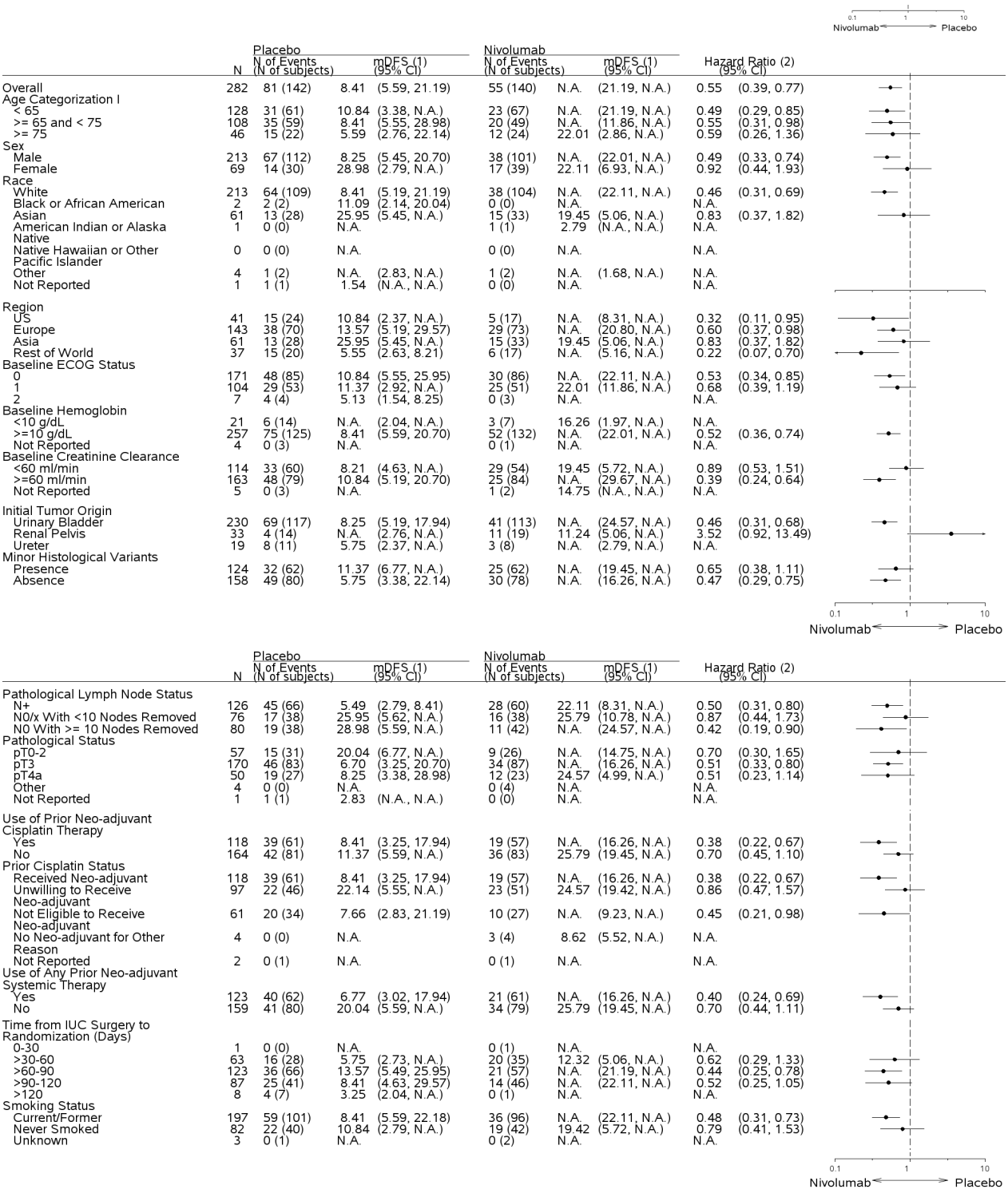


Figure 16: *Forest Plot of Treatment Effect on Disease-Free Survival in Pre-Defined Subsets - All Randomised Subjects with Tumour PD-L1 expression ≥ 1% (Updated with Reanalysis)*

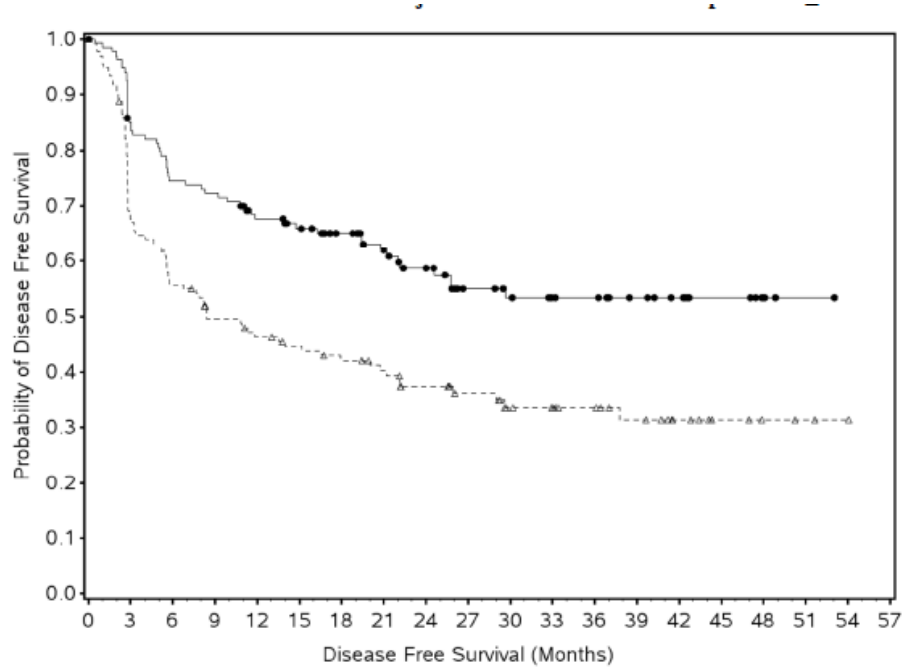


	N	Placebo N of Events (N of subjects)	mDFS (1) (95% CI)		Nivolumab N of Events (N of subjects)	mDFS (1) (95% CI)		Hazard Ratio (2) (95% CI)	
Overall	282	81 (142)	8.41	(5.59, 21.19)	55 (140)	N.A.	(21.19, N.A.)	0.55	(0.39, 0.77)
Age Categorization I									
< 65	128	31 (61)	10.84	(3.38, N.A.)	23 (67)	N.A.	(21.19, N.A.)	0.49	(0.29, 0.85)
>= 65 and < 75	108	35 (59)	8.41	(5.55, 28.98)	20 (49)	N.A.	(11.86, N.A.)	0.55	(0.31, 0.98)
>= 75	46	15 (22)	5.59	(2.76, 22.14)	12 (24)	22.01	(2.86, N.A.)	0.59	(0.26, 1.36)
Sex									
Male	213	67 (112)	8.25	(5.45, 20.70)	38 (101)	N.A.	(22.01, N.A.)	0.49	(0.33, 0.74)
Female	69	14 (30)	28.98	(2.79, N.A.)	17 (39)	22.11	(6.93, N.A.)	0.92	(0.44, 1.93)
Race									
White	213	64 (109)	8.41	(5.19, 21.19)	38 (104)	N.A.	(22.11, N.A.)	0.46	(0.31, 0.69)
Black or African American	2	2 (2)	11.09	(2.14, 20.04)	0 (0)	N.A.		N.A.	
Asian	61	13 (28)	25.95	(5.45, N.A.)	15 (33)	19.45	(5.06, N.A.)	0.83	(0.37, 1.82)
American Indian or Alaska Native	1	0 (0)	N.A.		1 (1)	2.79	(N.A., N.A.)	N.A.	
Native Hawaiian or Other Pacific Islander	0	0 (0)	N.A.		0 (0)	N.A.		N.A.	
Other	4	1 (2)	N.A.	(2.83, N.A.)	1 (2)	N.A.	(1.68, N.A.)	N.A.	
Not Reported	1	1 (1)	1.54	(N.A., N.A.)	0 (0)	N.A.		N.A.	
Region									
US	41	15 (24)	10.84	(2.37, N.A.)	5 (17)	N.A.	(8.31, N.A.)	0.32	(0.11, 0.95)
Europe	143	38 (70)	13.57	(5.19, 29.57)	29 (73)	N.A.	(20.80, N.A.)	0.60	(0.37, 0.98)
Asia	61	13 (28)	25.95	(5.45, N.A.)	15 (33)	19.45	(5.06, N.A.)	0.83	(0.37, 1.82)
Rest of World	37	15 (20)	5.55	(2.63, 8.21)	6 (17)	N.A.	(5.16, N.A.)	0.22	(0.07, 0.70)
Baseline ECOG Status									
0	171	48 (85)	10.84	(5.55, 25.95)	30 (86)	N.A.	(22.11, N.A.)	0.53	(0.34, 0.85)
1	104	29 (53)	11.37	(2.92, N.A.)	25 (51)	22.01	(11.86, N.A.)	0.68	(0.39, 1.19)
2	7	4 (4)	5.13	(1.54, 8.25)	0 (3)	N.A.		N.A.	
Baseline Hemoglobin									
<10 g/dL	21	6 (14)	N.A.	(2.04, N.A.)	3 (7)	16.26	(1.97, N.A.)	N.A.	
>=10 g/dL	257	75 (125)	8.41	(5.59, 20.70)	52 (132)	N.A.	(22.01, N.A.)	0.52	(0.36, 0.74)
Not Reported	4	0 (3)	N.A.		0 (1)	N.A.		N.A.	
Baseline Creatinine Clearance									
<60 ml/min	114	33 (60)	8.21	(4.63, N.A.)	29 (54)	19.45	(5.72, N.A.)	0.89	(0.53, 1.51)
>=60 ml/min	163	48 (79)	10.84	(5.19, 20.70)	25 (84)	N.A.	(29.67, N.A.)	0.39	(0.24, 0.64)
Not Reported	5	0 (3)	N.A.		1 (2)	14.75	(N.A., N.A.)	N.A.	
Initial Tumor Origin									
Urinary Bladder	230	69 (117)	8.25	(5.19, 17.94)	41 (113)	N.A.	(24.57, N.A.)	0.46	(0.31, 0.68)
Renal Pelvis	33	4 (14)	N.A.	(2.76, N.A.)	11 (19)	11.24	(5.06, N.A.)	3.52	(0.92, 13.49)
Ureter	19	8 (11)	5.75	(2.37, N.A.)	3 (8)	N.A.	(2.79, N.A.)	N.A.	
Minor Histological Variants									
Presence	124	32 (62)	11.37	(6.77, N.A.)	25 (62)	N.A.	(19.45, N.A.)	0.65	(0.38, 1.11)
Absence	158	49 (80)	5.75	(3.38, 22.14)	30 (78)	N.A.	(16.26, N.A.)	0.47	(0.29, 0.75)

	N	Placebo N of Events (N of subjects)	mDFS (1) (95% CI)		Nivolumab N of Events (N of subjects)	mDFS (1) (95% CI)		Hazard Ratio (2) (95% CI)	
Pathological Lymph Node Status									
N+	126	45 (66)	5.49	(2.79, 8.41)	28 (60)	22.11	(8.31, N.A.)	0.50	(0.31, 0.80)
N0/x With <10 Nodes Removed	76	17 (38)	25.95	(5.62, N.A.)	16 (38)	25.79	(10.78, N.A.)	0.87	(0.44, 1.73)
N0 With >= 10 Nodes Removed	80	19 (38)	28.98	(5.59, N.A.)	11 (42)	N.A.	(24.57, N.A.)	0.42	(0.19, 0.90)
Pathological Status									
pT0-2	57	15 (31)	20.04	(6.77, N.A.)	9 (26)	N.A.	(14.75, N.A.)	0.70	(0.30, 1.65)
pT3	170	46 (83)	6.70	(3.25, 20.70)	34 (87)	N.A.	(16.26, N.A.)	0.51	(0.33, 0.80)
pT4a	50	19 (27)	8.25	(3.38, 28.98)	12 (23)	24.57	(4.99, N.A.)	0.51	(0.23, 1.14)
Other	4	0 (0)	N.A.		0 (4)	N.A.		N.A.	
Not Reported	1	1 (1)	2.83	(N.A., N.A.)	0 (0)	N.A.		N.A.	
Use of Prior Neo-adjuvant Cisplatin Therapy									
Yes	118	39 (61)	8.41	(3.25, 17.94)	19 (57)	N.A.	(16.26, N.A.)	0.38	(0.22, 0.67)
No	164	42 (81)	11.37	(5.59, N.A.)	36 (83)	25.79	(19.45, N.A.)	0.70	(0.45, 1.10)
Prior Cisplatin Status									
Received Neo-adjuvant	118	39 (61)	8.41	(3.25, 17.94)	19 (57)	N.A.	(16.26, N.A.)	0.38	(0.22, 0.67)
Unwilling to Receive Neo-adjuvant	97	22 (46)	22.14	(5.55, N.A.)	23 (51)	24.57	(19.42, N.A.)	0.86	(0.47, 1.57)
Not Eligible to Receive Neo-adjuvant	61	20 (34)	7.66	(2.83, 21.19)	10 (27)	N.A.	(9.23, N.A.)	0.45	(0.21, 0.98)
No Neo-adjuvant for Other Reason	4	0 (0)	N.A.		3 (4)	8.62	(5.52, N.A.)	N.A.	
Not Reported	2	0 (1)	N.A.		0 (1)	N.A.		N.A.	
Use of Any Prior Neo-adjuvant Systemic Therapy									
Yes	123	40 (62)	6.77	(3.02, 17.94)	21 (61)	N.A.	(16.26, N.A.)	0.40	(0.24, 0.69)
No	159	41 (80)	20.04	(5.59, N.A.)	34 (79)	25.79	(19.45, N.A.)	0.70	(0.44, 1.11)
Time from IUC Surgery to Randomization (Days)									
0-30	1	0 (0)	N.A.		0 (1)	N.A.		N.A.	
>30-60	63	16 (28)	5.75	(2.73, N.A.)	20 (35)	12.32	(5.06, N.A.)	0.62	(0.29, 1.33)
>60-90	123	36 (66)	13.57	(5.49, 25.95)	21 (57)	N.A.	(21.19, N.A.)	0.44	(0.25, 0.78)
>90-120	87	25 (41)	8.41	(4.63, 29.57)	14 (46)	N.A.	(22.11, N.A.)	0.52	(0.25, 1.05)
>120	8	4 (7)	3.25	(2.04, N.A.)	0 (1)	N.A.		N.A.	
Smoking Status									
Current/Former	197	59 (101)	8.41	(5.59, 22.18)	36 (96)	N.A.	(22.11, N.A.)	0.48	(0.31, 0.73)
Never Smoked	82	22 (40)	10.84	(2.79, N.A.)	19 (42)	19.42	(5.72, N.A.)	0.79	(0.41, 1.53)
Unknown	3	0 (1)	N.A.		0 (2)	N.A.		N.A.	

Updated DFS analysis (primary definition) in the PD-L1⩾1% population (DBL 19-May-2021 with data cut on 01-Feb-2021) provided with during the procedure. The secondary DFS definition indicated similar results to the primary definition.

Figure 17 *Kaplan-Meier Plot of Disease-free Survival (Primary Definition) - All Randomised Subjects with Tumour PD-L1 expression ≥ 1% (DBL 19-May-2021)*



Number of Subjects at Risk

Placebo

142 90 74 62 57 53 49 44 36 29 23 21 18 14 9 5 3 2 1 0

Nivolumab

140 113 99 96 85 75 67 58 50 38 33 30 29 22 19 8 3 1 0 0

Placebo (events : 85/142), median and 95% CI : 8.41 (5.59, 20.04)

Nivolumab (events : 56/140), median and 95% CI : N.A. (22.11, N.A.)

Nivolumab vs Placebo - hazard ratio (95% CI) : 0.53 (0.38, 0.75)

Table 22 *DFS (primary definition) rates- all randomized subjects with tumor PD-L1 expression ≥1% (DBL 19-May-2021)*

Disease Free Survival Rate (95% CI)	Placebo N = 142	Nivolumab N = 140
3-MONTH	67.7 (59.1, 74.9)	85.1 (77.8, 90.1)
6-MONTH	55.7 (46.8, 63.6)	74.5 (66.2, 81.1)
9-MONTH	49.5 (40.7, 57.7)	72.3 (63.8, 79.1)
12-MONTH (A)	46.3 (37.6, 54.5)	67.6 (59.0, 74.9)
18-MONTH (B)	42.1 (33.5, 50.4)	65.0 (56.2, 72.5)
24-MONTH (C)	37.4 (29.0, 45.8)	58.6 (49.3, 66.9)
30-MONTH (D)	33.6 (25.2, 42.3)	53.4 (43.5, 62.3)

Based on Kaplan-Meier Estimates

(A) 12 patients in nivolumab arm and 14 patients in placebo arm were censored prior or at 12-months

(B) 27 patients in nivolumab arm and 17 patients in placebo arm were censored prior or at 18-months

(C) 38 patients in nivolumab arm and 25 patients in placebo arm were censored prior or at 24-months

(D) 51 patients in nivolumab arm and 35 patients in placebo arm were censored prior or at 30-months

Secondary endpoints

- **Survival events in the all randomised and PD-L1 expression ≥1% populations.**

At the 01-Feb-2021 DBL, 232 (57.4%) of the planned 404 OS events were observed for all randomized subjects and 84 (50.6%) of the planned 166 OS events were observed for all randomized subjects with tumour cell PD-L1 expression level ≥ 1%

- **Non-Urothelial Tract Recurrence Free Survival (NUTRFS) in All Randomised Subjects**

Nivolumab treatment resulted in an improvement in NUTRFS in all randomised subjects (see *Table 16*)

The number of subjects censored at the DBL (01-Feb-2021 DBL) was 191 (54.1%) and 166 (46.6%) in the nivolumab and placebo arms, respectively. Among those censored, most were in follow-up (134 [38.0%] in the nivolumab arm and 113 [31.7%] in the placebo arm).

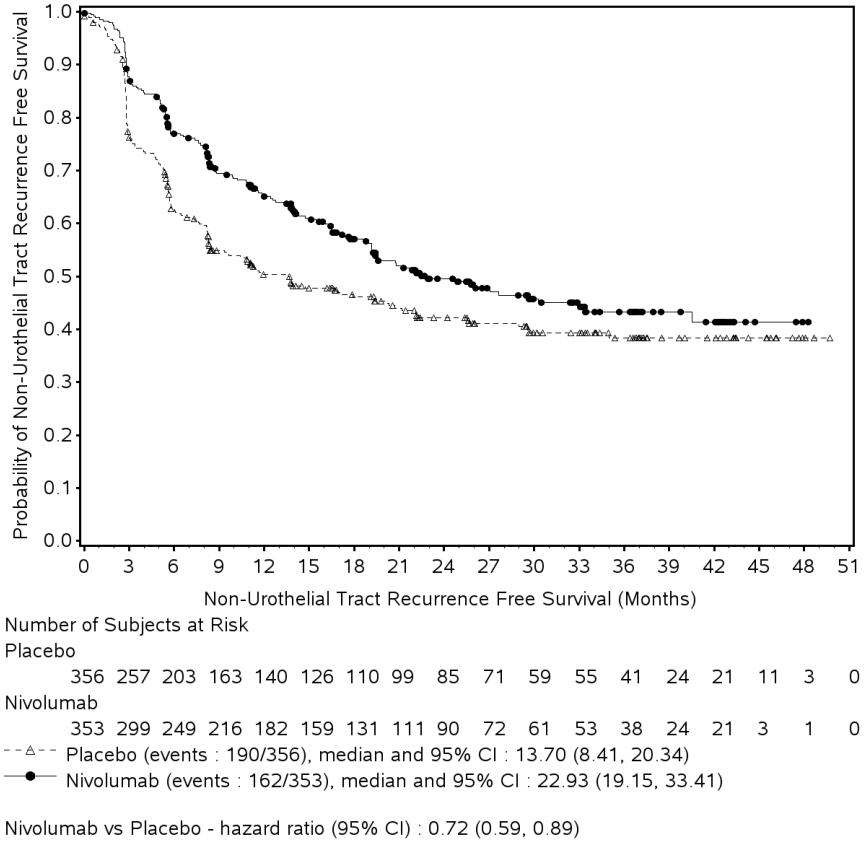
Table 23 *Reasons for censoring NUTRFS (Updated with Reanalysis)*

Reason for Censoring, Non-Urothelial Tract Recurrence Free Survival
All Randomized Subjects

	Placebo N = 356	Nivolumab N = 353
NUMBER OF EVENTS (%)	190 (53.4)	162 (45.9)
TYPE OF EVENTS (%)		
DISEASE AT BASELINE	3 (0.8)	1 (0.3)
RECURRENCE	175 (49.2)	147 (41.6)
DISTANT RECURRENCE	130 (36.5)	111 (31.4)
LOCAL NON-UROTHELIAL TRACT	45 (12.6)	36 (10.2)
DEATH	12 (3.4)	14 (4.0)
NUMBER OF SUBJECTS CENSORED (%)	166 (46.6)	191 (54.1)
CENSORED ON DATE OF RANDOMIZATION	13 (3.7)	11 (3.1)
NO BASELINE DISEASE ASSESSMENT (1)	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY DISEASE ASSESSMENT AND NO DEATH (1)	13 (3.7)	11 (3.1)
NEVER TREATED	6 (1.7)	2 (0.6)
NEW NON-UROTHELIAL CARCINOMA PRIMARY CANCER	0	1 (0.3)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY	0	1 (0.3)
OFF STUDY	6 (1.7)	7 (2.0)
OTHER	1 (0.3)	0

(1) Disease assessments and death if any, occurring after start of subsequent anti-cancer therapy or after new non-urothelial carcinoma primary cancer are not considered.
(2) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy or experienced new non-urothelial primary cancer without a prior reported NUTRFS event. Those subjects were censored at the last evaluable disease assessment prior to/on start date of subsequent anti-cancer therapy or new non-urothelial primary cancer.
Program Source: /opt/zfs002/prd/bms237954/stats/fa01relock/prog/tables/rt-ef-reascens.sas 22APR2021:11:16:10

***Figure 18*:** Kaplan-Meier Plot of NUTRFS - All Randomised Subjects (Updated with Reanalysis)



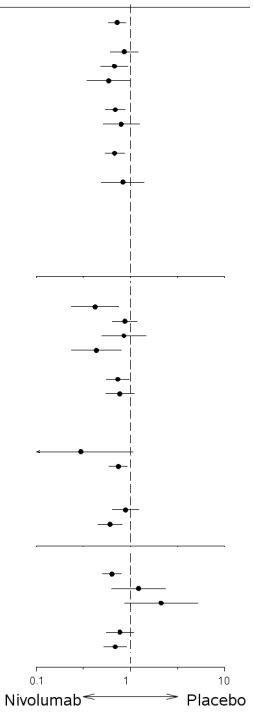
Updated analyses submitted during the procedure. At the 19-May-2021 DBL, median NUTRFS with nivolumab vs placebo treatment in all randomized subjects was 25.99 months (95% CI: 19.45, 41.13) and 13.70 months (95% CI: 8.41, 20.04), respectively (HR = 0.71, 95% CI: 0.58, 0.88).

NUTRFS rates were higher in the nivolumab arm than in the placebo arm at 30 months (48.0% [95% CI: 41.9, 53.8] vs 38.9% [95% CI: 33.3, 44.4]). The KM curves of the treatment arms do not appear to approach each other in the tails.

NUTRFS by Subgroups

***Figure 19**:Forest Plot of Treatment Effect on NUTRFS in Pre-Defined Subsets - All Randomised Subjects (Updated with Reanalysis)*

		Placebo			Nivolumab				
	N	N of Events (N of subjects)	mNUTRFS (1) (95% CI)		N of Events (N of subjects)	mNUTRFS (1) (95% CI)		Hazard Ratio (2) (95% CI)	
Overall	709	190 (356)	13.70	(8.41, 20.34)	162 (353)	22.93	(19.15, 33.41)	0.72	(0.59, 0.89)
Age Categorization I									
< 65	291	63 (136)	22.11	(8.41, N.A.)	71 (155)	25.79	(16.07, N.A.)	0.86	(0.61, 1.21)
>= 65 and < 75	295	93 (164)	11.07	(8.15, 20.70)	61 (131)	19.55	(17.35, N.A.)	0.68	(0.49, 0.94)
>= 75	123	34 (56)	11.10	(5.55, 22.14)	30 (67)	27.04	(11.24, N.A.)	0.59	(0.35, 0.99)
Sex									
Male	540	146 (275)	13.70	(8.41, 22.11)	118 (265)	24.57	(19.15, N.A.)	0.69	(0.54, 0.88)
Female	169	44 (81)	13.57	(6.05, 28.98)	44 (88)	21.88	(11.86, N.A.)	0.80	(0.52, 1.24)
Race									
White	536	154 (272)	11.20	(8.31, 17.94)	124 (264)	22.37	(18.89, 33.41)	0.68	(0.53, 0.86)
Black or African American	5	3 (3)	5.82	(2.14, 20.04)	1 (2)	N.A.	(2.92, N.A.)	N.A.	
Asian	155	29 (75)	N.A.	(8.41, N.A.)	31 (80)	N.A.	(14.16, N.A.)	0.83	(0.49, 1.41)
American Indian or Alaska Native	1	0 (0)	N.A.		1 (1)	2.79	(N.A., N.A.)	N.A.	
Native Hawaiian or Other Pacific Islander	0	0 (0)	N.A.		0 (0)	N.A.		N.A.	
Other	11	3 (5)	4.96	(2.73, N.A.)	5 (6)	4.01	(1.68, N.A.)	N.A.	
Not Reported	1	1 (1)	1.54	(N.A., N.A.)	0 (0)	N.A.		N.A.	
Region									
US	102	35 (53)	5.82	(5.09, 17.18)	23 (49)	20.76	(11.10, N.A.)	0.42	(0.24, 0.76)
Europe	341	92 (171)	13.83	(9.66, 22.18)	86 (170)	20.80	(16.07, 33.41)	0.87	(0.65, 1.17)
Asia	154	28 (74)	N.A.	(13.70, N.A.)	31 (80)	N.A.	(14.16, N.A.)	0.85	(0.50, 1.46)
Rest of World	112	35 (58)	6.05	(3.48, 19.35)	22 (54)	25.79	(13.80, N.A.)	0.43	(0.24, 0.80)
Baseline ECOG Status									
0	445	114 (221)	13.83	(9.36, 28.98)	98 (224)	25.99	(19.15, N.A.)	0.73	(0.56, 0.96)
1	247	69 (125)	11.37	(6.05, 20.34)	63 (122)	19.29	(12.75, 30.29)	0.78	(0.54, 1.10)
2	16	7 (9)	7.85	(1.54, N.A.)	1 (7)	N.A.	(11.01, N.A.)	N.A.	
Not Reported	1	0 (1)	N.A.		0 (0)	N.A.		N.A.	
Baseline Hemoglobin									
<10 g/dL	46	17 (27)	5.62	(2.79, N.A.)	8 (19)	30.29	(5.16, N.A.)	0.30	(0.08, 1.06)
>=10 g/dL	653	171 (321)	13.86	(9.63, 22.14)	154 (332)	22.93	(19.15, 40.54)	0.74	(0.60, 0.92)
Not Reported	10	2 (8)	N.A.	(0.03, N.A.)	0 (2)	N.A.		N.A.	
Baseline Creatinine Clearance									
<60 ml/min	309	83 (158)	13.86	(7.85, N.A.)	77 (151)	19.29	(13.80, 27.04)	0.89	(0.65, 1.22)
>=60 ml/min	388	105 (189)	11.50	(8.34, 21.19)	84 (199)	33.41	(19.42, N.A.)	0.60	(0.45, 0.81)
Not Reported	12	2 (9)	N.A.	(0.03, N.A.)	1 (3)	14.75	(N.A., N.A.)	N.A.	
Initial Tumor Origin									
Urinary Bladder	560	162 (281)	9.36	(7.62, 13.70)	129 (279)	21.88	(17.35, 40.54)	0.63	(0.50, 0.80)
Renal Pelvis	96	19 (52)	N.A.	(17.18, N.A.)	20 (44)	32.95	(11.24, N.A.)	1.23	(0.63, 2.37)
Ureter	53	9 (23)	N.A.	(5.62, N.A.)	13 (30)	25.99	(8.18, N.A.)	2.12	(0.87, 5.18)
Minor Histological Variants									
Presence	286	71 (141)	13.70	(8.41, N.A.)	69 (145)	21.19	(15.64, N.A.)	0.78	(0.55, 1.09)
Absence	423	119 (215)	13.57	(7.85, 22.18)	93 (208)	25.79	(18.89, N.A.)	0.69	(0.53, 0.91)
Pathological Lymph Node Status									
N+	335	113 (168)	7.62	(5.55, 8.41)	93 (167)	17.35	(11.60, 20.80)	0.64	(0.49, 0.86)
N0/x With <10 Nodes Removed	193	41 (99)	N.A.	(13.86, N.A.)	40 (94)	30.29	(14.75, N.A.)	0.92	(0.59, 1.44)
N0 With >= 10 Nodes Removed	179	35 (88)	N.A.	(11.50, N.A.)	29 (91)	N.A.	(25.99, N.A.)	0.70	(0.42, 1.16)
Not Reported	2	1 (1)	9.63	(N.A., N.A.)	0 (1)	N.A.		N.A.	
Pathological Status									
pT0-2	166	40 (86)	20.04	(11.37, N.A.)	34 (80)	33.41	(19.29, N.A.)	0.84	(0.51, 1.37)
pT3	410	109 (204)	11.66	(8.31, 20.70)	90 (206)	25.99	(19.15, N.A.)	0.65	(0.49, 0.86)
pT4a	119	37 (62)	8.25	(4.86, 28.98)	36 (57)	15.64	(7.62, 19.55)	0.84	(0.51, 1.37)
Other	12	3 (3)	5.09	(1.41, 7.26)	1 (9)	N.A.	(13.96, N.A.)	N.A.	
Not Reported	2	1 (1)	2.83	(N.A., N.A.)	1 (1)	11.43	(N.A., N.A.)	N.A.	
Use of Prior Neo-adjuvant Cisplatin Therapy									
Yes	308	94 (155)	8.31	(5.78, 11.66)	68 (153)	19.55	(16.26, N.A.)	0.55	(0.40, 0.76)
No	401	96 (201)	21.19	(13.70, N.A.)	94 (200)	24.57	(19.15, N.A.)	0.92	(0.69, 1.22)
Prior Cisplatin Status									
Received Neo-adjuvant	308	94 (155)	8.31	(5.78, 11.66)	68 (153)	19.55	(16.26, N.A.)	0.55	(0.40, 0.76)
Unwilling to Receive Neo-adjuvant	231	42 (108)	N.A.	(20.70, N.A.)	60 (123)	22.37	(15.05, N.A.)	1.22	(0.82, 1.82)
Not Eligible to Receive Neo-adjuvant	155	51 (85)	11.07	(6.05, 20.04)	30 (70)	30.29	(17.68, N.A.)	0.64	(0.40, 1.01)
No Neo-adjuvant for Other Reason	12	2 (6)	N.A.	(0.03, N.A.)	4 (6)	5.65	(3.81, N.A.)	N.A.	
Not Reported	3	1 (2)	N.A.	(2.89, N.A.)	0 (1)	N.A.		N.A.	
Use of Any Prior Neo-adjuvant Systemic Therapy									
Yes	319	98 (159)	8.28	(5.75, 11.20)	73 (160)	19.55	(15.64, N.A.)	0.56	(0.41, 0.76)
No	390	92 (197)	22.18	(13.70, N.A.)	89 (193)	25.79	(19.15, N.A.)	0.91	(0.68, 1.23)
Time from IUC Surgery to Randomization (Days)									
0-30	5	2 (3)	11.20	(4.99, 11.20)	0 (2)	N.A.		N.A.	
>30-60	149	39 (70)	13.70	(5.65, 28.98)	40 (79)	19.29	(9.95, N.A.)	0.64	(0.39, 1.05)
>60-90	342	85 (177)	22.11	(11.07, N.A.)	74 (165)	22.93	(17.35, N.A.)	0.78	(0.57, 1.08)
>90-120	198	57 (95)	9.63	(6.08, 14.72)	46 (103)	27.04	(16.26, N.A.)	0.74	(0.49, 1.11)
>120	15	7 (11)	5.62	(2.04, N.A.)	2 (4)	N.A.	(2.40, N.A.)	N.A.	
Smoking Status									
Current/Former	484	134 (247)	11.86	(8.31, 21.19)	112 (237)	22.11	(17.35, 33.41)	0.72	(0.56, 0.93)
Never Smoked	215	54 (104)	19.35	(5.68, 29.54)	49 (111)	25.99	(14.06, N.A.)	0.70	(0.47, 1.05)
Unknown	10	2 (5)	N.A.	(11.50, N.A.)	1 (5)	N.A.	(0.03, N.A.)	N.A.	
PD-L1 Status									
>=1%	280	76 (141)	10.87	(5.75, 22.18)	54 (139)	N.A.	(24.57, N.A.)	0.57	(0.40, 0.81)
<1%	419	110 (209)	13.86	(9.63, 25.66)	107 (210)	18.89	(14.16, 27.04)	0.85	(0.65, 1.12)
Indeterminate/Not Evaluable	8	3 (5)	5.82	(2.83, N.A.)	1 (3)	N.A.	(10.22, N.A.)	N.A.	
Not Reported	2	1 (1)	3.25	(N.A., N.A.)	0 (1)	N.A.		N.A.	

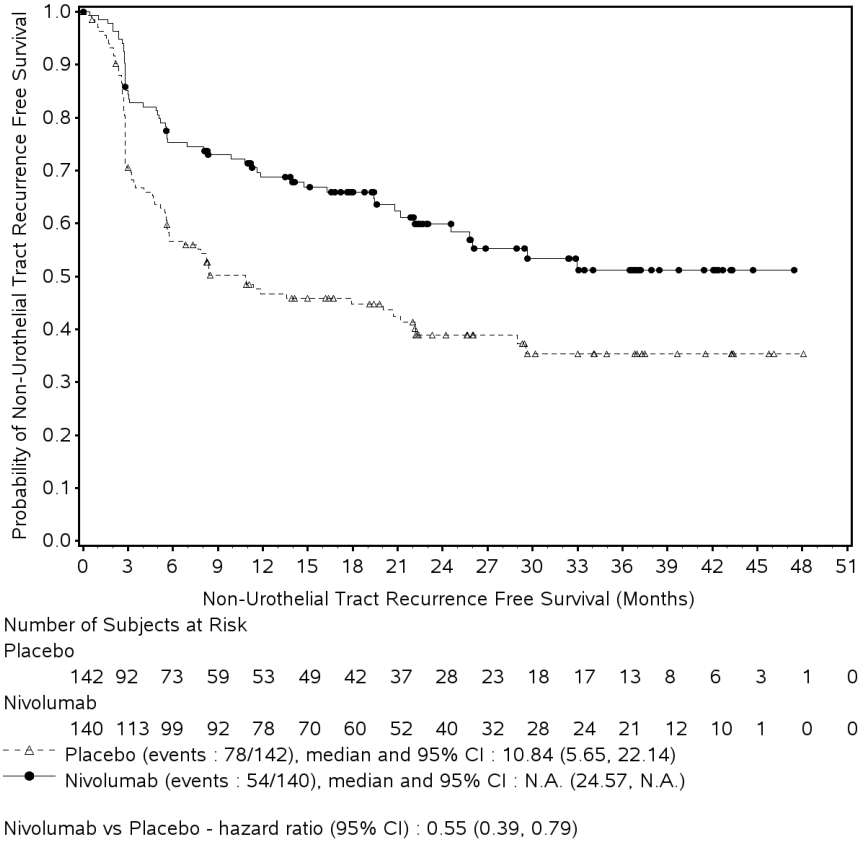


Note: HR is not computed for subset (except age, region, and sex) category with less than 10 subjects per treatment arm. PD-L1 status is based on clinical database.

- **NUTRFS in All Randomised Subjects with Tumour Cell PD-L1 Expression Level ⩾ 1%**

Nivolumab treatment resulted in an improvement in NUTRFS compared with placebo in subjects with tumour cell PD-L1 expression ≥ 1% (***Table 16***; ***Figure 20***)**.** At the time of the database lock, 86 (61.4%) subjects in the nivolumab arm and 64 (45.1%) subjects in the placebo arm were censored for NUTRFS. Among those censored, most were in follow-up (65 [46.4%] in the nivolumab arm and 44 [31.0%]in the placebo arm).

Figure 20: ***Kaplan-Meier Plot of NUTRFS - All Randomised Subjects with Tumour PD-L1 Expression ≥ 1% (Updated with Reanalysis)***

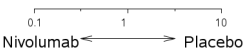


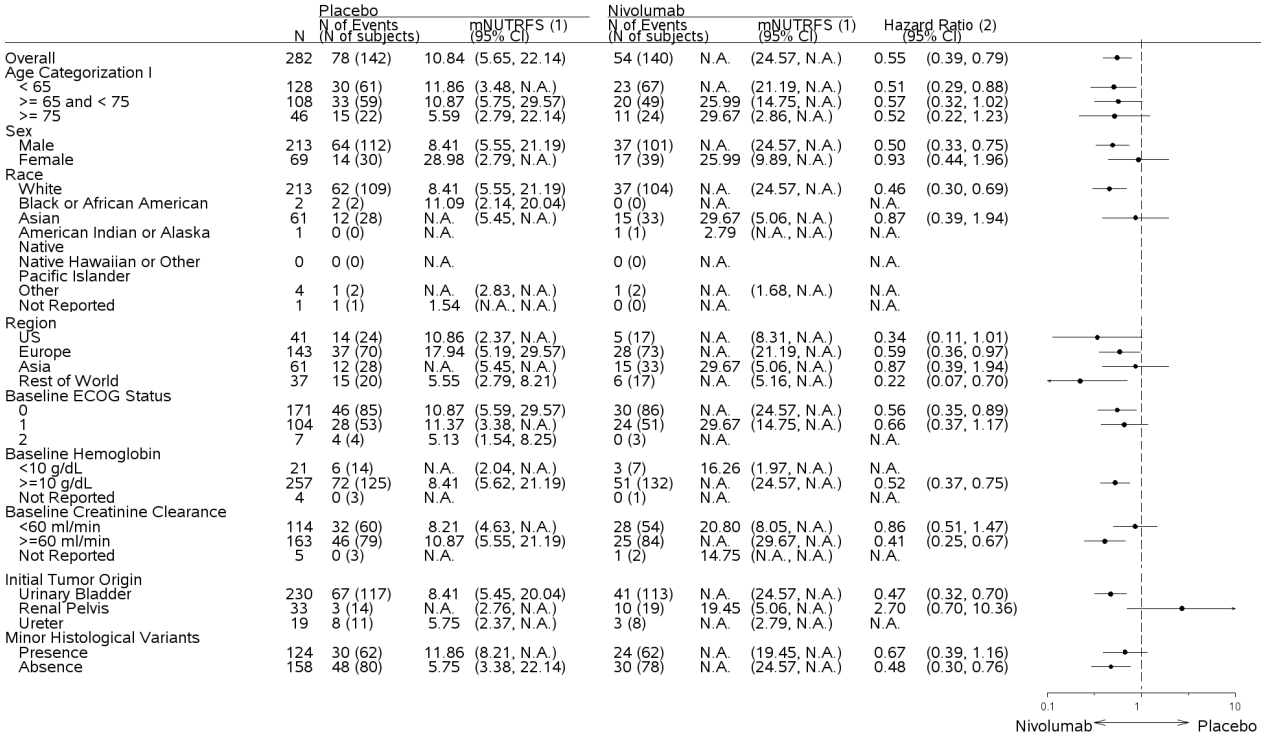
Updated analyses submitted during the procedure**:** At the 19-May-2021 DBL, median NUTRFS in subjects with tumor cell PD-L1 ≥ 1% was not reached in the nivolumab arm and 10.84 months (95% CI: 5.65, 20.70) in the placebo arm (HR = 0.54, 95% CI: 0.39, 0.77).

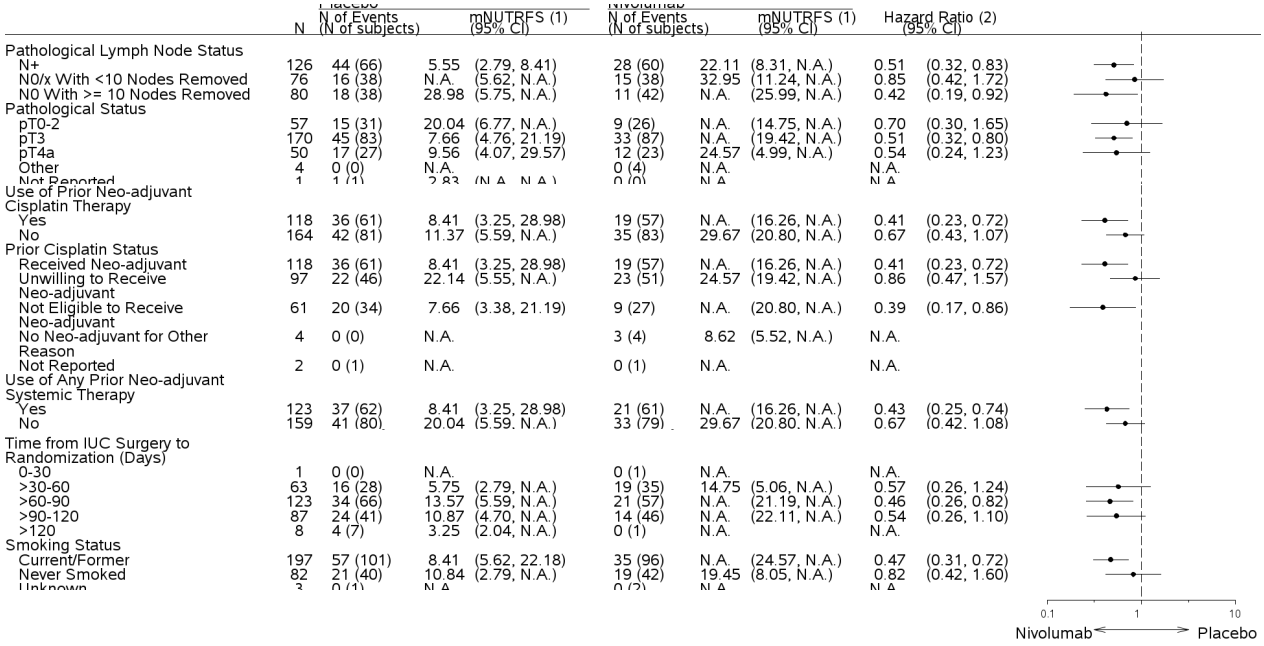
NUTRFS by Subgroups

In a subgroup analysis for all randomised subjects with tumour PD-L1 expression ≥ 1%, NUTRFS HRs for most subgroups favoured (HR < 1) nivolumab versus placebo.

Figure 21: ***Forest Plot of Treatment Effect on NUTRFS in Pre-Defined Subsets - All Randomised Subjects with Tumour PD-L1 expression ≥ 1% (Updated with Reanalysis)***







Note: HR is not computed for subset (except age, region, and sex) category with less than 10 subjects per treatment arm.

(1) Based on Kaplan-Meier estimates, (2) Stratified Cox proportional hazard model

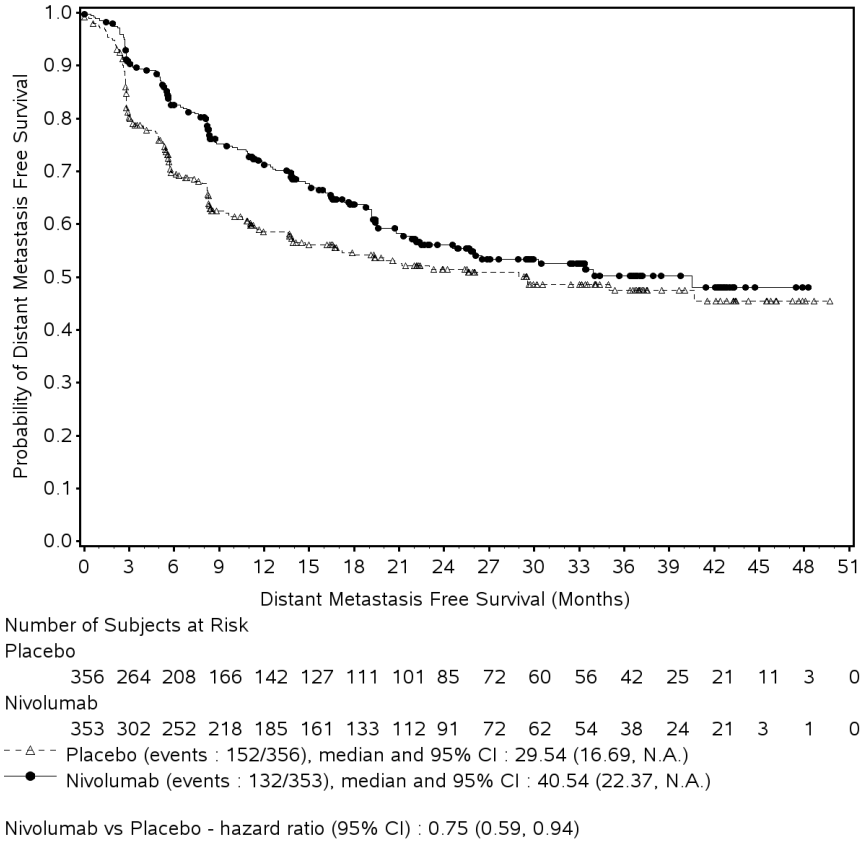
Exploratory endpoints

Distant Metastasis-free Survival (DMFS) in All Randomised Subjects (Exploratory Endpoint)

Nivolumab treatment resulted in an improvement in DMFS (*Figure 22*). DMFS rates were higher in the nivolumab arm than in the placebo arm at 6 months (82.5% vs 69.8%). At the time of the DBL, 221 (62.6%) subjects in the nivolumab arm and 204 (57.3%) subjects in the placebo arm were censored

for DMFS. Among those censored, most were in follow-up (139 [39.4%] in the nivolumab arm and 119 [33.4%] in the placebo arm).

Figure 22: Kaplan-Meier Plot of Distant Metastasis-Free Survival - All Randomised Subjects (Updated with Reanalysis)



The rate of subjects with local non-urothelial tract recurrence without distant recurrence exceeded 10% (81 subjects, i.e. 11.4%), for which a sensitivity analysis of DMFS was conducted where local non-urothelial tract recurrence was considered as a competing risk (no further scans being foreseen per the protocol) (HR = 0.74 (95% CI: 0.58, 0.94)).

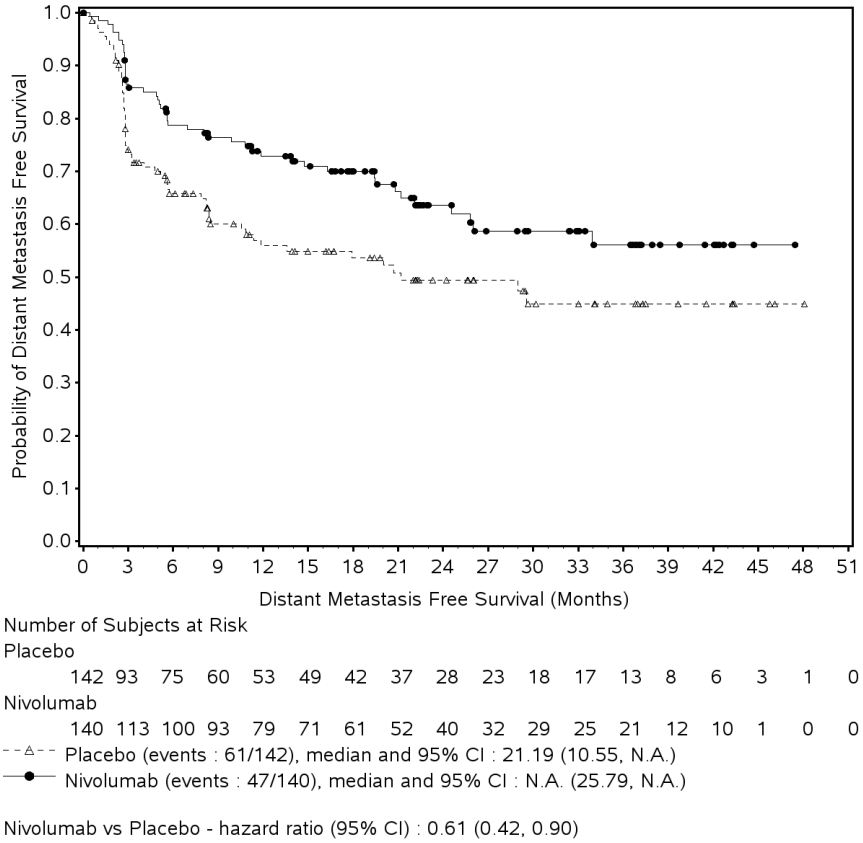
At the 19-May-2021 DBL, median DMFS with nivolumab vs placebo treatment in all randomized subjects was 41.13 months (95% CI: 25.99, N.A) and 29.21 months (95% CI: 15.21, N.A), respectively (HR = 0.73, 95% CI: 0.58, 0.92).

DMFS in All Randomised Subjects with Tumour Cell PD-L1 Expression Level ≥ 1%

Nivolumab treatment resulted in a clinically meaningful improvement in DMFS compared with placebo in subjects with tumour cell PD-L1 expression ≥ 1% (***Figure 23***, ***Table 16***). At the time of the 01-Feb-2021 DBL, 93 (66.4%) subjects in the nivolumab arm and 81 (57.0%) subjects in the placebo arm were censored for DMFS. Among those censored, most were in follow-up (67 [47.9%] in the nivolumab arm and 44 [31.0%] in the placebo arm).

At the 19-May-2021 DBL, median DMFS in subjects with tumor cell PD-L1 ≥ 1% was not reached in the nivolumab arm and 20.70 months (95% CI: 10.84, N.A.) in the placebo arm (HR = 0.60, 95% CI: 0.41, 0.88).

Figure 23: Kaplan-Meier Plot of Distant Metastasis-Free Survival - All Randomised Subjects Tumour PD-L1 Expression ≥ 1% (Updated with Reanalysis)

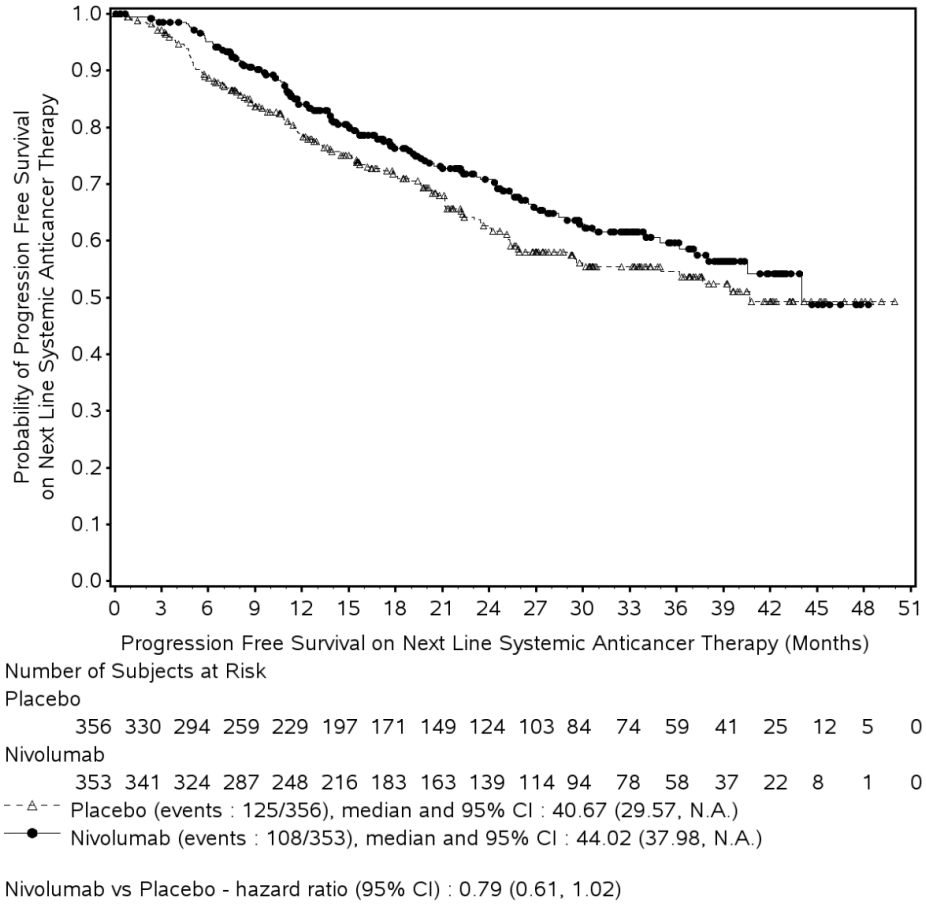


For the results of following Exploratory endpoints refer to Table 16: Time to Recurrence in All Randomised Subjects, Time to Recurrence in All Randomised Subjects with Tumour Cell PD-L1 Expression Level ≥ 1%, Time to Locoregional Recurrence in All Randomised Subjects, Locoregional Control in All Randomised Subjects with Tumour Cell PD-L1 Expression Level ≥ 1%, Locoregional Disease Free Survival in All Randomised Subjects, Locoregional Disease-free Survival in All Randomised Subjects with Tumour Cell PD-L1 Expression Level ≥ 1%.

Progression-free Survival on Next Line Systemic Therapy (PFS2) in All Randomised Subjects

Nivolumab treatment resulted in an improvement in PFS2 in all randomised subjects (**Table 16 and Figure 24).** PFS2 rates were higher in the nivolumab arm than in the placebo arm at 6 months (95.1% vs 88.7%, respectively). At the time of the 01-Feb-2021 DBL, 245 (69.4%) subjects in the nivolumab arm and 231 (64.9%) subjects in the placebo arm were censored for PFS2.

***Figure 24: Kaplan-Meier Plot of Progression-free Survival on Next Line Therapy (PFS2) - All Randomised Subjects* DBL 01-Feb-2021**

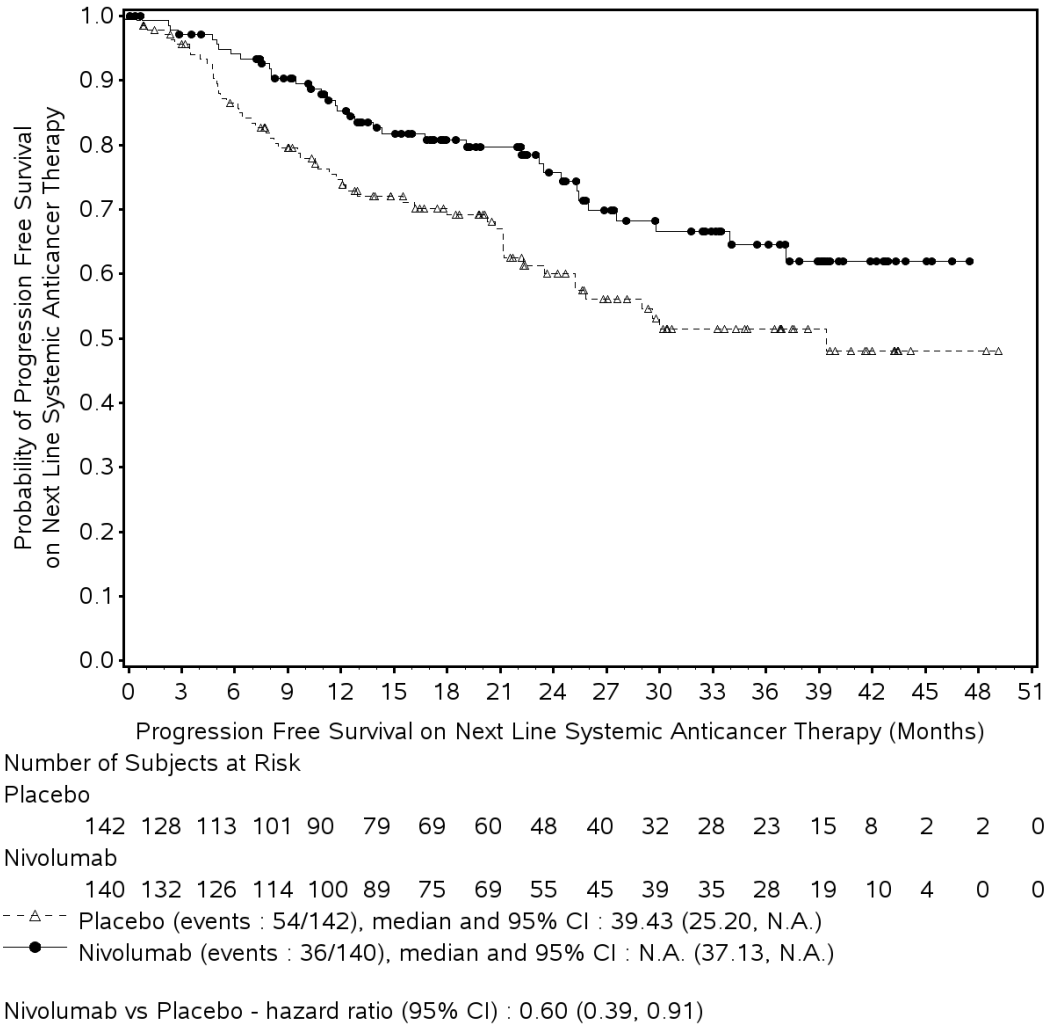


At the 01-Feb-2021 DBL, median PFS2 with nivolumab vs placebo treatment in all randomized subjects was 48.23 months (95% CI: 38.67, N.A.) and 47.93 months (95% CI: 29.96, N.A.), respectively (HR = 0.78, 95% CI: 0.61, 1.00).

Progression-free Survival on Next Line Systemic Therapy (PFS2) in All Randomised Subjects with Tumour Cell PD-L1 Expression Level ≥ 1%

Nivolumab treatment resulted in an improvement in PFS2 compared with placebo in subjects with tumour cell PD-L1 expression ≥ 1% (***Table 16* and *Figure 25***). PFS2 rates were higher in the nivolumab arm than in the placebo arm at 6 months (94.1% vs 86.5%, respectively). 104 (74.3%) subjects in the nivolumab arm and 88 (62.0%) subjects in the placebo arm were censored.

Figure 25: Kaplan-Meier Plot of Progression-free Survival on Next Line Systemic Anticancer Therapy (PFS2) - All Randomised Subjects with PD-L1 Expression ≥ 1%



At the 01-Feb-2021 DBL, median PFS2 in subjects with tumor cell PD-L1 ≥ 1% was not reached in the nivolumab arm and 39.43 months (95% CI: 23.49, N.A.) in the placebo arm (HR = 0.56, 95% CI: 0.37, 0.85).

Health-related Quality of Life in All Randomised Subjects and PD-L1≥1% subjects - Exploratory Endpoint

Several questionnaires have been used: QLQ-C30 and EQ-5D-3L. In all treatment groups baseline scores were comparable. Quality of life through Week 49 as measured by the EORTC QLQ-C30 Global Health Status scale remained stable in both treatment arms, with no mean change score from baseline reaching the minimal important difference for the subject (i.e. mean change ≥10 points) at any time point for either treatment arm. EQ-5D-3L utility index and EQ-5D VAS scores through Week 49 remained stable in both treatment arms, with no mean change score from baseline reaching the MID for the subject at any time point for either treatment arm.

Ancillary analyses

Efficacy in All Randomized Subjects with Tumor Cell PD-L1 < 1%

Separate analyses including KM curves of all the efficacy endpoints for randomized subjects with tumor cell PD-L1 < 1% are provided from the updated 19-May-2021 DBL.

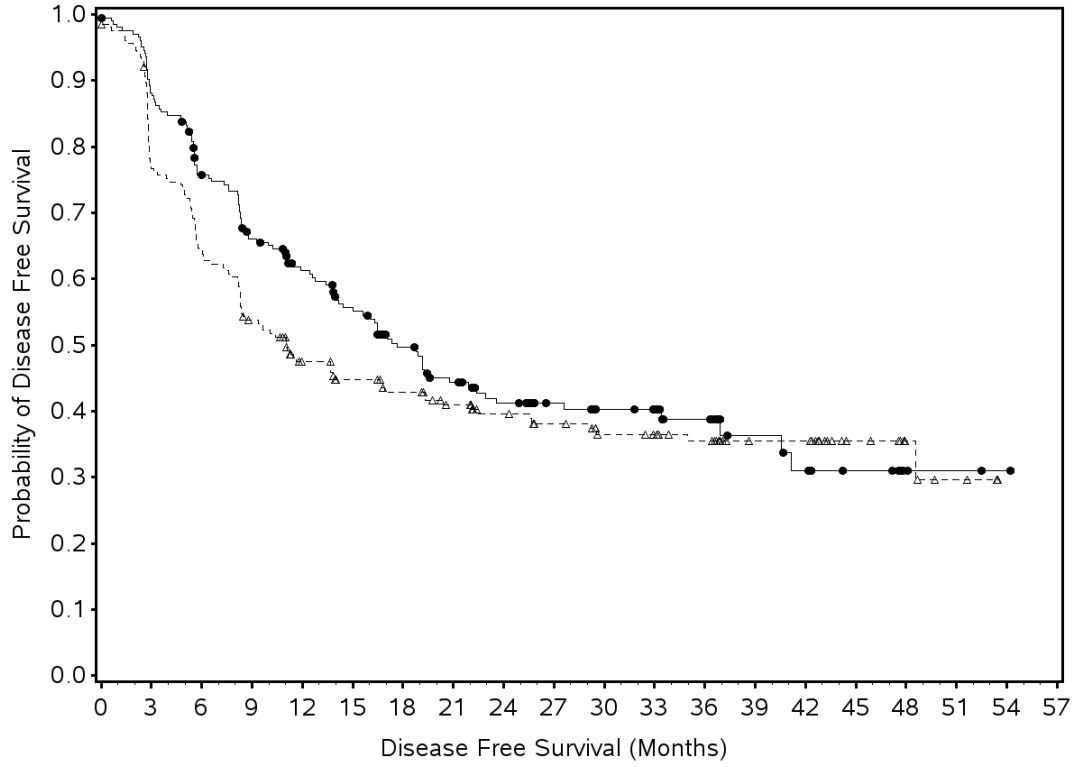
Table 24 Overall Summary of Efficacy - All Randomized Subjects with Tumor Cell PD L1 < 1% from 19-May-2021 DBL with data cut on 01-Feb-2021

Efficacy Parameter	Placebo (N = 207)	Nivolumab (N = 207)
PRIMARY ENDPOINTS		
DFS Primary Definition		
Events, n (%)	124 (59.9)	114 (55.1)
Median DFS (95% CI)[a], months	11.07 (8.31, 16.89)	17.68 (14.06, 22.37)
HR (95% CI) [b]	0.80 (0.62, 1.03)	
DFS Secondary Definition		
Events, n (%)	124 (59.9)	116 (56.0)
Median DFS (95% CI)[a], months	11.07 (8.31, 16.89)	17.68 (14.06, 22.37)
HR (95% CI) [b]	0.81 (0.63, 1.04)	
Secondary Endpoints		
NUTRFS		
Events, n (%)	114 (55.1)	105 (50.7)
Median NUTRFS (95% CI)[a], months	13.86 (9.66, 25.66)	19.15 (16.07, 37.16)
HR (95% CI) [b]	0.81 (0.62, 1.05)	
EXPLORATORY ENDPOINTS		
DMFS		
Events, n (%)	94 (45.4)	85 (41.1)
Median DMFS (95% CI)[a], months	29.54 (13.86, 53.65)	33.41 (19.15, N.A)
HR (95% CI) [b]	0.80 (0.60, 1.08)	
TTR		
Events, n (%)	119 (57.5)	109 (52.7)
Median TTR (95% CI)[c], months	11.50 (8.34, 22.11)	18.89 (14.42, 33.41)
HR (95% CI)[d]	0.79 (0.60, 1.02)	
LRDFS		
Events, n (%)	55 (26.6)	54 (26.1)
Median LRDFS (95% CI)[c], months	N.A	N.A
HR (95% CI)[d]	0.86 (0.59, 1.25)	
LRC		

Table 24 Overall Summary of Efficacy - All Randomized Subjects with Tumor Cell PD L1 < 1% from 19-May-2021 DBL with data cut on 01-Feb-2021

Efficacy Parameter	Placebo (N = 207)	Nivolumab (N = 207)
Events, n (%)	50 (24.2)	49 (23.7)
Median LRC (95% CI)[c], months	N.A	N.A
HR (95% CI) [d]	0.84 (0.56, 1.25)	
PFS2[e]		
Events, n (%)	77 (37.2)	80 (38.6)
Median PFS2 (95% CI)[a], months	47.93 (31.34, N.A)	40.11 (33.35, N.A)
HR (95% CI) [b]	0.94 (0.68, 1.29)	

Figure 26 *Kaplan-Meier Plot of Disease Free Survival (Primary definition) - All Randomized Subjects with Tumor Cell PD-L1 < 1% (*DBL 19-May-2021)



Number of Subjects at Risk

Placebo

207 154 129 106 86 76 70 62 55 50 42 40 35 23 23 12 6 3 0 0

Nivolumab

207 179 149 128 111 97 76 64 51 43 38 35 24 14 11 7 3 2 1 0

Placebo (events : 124/207), median and 95% CI : 11.07 (8.31, 16.89)

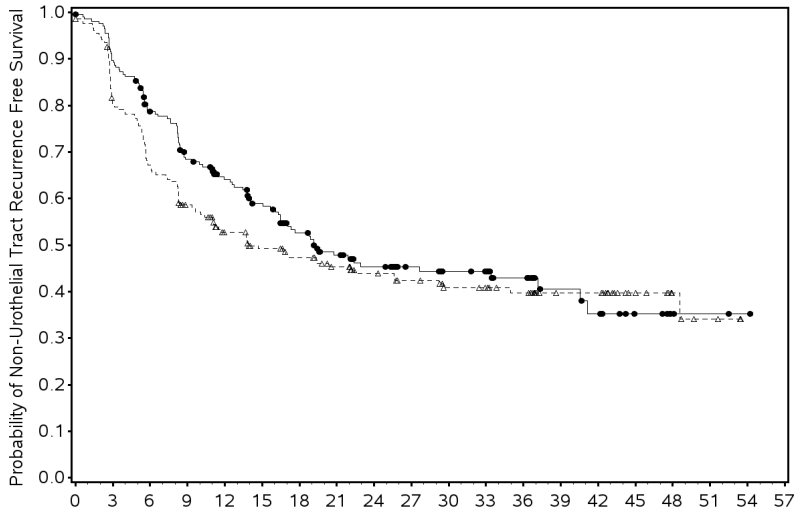
Nivolumab (events : 114/207), median and 95% CI : 17.68 (14.06, 22.37)

Nivolumab vs Placebo - hazard ratio (95% CI) : 0.80 (0.62, 1.03)

Table 25 *Disease Free Survival (Primary Definition) Rates - All Randomized Subjects with Tumor Cell PD-L1 < 1% (DBL* 19-May-2021)

Disease Free Survival Rate (95% CI)	Placebo N = 207	Nivolumab N = 207
3-MONTH	76.7 (70.2, 81.9)	88.2 (82.9, 91.9)
6-MONTH	64.2 (57.2, 70.4)	75.7 (69.2, 81.1)
9-MONTH	53.8 (46.6, 60.4)	66.1 (59.0, 72.2)
12-MONTH (A)	47.5 (40.4, 54.3)	61.3 (54.1, 67.7)
18-MONTH (B)	42.9 (35.9, 49.7)	49.6 (42.2, 56.6)
24-MONTH (C)	39.6 (32.6, 46.5)	41.2 (33.7, 48.4)
30-MONTH (D)	36.5 (29.5, 43.6)	40.2 (32.7, 47.5)

Figure 27 *Kaplan-Meier Plot of NUTRFS - All Randomized Subjects with Tumor PD-L1 < 1% (DBL* 19-May-2021)



Number of Subjects at Risk

Placebo

207 160 134 112 92 81 75 67 60 55 46 44 39 25 25 14 7 3 0 0

Nivolumab

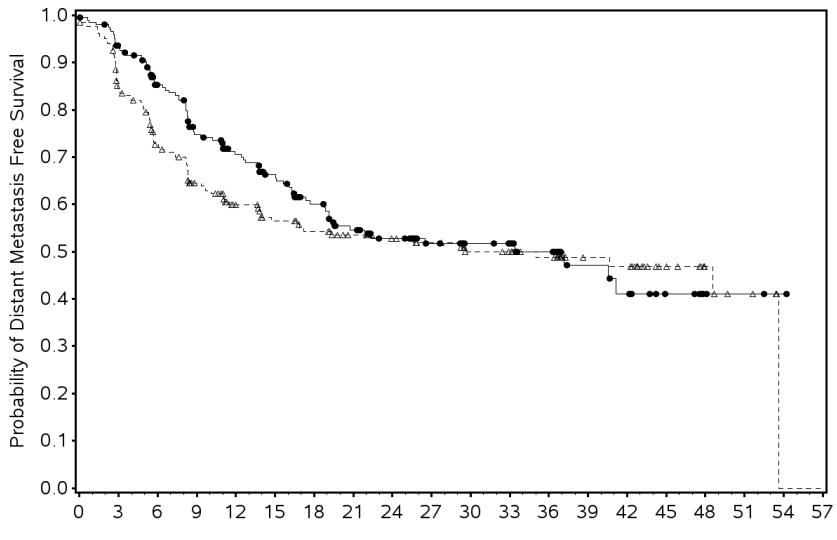
207 182 153 131 113 99 78 66 54 46 40 37 26 16 13 7 3 2 1 0

Placebo (events : 114/207), median and 95% CI : 13.86 (9.66, 25.66)

Nivolumab (events : 105/207), median and 95% CI : 19.15 (16.07, 37.16)

Nivolumab vs Placebo - hazard ratio (95% CI) : 0.81 (0.62, 1.05)

Figure 28 *Kaplan-Meier Plot of Distant Metastasis-Free Survival - All Randomized Subjects Tumor Cell PD-L1 < 1% (DBL* 19-May-2021)



Number of Subjects at Risk

Placebo

207 165 136 113 93 81 75 68 61 57 48 46 41 27 26 15 8 4 0 0

Nivolumab

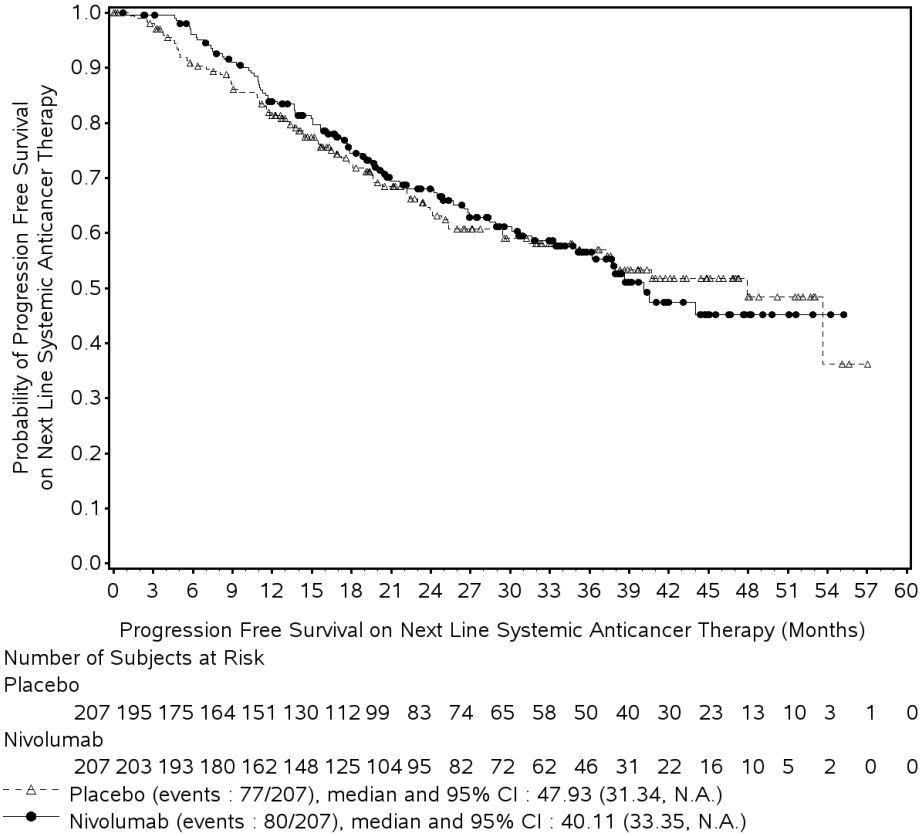
207 185 155 132 115 100 79 67 55 46 40 37 26 16 13 7 3 2 1 0

Placebo (events : 94/207), median and 95% CI : 29.54 (13.86, 53.65)

Nivolumab (events : 85/207), median and 95% CI : 33.41 (19.15, N.A.)

Nivolumab vs Placebo - hazard ratio (95% CI) : 0.80 (0.60, 1.08)

Figure 29 *Kaplan-Meier Plot of Progression-free Survival on Next Line Systemic Anticancer Therapy (PFS2) - All Randomized Subjects with Tumor Cell PD-L1 <1% DBL*



Nivolumab vs Placebo - hazard ratio (95% CI) : 0.94 (0.68, 1.29)

Multivariate analysis DFS

In a multivariate analysis of DFS in all randomised patients, the treatment effect when adjusted for age (< 65 years vs ≥ 65 years), gender (male vs female), baseline ECOG status (0 vs 1 vs 2), and pathological status (pT0-2 vs. pT3 vs. pT4), was consistent with the primary DFS analysis. Pathological status pT0-2 vs pT4 was a significant prognostic factor for DFS.

In a multivariate analysis of DFS in all randomised patients with tumour PD-L1 expression ≥1%, the treatment effect when adjusted for age (< 65 years vs ≥ 65 years), gender (male vs female), baseline ECOG status (0 vs 1 vs 2), and pathological status (pT0-2 vs. pT3 vs. pT4), was consistent with the primary DFS analysis. Pathological status pT0-2 vs pT4 was a significant prognostic factor for DFS.

Biomarker Analyses (Exploratory Endpoint)

Efficacy by Baseline PD-L1

Table 26 *Efficacy of Nivolumab by Baseline PD-L1 Tumour Cell Expression Levels - All Randomised Subjects 01 (*DBL on 27-Aug-2020)

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	PBO N = 209	Nivo N = 210	PBO N = 141	Nivo N = 139	PBO N = 244	Nivo N = 239	PBO N = 106	Nivo N = 110	PBO N = 255	Nivo N = 252	PBO N = 95	Nivo N = 97
DFS												
Events, n	120	113	78	52	141	126	57	39	148	131	50	34
Median DFS, mo.[a] (95% CI)	11.07 (8.31, 16.69)	16.49 (13.67, 20.76)	10.87 (5.75, 22.14)	N.A. (22.01, N.A.)	9.66 (8.25, 13.83)	18.79 (13.96, 22.01)	13.57 (5.82, 29.57)	N.A. (24.57, N.A.)	9.66 (8.25, 13.86)	18.89 (14.06, 22.01)	13.57 (5.75, N.A.)	N.A. (20.80, N.A.)

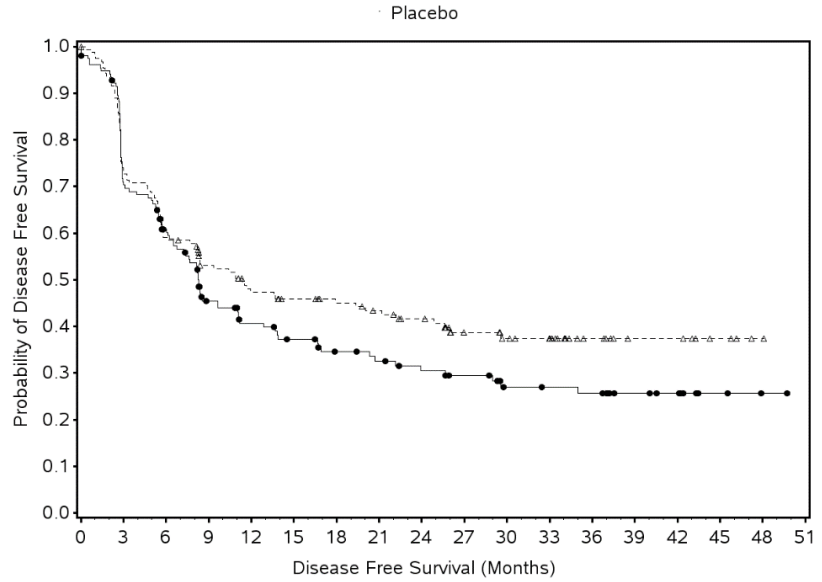
Efficacy by Baseline PD-L1 Combined Positive Score (CPS)

Table 27 *Efficacy of Nivolumab by Baseline PD-L1 CPS - All Randomised Subjects (*DBL on 27-Aug-2020)

	PD-L1 CPS < 1		PD-L1 CPS ≥ 1		PD-L1 CPS < 10		PD-L1 CPS ≥ 10	
	PBO N = 38	Nivo N = 34	PBO N = 280	Nivo N = 283	PBO N = 156	Nivo N = 152	PBO N = 162	Nivo N = 165
DFS								
Events, n	26	25	166	129	101	86	91	68
Median DFS, mo.[a] (95% CI)	9.63 (5.42, 13.83)	6.41 (5.13, 13.67)	8.41 (7.66, 13.70)	22.01 (18.89, 40.54)	8.31 (6.51, 11.10)	15.05 (11.01, 21.88)	11.37 (7.66, 22.18)	34.96 (19.29, N.A.)

[a] Based on Kaplan-Meier estimates

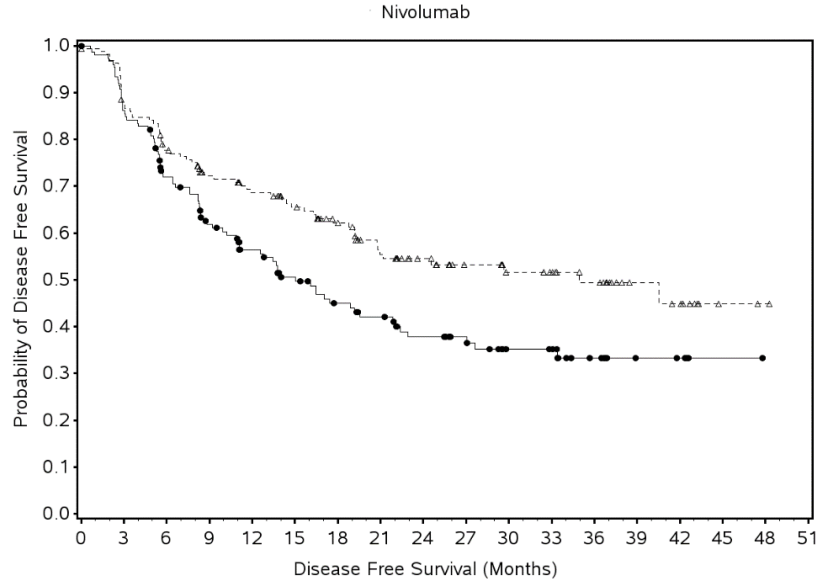
Figure 30 *Kaplan-Meier Plot of Disease-Free Survival, Primary Definition - by Baseline PD-L1 CPS at the Cutoff Value of 10% - All Randomised Quantifiable Subjects*



Number of Subjects at Risk

PD-L1 CPS >= 10%	162	113	91	76	65	60	54	50	45	33	28	25	13	8	8	4	1	0
PD-L1 CPS < 10%	156	106	85	58	49	43	36	33	29	26	20	19	18	12	10	3	1	0

PD-L1 CPS >= 10% (events : 91/162)
median and 95% CI : 11.37 (7.66, 22.18)
PD-L1 CPS < 10% (events : 101/156)
median and 95% CI : 8.31 (6.51, 11.10)



Number of Subjects at Risk

PD-L1 CPS >= 10%	165	136	119	101	92	82	70	55	46	35	30	27	22	11	9	2	1	0
PD-L1 CPS < 10%	152	130	101	83	68	57	47	42	34	30	22	21	11	6	5	1	0	0

PD-L1 CPS >= 10% (events : 68/165)
median and 95% CI : 34.96 (19.29, N.A.)
PD-L1 CPS < 10% (events : 86/152)
median and 95% CI : 15.05 (11.01, 21.88)

Post-hoc multivariate analyses to explore the results in subgroups based on prior neoadjuvant cisplatin-based chemotherapy and nodal status.

To further explore the results of the subgroup analyses, the MAH has conducted some multivariate Cox proportional hazard model analyses with respect to baseline covariates on DFS (primary definition) to explore reasons that caused different outcomes in the placebo arm and variability of treatment effect in the subgroups.

The following baseline covariates were considered in the full model: age (>= 65, < 65), sex (male, female), region (US, Europe, Asia, rest of world), ECOG PS (0, >=1), BMI (<= 25, > 25 to < 30, >= 30), smoking status (current/former, never), tumour origin type (upper tract - renal pelvis/ureter, urinary bladder), minor histological variants (yes, no), nodal status (N0/X <10 nodes removed, N0 >=10 nodes removed, N+), tumour stage (<=pT2, pT3-pT4a), prior neo-adjuvant cisplatin therapy (yes, no), baseline haemoglobin (<10 g/dL, >=10 g/dL), baseline creatine clearance (<60 mL/min, >= 60 mL/min), baseline tumour cell PD-L1 expression (>=1%, <1%). Race distribution was overlapping with region and was not considered in the model. All variables used case report form (CRF) source and values entered as "not reported", "not evaluable", "unknown", "indeterminate", etc. were considered as missing value and were excluded from model fitting.

For each multivariate model, the backward elimination method approach was used. This method of backward elimination starts with a full model including all baseline characteristics (as specified above) as covariates. The least significant variable is removed from the model until all covariates with a significance level greater or equal to 0.1 remain in the reduced model. The variable selection steps were done on the complete cases (non-missing for all baseline covariates in the full model) and repeated on the subjects with only non-missing baseline covariates in the reduced model.

The following multivariate models were analysed:

- multivariate model within placebo arm subjects
- multivariate model in the ITT population with treatment group (nivolumab versus placebo) as a fixed covariate
- multivariate model in the ITT population with treatment group (nivolumab versus placebo) and treatment-by-factor interaction as fixed covariates, where neoadjuvant cisplatin therapy and nodal status were investigated as treatment-by-factor interaction.

The multivariate model within placebo arm subjects with the significant covariates after variable selection are presented in ***Table 28***. In the placebo arm, the selected model comprised of 5 prognostic factors: age (p=0.1007), region (p=0.0637), nodal status (p<0.0001), tumour stage (p=0.0001), and prior neo-adjuvant cisplatin therapy (p=0.0177). As expected, the nodal status and prior neo-adjuvant cisplatin therapy, which were selected as randomization stratification factors, were found to be prognostic factors.

Table 28 *Multivariate model within placebo arm subjects with the significant covariates after variable selection*

Model	Parameter	DF	Estimate	Parameter Pr > ChiSq	Hazard Ratio (95% CI)
3 (n=354)	AGE (>= 65 VS < 65)	1	0.252	0.1007	1.286 (0.952, 1.738)
	REGION (US VS REST OF WORLD)	3	-0.018	0.0637	0.982 (0.617, 1.564)
	(EU VS REST OF WORLD)		-0.411		0.663 (0.454, 0.967)
	(ASIA VS REST OF WORLD)		-0.370		0.691 (0.435, 1.098)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+)	2	-0.710	<0.0001	0.492 (0.345, 0.700)
	(N0 >=10 NODES REMOVED VS N+)		-0.890		0.411 (0.283, 0.597)
	TUMOR STAGE (<= PT2 VS PT3-PT4A)	1	-0.684	0.0001	0.505 (0.355, 0.717)
	PRIOR NEO-ADJUVANT CISPLATIN (YES VS NO)	1	0.368	0.0177	1.445 (1.066, 1.958)

Model 3 is reduced model based on all randomized subjects with non-missing values for covariates in the reduced model only.

Table 29 shows the multivariate model in the ITT population with baseline characteristics and treatment as covariates included. The treatment effect remains highly significant (p=0.0005); in addition, 3 other prognostic factors were found to be significant: sex (p=0.0929), nodal status (p<0.0001) and tumor stage (p=0.0003). Those previously identified prognostic factors from the placebo arm (region, use of cisplatin neo-adjuvant therapy and age) were no longer significant in presence of above covariates. The nodal status showed consistent significance in all models within the placebo arm and in the ITT population. The adjusted HR on DFS decreased slightly from 0.706 to 0.691 after adjustment, suggesting that the treatment effect may be varying, in part, due to prognostic factors.

Table 29 *Multivariate model in the ITT population with baseline characteristics and treatment as covariates included*

Model	Parameter	DF	Estimate	Parameter Pr > ChiSq	Hazard Ratio (95% CI)
1 (n=709)	TREATMENT (NIVOLUMAB VS PLACEBO)	1	-0.349	0.0006	0.706 (0.578, 0.862)
2 (n=669)	TREATMENT (NIVOLUMAB VS PLACEBO)	1	-0.319	0.0023	0.727 (0.592, 0.892)
3 (n=669)	TREATMENT (NIVOLUMAB VS PLACEBO)	1	-0.369	0.0005	0.691 (0.562, 0.850)
	SEX (MALE VS FEMALE)	1	-0.205	0.0929	0.815 (0.642, 1.035)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+)	2	-0.624	<0.0001	0.536 (0.416, 0.690)
	(N0 >=10 NODES REMOVED VS N+)		-0.995		0.370 (0.278, 0.492)
	TUMOR STAGE (<= PT2 VS PT3-PT4A)	1	-0.470	0.0003	0.625 (0.483, 0.808)

Note: Model 1 is based on all randomized subjects. Model 2 is model with single covariate, "Treatment" restricted to complete cases in full model, including "Treatment". Model 3 is a reduced model with "Treatment" plus baseline covariates retained after backward elimination with significance level of 0.10 for retention.

Neoadjuvant Cisplatin therapy

Multivariate analyses were performed to evaluate neoadjuvant cisplatin therapy and its interaction with treatment group. ***Table 30*** presents the unadjusted model (without including other baseline covariates) and the adjusted model (including other baseline covariates and variable selection). From both models, the interaction between neoadjuvant cisplatin therapy and treatment group remains significant at a level of 0.05 regardless of presence of other baseline covariates. It should be noted that the study was not powered to detect interactions.

Table 30 *Multivariate analyses to evaluate neoadjuvant cisplatin therapy and its interaction with treatment group- unadjusted model*

Model	Parameter	DF	Parameter Estimate	Pr > ChiSq	Hazard Ratio (95% CI)
1 (n=709)	TREATMENT (NIVOLUMAB VS PLACEBO)	1	-0.164	0.2311	
	PRIOR NEO-ADJUVANT CISPLATIN (YES VS NO)	1	0.315	0.0218	
	TREATMENT * PRIOR NEO-ADJUVANT CISPLATIN	1	-0.422	0.0403	
	TREATMENT (NIVOLUMAB VS PLACEBO) AT PRIOR NEO-ADJUVANT CISPLATIN YES				0.556 (0.412, 0.752)
	TREATMENT (NIVOLUMAB VS PLACEBO) AT PRIOR NEO-ADJUVANT CISPLATIN NO				0.848 (0.648, 1.110)
	PRIOR NEO-ADJUVANT CISPLATIN (YES VS NO) AT TREATMENT NIVOLUMAB				0.899 (0.665, 1.214)
	PRIOR NEO-ADJUVANT CISPLATIN (YES VS NO) AT TREATMENT PLACEBO				1.371 (1.047, 1.794)
3 (n=669)	TREATMENT (NIVOLUMAB VS PLACEBO)	1	-0.162	0.2511	
	AGE (>= 65 VS < 65)	1	0.184	0.0937	
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+)	2	-0.604	<0.0001	
	(N0 >=10 NODES REMOVED VS N+)		-0.978		
	TUMOR STAGE (<= PT2 VS PT3-PT4A)	1	-0.511	0.0001	
	PRIOR NEO-ADJUVANT CISPLATIN (YES VS NO)	1	0.378	0.0104	
	TREATMENT * PRIOR NEO-ADJUVANT CISPLATIN	1	-0.447	0.0346	
	TREATMENT (NIVOLUMAB VS PLACEBO) AT PRIOR NEO-ADJUVANT CISPLATIN YES				0.544 (0.399, 0.741)
	TREATMENT (NIVOLUMAB VS PLACEBO) AT PRIOR NEO-ADJUVANT CISPLATIN NO				0.850 (0.645, 1.122)
	PRIOR NEO-ADJUVANT CISPLATIN (YES VS NO) AT TREATMENT NIVOLUMAB				0.933 (0.683, 1.275)
	PRIOR NEO-ADJUVANT CISPLATIN (YES VS NO) AT TREATMENT PLACEBO				1.460 (1.093, 1.950)

Note: Model 1 includes main effects of "Treatment" and variable of interest plus their interaction, restricted to complete cases based on these effects, among all randomized subjects.
Model 3 is reduced model from backward elimination, with significance level of 0.10 for retention, based on complete cases in full model among all randomized subjects. Main effects of treatment and variable and interaction always stay.

Nodal Status / Number of Resected Nodes

Multivariate analyses were performed to evaluate nodal status and number of resected nodes and its interaction with treatment group. ***Table 31*** presents the unadjusted model (without including other baseline covariates) and the adjusted model (including other baseline covariates and variable selection). The multivariate analysis evaluating the impact of nodal status and number of resected nodes confirms the initial clinical interpretation of the results and the published data. It showed that the interaction between nodal status and treatment group is not significant in either the final or reduced model (***Table 31***).

Table 31 *Multivariate analyses were performed to evaluate nodal status and number of resected nodes and its interaction with treatment group*

Model	Parameter	DF	Parameter Estimate	Pr > ChiSq	Hazard Ratio (95% CI)
1 (n=707)	TREATMENT (NIVOLUMAB VS PLACEBO)	1	-0.453	0.0009	
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+)	2	-0.578	<0.0001	
	(N0 >=10 NODES REMOVED VS N+)		-0.815		
	TREATMENT * NODAL STAGE (NIVOLUMAB, N0/X <10 NODES REMOVED)	2	0.374	0.2768	
	TREATMENT * NODAL STAGE (NIVOLUMAB, N0 >=10 NODES REMOVED)		0.010		
	TREATMENT (NIVOLUMAB VS PLACEBO) AT NODAL STAGE N0/X <10 NODES REMOVED				0.924 (0.625, 1.366)
	TREATMENT (NIVOLUMAB VS PLACEBO) AT NODAL STAGE N0 >=10 NODES REMOVED				0.642 (0.398, 1.036)
	TREATMENT (NIVOLUMAB VS PLACEBO) AT NODAL STAGE N+				0.636 (0.486, 0.831)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+) AT TREATMENT NIVOLUMAB				0.816 (0.577, 1.154)
	NODAL STAGE (N0 >=10 NODES REMOVED VS N+) AT TREATMENT NIVOLUMAB				0.447 (0.297, 0.673)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N0 >=10 NODES REMOVED) AT TREATMENT NIVOLUMAB				1.826 (1.157, 2.881)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+) AT TREATMENT PLACEBO				0.561 (0.406, 0.776)
	NODAL STAGE (N0 >=10 NODES REMOVED VS N+) AT TREATMENT PLACEBO				0.443 (0.307, 0.638)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N0 >=10 NODES REMOVED) AT TREATMENT PLACEBO				1.268 (0.836, 1.923)
3 (n=669)	TREATMENT (NIVOLUMAB VS PLACEBO)	1	-0.497	0.0004	
	SEX (MALE VS FEMALE)	1	-0.220	0.0711	
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+)	2	-0.836	<0.0001	
	(N0 >=10 NODES REMOVED VS N+)		-1.022		
	TUMOR STAGE (<= PT2 VS PT3-PT4A)	1	-0.485	0.0002	
	TREATMENT * NODAL STAGE (NIVOLUMAB, N0/X <10 NODES REMOVED)	2	0.466	0.1649	
	TREATMENT * NODAL STAGE (NIVOLUMAB, N0 >=10 NODES REMOVED)		0.046		
	TREATMENT (NIVOLUMAB VS PLACEBO) AT NODAL STAGE N0/X <10 NODES REMOVED				0.970 (0.647, 1.454)
	TREATMENT (NIVOLUMAB VS PLACEBO) AT NODAL STAGE N0 >=10 NODES REMOVED				0.637 (0.387, 1.048)
	TREATMENT (NIVOLUMAB VS PLACEBO) AT NODAL STAGE N+				0.609 (0.463, 0.800)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+) AT TREATMENT NIVOLUMAB				0.691 (0.483, 0.988)
	NODAL STAGE (N0 >=10 NODES REMOVED VS N+) AT TREATMENT NIVOLUMAB				0.377 (0.247, 0.576)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N0 >=10 NODES REMOVED) AT TREATMENT NIVOLUMAB				1.833 (1.142, 2.942)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N+) AT TREATMENT PLACEBO				0.434 (0.307, 0.612)
	NODAL STAGE (N0 >=10 NODES REMOVED VS N+) AT TREATMENT PLACEBO				0.360 (0.245, 0.528)
	NODAL STAGE (N0/X <10 NODES REMOVED VS N0 >=10 NODES REMOVED) AT TREATMENT PLACEBO				1.205 (0.780, 1.860)

Note: Model 1 includes main effects of "Treatment" and variable of interest plus their interaction, restricted to complete cases based on these effects, among all randomized subjects.
Model 3 is reduced model from backward elimination, with significance level of 0.10 for retention, based on complete cases in full model among all randomized subjects. Main effects of treatment and variable and interaction always stay.

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 32 Summary of efficacy for trial CA209274

Title: A Phase 3 Randomised, Double-blind, Multi-center Study of Adjuvant Nivolumab Versus Placebo in Subjects With High Risk Invasive Urothelial Carcinoma (CheckMate 274: CHECKpoint Pathway and nivoluMAb Clinical Trial Evaluation 274)			
Study identifier	CA209274		
Design	Phase 3 multicentre randomised double-blind nivolumab/placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		47 months(Mar-2016 – Jan-2020) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	**Nivolumab**		adjuvant 240 mg Q2W 1 year unless recurrence, toxicity **N= 353**
	Placebo		adjuvant Q2W 1 year unless recurrence, toxicity **N=356**
Endpoints and definitions	Primary endpoint	DFS for 'all randomised' and for PD-L1≥ 1% patients (dual-primary)	Disease Free Survival- Time from randomization date and date of the first documented recurrence or death
	Secondary endpoint	for 'all randomised' and for PD-L1≥ 1% patients: OS NUTRFS DSS	 Overall survival- the time between the date of randomization and the date of death (of any cause). Non Urothelial Tract Recurrence Free Survival- Time between the date of randomization and the date of first documented recurrence (local non urothelial tract or distant), or death (from any cause), whichever occurred first. Disease Specific Survival- the time between the date of randomization and the date of death due to disease (urothelial cancer).
Database lock	27 August 2020		

Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat (ITT) for DFS 'all randomised' patients and PD-L1≥1%. Clinical cut-off 17 July 2020; minimum follow-up 5.9 months.				
Descriptive statistics and estimate variability	Treatment group	**Nivolumab-all randomised patients**	**Placebo-control-all randomised patients**	**Nivolumab-PD-L1≥1% patients**	**Placebo-control-PD-L1≥1% patients**
	Number of subject	N=353	N=356	N=140	142
	Median DFS primary definition	20.76	10.84	NA	8.41
	95% confidence interval (CI)	(16.49, 27.63)	(8.25, 13.86)	(21.19, N.A.)	(5.59, 21.19)
	Median NUTRFS	22.93	13.70	NA	10.84
	(95% CI)	(19.15, 33.41)	(8.41, 20.34)	(24.57, N.A.)	(5.65, 22.14)
Effect estimate per comparison	Dual-Primary endpoint: DFS in all randomised' and PD-L1≥ 1% patients	Comparison groups	Nivolumab vs placebo	Comparison groups	Nivolumab vs placebo
		HR	0.70	HR	0.55
		98.22% CI	0.55, 0.90	98.72% CI:	0.35, 0.85
		P-value	0.0008	P-value	0.0005
	Secondary endpoint: NUTRFS all randomised' and for PD-L1≥ 1% patients	Comparison groups	Nivolumab vs placebo	Comparison groups	Nivolumab vs placebo
		HR	0.72	HR	0.55
		95%CI	0.59, 0.89	95% CI	0.39, 0.79
		P-value	No formal comparison	P-value	No formal comparison

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study design

The randomised, double-blinded, nivolumab-placebo controlled study design that was used in study CA209274 is considered adequate to evaluate the benefits and risks of adjuvant nivolumab in patients who have undergone radical resection of MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence.

Study population

The inclusion and exclusion criteria for study CA209274 appear overall acceptable. However, it is uncertain whether the results obtained in MIBC patients can be regarded relevant for the UTUC

patients considering differences in the anatomic site, lymphogenic spreading pattern, early onset of (obstructive) symptoms and only a thin muscle layer in contrast to the bladder muscle layer. The course of disease and metastasis pattern might differ.

The temporarily capped at 20% of the UTUC population is considered acceptable considering the general MIUC population.

Both patients who have received cisplatin-based neo-adjuvant chemotherapy and who have not received neo-adjuvant chemotherapy were allowed in the study. According to guidelines, neoadjuvant cisplatin-based chemotherapy is the treatment of choice, based on a meta-analysis that showed an improvement in OS of 50% versus 45%, HR 0.87 (95% CI 0.78-0.98) and a lower risk of recurrence (HR 0.81, 95% CI 0.74-0.90), resulting in a DFS advantage of 7% (Stadler, 2003). Patients who did not receive cisplatin-based neoadjuvant chemotherapy either because non-eligible or because refusing adjuvant cisplatin chemotherapy were eligible to enter the study with an ECOG PS score of 2. This could potentially have led to the inclusion of patients who had a poorer health status compared to those eligible for neoadjuvant therapy, however this is excluded by demographics data.

Treatments

Since there is not a widely accepted adjuvant treatment regimen for this study population (ESMO guidelines 2019), a placebo is an acceptable comparator. The nivolumab dose of 240 mg Q2W is similar to the dose approved for locally advanced inoperable or metastatic urothelial carcinoma and therefore adequate. The additional 480 mg Q4W regimen is considered sufficiently substantiated and therefore acceptable (see clinical pharmacology section).

Objectives and endpoints

The objective of this study was to compare DFS for nivolumab versus placebo. The primary endpoint was DFS analysed in two different populations (dual-primary): **subjects with PD-L1 expression level ≥1% and all randomised subjects**.

DFS as a primary endpoint of the pivotal study might be sufficient for registrational purposes when there is a clear treatment effect supported by a difference in plateaus in the Kaplan-Meier curves suggesting long-term benefit, and thus likely a higher cure rate. If this is not evident, OS data are normally needed for interpretation of the benefit of the investigational product in the adjuvant setting at hand (EMA/CHMP/205/95 Rev.5). This is of the utmost importance to prevent patients to be treated with an adjuvant therapy in the absence of benefit, while being exposed to safety risks.

Other endpoints were also analysed for the all-randomised and for the PD-L1≥1% group.

The key secondary endpoint was OS. However, at the time of the 01-Feb-2021 cut-off date OS data were not mature [57.4% of the planned 404 OS events were observed for all randomized subjects and 84 (50.6%) of the planned 166 OS events were observed for all randomized subjects with tumour cell PD-L1 expression level ≥ 1%] and did not meet the pre-specified boundary for declaring the statistical significance. The Data Monitoring Committee (DMC) therefore recommended to not release this information to BMS in alignment with the DMC charter. Following this recommendation, the study OS data remains blinded. Consequently, no OS summary is included in this report. OS data will however be reported upon formal submission when mature data become available.

The other secondary endpoints, i.e. NUTRFS and DSS, were only supportive since their relation to clinical benefit is unclear and no formal comparison was done for these endpoints. DMFS was defined as an exploratory endpoint without correction for multiplicity testing and can be used only as supportive data. The same holds for PFS2. The exploratory endpoints for 'safety and tolerability', TTR,

LRDFS, LRC are acceptable, however LRDFS and LRC are not commonly used endpoints in urothelial carcinoma.

Statistical methods

Only DFS and then OS were tested hierarchically, all other endpoints were only descriptive. DFS in PD-L1 ≥1% and DFS in all randomised were dual endpoints (both of each were allocated half of the total type I error, 0.025 two-sided each).

A stratified log-rank test (primary analysis) and Fleming-Harrington test (supportive analysis) for DFS were used. However, the Fleming-Harrington test downweighs early events and upweights late events and can therefore give statistically significant results without being clinically relevant, while for interpretation the Kaplan-Meier curves are needed.

DFS in the primary definition was censored for both new subsequent therapy and new non-urothelial primary carcinoma. This may have led to informative censoring. The secondary definition of DFS which does not censor new subsequent therapy is more in line with the recommendation in EMA's oncology guideline (CHMP/27994/2008 Rev. 1) and is therefore preferred. However, although it is recommended to not censor for subsequent therapy, subsequent therapy use is negligible and the primary definition results for DFS are very similar to those of the secondary definition.

An interim analysis was conducted for DFS which is not recommended (CHMP/27994/2008 Rev. 1) in general, and specifically for the adjuvant setting where there is the risk that the desired long-term effects cannot be interpreted.

Exploratory endpoint like disease specific survival and time to recurrence have death-not-due-to-disease as a competing risk. Therefore, a beneficial effect on the event(s) of interest (in a certain time frame) may be at the cost of an adverse effect in the competing risk event (in that time frame), and vice versa. Therefore, endpoints with their competing risk analyses should be evaluated together with their competing risk.

Efficacy data and additional analyses

Participant flow and recruitment

In total 1075 subjects were enrolled at 170 sites in 30 countries and 709 subjects were randomised. The most common reason for not being randomised was due to patients no longer meeting the study criteria. This is considered acceptable.

Study conduct

During the study several amendments have been implemented such as increase of sample size, capping and de-capping to steer towards a realistic percentage of PD-L1 positive patients, changing the hierarchical testing procedure (OS became key secondary endpoint), and addition of a formal early OS interim analysis (FDA request) at the time of the DFS IA or when the final DFS analysis would have crossed the pre-specified boundary for statistical significance. Given the double-blind character of the study, these amendments are not likely to have affected the results of the study

While the procedure was ongoing, the MAH discovered that the DFS data in the original CSR contained an error for 24 subjects in data capture on the case report form (CRF) that impacted either the status of DFS (censored vs event: recurrence or death) and/or time (date of recurrence). A restricted database re-lock and reanalysis were performed, and updated results for DFS, NUTRFS, and DMFS were provided in an erratum. The main cause for the DFS errors was determined to be the complexity in the collection of these data in the eCRF, resulting in some sites incorrectly recording the date and/or type of DFS event in the disease recurrence page. Further, data monitoring and risk mitigation were

not sufficiently adequate on this subject, particularly since these errors were discovered after questions by the FDA. Thus, trial oversight/data management has been suboptimal for this study. DFS errors specifically, were related to discordance between the first date a suspect lesion was identified and the date of recurrence confirmation at a later timepoint e.g. by additional procedures. As the time between the date of first identification of a lesion and the confirmation of that lesion by additional investigation is generally expected to be short, the errors are not considered to lead to major changes in the DFS data at least not when occurring in a low frequency, as was the case in the pivotal study. In conclusion, the data are considered sufficiently reliable for assessment.

Demographics and other baseline characteristics

Overall, the median age of all randomised subjects was 67.0 years. Most subjects were white (75.6%), male (76.2%) and had an ECOG PS of 0 (62.8%). The predominant tumour type was urinary bladder (79.0% of subjects). The demographics and other baseline characteristics were well balanced between both treatment arms in both the all randomised and the PD-L1≥1% populations. The population might be considered representative for the European patient population. Few patients with an ECOG =2 were included in the study (2.3%). Baseline demographic and disease characteristics in randomised subjects with tumour cell PD-L1 expression level ≥1% were consistent with that in all randomised subjects.

Overall, in daily practice around half of patients are eligible for/willing to have such neoadjuvant treatment and this is reflected in the study population (43% having been pre-treated with cisplatin-based chemotherapy).

Primary endpoint-DFS

Efficacy data presented is based on the clinical DBL on 27-Aug-2020 for the planned IA of DFS as specified in the protocol, with a median follow-up time of 20.90 months and 19.48 months (48% and 57% events) for all randomised patients and 22.11 months and 18.69 months (39% and 57% events) for PD-L1 expression ≥1% patients in the nivolumab and placebo arms, respectively.

Nivolumab as adjuvant therapy demonstrated a statistically significant advantage in the dual-primary endpoint of DFS vs placebo in **subjects with tumour cell PD-L1 ≥1%:** HR = 0.55 [98.72% CI: 0.35, 0.85]; p-value = 0.0005). Median DFS was not reached in the nivolumab arm and was of 8.41 months in the placebo arm. DFS event- and censoring rates per 6 months to assess plateau formation in the KM curves were provided on request. The results indicate that while a definitive conclusion that DFS plateaus have been reached cannot be drawn yet for both study arms, the data are indicative that there is a trend towards such situation.

The KM-curve for **PD-L1 ≥1% patients** show clear early separation of the curves and a plateau appears to be reached for DFS from 27 months onwards, however the small numbers at risk at that time do not allow for a definitive conclusion. A similar pattern is observed for the NUTRFS, DMFS and PFS2 results. Nonetheless, it appears that the efficacy in terms of DFS in the PD-L1 ≥ 1% patients is suggestive for long-term benefit. During the procedure updated efficacy data was provided from a DBL on 19-May-2021 which translated into approximately 5 additional months of follow-up since the previous DBL. Updated DFS data continue to support a long term DFS effect in PD-L1 ≥ 1% patients.

Also in the **all randomised subject population** a statistically significant outcome of the dual-primary endpoint of DFS was observed for nivolumab over placebo: HR = 0.70 [98.22% CI: 0.55, 0.90]; p = 0.0008; median DFS of 20.76 months vs 10.84 months. However, there is extensive censoring in the KM curves. A similar pattern is observed in the KM-curves for NUTRFS (secondary endpoint) and for DMFS and PFS2 (exploratory endpoints). Updated DFS results are comparable to the primary analysis. DFS event and censoring rates were not provided, thus not allowing to evaluate a difference in plateaus in the DFS KM-curves that would be suggestive of long-term benefit.

Note that around 60% of the study population does not have a PD-L1 expression ≥1%. Regretfully no formal analyses were planned in the **PD-L1<1% patients**. The DFS subgroup results for these patients indicate a HR point estimate of 0.80 (95% CI: 0.62, 1.03) with a median DFS of 17.68 months (95% CI: 14.06-22.37) in the nivolumab group versus 11.07 months (95% CI: 8.31-16.89) in the placebo group and overlapping CIs with similar updated results. The DFS KM-curve provided during the procedure indicates no clinically meaningful treatment effect in this subgroup, as the curves initially shows some separation, however after 18 months the curves converge with comparable event rates after 22 months in both study arms. KM-curves for the secondary endpoints also do not indicate clinically relevant efficacy in the PD-L1<1% population. Thus, the efficacy of nivolumab in 'all randomised patients' is driven by the efficacy in PD-L1≥1% patients. A pattern which is also apparent in the secondary and exploratory time to event endpoints (though not formally tested).

To explore further the benefit in PD-L1<1% patients, the MAH performed a post-hoc exploratory analysis in this PD-L1 subgroup excluding UTUC patients (focussing on bladder cancer only patients) and observed a DFS HR of 0.70 (95% CI 0.53, 0.94). Notably, this exploratory analysis was conducted following explicit confirmation by the MAH that UTUC should be regarded as the same disease entity as MIBC and therefore included in the indication. Furthermore, it is not considered acceptable to deduce from a post-hoc analysis of a subgroup of a subgroup of patients (i.e. PD-L1<1%, bladder cancer only), that a beneficial effect can be shown while it is not shown for the entire PD-L1<1% population, particularly not in the absence of pre-planning, a biological rationale and/or replication.

In conclusion, it remains unlikely that adjuvant nivolumab treatments results into a long-term benefit/ a higher cure rate in PD-L1<1% patients. Also taking into account that administration of this drug is associated with toxicity, it cannot be concluded that the B/R is positive in the PD-L1<1% population.

Although it is recommended to not censor for subsequent therapy, subsequent therapy use is negligible and the primary definition results for DFS are very similar to those of the secondary definition.

At the same time the HR for other subgroups showed substantial variability in the **all randomised subjects population**, which may be explained by several factors. The HR point estimate for DFS in the subgroup with neoadjuvant cisplatin was 0.52 while without cisplatin it was 0.92 (95% CI: 0.69, 1.21). This may be explained by the fact that subjects with excellent response to neoadjuvant therapy (i.e., ypT0/Ta/Tcis/T1 and N0) were excluded from the study, thus selecting subjects with worse outcomes among those who had received neoadjuvant therapy. Post hoc models provided by the MAH indicate that the difference in effect depending on neoadjuvant cisplatin therapy is likely not a chance finding.

In the **PD-L1≥1% patients** HR point estimates were 0.37 (95% CI: 0.22; 0.64) and 0.69 (95%CI: 0.44; 1.08), respectively, showing the same pattern with prior cisplatin performing better. As these data are relevant for prescribers in clinical practice the data is reported in the SmPC.

For patients with N0/x with less than 10 nodes removed the HR is 0.85 in all randomised and 0.87 in PD-L1≥1% patients. There is no clinical or mechanistical reason for a different effect and post hoc analyses provided by the MAH indicate that this may be a chance finding as there is no major difference in treatment effect within each subcategory of nodal status. The multivariate analyses confirmed subjects with N+ tumors have the worst treatment effect and benefit from nivolumab. It also showed that resecting less than 10 lymph nodes (or when the N status is unknown) is associated with a worse treatment effect compared to subjects with N0 status and 10 or more lymph nodes removed, observed in both treatment arms but emphasized in the nivolumab arm. It is questioned whether information on subgroups based on nodal status is useful considering the difficulty in reliably establishing the "true" nodal status and the likelihood of a chance finding.

Secondary Endpoints

No data on key secondary endpoint OS were provided in the initial submission, as at the first pre-specified interim analysis the pre-specified boundary for declaring the statistical significance was not met. Even if the absence of mature OS data constitutes a limitation in the context of the proposed adjuvant treatment, the size of the DFS effect in the PD-L1 ≥1% population is such that it is reasonably likely that a favourable effect on the long-term, including a higher cure rate, is achieved, while this is not the case for the PD-L1 <1% population. At least a detrimental effect on OS is considered very unlikely and the updated DFS together with the known safety profile of nivolumab result are sufficient to support clinical benefit in the PD-L1 ≥1% population.

In order to further characterize the efficacy of nivolumab as adjuvant treatment of adults with muscle invasive urothelial carcinoma the MAH should submit the OS data from the 2nd IA and the final OS analysis of the Phase 3 CA209274 study for the PD-L1 ≥1% populations.

NUTRFS

No formal comparisons were planned for the secondary NUTRFS or exploratory endpoints, so these endpoints are merely descriptive for both primary populations.

NUTRFS results in patients with PD-L1 ≥1% appears in support of DFS in patients with PD-L1 ≥1%, but the importance of this endpoint for clinical benefit in the target population is unclear and considering the chosen statistical strategy, results are descriptive.

Exploratory endpoints

DMFS, TTR, LRDFS, LRC, PFS2,

The HR point estimate for DMFS (i.e. 0.75) in the **all randomised patients** showed a similar effect as DFS in favour of nivolumab over placebo. No formal comparison was done. Furthermore, the DMFS KM curves bend towards each other over time and also the CI of the median DFS overlap between the nivolumab and placebo arm. A similar notion can be made for the other exploratory endpoints, though merely descriptive.

For **patients with PD-L1 ≥1%** the HR point estimates of the exploratory endpoints, show a similar effect as was observed for DFS in patients with PD-L1 ≥1%. Updated data support the primary analyses.

However, in **patients with PD-L1<1%** the results in exploratory endpoints and the Kaplan-Meier plots are not indicative of benefit for this population.

In conclusion, also for DMFS and the others exploratory endpoints (**TTR, LRDFS, LRC, PFS2)** these the results seem to be driven by PD-L1 ≥ 1% patients.

Biomarker analysis

The DFS efficacy of nivolumab vs placebo was considered in relation to PD-L1 tumour cell expression status (< 1%, ≥ 1%, < 5%, ≥ 5%, < 10%, and ≥ 10%) and to PD-L1 CPS populations (≥ 1, < 10, ≥ 10), however, no optimal cut-off value could be defined with respect to PD-L1 expression.

Quality of life

Baseline data of QoL were comparable in both treatment groups and did not show a different effect from treatment between nivolumab and placebo during follow-up. Further, since results provided are merely descriptive for HrQoL exploratory endpoints, they are not reflected in section 5.1 of the SmPC.

Patients with a baseline performance score of ≥2 (except patients with a baseline performance score of 2 who have not received cisplatin based neoadjuvant chemotherapy and are considered ineligible for cisplatin adjuvant chemotherapy), evidence of disease after surgery, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trial of adjuvant treatment of urothelial carcinoma. 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 (see section 4.4 of the SmPC).

2.4.4. Conclusions on the clinical efficacy

DFS results in the **PD-L1≥1% population** showed a statistically significant and clinically meaningful improvement in DFS in patients treated with one year adjuvant nivolumab compared to placebo. Statistical significant and clinically meaningfulness are based on the HR, the median DFS and the pattern of the curve showing a plateau. Results in the secondary/exploratory endpoints provide confirmation support of long-term benefit in these patients.

Even if lack of mature OS data constitutes a limitation in the context of the proposed adjuvant treatment, the size of the DFS effect in the PD-L1 ≥1% population is such that it is reasonably likely that a favourable effect on the long-term, including a higher cure rate, is achieved, while this is not the case for the PD-L1 <1% population. Based on the DFS results (extent and duration) at least a detrimental effect on OS is considered very unlikely and the updated DFS together with the known safety profile of nivolumab result are sufficient to support clinical benefit in the PD-L1 ≥1% population.

This having said, the results of the planned 2nd OS IA in all randomised subjects with tumour cell PD-L1 expression level ≥ 1% and final analysis for OS remain key to confirm the data showed by the DFS endpoint and should be provided as soon as available as an Annex II condition.

The beneficial DFS effect for the **all randomised patients** (irrespective of PD-L1 expression) is driven by the PD-L1≥1% patients. In the all randomised patient population there is uncertainty about the sustainability of the treatment effect and taking into account that administration of this drug is associated with toxicity, it cannot be concluded that the B/R is positive in the PD-L1<1%.

The finally agreed indication is as follows (**text added**):

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) **with tumour cell PD-L1 expression ⩾ 1%,** who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).

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

Post authorisation efficacy study (PAES): In order to further characterize the efficacy of nivolumab as adjuvant treatment of adults with muscle invasive urothelial carcinoma the MAH should submit the OS data from the 2nd IA and the final OS analysis of the Phase 3 CA209274 study for the PD-L1 ≥1% population.

2.5. Clinical safety

Introduction

The existing safety profile of nivolumab monotherapy (240mg Q2W or 480 mg Q4W) has been established across several tumour types, including of locally advanced unresectable or metastatic urothelial carcinoma adults after failure of prior platinum containing therapy.

The safety data for this extension of indication in patients with high risk muscle invasive urothelial carcinoma at radical resection is derived from Study CA209274 a Phase 3, randomised, double-blind, placebo-controlled study of nivolumab versus placebo in subjects who have undergone radical resection of MIUC originating in the bladder or upper urinary tract and are at a high risk of recurrence. Pooled safety data for all approved monotherapy indications are provided in the section "Safety in the SmPC".

Patient exposure

Safety data in subjects treated with nivolumab monotherapy (N = 351) and placebo (N = 348) are based on the clinical cut-off date of 17-Jul-2020 and database lock (DBL) date of 27 Aug 2020. The all treated population who received at least 1 dose of study drug was the primary population for safety analyses. The median follow-up time was 20.90 months and 19.48 months for all randomised subjects in the nivolumab and placebo arms, respectively. The minimum follow up time was 5.9 months for all randomised subjects.

For a summary on cumulative dose and dose intensity refer to **Table 33**. The median duration of therapy for all treated subjects was 8.77 months in the nivolumab arm and 8.21 months in the placebo arm, see also **Table 34**.

Table 33 *Cumulative Dose and Relative Dose Intensity Summary - All Treated Subjects*

	Placebo N = 348	Nivolumab N = 351
NUMBER OF DOSES RECEIVED		
MEAN (SD)	16.5 (8.9)	16.7 (9.0)
MEDIAN (MIN - MAX)	18.0 (1 - 27)	19.0 (1 - 27)
CUMULATIVE DOSE (MG)		
MEAN (SD)	N.A.	3997.66 (2155.95)
MEDIAN (MIN - MAX)	N.A.	4560.00 (240.0 - 6480.0)
RELATIVE DOSE INTENSITY (%)		
>= 110%	N.A.	0
90% TO < 110%	N.A.	297 (84.6)
70% TO < 90%	N.A.	49 (14.0)
50% TO < 70%	N.A.	3 (0.9)
< 50%	N.A.	2 (0.6)

Abbreviations: MAX = maximum, MIN = minimum, SD = standard deviation.

Table 34 *Duration of Study Therapy Summary - All Treated Subjects*

	Placebo N = 348	Nivolumab N = 351
DURATION OF THERAPY (MONTHS)		

MEAN (MIN, MAX)	7.50 (0.0, 12.6)	7.63 (0.0, 12.5)
MEDIAN	8.21	8.77
N OFF TRT/N TREATED (%)	328/348 (94.3)	330/351 (94.0)
> 3 MONTHS (%)	255 (73.3)	271 (77.2)
> 6 MONTHS (%)	209 (60.1)	212 (60.4)
> 9 MONTHS (%)	160 (46.0)	173 (49.3)
> 12 MONTHS (%)	13 (3.7)	7 (2.0)

Abbreviations: MAX = maximum, MIN = minimum

Adverse events

A summary of the safety data in Study CA209274 is provided below in ***Table 35***.

Table 35 *Summary of Safety - All Treated Subjects*

	No. of Subjects (%)			
Safety Parameters	**Placebo (N = 348)**		**Nivolumab (N = 351)**	
Deaths	107 (30.7)		95 (27.1)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	105 (30.2)	73 (21.0)	104 (29.6)	81 (23.1)
Drug-related SAEs	7 (2.0)	6 (1.7)	32 (9.1)	26 (7.4)
All-causality AEs leading to DC	32 (9.2)	21 (6.0)	64 (18.2)	39 (11.1)
Drug-Related AEs leading to DC	7 (2.0)	5 (1.4)	45 (12.8)	25 (7.1)
All-causality AEs	332 (95.4)	122 (35.1)	347 (98.9)	148 (42.2)
≥ 15% of Subjects in Any Treatment Arm				
Pruritus	56 (16.1)	0	106 (30.2)	0
Diarrhoea	91 (26.1)	4 (1.1)	102 (29.1)	6 (1.7)
Fatigue	85 (24.4)	1 (0.3)	96 (27.4)	2 (0.6)
Urinary tract infection	66 (19.0)	22 (6.3)	70 (19.9)	19 (5.4)
Rash	34 (9.8)	0	66 (18.8)	2 (0.6)
Nausea	44 (12.6)	0	57 (16.2)	2 (0.6)
Constipation	53 (15.2)	1 (0.3)	47 (13.4)	1 (0.3)
Drug-related AEs	193 (55.5)	25 (7.2)	272 (77.5)	63 (17.9)
≥ 15% of Subjects in Any Treatment Arm Events				
Pruritus	40 (11.5)	0	81 (23.1)	0
Fatigue	42 (12.1)	0	61 (17.4)	1 (0.3)
Diarrhoea	38 (10.9)	1 (0.3)	59 (16.8)	3 (0.9)
Rash	19 (5.5)	0	53 (15.1)	2 (0.6)

MedDRA version 23.0; CTC version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated. Abbreviations: AE = adverse event, DC = discontinuation, IMAE = immune-mediated adverse event, MedDRA = Medical Dictionary for Regulatory Activities, CTC = Common Terminology Criteria, OESI = other event of special interest, SAE = serious adverse event.

Adverse events (regardless of causality)

Any-grade AEs (regardless of causality) were reported in 347 (98.9%) subjects in the nivolumab arm and 332 (95.4%) subjects in the placebo arm (refer to ***Table 36 Table 36***).

Table 36 *Adverse Events by Worst CTC Grade with 5% Cut-off - All Treated Subjects*

System Organ Class (%) Preferred Term (%)	Placebo N = 348			Nivolumab N = 351		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	332 (95.4)	122 (35.1)	6 (1.7)	347 (98.9)	148 (42.2)	2 (0.6)
Gastrointestinal disorders	188 (54.0)	20 (5.7)	0	198 (56.4)	22 (6.3)	0
Diarrhoea	91 (26.1)	4 (1.1)	0	102 (29.1)	6 (1.7)	0
Nausea	44 (12.6)	0	0	57 (16.2)	2 (0.6)	0
Constipation	53 (15.2)	1 (0.3)	0	47 (13.4)	1 (0.3)	0
Abdominal pain	40 (11.5)	2 (0.6)	0	36 (10.3)	2 (0.6)	0
Vomiting	29 (8.3)	1 (0.3)	0	29 (8.3)	0	0
Dry mouth	2 (0.6)	0	0	18 (5.1)	0	0
Skin and subcutaneous tissue disorders	120 (34.5)	1 (0.3)	0	194 (55.3)	7 (2.0)	0
Pruritus	56 (16.1)	0	0	106 (30.2)	0	0
Rash	34 (9.8)	0	0	66 (18.8)	2 (0.6)	0
Dry skin	16 (4.6)	0	0	25 (7.1)	0	0
Rash maculo-papular	9 (2.6)	0	0	21 (6.0)	2 (0.6)	0
General disorders and administration site conditions	162 (46.6)	4 (1.1)	2 (0.6)	185 (52.7)	6 (1.7)	0
Fatigue	85 (24.4)	1 (0.3)	0	96 (27.4)	2 (0.6)	0
Asthenia	29 (8.3)	0	0	38 (10.8)	2 (0.6)	0
Pyrexia	36 (10.3)	1 (0.3)	0	36 (10.3)	1 (0.3)	0
Oedema peripheral	22 (6.3)	1 (0.3)	0	31 (8.8)	0	0
Infections and infestations	162 (46.6)	38 (10.9)	2 (0.6)	163 (46.4)	34 (9.7)	0
Urinary tract infection	66 (19.0)	22 (6.3)	0	70 (19.9)	19 (5.4)	0
Upper respiratory tract infection	25 (7.2)	2 (0.6)	0	31 (8.8)	1 (0.3)	0
Nasopharyngitis	25 (7.2)	0	0	23 (6.6)	0	0
Investigations	119 (34.2)	24 (6.9)	0	152 (43.3)	47 (13.4)	0
Blood creatinine increased	48 (13.8)	2 (0.6)	0	48 (13.7)	2 (0.6)	0
Amylase increased	28 (8.0)	6 (1.7)	0	44 (12.5)	16 (4.6)	0
Lipase increased	29 (8.3)	13 (3.7)	0	41 (11.7)	22 (6.3)	0
Alanine aminotransferase increased	16 (4.6)	1 (0.3)	0	23 (6.6)	2 (0.6)	0
Aspartate aminotransferase increased	14 (4.0)	1 (0.3)	0	19 (5.4)	3 (0.9)	0
Musculoskeletal and connective tissue disorders	134 (38.5)	7 (2.0)	0	136 (38.7)	6 (1.7)	0
Back pain	44 (12.6)	1 (0.3)	0	45 (12.8)	1 (0.3)	0
Arthralgia	44 (12.6)	0	0	39 (11.1)	1 (0.3)	0
Myalgia	12 (3.4)	0	0	22 (6.3)	1 (0.3)	0
Pain in extremity	18 (5.2)	1 (0.3)	0	22 (6.3)	0	0
Metabolism and nutrition disorders	91 (26.1)	17 (4.9)	0	125 (35.6)	20 (5.7)	0
Decreased appetite	25 (7.2)	1 (0.3)	0	44 (12.5)	3 (0.9)	0
Hyperkalaemia	24 (6.9)	4 (1.1)	0	21 (6.0)	5 (1.4)	0
Hyperglycaemia	26 (7.5)	5 (1.4)	0	19 (5.4)	2 (0.6)	0
Respiratory, thoracic and mediastinal disorders	85 (24.4)	5 (1.4)	0	114 (32.5)	9 (2.6)	0
Cough	38 (10.9)	0	0	45 (12.8)	0	0
Dyspnoea	18 (5.2)	1 (0.3)	0	37 (10.5)	1 (0.3)	0
Nervous system disorders	93 (26.7)	3 (0.9)	1 (0.3)	88 (25.1)	8 (2.3)	0
Headache	29 (8.3)	0	0	33 (9.4)	1 (0.3)	0
Dizziness	26 (7.5)	0	0	31 (8.8)	1 (0.3)	0
Endocrine disorders	11 (3.2)	0	0	69 (19.7)	1 (0.3)	0
Hyperthyroidism	4 (1.1)	0	0	37 (10.5)	0	0
Hypothyroidism	8 (2.3)	0	0	37 (10.5)	0	0
Blood and lymphatic system disorders	46 (13.2)	1 (0.3)	0	58 (16.5)	6 (1.7)	0
Anaemia	35 (10.1)	1 (0.3)	0	47 (13.4)	4 (1.1)	0
Vascular disorders	37 (10.6)	7 (2.0)	0	38 (10.8)	4 (1.1)	1 (0.3)
Hypertension	19 (5.5)	7 (2.0)	0	15 (4.3)	4 (1.1)	0
Psychiatric disorders	33 (9.5)	1 (0.3)	0	36 (10.3)	0	0
Insomnia	16 (4.6)	0	0	23 (6.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	36 (10.3)	19 (5.5)	1 (0.3)	19 (5.4)	10 (2.8)	1 (0.3)
Malignant neoplasm progression	20 (5.7)	13 (3.7)	1 (0.3)	8 (2.3)	6 (1.7)	1 (0.3)

MedDRA Version: 23.0
CTC Version: 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.1.31.1

Table 37 *Drug-related Adverse Events by Worst CTC Grade Reported in ≥ 5% of All Treated Subjects*

System Organ Class (%) Preferred Term (%)	Placebo N = 348			Nivolumab N = 351		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	193 (55.5)	25 (7.2)	0	272 (77.5)	63 (17.9)	0
Skin and subcutaneous tissue disorders	73 (21.0)	0	0	147 (41.9)	6 (1.7)	0
Pruritus	40 (11.5)	0	0	81 (23.1)	0	0
Rash	19 (5.5)	0	0	53 (15.1)	2 (0.6)	0
Rash maculo-papular	4 (1.1)	0	0	19 (5.4)	2 (0.6)	0
General disorders and administration site conditions	64 (18.4)	0	0	104 (29.6)	3 (0.9)	0
Fatigue	42 (12.1)	0	0	61 (17.4)	1 (0.3)	0
Asthenia	17 (4.9)	0	0	24 (6.8)	2 (0.6)	0
Gastrointestinal disorders	58 (16.7)	3 (0.9)	0	102 (29.1)	8 (2.3)	0
Diarrhoea	38 (10.9)	1 (0.3)	0	59 (16.8)	3 (0.9)	0
Nausea	13 (3.7)	0	0	24 (6.8)	0	0
Investigations	58 (16.7)	15 (4.3)	0	90 (25.6)	32 (9.1)	0
Lipase increased	20 (5.7)	9 (2.6)	0	34 (9.7)	18 (5.1)	0
Amylase increased	20 (5.7)	5 (1.4)	0	33 (9.4)	13 (3.7)	0
Blood creatinine increased	11 (3.2)	0	0	20 (5.7)	1 (0.3)	0
Endocrine disorders	7 (2.0)	0	0	63 (17.9)	0	0
Hypothyroidism	5 (1.4)	0	0	34 (9.7)	0	0
Hyperthyroidism	3 (0.9)	0	0	33 (9.4)	0	0
Metabolism and nutrition disorders	27 (7.8)	3 (0.9)	0	43 (12.3)	5 (1.4)	0
Decreased appetite	11 (3.2)	0	0	20 (5.7)	2 (0.6)	0

MedDRA Version: 23.0
CTC Version: 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.1.32.1

Exposure-adjusted adverse events rates

When incidence rates (IR) were exposure adjusted, all-causality any grade AE IR within 30 days follow-up were 1337.8 (events per 100 person-years) in the nivolumab arm and 1158.7 in the placebo arm. The most frequently reported AEs were within the SOC of gastrointestinal disorders (206.8 in the nivolumab arm and 208.5 in the placebo arm). Diarrhoea was the most frequently reported PT (62.8 in the nivolumab arm and 61.7 in the placebo arm). When IR were exposure-adjusted, drug-related AE IR within 30 days follow-up were 511.1 (events per 100 person years) with nivolumab treatment and 274.3 with placebo treatment. Endocrine disorders (36.8 vs 4.9 events per 100 person years) and skin and subcutaneous tissue disorders (80.2 vs 144.0 events per 100 person years) were observed more frequent in the nivolumab arm compared to placebo.

Subgroup analyses of adverse events

The frequencies of all-causality and drug-related AEs in the nivolumab and placebo arms for subgroups of age, gender, and geographic region were similar to the AE frequencies reported for the overall study population by treatment.

The following numerical differences were observed:

- In the Musculoskeletal and Connective Tissue Disorder system organ class (SOC), more all-causality and drug related AEs were reported in female subjects compared with male subjects in the nivolumab arm:

  - Any grade all-causality AEs were reported in 47.1% female subjects and 36.0% male subjects.
  - Any grade drug-related AEs were reported in 19.5% female subjects and 10.6% male subjects.

- In the Nervous Systems Disorder SOC, more all-causality AEs were reported in female subjects compared with male subjects in the nivolumab arm:

  - Any grade all-causality AEs were reported in 31.0% female subjects and 23.1% male subjects.

- In the Respiratory, Thoracic, and Mediastinal Disorders SOC, more all-causality AEs were reported in female subjects compared with male subjects in the nivolumab arm:

- Any grade all-causality AEs were reported in 39.1% female subjects and 30.3% male subjects.

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

- The frequencies of all-causality and drug-related AEs in the nivolumab and placebo arms for each geographic region subgroup (US or Europe or Asia) were similar to the frequencies of these types of AEs reported for the rest of the world (ROW) by treatment.

Serious adverse event/deaths/other significant events

Serious adverse events

Any-grade all-causality SAEs (within 30 days of last dose) were reported in 104 (29.6%) subjects in the nivolumab arm and 105 (30.2%) subjects in the placebo arm (***Table 38***). Grade 3-4 SAEs were reported in 81 (23.1%) subjects in the nivolumab arm and 73 (21.0%) subjects in the placebo arm.

Table 38 *Serious Adverse Events Reported in ≥ 1% of All Treated Subjects*

System Organ Class (%) Preferred Term (%)	Placebo N = 348			Nivolumab N = 351		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	105 (30.2)	73 (21.0)	6 (1.7)	104 (29.6)	81 (23.1)	2 (0.6)
Infections and infestations	40 (11.5)	28 (8.0)	2 (0.6)	27 (7.7)	22 (6.3)	0
Urinary tract infection	21 (6.0)	17 (4.9)	0	9 (2.6)	7 (2.0)	0
Sepsis	1 (0.3)	0	1 (0.3)	4 (1.1)	3 (0.9)	0
Urosepsis	6 (1.7)	4 (1.1)	0	2 (0.6)	2 (0.6)	0
Gastrointestinal disorders	15 (4.3)	13 (3.7)	0	18 (5.1)	15 (4.3)	0
Intestinal obstruction	5 (1.4)	3 (0.9)	0	5 (1.4)	4 (1.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28 (8.0)	18 (5.2)	1 (0.3)	13 (3.7)	10 (2.8)	1 (0.3)
Malignant neoplasm progression	19 (5.5)	12 (3.4)	1 (0.3)	8 (2.3)	6 (1.7)	1 (0.3)
Renal and urinary disorders	15 (4.3)	12 (3.4)	0	11 (3.1)	8 (2.3)	0
Acute kidney injury	1 (0.3)	0	0	5 (1.4)	3 (0.9)	0
Hydronephrosis	4 (1.1)	3 (0.9)	0	2 (0.6)	2 (0.6)	0
Urinary tract obstruction	4 (1.1)	3 (0.9)	0	1 (0.3)	1 (0.3)	0

MedDRA Version: 23.0
CTC Version: 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.3.1.2.1

Any-grade drug-related SAEs (within 30 days of last dose) were reported in 32 (9.1%) subjects in the nivolumab arm and 7 (2.0%) subjects in the placebo arm. Grade 3-4 drug related SAEs were reported in 26 (7.4%) subjects in the nivolumab arm and 6 (1.7%) subjects in the placebo arm.

The most frequently reported drug-related SAEs were:

- Nivolumab: pneumonitis, colitis, and acute kidney injury (0.9% each).
- Placebo: colitis (0.6%).

Deaths

As of the 27-Aug-2020 DBL, 95 (27.1%) subjects in the nivolumab arm and 107 (30.7%) subjects in the placebo arm had died (***Table 39***). Disease progression was the most common cause of death for both arms.

Table 39 *Death Summary - All Treated Subjects*

	Placebo N = 348	Nivolumab N = 351
NUMBER OF SUBJECTS WHO DIED (%)	107 (30.7)	95 (27.1)
PRIMARY REASON FOR DEATH (%)		
DISEASE	90 (25.9)	73 (20.8)
STUDY DRUG TOXICITY	0	2 (0.6)
UNKNOWN	3 (0.9)	3 (0.9)
OTHER	14 (4.0)	17 (4.8)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	9 (2.6)	4 (1.1)
PRIMARY REASON FOR DEATH (%)		
DISEASE	3 (0.9)	2 (0.6)
STUDY DRUG TOXICITY	0	1 (0.3)
UNKNOWN	1 (0.3)	0
OTHER	5 (1.4)	1 (0.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	35 (10.1)	16 (4.6)
PRIMARY REASON FOR DEATH (%)		
DISEASE	24 (6.9)	8 (2.3)
STUDY DRUG TOXICITY	0	1 (0.3)
UNKNOWN	1 (0.3)	0
OTHER	10 (2.9)	7 (2.0)

Source: Table S.6.15.1

There were 2 (0.6%) deaths in the nivolumab arm (1 immune-mediated pneumonitis (initially Grade 3) and 1 pneumonitis (initially Grade 4)), and 0 deaths in the placebo arm that were attributed to study drug toxicity by the investigator (***Table 40***).

Table 40 *Study Drug Toxicity Deaths - All Enrolled Subjects*

Unique Subject ID (Age/Sex/Race)	Randomization Date	First Dose Date	Last Dose Date	Death Date	Days Since Last Dose	CRF Source	Cause of Death Specify
Nivolumab							
26SEP2019 (70/M/I)	27SEP2019	06DEC2019	19DEC2019	14	DEATH	STUDY DRUG	IMMUNOMEDIATED TOXICITY PNEUMONITIS
						AE/SAE	COMPLICATION OF IMMNOMEDIATED Immune-mediated pneumonitis: PNEUMONITIS
09MAY2018 (75/M/A)	09MAY2018	26SEP2018	08JAN2019	105	DEATH	STUDY DRUG	PNEUMONITIS TOXICITY

Deaths may be captured on death, adverse event, ECOG status, status and follow-up case report form pages. The primary source of death date is the death case report form. If the date is missing, the death date reported on the adverse event case report form is reported.

Abbreviations: A = Asian, AE = adverse event, CRF = case report form, ECOG = Eastern Cooperative Oncology Group, I = American Indian, ID = identification, M = male, SAE = serious adverse event

Deaths attributed to other reasons were reported in 17 (4.8%) subjects in the nivolumab arm, and 14 (4.0%) subjects in the placebo arm. The verbatim terms reported for the "other" reasons for death are provided below (***Table 41***).

Table 41 *Verbatim Terms for Deaths Attributed to "Other" - All Treated Subjects*

Placebo		**Nivolumab**	
Subject ID	**Verbatim Term**	**Subject ID**	**Verbatim Term**
	Cardiac arrest		Disease progression in new lung primary
	Pulmonary thromboembolism		Overall clinical deterioration
	Pneumonia		Sudden death
	Diverticulitis complications		Septic shock of respiratory origin
	Intracranial hemorrhage		Pulmonary thromboembolism
	Sepsis		Surgery related complications
	Esophageal necrosis		Fatal bowel perforation
	Hemorrhagic stroke		Rupture of the abdominal aorta
	Basal pneumonia staphylococci, and candida albicans infection		Sepsis
	Hypercalcemia		Meningitis
	Sudden death		Terminal kidney failure, sepsis with enterobacter cloacae
	Septic shock with cardiac decompensation		Syncope and heart failure
	Bladder malignancy, intestinal obstruction, septic shock		Suspected pulmonary thromboembolism
	Unknown: no death certificate provided		Atrial fibrillation with RVR
			Cardiopulmonary failure
			Liver failure and death
			Sepsis

Abbreviation: ID = identification, RVR = rapid ventricular rate

Dose delays, infusion interruptions and infusion rate reductions

Among all treated subjects, 162 (46.2%) subjects in the nivolumab arm had at least one dose delayed compared with 146 (42.0%) subjects in the placebo arm (***Table 42***).

Among all treated subjects, 12 (3.4%) subjects in the nivolumab arm had at least 1 infusion interruption compared with 6 (1.7%) subjects in the placebo arm. The most common reason for infusion interruptions in both treatment arms was a hypersensitivity reaction (16 (59.3%) subjects in the nivolumab arm and 3 (42.9%) subjects in the placebo arm). Among all treated subjects, 6 (1.7%) subjects in the nivolumab arm had an infusion rate reduction compared with 2 (0.6%) subjects in the placebo arm. The most common reason in both treatment arms was other (12 (60.0%) in the nivolumab arm and 2 (100.0%) subjects in the placebo arm).

Table 42 *Dose Delays of Study Therapy - All Treated Subjects*

	Placebo N = 348	Nivolumab N = 351
DOSE DELAYS		
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	146 (42.0)	162 (46.2)
NUMBER OF DOSES DELAYED PER SUBJECT (%)		
0	202 (58.0)	189 (53.8)
1	84 (24.1)	91 (25.9)
2	38 (10.9)	36 (10.3)
3	15 (4.3)	19 (5.4)
>= 4	9 (2.6)	16 (4.6)
TOTAL NUMBER OF DOSES DELAYED / TOTAL NUMBER OF DOSES RECEIVED (%)	249/5395 (4.6)	293/5497 (5.3)
REASON FOR DOSE DELAY (%) (A)		
ADVERSE EVENT	102 (41.0)	139 (47.4)
OTHER	123 (49.4)	117 (39.9)
NOT REPORTED	24 (9.6)	37 (12.6)
LENGTH OF DOSE DELAY (%) (A)		
4 - 7 DAYS	99 (39.8)	120 (41.0)
8 - 14 DAYS	94 (37.8)	105 (35.8)
15 - 42 DAYS	51 (20.5)	62 (21.2)
> 42 DAYS	5 (2.0)	6 (2.0)

Adverse events leading to dose delay

Any-grade all-causality AEs leading to dose delay were reported in 117 (33.3%) subjects in the nivolumab arm and 90 (25.9%) subjects in the placebo arm. Grade 3-4 AEs leading to dose delay were reported in 49 (14.0%) subjects in the nivolumab arm and 32 (9.2%) subjects in the placebo arm.

The most frequently reported all-causality AEs leading to dose delay were:

- Nivolumab: urinary tract infection (4.0%), diarrhoea (3.4%), increased blood creatinine (2.6%), increased lipase (2.0%), increased alanine aminotransferase (1.7%), and pneumonia (1.7%).
- Placebo: diarrhoea (4.3%), urinary tract infection (3.4%), increased blood creatinine (2.6%), and hydronephrosis (1.4%).

Any-grade drug-related AEs leading to dose delay were reported in 55 (15.7%) subjects in the nivolumab arm and 34 (9.8%) subjects in the placebo arm. Grade 3-4 AEs leading to dose delay were reported in 16 (4.6%) subjects in the nivolumab arm and 7 (2.0%) subjects in the placebo arm.

The most frequently reported drug-related AEs leading to dose delay were:

- Nivolumab: diarrhoea (3.1%), increased alanine aminotransferase, and increased lipase (1.4% each).

- Placebo: diarrhoea (3.2%), and increased lipase (1.1%).

Select adverse events

In order to characterize adverse events (AEs) of special clinical interest that are potentially associated with the use of nivolumab, the MAH identified select AEs based on the following 4 guiding principles: AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies, AEs that may require immunosuppression (e.g., corticosteroids) as part of their management, AEs whose early recognition and management may mitigate severe toxicity and AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization. A summary of drug-related select AEs is shown in ***Table 43***.

Table 43 *Summary of drug-related select AEs, IMAEs and OESIs*

	No. of Subjects (%)			
Safety Parameters	**Placebo (N = 348)**		**Nivolumab (N = 351)**	
Drug-Related Select AEs				
Endocrine	13 (3.7)	0	67 (19.1)	1 (0.3)
Gastrointestinal	39 (11.2)	3 (0.9)	65 (18.5)	6 (1.7)
Hepatic	17 (4.9)	1 (0.3)	29 (8.3)	6 (1.7)
Pulmonary	5 (1.4)	0	19 (5.4)	5 (1.4)
Renal	12 (3.4)	0	25 (7.1)	4 (1.1)
Skin	62 (17.8)	0	143 (40.7)	6 (1.7)
Hypersensitivity/Infusion Reactions	3 (0.9)	0	16 (4.6)	2 (0.6)
All-causality IMAEs within 100 days of last dose				
Treated with Immune Modulating Medication				
Rash	8 (2.3)	0	40 (11.4)	9 (2.6)
Pneumonitis	2 (0.6)	0	17 (4.8)	8 (2.3)
Diarrhoea/Colitis	3 (0.9)	1 (0.3)	14 (4.0)	8 (2.3)
Hepatitis	1 (0.3)	1 (0.3)	10 (2.8)	7 (2.0)
Nephritis/Renal Dysfunction	3 (0.9)	0	7 (2.0)	4 (1.1)
Hypersensitivity/Infusion Reactions	0	0	2 (0.6)	0
All-causality Endocrine IMAEs within 100 days of last dose				
With or Without Immune Modulating Medication				
Hypothyroidism	5 (1.4)	0	37 (10.5)	0
Hyperthyroidism	3 (0.9)	0	32 (9.1)	0
Adrenal Insufficiency	0	0	3 (0.9)	1 (0.3)
Thyroiditis	0	0	3 (0.9)	0
Diabetes Mellitus	0	0	1 (0.3)	1 (0.3)
Hypophysitis	0	0	0	0

The most frequently reported drug-related select AE events by PT (any-grade) by treatment arm were:

- Nivolumab: pruritus (23.1%), diarrhoea (16.8%), and rash (15.1%).
- Placebo: pruritus (11.5%), diarrhoea (10.9%), and rash (5.5%).

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

- Nivolumab: pneumonitis, colitis, and acute kidney injury (0.9% each).

- Placebo: colitis (0.6%).

Across the select AE categories, the majority of events were manageable using the established algorithms in the nivolumab arm (***Table 44***), with resolution occurring when IMMs (mainly systemic corticosteroids) were administered. Most drug related select AEs with nivolumab treatment (ranging from 58.2% to 100.0% across categories) had resolved at time of the DBL. Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Table 44 *Onset, Management, and Resolution of Drug-Related Select AEs - Nivolumab Treated Subjects (N = 351)*

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), wks	% Treated Subj. with Drug-related Select AE Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median Time[b] to Resolution of Drug-related Select AE[c,d] (range[e]), wks[b]	% Subj. with Drug-related Select AE that Resolved[c,d]
Endocrine	19.1 / 0.3	8.71 (0.1 - 44.4)	0.3	9.0 / 1.5	35.14. (1.0 - 204.4+)	58.2
Gastrointestinal	18.5 / 1.7	9.71 (0.1 - 49.4)	1.7	18.5 / 16.9	3.21 (0.1 - 108.6+)	96.9
Hepatic	8.3 / 1.7	12.43 (0.1 - 52.1)	1.4	27.6 / 20.7	7.14 (0.6 - 57.6)	89.7
Pulmonary	5.4 / 1.4	19.14 (3.9 - 50.7)	2.3	63.2 / 52.6	11.71 (0.1+ - 109.1+)	63.2
Renal	7.1 / 1.1	11.43 (2.0 - 51.9)	0.9	20.0 / 16.0	4.14 (0.4 - 69.4+)	79.2
Skin	40.7 / 1.7	7.14 (0.1 - 46.1)	1.4	38.5 / 3.5	16.14 (0.1 - 192.7+)	71.3
Hypersensitivity/ Infusion Reaction	4.6 / 0.6	2.14 (0.1 - 14.1)	0	25.0 / 12.5	0.14 (0.1 - 34.0)	100.0

MedDRA Version: 23.0 CTC Version: 4.0. Includes events reported after the first dose and within 30 days of last dose of study therapy.

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

[b] From Kaplan-Meier estimation.

[c] Subjects who experienced select adverse event without worsening from baseline grade were excluded from time to resolution analysis.

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

[e] Symbol + indicates a censored value.

Abbreviations: AE = adverse event; DC = discontinuation; IMM = immune-modulating medication; Subj. = subject; wks = weeks

Source: Refer to Table 8.2.6-1 of the CA209274 Primary CSR[2]

Immune-mediated adverse events

IMAEs are specific events (or groups of PTs describing specific events) that include diarrhoea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, and endocrine (adrenal insufficiency, hypophysitis, hypothyroidism/thyroiditis, hyperthyroidism, and diabetes mellitus). IMAE analyses included events, regardless of causality, occurring within 100 days of the last dose (i.e., with extended follow-up). These analyses were limited to subjects who received an IMM for treatment of the event, with the exception of endocrine events, which were included in the analysis regardless of treatment since these events are often managed without immunosuppression. In addition, these events were identified by the investigator as IMAEs with no clear alternate aetiology and an immune mediated component.

The majority of IMAEs were Grade 1-2 (***Table 45***).

Across IMAE categories, the majority of events were manageable using established management algorithms, with resolution occurring when IMMs (mostly systemic corticosteroids) were administered. Some endocrine IMAEs, were not considered resolved due to the continuing need for hormone replacement therapy. A re-challenge was considered as an unsuccessful or positive re-challenge if, after resolution of the IMAE, a new IMAE of the same type occurred with re treatment. A re-challenge

was considered as a successful or negative re challenge if, after resolution of the IMAE, no new IMAEs of the same type occurred with re treatment.

Table 45 *Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - Nivolumab Treated Subjects (N = 351)*

IMAE Category	% Treated Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Treated Subj. with IMAE leading to DC / Dose Delay	% Treated Subj. with IMAEs Receiving IMM / High-dose Corticosteroids[a]	Median Duration IMM (range), wks	% Treated Subj. with Resolution of IMAE[b,c,d]	Median[e] Time to Resolution (range)[f], wks	% Treated Subj. with Recurrence after Reinitiation[g]
Pneumonitis	4.8 / 2.3	36.57 (5.3 - 61.1)	2.3 / 0.6	100.0 / 88.2	6.71 (1.6 - 24.7)	70.6	19.00 (0.7 - 39.6)	0 (0/1)
Diarrhea/Colitis	4.0 / 2.3	19.07 (0.7 - 64.7)	1.7 / 0.6	100.0 / 92.9	6.71 (0.7 - 36.7)	92.9	4.64 (0.3 - 69.6)	0
Hepatitis	2.8 / 2.0	13.36 (2.0 - 57.9)	1.4 / 1.1	100.0 / 80.0	5.21 (0.6 - 20.7)	90.0	7.14 (0.6 - 79.1+)	33.3 (1/3)
Nephritis/Renal Dysfunction	2.0 / 1.1	18.14 (4.4 - 25.3)	0.9 / 0.6	100.0 / 85.7	9.29 (1.7 - 18.0)	57.1	5.29 (0.6 - 163.0+)	100.0 (1/1)
Rash	11.4 / 2.6	7.07 (0.1 - 57.7)	1.4 / 1.1	100.0 / 17.5	10.50 (0.6 - 146.0)	75.0	17.86 (1.1 - 192.7+)	100 (1/1)
Hypersensitivity	0.6 / 0	30.64 (21.3 - 40.0)	0 / 0	100.0 / 0	6.57 (0.4 - 12.7)	100.0	17.21 (0.4 - 34.0)	0
Adrenal Insufficiency	0.9 / 0.3	44.43 (34.0 - 50.9)	0 / 0.6	100.0 / 33.3	16.86 (12.1 - 128.3)	0	N.A (46.6+ - 128.3+)	0
Hypophysitis	0 / 0	N.A.	0 / 0	0 / 0	0	0	0	0
Hypothyroidism	10.5 / 0	12.00 (0.1 - 33.9)	0 / 0.9	0 / 0	0 / 0	43.2	N.A (2.3 - 204.4+)	0
Thyroiditis	0.9 / 0	3.86 (2.0 - 24.3)	0 / 0	66.7 / 33.3	4.36 (3.0 - 5.7)	66.7	16.00 (15.9 - 32.6+)	0
Hyperthyroidism	9.1 / 0	6.00 (1.9 - 31.9)	0 / 1.1	6.3 / 0	4.07 (2.7 - 5.4)	87.5	8.14 (1.9 - 62.0+)	0
Diabetes Mellitus	0.3 / 0.3	4.86 (4.9 - 4.9)	0.3 / 0	0 / 0	0	0	N.A (56.3+ - 56.3+)	0

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

[a]Denominator is based on the number of subjects who experienced the event. [b]Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis. [c]Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved. [d]For each subject, the longest duration of immune-mediated AEs where immune modulation is considered. [e]From Kaplan-Meier estimation. [f]Symbol + indicates a censored value. [g]Percentages are based on subjects who were re-challenged. A positive re-challenge/recurrence is defined as any occurrence of new event(s) or worsening of any severity grade IMAE on or after study therapy re-initiation. Abbreviations: DC = discontinuation; IMAE = immune-mediated adverse event; IMM = immune-modulating medication; N.A. = not applicable; Subj. = subject; wks = weeks

Other Events of Special Interest

Other events of special interest (OESIs) are events that do not fulfil all criteria to qualify as select AEs or IMAEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management.

Overall, OESIs were reported in 8/351 (2.3%) subjects (10 OESIs) in the nivolumab arm and 4/348 (1.1%) subjects in the placebo arm. 9/10 (90.0%) OESIs in the nivolumab arm and 3/4 (75.0%) OESIs in the placebo arm were resolved at the time of the DBL.

Among both treatment arms, the following OESI categories had no reported events: encephalitis, Guillain-Barré syndrome, and graft versus host disease.

Drug-related OESIs are summarized in ***Table 46***

Table 46 *Treatment, Onset, and Resolution Information for Other Events of Special Interest by Subject - All Treated Subjects*

PID	Event Description	Immune-modulating Medication	Onset Date (Study Day)	Duration of Event (Days)	Resolution (Yes/No)
Placebo					
Pancreatitis					
	Grade 2 unrelated SAE of pancreatitis	None	21-Jun-2018 (364)	9	Yes
	Grade 3 unrelated SAE of pancreatitis	None	21-Jun-2019 (122)	12	Yes
	Grade 2 unrelated AE of pancreatitis	None	22-Jun-2019 (348)	Continuing	No
Rhabdomyolysis					
	Grade 3 unrelated AE of rhabdomyolysis	None	19-Mar-2019 (141)	12	Yes
Nivolumab					
Myasthenic Syndrome					
	Grade 3 drug-related SAE of myasthenia gravis	Methylprednisolone	24-May-2018 (21)	20	Yes
	Grade 3 drug-related SAE of myasthenia gravis	Dexamethasone	20-Oct-2018 (31)	118	Yes
Demyelination					
	Grade 3 drug-related SAE of demyelination	Dexamethasone	18-Aug-2016 (84)	Continuing	No
Pancreatitis					
	Grade 3 drug-related SAE of pancreatitis	None	02-Feb-2018 (16)	5	Yes
Uveitis					
	Grade 2 drug-related AE of uveitis	Prednisone	08-Feb-2018 (172)	106	Yes
Myocarditis					
	Grade 2 drug-related SAE of myocarditis	Cortisone	03-Sep-2018 (144)	149	Yes
	Grade 4 drug-related SAE of immune-associated myocarditis	Methylprednisolone	29-May-2018 (26)	10	Yes
	Grade 3 drug-related SAE of myocarditis	Dexamethasone	20-Oct-2018 (31)	28	Yes
Myositis					
	Grade 2 drug-related AE of myositis	Prednisone	11-Dec-2018 (44)	371	Yes
	Grade 2 drug-related AE of immune-associated myositis	Methotrexate	29-May-2018 (26)	277	Yes

Laboratory findings

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2 in the nivolumab and placebo arms.

Serum chemistry

A total of 4/351 (1.2%) subjects in the nivolumab arm and no subjects in the placebo arm had concurrent alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN with total bilirubin > 2 x ULN within 1 day and within 30 days based on laboratory results reported after the first dose and within 30 days of last dose of study therapy (***Table 47***).

Table 47 *Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests (SI Units) - All Treated Subjects*

Abnormality (%)	Placebo N = 348	Nivolumab N = 351	Total N = 699
	N = 339	N = 345	N = 684
ALT OR AST > 3XULN	8 (2.4)	26 (7.5)	34 (5.0)
ALT OR AST > 5XULN	4 (1.2)	15 (4.3)	19 (2.8)
ALT OR AST > 10XULN	1 (0.3)	5 (1.4)	6 (0.9)
ALT OR AST > 20XULN	0	2 (0.6)	2 (0.3)
	N = 339	N = 345	N = 684
TOTAL BILIRUBIN > 2XULN	2 (0.6)	6 (1.7)	8 (1.2)
	N = 339	N = 344	N = 683
ALP > 1.5XULN	19 (5.6)	35 (10.2)	54 (7.9)
	N = 339	N = 345	N = 684
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN ONE DAY	0	5 (1.4)	5 (0.7)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 1.5XULN WITHIN 30 DAYS	0	5 (1.4)	5 (0.7)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	0	4 (1.2)	4 (0.6)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	0	4 (1.2)	4 (0.6)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter
Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal

There were in total 6 subjects with concurrent ALT or AST > 3x ULN with T.BILI > 2x ULN within one day of which 4 cases within 30 days of last dose of nivolumab, and 2 cases occurred > 30 days of the last dose of nivolumab. From these patients there were two patients with a DILI related to nivolumab treatment. The events occurred 72 days after the 5th (last) nivolumab infusion and 19 days after the 7th nivolumab infusion respectively. For both patients the abnormal liver functions resolved after treatment.

The other cases were assessed as not related to nivolumab treatment. The abnormal liver functions were caused by cholecystitis (2 patients), a bile duct stone and a biliary/pancreatic duct dilatation due to a possible pancreatic malignancy. In 3 out of 4 patients these events resolved after treatment. One patient died due to the consequences of a sepsis caused by a cholecystitis.

Most subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period.

The abnormalities in creatinine (increased) were primarily reported as Grade 1 to 2 in severity. 6 (1.7%) subjects in the nivolumab arm and 8 (2.4%) subjects in the placebo arm had a Grade 3 increased creatinine level, and 1 subject in the placebo arm had a Grade 4 increased creatinine level.

Thyroid stimulating hormone (TSH) increases (> ULN) from baseline (≤ ULN) were reported in 73/339 (21.5%) subjects in the nivolumab arm, and 37/335 (11.0%) subjects in the placebo arm (***Table 48***). The proportion of subjects with TSH increases (> ULN) was higher in the nivolumab arm than the placebo arm. Decreases (< lower limit of normal (LLN)) from baseline (≥ LLN) were reported in 85/339 (25.1%) subjects in the nivolumab arm, and 32/335 (9.6%) subjects in the placebo arm.

Table 48 *Summary of On-Treatment Laboratory Abnormalities in Specific Thyroid Tests - (SI Units) - All Treated Subjects with at Least One On-Treatment TSH*

Abnormality (%)	Placebo N = 335	Nivolumab N = 339	Total N = 674
TSH > ULN	63(18.8)	94(27.7)	157(23.3)
TSH > ULN WITH TSH <= ULN AT BASELINE	37(11.0)	3(21.5)	110(16.3)
TSH > ULN WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	17 5.1)	41(2.1)	58(8.6)
TSH > ULN WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	27 8.1)	30(8.8)	57(8.5)
TSH > ULN WITH FT3/FT4 TEST MISSING (A)(B)	19(5.7)	23(6.8)	42(6.2)
TSH < LLN	48(14.3)	96(28.3)	144(21.4)
TSH < LLN WITH TSH >= LLN AT BASELINE	32(9.6)	85(25.1)	117(17.4)
TSH < LLN WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	13(3.9)	41(12.1)	54(8.0)
TSH < LLN WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	19(5.7)	28(8.3)	47(7.0)
TSH < LLN WITH FT3/FT4 TEST MISSING (A)(B)	16(4.8)	27(8.0)	43(6.4)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy. (A) Within a 2-week window after the abnormal TSH test date. (B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test. Abbreviations: FT3 = free triiodothyronine, FT4 = free thyroxine, SI = International System of Units, TSH = thyroid stimulating hormone, ULN = upper limit of normal Source: Table S.7.6.5 (SI units)

The following Grade 3 abnormalities in amylase and lipase were observed in ≥ 5% of treated subjects with on-treatment laboratory results:

- Nivolumab: lipase (10.2% Grade 3) and amylase (8.3% Grade 3)
- Placebo: lipase (9.3% Grade 3)

Most subjects had normal electrolyte levels during the treatment reporting period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity.

Vital signs

Vital signs were provided as patient listings and a summary was provided with the response to the 1st RSI. No post-baseline vital signs were collected in the CRF. If subsequent vital signs were abnormal and deemed to be clinically significant, abnormalities should be reported as an adverse event (AE) as appropriate.

Table 49: *Adverse Events Associated with Vital Signs by Worst CTC Grade - All Treated Subjects*

1. Preferred Term (%)	2. Grade 1	3. Grade 2	4. Grade 3	5. Grade 4	6. Grade 5	7. Total
Nivolumab						
Hypertension[a]	4 (1.1)	7 (2.0)	4 (1.1)	0	0	15 (4.3)
Hypotension (symptomatic)	5 (1.4)	3 (0.9)	0	0	0	8 (2.3)
Tachycardia	1 (0.3)	0	1 (0.3)	0	0	2 (0.6)
Arrhythmia	0	1 (0.3)	0	0	0	1 (0.3)
Atrioventricular block	0	0	1 (0.3)	0	0	1 (0.3)
Atrioventricular block complete	0	0	1 (0.3)	0	0	1 (0.3)
Pyrexia	30 (8.5)	5 (1.4)	1 (0.3)	0	0	36 (10.3)
Hyperthermia	1 (0.3)	0	0	0	0	1 (0.3)
Placebo						
Hypertension	5 (1.4)	7 (2.0)	7 (2.0)	0	0	19 (5.5)
Hypotension (symptomatic)	2 (0.6)	3 (0.9)	0	0	0	5 (1.4)
Tachycardia	1 (0.3)	0	0	0	0	1 (0.3)
Bradycardia	1 (0.3)	0	0	0	0	1 (0.3)
Arrhythmia	1 (0.3)	0	2 (0.6)	0	0	3 (0.9)
Atrial flutter	1 (0.3)	1 (0.3)	0	0	0	2 (0.6)
Atrioventricular block complete	0	0	1 (0.3)	0	0	1 (0.3)
Pyrexia	23 (6.6)	12 (3.4)	1 (0.3)	0	0	36 (10.3)
Hyperthermia	1 (0.3)	0	0	0	0	1 (0.3)

[a] Grade 1 is considered pre-hypertension

The following PTs had no cases in the nivolumab arm: hypothermia, bradycardia, atrial flutter, supraventricular tachycardia, paroxysmal atrial tachycardia, sick sinus syndrome, sinus bradycardia, dysrhythmia, ventricular fibrillation, ventricular tachycardia, atrial tachycardia, atrioventricular block first degree, bundle branch block right, cardiac flutter, tachyarrhythmia, and ventricular arrhythmia

The following PTs had no cases in the placebo arm: hypothermia, supraventricular tachycardia, paroxysmal atrial tachycardia, sick sinus syndrome, sinus bradycardia, dysrhythmia, ventricular fibrillation, ventricular tachycardia, atrioventricular block, atrial tachycardia, atrioventricular block first degree, bundle branch block right, cardiac flutter, tachyarrhythmia, and ventricular arrhythmia.

Immunogenicity

Of the 305 nivolumab ADA evaluable subjects in the nivolumab arm, 13 (4.3%) subjects were nivolumab ADA positive at baseline and 42 (13.8%) subjects were treatment-induced nivolumab ADA positive after the start of treatment.

- No subjects were considered persistent positive and 5 (1.6%) subjects were neutralizing ADA positive.

- The highest titer value observed in nivolumab ADA positive subjects was 128, which occurred in 1 subject. All other titers were low, ranging from 0 to 32.

Based on the assessment of the presence of ADA and neutralizing antibodies in relation to DFS per investigator, there was no apparent trend showing an effect of ADA or neutralizing antibodies on the efficacy of nivolumab. Overall, the incidence of nivolumab ADA was 13.8%, and did not appear to have an effect on safety of the tested regimen. Of all the nivolumab treated subjects who were evaluable for ADA, hypersensitivity/infusion reaction select AEs were experienced by 12 (4.6%) nivolumab ADA negative subjects, and 1 (2.4%) nivolumab ADA-positive subject.

Safety in special populations

The MAH has provided safety data comparing all treated subjects to all treated subjects with tumour cell PD-L1 expression level ≥ 1%. The safety data in the latter subgroup was consistent with that reported in the all treated population.

The frequencies of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/standardized MedDRA queries (SMQs)/SOC by age group (< 65, 65 to 74, and 75 to 84 years) are presented for nivolumab and placebo-treated subjects in CA209274 (***Table 50***), and pooled monotherapy studies (***Table 51***).

Table 50 *Summary of On-treatment Adverse Events by Age Group - All Treated Subjects in CA209274*

	Placebo				Nivolumab			
	Age Group (Years)				Age Group (Years)			
MedDRA Terms (%)	< 65 N = 131	65–74 N = 162	75–84 N = 53	>= 85 N = 2	< 65 N = 155	65–74 N = 130	75–84 N = 62	>= 85 N = 4
TOTAL SUBJECTS WITH AN EVENT	124 (94.7)	156 (96.3)	50 (94.3)	2 (100.0)	153 (98.7)	128 (98.5)	62 (100.0)	4 (100.0)
SERIOUS AE - TOTAL	30 (22.9)	56 (34.6)	19 (35.8)	0	42 (27.1)	33 (25.4)	26 (41.9)	3 (75.0)
FATAL (DEATH)[a]	3 (2.3)	6 (3.7)	4 (7.5)	0	3 (1.9)	2 (1.5)	3 (4.8)	0
HOSPITALIZATION/PROLONGATION	26 (19.8)	54 (33.3)	14 (26.4)	0	39 (25.2)	30 (23.1)	25 (40.3)	3 (75.0)
LIFE THREATENING	2 (1.5)	4 (2.5)	1 (1.9)	0	1 (0.6)	2 (1.5)	1 (1.6)	0
CANCER	0	4 (2.5)	1 (1.9)	0	0	1 (0.8)	1 (1.6)	0
DISABILITY/INCAPACITY	0	0	0	0	0	0	0	0
IMPORTANT MEDICAL EVENT	3 (2.3)	3 (1.9)	2 (3.8)	0	2 (1.3)	4 (3.1)	2 (3.2)	0
AE LEADING TO DISCONTINUATION	11 (8.4)	16 (9.9)	5 (9.4)	0	21 (13.5)	25 (19.2)	18 (29.0)	0
PSYCHIATRIC DISORDERS	12 (9.2)	14 (8.6)	7 (13.2)	0	17 (11.0)	10 (7.7)	7 (11.3)	2 (50.0)
NERVOUS SYSTEM DISORDERS	41 (31.3)	35 (21.6)	15 (28.3)	1 (50.0)	32 (20.6)	37 (28.5)	15 (24.2)	3 (75.0)
ACCIDENT AND INJURIES	5 (3.8)	13 (8.0)	4 (7.5)	0	10 (6.5)	8 (6.2)	4 (6.5)	0
CARDIAC DISORDERS	5 (3.8)	13 (8.0)	5 (9.4)	0	6 (3.9)	7 (5.4)	7 (11.3)	0
VASCULAR DISORDERS	13 (9.9)	16 (9.9)	8 (15.1)	0	17 (11.0)	11 (8.5)	9 (14.5)	1 (25.0)
CEREBROVASCULAR DISORDERS	0	2 (1.2)	3 (5.7)	0	0	1 (0.8)	2 (3.2)	2 (50.0)
INFECTIONS AND INFESTATIONS	64 (48.9)	74 (45.7)	24 (45.3)	0	74 (47.7)	57 (43.8)	29 (46.8)	3 (75.0)
ANTICHOLINERGIC SYNDROME	30 (22.9)	33 (20.4)	14 (26.4)	0	36 (23.2)	32 (24.6)	15 (24.2)	2 (50.0)
QUALITY OF LIFE DECREASED	0	0	0	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE DIZZINESS, ATAXIA, FRACTURES	12 (9.2)	19 (11.7)	9 (17.0)	0	18 (11.6)	17 (13.1)	6 (9.7)	1 (25.0)

[a] Deaths reported are only AE related, representing a subset of total deaths.

Table 51 *Summary of On-treatment Adverse Events by Age Group - All Treated Subjects - Nivolumab Monotherapy Data Integrated Across Indications, Including CA209274*

	Age Group (Years)			
MedDRA Terms (%)	< 65 N = 2230	65-74 N = 1017	75-84 N = 314	>= 85 N = 29
TOTAL SUBJECTS WITH AN EVENT	2178 (97.7)	987 (97.1)	308 (98.1)	29 (100.0)
SERIOUS AE - TOTAL	836 (37.5)	440 (43.3)	146 (46.5)	17 (58.6)
FATAL (DEATH)	187 (8.4)	95 (9.3)	31 (9.9)	3 (10.3)
HOSPITALIZATION/PROLONGATION	739 (33.1)	389 (38.2)	134 (42.7)	14 (48.3)
LIFE THREATENING	32 (1.4)	16 (1.6)	3 (1.0)	0
CANCER	29 (1.3)	24 (2.4)	12 (3.8)	2 (6.9)
DISABILITY/INCAPACITY	1 (<0.1)	1 (<0.1)	0	0
IMPORTANT MEDICAL EVENT	74 (3.3)	40 (3.9)	10 (3.2)	1 (3.4)
AE LEADING TO DISCONTINUATION	290 (13.0)	179 (17.6)	76 (24.2)	5 (17.2)
PSYCHIATRIC DISORDERS	395 (17.7)	146 (14.4)	46 (14.6)	9 (31.0)
NERVOUS SYSTEM DISORDERS	765 (34.3)	313 (30.8)	99 (31.5)	17 (58.6)
ACCIDENT AND INJURIES	164 (7.4)	89 (8.8)	30 (9.6)	3 (10.3)
CARDIAC DISORDERS	174 (7.8)	84 (8.3)	27 (8.6)	5 (17.2)
VASCULAR DISORDERS	346 (15.5)	158 (15.5)	50 (15.9)	11 (37.9)
CEREBROVASCULAR DISORDERS	28 (1.3)	29 (2.9)	12 (3.8)	3 (10.3)
INFECTIONS AND INFESTATIONS	951 (42.6)	444 (43.7)	127 (40.4)	16 (55.2)
ANTICHOLINERGIC SYNDROME	749 (33.6)	318 (31.3)	101 (32.2)	13 (44.8)
QUALITY OF LIFE DECREASED	1 (<0.1)	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	254 (11.4)	116 (11.4)	37 (11.8)	5 (17.2)

CTC version: 4.0; MedDRA version: 23.0
Includes events reported after the first dose and within 30 days after last dose of study therapy, except for ONO-4538-24.
ONO-4538-24 includes events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period.

Safety related to drug-drug interactions and other interactions

No formal pharmacokinetic drug interaction studies have been conducted with nivolumab. No new information has been generated in support of this submission.

Discontinuation due to adverse events

Any-grade AEs leading to discontinuation (regardless of causality) were reported in 64 (18.2%) subjects in the nivolumab arm, and 32 (9.2%) subjects in the placebo arm (***Table 52***). Grade 3-4 AEs leading to discontinuation were reported in 39 (11.1%) subjects in the nivolumab arm, and 21 (6.0%) subjects in the placebo arm.

The most frequently reported AEs leading to discontinuation were:

- Nivolumab: pneumonitis (1.7%), malignant neoplasm progression (1.4%), and rash (1.1%).
- Placebo: malignant neoplasm progression (2.6%).

Any grade drug-related AEs leading to discontinuation were reported in 45 (12.8%) subjects in the nivolumab arm and 7 (2.0%) subjects in the placebo arm. Grade 3-4 drug related AEs leading to discontinuation were reported in 25 (7.1%) subjects in the nivolumab arm and 5 (1.4%) subjects in the placebo arm, respectively.

The most frequently reported drug-related AEs leading to discontinuation:

- Nivolumab: pneumonitis (1.7%) and rash (1.1%).
- Placebo: colitis (0.6%).

Table 52 *Adverse Events Leading to Discontinuation in ≥ 2 Subjects - All Treated Subjects*

System Organ Class (%) Preferred Term (%)	Placebo N = 348			Nivolumab N = 351		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	32 (9.2)	21 (6.0)	2 (0.6)	64 (18.2)	39 (11.1)	1 (0.3)
Gastrointestinal disorders	7 (2.0)	5 (1.4)	0	9 (2.6)	7 (2.0)	0
Colitis	2 (0.6)	2 (0.6)	0	3 (0.9)	2 (0.6)	0
Diarrhoea	1 (0.3)	0	0	3 (0.9)	2 (0.6)	0
Investigations	2 (0.6)	1 (0.3)	0	8 (2.3)	4 (1.1)	0
Alanine aminotransferase increased	0	0	0	3 (0.9)	1 (0.3)	0
Amylase increased	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Aspartate aminotransferase increased	0	0	0	2 (0.6)	1 (0.3)	0
Blood creatinine increased	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (4.0)	10 (2.9)	1 (0.3)	8 (2.3)	6 (1.7)	1 (0.3)
Malignant neoplasm progression	9 (2.6)	6 (1.7)	1 (0.3)	5 (1.4)	3 (0.9)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	0	0	8 (2.3)	4 (1.1)	0
Pneumonitis	1 (0.3)	0	0	6 (1.7)	2 (0.6)	0
Musculoskeletal and connective tissue disorders	1 (0.3)	1 (0.3)	0	6 (1.7)	1 (0.3)	0
Myalgia	0	0	0	2 (0.6)	0	0
Skin and subcutaneous tissue disorders	0	0	0	6 (1.7)	3 (0.9)	0
Rash	0	0	0	4 (1.1)	1 (0.3)	0
Cardiac disorders	1 (0.3)	1 (0.3)	0	4 (1.1)	3 (0.9)	0
Myocarditis	0	0	0	2 (0.6)	1 (0.3)	0
General disorders and administration site conditions	2 (0.6)	0	0	4 (1.1)	1 (0.3)	0
Fatigue	2 (0.6)	0	0	2 (0.6)	1 (0.3)	0
Nervous system disorders	2 (0.6)	1 (0.3)	1 (0.3)	4 (1.1)	3 (0.9)	0
Myasthenia gravis	0	0	0	2 (0.6)	2 (0.6)	0
Metabolism and nutrition disorders	1 (0.3)	1 (0.3)	0	3 (0.9)	1 (0.3)	0
Decreased appetite	0	0	0	2 (0.6)	1 (0.3)	0

MedDRA Version: 23.0
CTC Version: 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table S.6.4.2.1

Post marketing experience

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and in the European Union (EU), and for other indications as monotherapy (e.g. metastatic non-small cell lung cancer (NSCLC), advanced renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell carcinoma of the head and neck (SCCHN), urothelial carcinoma (UC), and oesophageal squamous cell carcinoma (ESCC). In US, nivolumab monotherapy was also approved for hepatocellular carcinoma (HCC), microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC), and small cell lung cancer (SCLC)).

Based on pharmacovigilance activities conducted by Bristol Myers Squibb (BMS) World Wide Patient Safety, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab.

Safety in SmPC

Safety data to support Section 4.8 of the SmPC were integrated by the MAH across completed studies in multiple indications using the intended dose and regimen for nivolumab monotherapy. Also the

following methodology was used to generate the adverse drug reactions table with nivolumab monotherapy in Section 4.8 of the SmPC:

1) Programmatically remap MedDRA PTs representing the same or similar clinical conditions for the integrated AE data and generate summary tables.

2) Identify clinical relevant events based on BMS medical review of the drug-related remapped AE summary table.

3) Present resulting clinically relevant remapped events by SOC and all-causality frequency in the final adverse drug reaction (ADR) table.

In the ADR table in Section 4.8 of the proposed OPDIVO SmPC for the current application, some footnotes have been revised or deleted for the following reasons:

- The footnote on cardiac disorders system organ class (previously treated melanoma indication only) has been deleted to simplify the ADR table footnotes and to align with the approved Risk Mitigation Plan as cardiac arrhythmias was removed from the list of important potential risks based on the Periodic Safety Update Report (PSUR) procedure 9. 'Arrhythmia (including ventricular arrhythmia)' PT is included in the ADR table. 'Ventricular arrhythmia' is remapped under 'arrhythmia' per remapping definition output.

- 'Rash generalized' and 'rash papulosquamous' were deleted from the 'rash' footnote as these PTs were not included in the remapping definition output. Although 'Pemphigoid' is not included in the remapping definition output, it is included under 'rash' for frequency calculation purpose.

A comparison between the safety in nivolumab treated subjects in CA209274 and the safety in pooled nivolumab monotherapy studies excluding CA209274 is made in **Table 53**

- Any grade all-causality AEs frequencies were higher in nivolumab monotherapy treated subjects in CA209274 vs the pooled nivolumab monotherapy studies, excluding CA209274 for; diarrhea (29.1% vs 25.7%), rash (28.8% vs 24.0%), pruritus (30.2% vs 18.4%), urinary tract infection (20.2% vs 5.0%), hyperkalemia (6.8% vs 2.4%), blood creatinine increased (13.7% vs 5.0%), lipase increased (11.7% vs 4.1%), amylase increased (12.5% vs 3.3%), weight increased (3.7% vs 2.0%), hypothyroidism (10.5% vs 9.0%), hyperthyroidism (10.5% vs 4.1%), renal failure (3.7% vs 1.8%), haematuria (4.0% vs 1.5%), dizziness (10.5% vs 8.8%), respectively
- Drug-related AEs frequencies were higher in nivolumab monotherapy treated subjects in CA209274 vs the pooled nivolumab monotherapy studies, excluding CA209274 for; rash (23.6% vs 18.1%), pruritus (23.1% vs 14.1%), diarrhea (16.8% vs 14.6%), lipase increased (9.7% vs 3.1%), amylase increased (9.4% vs 2.7%), blood creatinine increased (5.7% vs 1.7%), pneumonitis (5.1% vs 3.3%), hypothyroidism (9.7% vs 7.6%), hyperthyroidism (9.4% vs 3.6%), respectively

Table 53 *Summary of Adverse Events (Re-mapped Terms) Occurring in at Least 10% of Subjects, by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with 30 Days Follow-up - All Treated Subjects with Nivolumab Monotherapy*

System Organ Class (%) Preferred Term (%)	CA209274 Nivolumab 240 mg Q2W N = 351			Monotherapy Pooled (excluding CA209274) Nivolumab 3 mg/kg or 240 mg N = 3771		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	347 (98.9)	148 (42.2)	2 (0.6)	3665 (97.2)	1570 (41.6)	210 (5.6)
General disorders and administration site conditions	184 (52.4)	6 (1.7)	0	2385 (63.2)	218 (5.8)	13 (0.3)
Fatigue	125 (35.6)	4 (1.1)	0	1744 (46.2)	125 (3.3)	0
Pyrexia	36 (10.3)	1 (0.3)	0	532 (14.1)	13 (0.3)	0
Oedema	31 (8.8)	0	0	397 (10.5)	13 (0.3)	0
Gastrointestinal disorders	199 (56.7)	22 (6.3)	0	2349 (62.3)	292 (7.7)	3 (<0.1)
Diarrhoea	102 (29.1)	6 (1.7)	0	970 (25.7)	69 (1.8)	0
Nausea	57 (16.2)	2 (0.6)	0	892 (23.7)	26 (0.7)	0
Constipation	47 (13.4)	1 (0.3)	0	638 (16.9)	12 (0.3)	0
Abdominal pain	53 (15.1)	3 (0.9)	0	589 (15.6)	43 (1.1)	0
Vomiting	29 (8.3)	0	0	526 (13.9)	29 (0.8)	0
Respiratory, thoracic and mediastinal disorders	114 (32.5)	9 (2.6)	0	1764 (46.8)	261 (6.9)	16 (0.4)
Cough	47 (13.4)	0	0	923 (24.5)	9 (0.2)	0
Dyspnoea	40 (11.4)	1 (0.3)	0	671 (17.8)	92 (2.4)	1 (<0.1)
Skin and subcutaneous tissue disorders	195 (55.6)	7 (2.0)	0	1697 (45.0)	70 (1.9)	0
Rash	101 (28.8)	5 (1.4)	0	906 (24.0)	44 (1.2)	0
Pruritus	106 (30.2)	0	0	695 (18.4)	7 (0.2)	0
Musculoskeletal and connective tissue disorders	136 (38.7)	6 (1.7)	0	1603 (42.5)	148 (3.9)	1 (<0.1)
Musculoskeletal pain	98 (27.9)	2 (0.6)	0	1172 (31.1)	89 (2.4)	1 (<0.1)
Arthralgia	39 (11.1)	1 (0.3)	0	547 (14.5)	18 (0.5)	0
Infections and infestations	163 (46.4)	34 (9.7)	0	1546 (41.0)	293 (7.8)	9 (0.2)
Upper respiratory tract infection	57 (16.2)	1 (0.3)	0	594 (15.8)	7 (0.2)	0
Urinary tract infection	71 (20.2)	19 (5.4)	0	188 (5.0)	44 (1.2)	0
Metabolism and nutrition disorders	131 (37.3)	21 (6.0)	0	1307 (34.7)	284 (7.5)	1 (<0.1)
Decreased appetite	44 (12.5)	3 (0.9)	0	693 (18.4)	34 (0.9)	0
Nervous system disorders	93 (26.5)	8 (2.3)	0	1254 (33.3)	117 (3.1)	4 (0.1)
Headache	33 (9.4)	1 (0.3)	0	500 (13.3)	14 (0.4)	0
Dizziness	37 (10.5)	1 (0.3)	0	332 (8.8)	5 (0.1)	0
Investigations	144 (41.0)	46 (13.1)	0	1224 (32.5)	297 (7.9)	0
Blood creatinine increased	48 (13.7)	2 (0.6)	0	189 (5.0)	11 (0.3)	0
Lipase increased	41 (11.7)	22 (6.3)	0	153 (4.1)	85 (2.3)	0
Amylase increased	44 (12.5)	16 (4.6)	0	124 (3.3)	56 (1.5)	0
Blood and lymphatic system disorders	70 (19.9)	7 (2.0)	0	795 (21.1)	220 (5.8)	0
Anaemia	50 (14.2)	4 (1.1)	0	524 (13.9)	128 (3.4)	0
Endocrine disorders	69 (19.7)	1 (0.3)	0	519 (13.8)	26 (0.7)	0
Hypothyroidism	37 (10.5)	0	0	341 (9.0)	3 (<0.1)	0
Hyperthyroidism	37 (10.5)	0	0	156 (4.1)	2 (<0.1)	0

System Organ Class (%) Preferred Term (%)	Monotherapy Pooled Nivolumab 3 mg/kg or 240 mg N = 4122		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	4012 (97.3)	1718 (41.7)	212 (5.1)
General disorders and administration site conditions	2569 (62.3)	224 (5.4)	13 (0.3)
Fatigue	1869 (45.3)	129 (3.1)	0
Pyrexia	568 (13.8)	14 (0.3)	0
Oedema	428 (10.4)	13 (0.3)	0
Gastrointestinal disorders	2548 (61.8)	314 (7.6)	3 (<0.1)
Diarrhoea	1072 (26.0)	75 (1.8)	0
Nausea	949 (23.0)	28 (0.7)	0
Constipation	685 (16.6)	13 (0.3)	0
Abdominal pain	642 (15.6)	46 (1.1)	0
Vomiting	555 (13.5)	29 (0.7)	0
Respiratory, thoracic and mediastinal disorders	1878 (45.6)	270 (6.6)	16 (0.4)
Cough	970 (23.5)	9 (0.2)	0
Dyspnoea	711 (17.2)	93 (2.3)	1 (<0.1)
Skin and subcutaneous tissue disorders	1892 (45.9)	77 (1.9)	0
Rash	1007 (24.4)	49 (1.2)	0
Pruritus	801 (19.4)	7 (0.2)	0
Musculoskeletal and connective tissue disorders	1739 (42.2)	154 (3.7)	1 (<0.1)
Musculoskeletal pain	1270 (30.8)	91 (2.2)	1 (<0.1)
Arthralgia	586 (14.2)	19 (0.5)	0
Infections and infestations	1709 (41.5)	327 (7.9)	9 (0.2)
Upper respiratory tract infection	651 (15.8)	8 (0.2)	0
Urinary tract infection	259 (6.3)	63 (1.5)	0
Metabolism and nutrition disorders	1438 (34.9)	305 (7.4)	1 (<0.1)
Decreased appetite	737 (17.9)	37 (0.9)	0
Nervous system disorders	1347 (32.7)	125 (3.0)	4 (<0.1)
Headache	533 (12.9)	15 (0.4)	0
Dizziness	369 (9.0)	6 (0.1)	0
Investigations	1368 (33.2)	343 (8.3)	0
Blood creatinine increased	237 (5.7)	13 (0.3)	0
Lipase increased	194 (4.7)	107 (2.6)	0
Amylase increased	168 (4.1)	72 (1.7)	0
Blood and lymphatic system disorders	865 (21.0)	227 (5.5)	0
Anaemia	574 (13.9)	132 (3.2)	0
Endocrine disorders	588 (14.3)	27 (0.7)	0
Hypothyroidism	378 (9.2)	3 (<0.1)	0
Hyperthyroidism	193 (4.7)	2 (<0.1)	0

2.5.1. Discussion on clinical safety

The safety profile for nivolumab monotherapy (240mg Q2W or 480 mg Q4W) has previously been established across several tumour types, including urothelial carcinoma. The safety profile described in

this procedure is based on the safety data derived from study CA209274; a phase 3, randomised, double-blind, placebo-controlled study of nivolumab vs placebo in adult subjects who have undergone radical resection of MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence.

Exposure

The median follow-up time was comparable for both study arms (20.90 months and 19.48 months for all in the nivolumab and placebo arms, respectively). The median duration of therapy was comparable between the treatment arms 8.77 months in the nivolumab arm and 8.21 months in the placebo arm. In relation to the proposed target population and posology (up to 1 year) the extent of exposure in the nivolumab arm is considered to be a bit short, however can be considered acceptable for assessment of the B/R considering the available safety data from other approved indications. The number of dose delays was comparable between the two study arms (46.2% in the nivolumab arm vs 42.0% in the placebo arm).

Adverse Events (AEs)

Nearly all patients experienced an AE (98.9% patients in the nivolumab arm and 95.4% in the placebo arm). The most frequent any-Grade all-causality AEs in the nivolumab arm were pruritus (30.2% vs 16.2%), diarrhoea (29.1% vs 26.1%), fatigue (27.4%vs 24.4%), urinary tract infection (19.9% vs 19.0%), and rash (18.8% vs 9.8%). The most frequently reported drug-related AEs were pruritus (23.1% vs 11.5%), fatigue (17.4% vs 12.1%), and diarrhoea (16.8% vs 10.9%) in the nivolumab and placebo arm, respectively. There were more Grade 3-4 AEs (regardless of causality) observed in the nivolumab arm (42.2%) compared to the placebo arm (35.1%). The most frequently reported Grade 3-4 AEs were increased lipase (6.3%), urinary tract infection (5.4%vs 6.4%), increased amylase (4.6% vs 1.7%), malignant neoplasm progression (1.7% vs 3.7%), and diarrhoea (1.7% vs 1.1%).

When incidence rates (IR) were exposure adjusted, all-causality any grade AE were more frequent in the nivolumab arm (1337.8 events per 100 person-years) compared to the placebo arm (1158.7). Particularly endocrine disorders and skin and subcutaneous tissue disorders were observed more frequent in the nivolumab arm compared to the placebo arm. This is in line with the known safety profile of nivolumab monotherapy.

No new safety concerns have arisen from this study, however some AE are more frequently observed in this population compared to the pooled nivolumab monotherapy population. These data were also compared for the purpose of assessment of the proposal for pooled safety data in the SmPC. The most notable differences in frequencies of any grade all-causality AEs between study CA209274 and the pooled nivolumab monotherapy studies, excluding CA209274, were AEs pruritus (30.2% vs 18.4%), urinary tract infection (20.2% vs 5.0%), hyperkalemia (6.8% vs 2.4%), blood creatinine increased (13.7% vs 5.0%), lipase increased (11.7% vs 4.1%) and amylase increased (12.5% vs 3.3%). These AE are considered to be specific for the disease setting of urothelial cancer. Besides these disease-specific AEs, the safety profile of nivolumab in study CA209274 is similar to the safety profile of the pooled nivolumab monotherapy population. Therefore, pooling the safety data of nivolumab from study CA209274 with data from other nivolumab monotherapy indications in the SmPC is considered acceptable.

Serious Adverse Events and deaths

A comparable number of SAEs were observed in the nivolumab and placebo arm (29.6% vs 30.2%). The most frequently reported all-causality SAEs in the nivolumab arm were urinary tract infection (2.6% vs 6.0%), malignant neoplasm progression (2.3% vs 5.5%), intestinal obstruction (1.4% vs 1.4%), acute kidney injury (1.4% vs 0.3%). Also the number of severe SAEs was comparable between

the study arms (23.1% vs 21.0%). More SAEs were related to treatment in the nivolumab arm (9.1%) compared to placebo (2.0%), however the increased number could not be attributed to specific SAEs.

Due to the immaturity of OS data at the time of this IA, the MAH remained blinded to deaths by treatment arm so no information about these events has been included at the initial submission however the number of deaths was comparable between the study arms (nivolumab: 27.1% vs placebo 30.7%). In the nivolumab arm there were less deaths due to the disease (20.8% vs 25.9%). Of note, 2 patients died due to study drug toxicity in the nivolumab arm (one for immune-mediated pneumonitis and one for pneumonitis). The number of deaths due to other reasons was comparable (nivolumab: 4.8% vs placebo: 4.0%) between the study arms.

Other AEs of interest

AEs with potential immune-related aetiology consistent with the mechanism of action of immunotherapies/ nivolumab (select AEs (74.9% vs 55.5%), immune-mediate AEs (IMAEs; non-endocrine IMAEs treated with immune-modulating medication and endocrine IMAEs with or without immune-modulating medication: 34.5% vs. 6.9%and other AEs of special interest (OESIs; 2.0% vs 1.1%) were observed more frequently in the nivolumab arm compared to the placebo arm. The majority of the select AEs and IMAEs were low grade and resolved mostly by dose interruptions and corticosteroid therapy prior to database lock.

Dose delays

The number of dose delays was comparable between the nivolumab and placebo arm (46.2% vs 42.0%), however there were slightly more dose interruptions in the nivolumab arm compared to the placebo arm. (3.4% vs 1.7%). There were also slightly more any grade all-causality AEs leading to dose delay in the nivolumab arm (33.3%) compared to the placebo arm (25.9%), this was also seen for severe AEs (14.0% vs 9.2%).

Laboratory abnormalities, vital signs

In general, most laboratory abnormalities were low grade. There were 6 patients in the nivolumab arm, who had concurrent ALT or AST > 3 x ULN with total bilirubin > 2 x ULN within one day. From these patients there were two patients with a DILI related to nivolumab treatment. The events occurred 72 days after the 5th (last) nivolumab infusion and 19 days after the 7th nivolumab infusion respectively. For both patients the abnormal liver functions resolved after treatment. This is considered acceptable. Vital signs were not systematically collected but reported as AE when abnormal and deemed to be clinically significant. It is acknowledged that this is a limitation to the above data. The presented data in itself do not indicate large differences between the two study arms and are therefore considered acceptable.

Immunogenicity

In the nivolumab arm there were no patients who were consistently Anti-Drug Antibody (ADA) positive and the number of patients with neutralizing ADAs was small (1.6%). Therefore, no conclusion can be made regarding the impact in the efficacy and safety of neutralizing ADAs in these patients -, however considering the very low number of neutralizing ADAs, this is considered acceptable.

Special populations

The MAH provided safety data by age group. From these data it appears that patients ≥75 years of age in the nivolumab arm experience certain type of AEs more frequent, such as SAEs, psychiatric and nervous system disorders. The number of patients ≥75 years, however, is too limited to draw a definitive conclusion on these patients.

Discontinuation due to AEs

Nivolumab treatment was less tolerable compared to placebo, as shown by the higher number of discontinuations due to AEs (18.2% vs 9.2% respectively). The discontinuations due to AEs were mostly due to severe AEs in both study arms and mostly treatment related in the nivolumab arm. The discontinuations could not be attributed to a certain AE.

SmPC

Safety data from the pivotal study was combined with multiple indications using the intended dose and regimen for nivolumab monotherapy. In addition, the MAH remapped similar MeDRA PTs, which is considered acceptable.

2.5.2. Conclusions on clinical safety

No new safety concerns have arisen for nivolumab monotherapy in the adjuvant treatment for adult subjects who have undergone radical resection of MIUC originating in the bladder or upper urinary tract (renal pelvis or ureter) and are at high risk of recurrence.

The toxicity of treatment with nivolumab is slightly worse as shown in the higher number of severe AEs and exposure adjusted, all-causality any grade AE in the nivolumab arm compared to the placebo arm. Nivolumab treatment was also slightly less tolerable as could be seen in the higher number of dose delays and discontinuations due to AEs. Nonetheless, this is considered acceptable since overall the toxicity profile is manageable, and the differences between the nivolumab arm and placebo arm were generally small. Overall, no critical safety issues were identified.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 26.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 26.2 with the following content:

Safety concerns

Table -54: 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

Table -54:	Summary of Safety Concerns
	Immune-related skin ARs
	Other immune-related ARs
	Severe infusion reactions
Important potential risks	Embryofetal toxicity
	Immunogenicity
	Complications of allogeneic HSCT following nivolumab therapy in cHL
	Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab

Pharmacovigilance plan

Table 55: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and VKH), and infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCTOngoing	To assess transplant-related complications following prior nivolumab use	Postmarketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission	With PSUR starting at DLP 03-Jul-2017 06-2019 4Q2022

Risk minimisation measures

Table 56: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8 Additional risk minimization measures: Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Table 56: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and Annex II are being updated to add the data of study CA209274 in high risk MIUC patients. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The inclusion of the new proposed indication for Opdivo (i.e. adjuvant treatment of adult patients with muscle invasive urothelial carcinoma (MIUC).) does not have a relevant impact on the PIL and therefore it is agreed with the MAH that there is no need to conduct additional consultation with target patients groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The final approved indication is*: "OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC)* ***with tumour cell PD-L1 expression ⩾ 1%,*** *who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1).*

3.1.1. Disease or condition

Urothelial carcinoma (UC) originates in the urothelial cells that line the bladder, ureter, and renal pelvis. The majority (90%) of UCs originate in the urinary bladder, while up to 10% originate in the upper urinary tract (ureters and/or renal pelvis) (Hepp et al, 2020; Miyazaki & Nishiyama, 2017). Around 20% of UCs present with or eventually progress to muscle invasive or metastatic disease. Muscle invasive bladder cancer (MIBC) is an aggressive disease that requires multimodal treatment,

which includes radical surgery or radiation therapy with or without chemotherapy. Studies report a median survival which ranges between 3.8-5.2 years (Supit 2014, Mitra 2011; Barton Grossman 2003).

Muscle invasive upper tract urothelial carcinoma (UTUC) is less common. From the literature it is not clear whether UTUC is the same or a different disease entity as MIBC. However, due to the different anatomic site and lymphogenic spreading pattern the course of disease and metastasis pattern may differ. Similar to MIBC, muscle invasive UTUC is an aggressive disease that requires radical surgery with a median disease-free survival (DFS) of 30 months. Cisplatin-based adjuvant chemotherapy could improve DFS in muscle invasive UTUC based on the results of the POUT (Peri-Operative chemotherapy versus surveillance in UTUC) study, but OS data were not available (Birtle A,2020).

3.1.2. Available therapies and unmet medical need

Despite multimodal treatment, more than 50% of patients with MIBC will eventually develop metastases; upon metastatic relapse, the prognosis is dismal, with a median overall survival (OS) up to 15 months with chemotherapy alone and to up to 21 months when maintenance checkpoint inhibitor is added for patients without disease progression after completing first line therapy.

The ultimate goal of adjuvant therapy is to demonstrate a favourable and sustained effect on DFS, i.e. in analyses conducted when recurrence rates have reached an apparent plateau, likely to translate in an OS benefit. Currently, no agent is approved in the adjuvant treatment for MIUC. Of note, recently the results of the IMvigor010 study with adjuvant atezolizumab in a similar patient population did not show a statistically significant improvement of DFS (Bellmunt, 2021).

There exists an unmet need in patients who have high risk residual disease following RC, regardless of whether they received neo-adjuvant chemotherapy, in particular if they are not eligible for cisplatin-based adjuvant chemotherapy due to the dismal prognosis of these patients.

3.1.3. Main clinical studies

The CA209274 study is a 1:1 randomised, double-blinded, placebo-controlled study to determine the efficacy of 1 year adjuvant nivolumab in high risk MIUC patients who have undergone radical surgery, with or without neoadjuvant cisplatin-based chemotherapy. There were N=353 patients included in the nivolumab arm and N=356 in the placebo arm. These numbers were respectively N=140 and N=142 for the PD-L1≥1% patients. The dual-primary endpoint was DFS in patients with PD-L1≥ 1% and in the all randomised patients group. Secondary endpoints were OS, NUTRFS and DSS also to be determined in patients with PD-L1≥ 1% and in all randomised patients. No formal comparison was planned for NUTRFS, DSS and exploratory endpoints (including DMFS).

Efficacy data presented are based on the clinical DBL on 27-Aug-2020 for the planned IA of DFS as specified in the protocol, with a median follow-up time of 20.90 months and 19.48 months (48% and 57% events) for all randomised patients and 22.11 months and 18.69 months (39% and 57% events) for PD-L1 expression ≥ 1% patients in the nivolumab and placebo arms, respectively. In the requested updated analysis the DBL is 19-May-2021, which translates into approximately 5 additional months of follow-up since the previous DBL.

The dosing regimen evaluated in study CA209274 was nivolumab 240 mg Q2W but an additional dose 480 mg Q4W is proposed based on a model-based bridge.

3.2. Favourable effects

DFS

In the **PD-L1≥ 1% patients** the dual-primary endpoint DFS showed a statistically significant effect favouring nivolumab over placebo (HR = 0.55 [98.72% CI: 0.35, 0.85]; p = 0.0005) (DBL 27-Aug-2020). The median DFS was 8.41 (95% CI: 5.59, 21.19) months in the placebo group and N.A. (95% CI 21.19, N.A) in the nivolumab group. The DFS KM curves for PD-L1≥ 1% patients show a clear separation of the curves and plateaus appear to be reached at the end of the curves.

The DFS results analysed according to the secondary definition of DFS (EMA preferred analyses) are comparable to the primary definition in both populations.

Updated DFS data (DBL 19-May-2021) continue to support a long term DFS effect in PD-L1 ≥ 1% patients (SmPC Table 36)

NUTRFS

In **the PD-L1≥ 1% population** the NUTRFS HR is 0.55 (95% CI: 0.39, 0.79) and the median was N.A. (95% CI: 24.57, N.A.) in the nivolumab arm and 10.84 (95% CI: 5.65, 22.14) in the placebo arm (no formal comparison). The NUTRFS KM curve for PD-L1≥ 1% patients showed a clear separation of the curve and plateaus.

Updated NUTRFS data (DBL 19-May-2021) continue to support the NUTRFS effect in PD-L1 ≥ 1% patients

Exploratory endpoints

Exploratory endpoints DMFS, TTR, LRDFS, LRC and PFS2 have a comparable HR to the dual-primary endpoints in **PD-L1≥ 1% patients**. In PD-L1≥ 1% patients the KM curves for DMFS and PFS2 separated and appear to reach plateaus.

Posology

To support the 480 mg Q4W dosing, nivolumab exposures were compared with 240 mg Q2W dosing considering the adjuvant MIUC population and the advanced UC population (already approved). Similar or higher exposures Cmin and Cave (steady-state) of nivolumab are expected in subjects with adjuvant treatment of MIUC with 480 mg Q4W compared to subjects with advanced UC treated with 240 mg Q2W, which is approved in the EU. Since the site of action is the same for the adjuvant treatment of MIUC as for treatment of advanced UC, these comparable nivolumab exposure data from advanced UC are considered supportive for efficacy for the 480 mg Q4W dosing regimen for the adjuvant treatment of MIUC.

3.3. Uncertainties and limitations about favourable effects

The absence of mature OS data constitutes a limitation in the context of the proposed adjuvant treatment.

3.4. Unfavourable effects

The most frequent any-Grade all-causality AE in the nivolumab arm were pruritus (30.2% vs 16.2%), diarrhoea (29.1% vs 26.1%), fatigue (27.4% vs 24.4%), urinary tract infection (19.9% vs 19.0%), and rash (18.8% vs 9.8%). When incidence rates (IR) were exposure adjusted, all-causality any grade

AE were more frequent in the nivolumab arm (1337.8 events per 100 person-years) compared to the placebo arm (1158.7).

There were more **Grade 3-4 all causality AEs** observed in the nivolumab arm (42.2%) compared to the placebo arm (35.1%). The most frequently reported Grade 3-4 AEs were increased lipase (6.3%), urinary tract infection (5.4%vs 6.4%), increased amylase (4.6% vs 1.7%), malignant neoplasm progression (1.7% vs 3.7%), and diarrhoea (1.7% vs 1.1%).

A comparable number of **SAEs** were observed in the nivolumab and placebo arm (29.6% vs 30.2%). The most frequently reported all-causality SAEs in the nivolumab arm were urinary tract infection (2.6% vs 6.0%), malignant neoplasm progression (2.3% vs 5.5%), intestinal obstruction (1.4% vs 1.4%), acute kidney injury (1.4% vs 0.3%).

There were 2 **deaths** due to study drug toxicity in the nivolumab arm (one immune-mediated pneumonitis and one pneumonitis).

The number of **discontinuation due to AEs** was higher in the nivolumab arm compared to the placebo arm (18.2% vs 9.2% respectively).

AEs with potential immune-related aetiology occurred more frequently in the nivolumab arm. The majority of these AEs were low Grade and most AEs resolved with dose delays and/or immune modulating medication. An exception were endocrine select AEs, in this category most AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Posology

To support the 480 mg Q4W dosing regimen, the predicted 6 month and 1 year probabilities of Gr2+ IMAE were approximately 6% and 8%, respectively, higher for the nivolumab 480 mg Q4W compared to nivolumab 240 mg Q2W for adjuvant muscle invasive urothelial carcinoma. The small differences in probability in Grade 2+ IMAEs for 480 mg Q4W compared to 240 mg Q2W, based on Cmax1 as predictor as worst case scenario, are similar to those predicted for other indications and were found acceptable for melanoma and RCC indications. Therefore, the 480 mg Q4W dosing regimen can be accepted.

3.5. Uncertainties and limitations about unfavourable effects

There are no new safety concerns identified and no major uncertainties were identified with regard to the safety results.

3.6. Effects Table

Table 57. Effects Table for nivolumab adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC (DBL 19-May-2021)

Effect	Short description	Unit	Nivolumab	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
DFS PD-L1≥ 1%	median	months	N.A. (22.11 N.A.)	8.41 (5.59, 20.04)	HR 0.53 (98.72% CI: 0.38, 0.75) Clear separation of the curves.	
Unfavourable Effects						
Gr 3-4 AEs	Grade 3-4 all causality	%	42.2%	35.1%	**Strengths**:	Adverse events

	AEs				- Safety data derived from phase 3 RCT vs standard of care placebo - Double blind study **Uncertainties:** - No major uncertainties identified with regards to safety	
Drug-related Deaths	Deaths	n	2	0		SAEs, deaths and other significant events
Discontinuations	Discontinuations due to AEs	%	18.2%	9.2%		Discontinuations due to AEs

Abbreviations: AE- adverse event, Gr- grade, n- number, RCT- randomised controlled trial, SAE- serious adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The reported DFS results in study CA209274 showed an advantage for nivolumab compared to placebo in **the PD-L1≥ 1% population** for the dual primary endpoint. This effect is sustained over time as showed by the clear separation of the KM curves which appears to reach a plateau from 30 months onwards indicative of long-term benefit. Secondary endpoints such as DMFS and PFS2 for which the KM curves also indicate sustained effects and plateaus provide further support for a benefit of nivolumab in PD-L1≥ 1% patients.

OS data are still immature. Even if this constitutes a limitation in the context of an adjuvant treatment a detrimental effect on OS is considered unlikely for the reasons aforementioned and the provided updated DFS results (effect size and duration) and additional analyses (secondary endpoints) are considered sufficient to support clinical benefit in the intended treatment setting.
The MAH will provide the results of the planned 2nd IA and the final OS analysis to further characterize the efficacy of nivolumab in subjects with tumour cell PD-L1 expression level ≥ 1% by December 2027 (see Annex II).

There are no new safety concerns and no major uncertainties related to safety identified. The toxicity and tolerability of treatment with adjuvant nivolumab is somewhat worse compared to placebo as shown by the higher number of severe AEs, dose delays and discontinuations due to AEs, but appears manageable and could be acceptable in light of an effective therapy.

Complexities in the eCRF and a suboptimal trial oversight/data management led to a small number of errors in the DFS data, which were corrected during this procedure. The data are considered sufficiently reliable for assessment.

3.7.2. Balance of benefits and risks

Nivolumab has demonstrated a statistically significant and clinically relevant improvement in DFS in adults with MIUC with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC, supported by updated analysis and secondary endpoints. Even though there are currently uncertainties on the magnitude of the benefit in terms of OS, the results are

considered clinically relevant and sufficient to conclude on (long-term) clinical benefit in the intended treatment setting.

The safety data from study CA209274 are consistent with the already known safety profile of nivolumab and no new risks have been identified.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of nivolumab as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) **with tumour cell PD-L1 expression ⩾ 1%,** who are at high risk of recurrence after undergoing radical resection of MIUC is positive.

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

Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adult patients with muscle invasive urothelial carcinoma the MAH should submit the OS data from the 2nd IA and the final OS analysis of the phase 3 CA209274 study for the PD-L1 ≥1% population.

4. Recommendations

Outcome

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

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

Extension of indication for Opdivo to include as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1); as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and Annex II are updated. The Package Leaflet is updated in accordance. Version 26.2 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

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

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

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

Description	Due date
Post authorisation efficacy study (PAES): In order to further characterize the efficacy of nivolumab as adjuvant treatment of adults with muscle invasive urothelial carcinoma, the MAH should submit the OS data from the 2nd IA and the final OS analysis of the Phase 3 CA209274 study in the PD-L1 ≥1% population.	By 31st December 2027

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'OPDIVO-H-C-3985-II-0100'