25 April 2024
EMA/225115/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: Nivolumab

Procedure No. EMEA/H/C/003985/II/0137

Note

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

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List of abbreviations

1L	first-line
ADA	anti-drug antibody
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
B/R	benefit-risk
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
cHL	classic Hodgkin Lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CPI	checkpoint inhibitor
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DC	discontinuation
DCO	data cut-off
ddMVAC	Dose dense methotrexate, vinblastine, doxorubicin, and cisplatin
dMMR	mismatch repair deficient
DoR	duration of response
EAC	esophageal adenocarcinoma
EC	esophageal cancer
ECL	electrochemiluminescence
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30
EQ-5D	European Quality of Life 5 Dimension
E-R	exposure-response

ESCC	esophageal squamous cell carcinoma
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GC	gastric cancer
GCP	Good Clinical Practice
GEJC	gastro-esophageal junction cancer
HCC	hepatocellular carcinoma
HR	hazard ratio
HRQoL	health related quality of life
IHC	immunohistochemistry
IHC	immunohistochemistry
IMAE(s)	immune-mediated adverse event(s)
IMM	immune-modulating medication
IO	immuno-oncology
IPD	important protocol deviation
irAR	immune-related adverse event
IRT	interactive response technology
KM	Kaplan-Meier
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
MPM	malignant plural mesothelioma
MSI H	microsatellite instability-high
nivo	nivolumab
NSCLC	non-small cell lung cancer
OESI(s)	other event(s) of special interest
ORR	objective response rate
OS	overall survival
PD-1	programmed death receptor 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PRO	patient-reported outcome

PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RCC	renal cell carcinoma
RPD	relevant protocol deviation
SAE(s)	serious adverse event(s)
SCCHN	squamous cell carcinoma of head and neck
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
SOC	standard of care gemcitabine-cisplatin chemotherapy arm; system organ class
TCC	transitional cell carcinoma
TTR	time to recurrence
UC	urothelial carcinoma
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
VAS	visual analogue scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 10 October 2023 an application for a variation.

The following variation was requested:

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

Extension of indication to include in combination with cisplatin based chemotherapy the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC) for OPDIVO, based on interim results from study CA209901 (CheckMate901); this is a Phase 3, open-label, randomized study of nivolumab combined with ipilimumab, or with standard of care chemotherapy, versus standard of care chemotherapy in participants with previously untreated unresectable or metastatic urothelial cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 35.0 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0432/2020 and P/0339/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0432/2020 was completed and the PIP P/0339/2023 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 received Scientific Advice (SA) on the development of nivolumab in urothelial cancer from the CHMP on 28 May 2020 regarding amendments in the ongoing CA209901 primary and substudy (EMEA/H/SA/2253/13/2020/II).

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: Peter Mol

Timetable	Actual dates
Submission date	10 October 2023
Start of procedure:	28 October 2023
CHMP Rapporteur Assessment Report	20 December 2023
PRAC Rapporteur Assessment Report	3 January 2024
PRAC Outcome	11 January 2024
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 January 2024
Request for supplementary information (RSI)	25 January 2024
CHMP Rapporteur Assessment Report	2 April 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur Assessment Report	19 April 2024
Opinion	25 April 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The clinical data in this application are intended to support the use of nivolumab, in combination with cisplatin-based chemotherapy, for first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC).

State the claimed the therapeutic indication

Proposed indication

OPDIVO, in combination with cisplatin-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

Proposed dosage and administration

Nivolumab 360 mg (over 30 minutes) in combination with cisplatin-based chemotherapy administered Q3W for up to 6 cycles, followed by nivolumab 240 mg Q2W or 480 mg Q4W (over 30 minutes) for up to 24 months from first dose.

Epidemiology and risk factors

UC of the bladder is among the top 10 most common cancers in the world, with approximately 550,000 new cases annually. In 2020, the prevalence of bladder cancer in the EU was 27.2 per 100,000 people per year. Bladder cancer is the fifth most common cancer in the EU, with an estimated 203,983 new cases and 67,289 deaths from UC in 2020. The age-standardised incidence rate (per 100,000 person/years) is 20 for men and 4.6 for women[1].

Risk factors for UC include tobacco smoking, occupational exposure to chemicals, radiotherapy and bladder schistosomiasis and chronic urinary tract infection[2].

Clinical presentation and prognosis

The majority (90%) of UC originates in the urinary bladder, while up to 10% originate in the upper urinary tract (ureters and/or renal pelvis UC)[3]. UC is characterised by multiple non-muscle invasive recurrences, however approximately 15% to 25% of UCs either present with or eventually progress to muscle invasive or metastatic disease[4]. For patients with muscle invasive disease more than 50% of patients with MIBC will eventually develop metastases. The prognosis for patients with locally advanced unresectable or metastatic UC is dismal. Cisplatin-based chemotherapy became the standard first-line treatment for metastatic UC in the 1980s, with long-term remission possible in around 10% of patients[5].

Management

Chemotherapy as first-line treatment for metastatic urothelial carcinoma

Cisplatin-based chemotherapy regimens such as gemcitabine plus cisplatin or ddMVAC are standard first-line 1L regimens for patients with locally advanced/metastatic UC who can tolerate cisplatin-based therapy (i.e., the cisplatin-eligible population[6;7]). While the toxicity of ddMVAC limits its widespread use, gemcitabine plus cisplatin has been established as the preferred regimen in this 1L setting based on the observed survival benefit, with median OS of 14-15 months and median PFS of approximately 7 months[8].

Around 50% of patients with metastatic UC cannot receive cisplatin due to a poor performance status, comorbidities, or impaired renal function. These patients generally receive oncological inferior carboplatin-based regimens. Carboplatin-based chemotherapy seems to be less effective than cisplatin based, with published median OS of 9 months and median PFS of 6 months[9].

[1] International Agency for Research on Cancer. (2020). GLOBOCAN 2020: Estimated cancer incidence, mortality and prevalence worldwide. IARC. https://gco.iarc.fr/today
[2] Burger, M., et al. (2012). Epidemiology and risk factors of urothelial bladder cancer. European Urology, 63(2), 234-241. doi:10.1016/j.eururo.2012.07.033
[3] National Cancer Institute (2022). SEER Cancer Stat Facts: Bladder Cancer
[4] Balasubramanian, A., et al. (2022). Adjuvant therapies for non-muscle-invasive bladder cancer: Advances during BCG shortage. World Journal of Urology, 40, 1111–1124. https://doi.org/10.1007/s00345-021-03908-x
[5] Tian, J., et al. (2021). Population-based outcome of muscle-invasive bladder cancer following radical cystectomy: who can benefit from adjuvant chemotherapy? Translational Andrology and Urology, 10(1), 356-373. https://doi.org/10.21037/tau-20-960
[6] Powles, T. et al. (2021). Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology, 32(12), 1619-1648.
[7] Witjes, J. A., Bruins, H., Carrion, A., et al. (2023). European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2023 guidelines. European Urology, 85(1), 17-31.
[8] NCCN Clinical Practice guidelines in Oncology. Bladder Cancer Version 4.2019. www.nccn.org.
[9] De Santis, M., et al. (2012). Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. Journal of Clinical Oncology, 30(2), 191-199. https://doi.org/10.1200/JCO.2011.37.3571

Immune checkpoint inhibitors

Recently, study Javelin 100 demonstrated that the sequential addition of avelumab maintenance after 1L platinum-based chemotherapy improved outcomes of patients with metastatic UC, but only for patients that did not show progression of disease during or immediately after the platinum-based induction part of their treatment[10]. The Javelin 100 study reported a median OS of 21.4 months vs. 14.3 months in the control arm (HR 0.69; 95% CI 0.56 - 0.86; p = 0.001). Avelumab maintenance, therefore, became a standard of care for non-progressing patients after platinum-based chemotherapy (Bavencio II/18 EPAR).

For patients who are unable to receive cisplatin, atezolizumab (ORR 24-28%) or pembrolizumab (ORR 47%) may also be considered in patients with PD-L1 positive tumors[11,12].

Unmet medical need for metastatic urothelial carcinoma

Platinum-based chemotherapy remains the standard treatment for metastatic UC. Although response rates to cisplatin-based chemotherapy in 1L metastatic UC are relatively high (>40%), they are rarely durable[9].

The top priorities in treating metastatic UC continue to be improvement in OS with a manageable safety profile while not deteriorating the patients' quality of life. To achieve those goals, identifying novel approaches to increase survival, response, and response durability with manageable toxicities is paramount.

The introduction (June 2020) of avelumab maintenance for patients who did not progress during or after 1L platinum-based chemotherapy represents an improvement in the treatment landscape for metastatic UC patients. Importantly, avelumab 1L maintenance does not offer a solution for patients who have a more aggressive disease (progressing before completing a full course of 1L platinum-based chemotherapy) and, thus, would miss the benefit from immunotherapy in the 1L of treatment (Bavencio II/18 EPAR).

Concurrent 1L immunotherapy plus chemotherapy combinations have demonstrated OS and PFS benefits compared with chemotherapy alone in several tumour types. However, this has not been the case for UC, where published Phase 3 trials have failed to demonstrate OS and PFS benefit.

In the KEYNOTE-361 trial of pembrolizumab in combination with either gemcitabine-cisplatin or gemcitabine-carboplatin, pembrolizumab did not significantly improve either OS or PFS[13]. Similarly, atezolizumab in combination with chemotherapy failed to improve OS vs. placebo plus chemotherapy in the overall population in the IMvigor130 trial despite improvement in PFS[14].

However, exploratory analyses of both KEYNOTE-361[14] and IMvigor130[15] revealed improvements in PFS (and OS in IMvigor130) in patients receiving PD-1/PD-L1 blockade added to cisplatin–, but not carboplatin–, based chemotherapy. These results may, in part, be explained by differences in the immunomodulatory effects of cisplatin versus carboplatin and highlight the importance of the particular

[10] Powles, T., et al. (2020). Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. The New England Journal of Medicine, 383(13), 1218–1230. https://doi.org/10.1056/NEJMoa2002788
[11] European Medicines Agency. Tecentriq: EPAR - Product Information
[12] European Medicines Agency. Keytruda: EPAR - Product Information
[13] Powles, T., et al. (2021). Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. The Lancet Oncology, 22(6), 792–802
[14] Galsky, M. D., et al. (2020). Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. The Lancet Oncology, 21(5), 631-644
[15] Grande, E., et al. (2023). Atezolizumab plus chemotherapy versus placebo plus chemotherapy in untreated locally advanced or metastatic urothelial carcinoma (IMvigor130): final overall survival analysis results from a randomised, controlled, phase 3 study. The Lancet Oncology, 24(12), 1802-1814

cytotoxic chemotherapy backbones in combination regimens with immune checkpoint blockade. The current CA209901 substudy is the only trial in this setting specifically addressing the benefit of adding PD-1 blockade to cisplatin-based chemotherapy.

2.1.2. About the product

Opdivo (nivolumab; pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein-1/ death ligand-1) inhibitors; ATC code: L01FF01) is a human immunoglobulin G4 (IgG4) monoclonal antibody, which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

In the European Union (EU) Opdivo is approved for the treatment of multiple solid tumours and for the treatment of classical Hodgkin lymphoma (Opdivo SmPC). The indications for the treatment of solid tumours include the treatment of melanoma, non-small cell lung cancer (NSCLC), malignant pleural mesothelioma, renal cell carcinoma, urothelial carcinoma, colorectal cancer, oesophageal squamous cell carcinoma, oesophageal or gastro-oesophageal junction cancer, and gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

The approvals for the treatment of urothelial cancer are the following:

- OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.
- 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.

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

The nivolumab clinical program was initiated in 2006 and spans across multiple solid tumours and haematological malignancies. The current application is based on data from the ongoing clinical study, CA209901 (NCT03036098). Study CA209901 is a phase 3, open-label, randomised study of nivolumab combined with ipilimumab, or with SOC chemotherapy vs. SOC chemotherapy in subjects with previously untreated unresectable or metastatic UC. Study CA209901 consists of a primary study (Arm A vs. Arm B) and substudy (Arm C vs. Arm D).

Scientific advice

The MAH received SA from the CHMP on 28 May 2020 on revision of the ongoing study CA209901 (EMEA/H/SA/2253/13/2020/II), mainly related to the revision of the primary study but also to the substudy. The primary study aimed to demonstrate that treatment with nivolumab combined with ipilimumab will improve OS in cisplatin-ineligible PD-L1 positive (≥ 1%) and/or all randomised participants with previously untreated unresectable or metastatic UC. The substudy aimed to demonstrate that treatment with nivolumab combined with SOC chemotherapy will improve PFS in

cisplatin-eligible participants with previously untreated, unresectable or metastatic UC. For the substudy it was proposed to make OS a primary endpoint with PFS, remove the PFS interim analysis, add an OS interim analysis, and increase the sample size for sufficient power. Of note, at that time the Applicant had already amended the primary study in a prior protocol revision; PFS was removed as a co-primary objective and OS in PD-L1 positive (≥ 1%) was added as a primary population. Prior to that amendment, for the primary study OS and PFS in cisplatin-ineligible patients were co-primary endpoints. Issues related to the substudy are discussed below.

- The CHMP would have supported the upgrading of OS as a co-primary endpoint and increasing the sample size, if this decision had been taken before data reached maturity. Noting that considering the poor prognosis of urothelial cancer an established effect on PFS only would not necessarily allow to conclude to a relevant benefit. In the context of an open-label trial it was considered unlikely that the MAH can provide sufficient reassurance that data have not driven the proposed changes, resulting in an unknown statistical risk and unreliable conclusions.
- The CHMP did not recommend the proposed OS interim analysis to be submitted or even performed. The interim analysis of OS would include 44.5% of the total expected events, which was considered as premature and at risk of over-representing patients with a poor prognosis. Removal of a PFS interim analyses could in principle be supported.
- The CHMP concluded that in the CA209901 primary study and its substudy several hypotheses of drug-combinations and target populations are tested and the succession of amendments may provide different combinations of results. If the Applicant, instead of prospectively defining the treatment the endpoints and target populations under testing, opts for a post-hoc choice of the most favourable one(s), this may cause unacceptable problems of multiplicity.

Paediatric investigation plan

See 'Information on paediatric requirements' in section 1.

Orphan indication

Not applicable.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with Good Clinical Practice (GCP) as claimed by the MAH.

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

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Nivolumab is a protein composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk. As a protein, nivolumab is exempt from preparation of an Environmental Risk Assessment under the 1 June 2006 "Guideline on the Environmental Risk

Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00). Nivolumab and the product excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Primary Objective of the Study	Study Design and Type of Control	Treatment Cohorts (Test Product(s): Dosage Regimen, Route of Administration)	Number of Subjects (treated)	Diagnosis of Patients (Study Population)	Study Status Type of Report
Efficacy/ Safety	CA209901 Substudy (NCT03036098)	Module 5.3.5.1	The primary objectives of the CA209901 substudy were: • to compare overall survival of nivolumab combined with SOC chemotherapy versus SOC chemotherapy. • to compare progression-free survival of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	Phase 3, open-label, randomized, cisplatin-based chemotherapy controlled.	Arm C: Nivolumab (360 mg) Day 1 of each 3 week cycle plus gemcitabine (1000 mg/m^2) on Days 1 and 8 of each 3 week cycle plus cisplatin (70 mg/m^2) on Day 1 of each 3 week cycle for up to 6 cycles, followed by nivolumab (480 mg) beginning 3 weeks following last combination dose, Q4W. Arm D: Gemcitabine (1000 mg/m^2) on Days 1 and 8 of each 3-week cycle plus cisplatin (70 mg/m^2) Day 1 of each 3-week cycle for up to 6 cycles.	**Nivolumab + SOC:** 304 **SOC:** 288	Cisplatin-eligible patients with previously untreated locally advanced unresectable or metastatic urothelial carcinoma.	Study Status: Ongoing Type of Report: Interim CSR

Abbreviations: SOC = gemcitabine-cisplatin standard of care chemotherapy, Q4W = every 4 weeks

2.3.2. Pharmacokinetics

No new clinical pharmacology data are submitted in the current application as agreed with the Rapporteurs and EMA during the pre-submission meeting held on 25-Sep-2023.

The previous extensive characterisation of the nivolumab clinical pharmacology profile supports the proposed posology for this indication.

Rationale for dosing regimen selection for pivotal phase 3 CA209901 substudy

The dosing regimen selected for the CA209901 substudy was based on available PK, safety and efficacy data across the nivolumab program and was nivolumab 360 mg (over 30 minutes) in combination with platinum-doublet chemotherapy gemcitabine-cisplatin administered Q3W for up to 6 cycles, followed by nivolumab 480 mg Q4W (over 30 minutes) for up to 24 months from the first dose. Nivolumab 360 mg Q3W is an interpolated dosing regimen between the approved monotherapy dosing regimens 240 mg Q2W and 480 mg Q4W with a similar time-averaged exposure over the dosing interval at steady state (Cavgss). Nivolumab 360 mg Q3W allowed for more convenient dosing in combination with chemotherapy and was evaluated in NSCLC in combination with chemotherapy and ipilimumab in study CA2099LA, in combination with chemotherapy in neoadjuvant NSCLC in study

CA209816 (Opdivo II/117 EPAR), and in GC/GEJC/EAC in combination with chemotherapy in study CA209649 (Opdivo II/96 EPAR) that resulted in a favourable benefit-risk profile supporting approvals.

Dose Confirmation

The selected dosage and regimen is supported by the clinical efficacy and safety results in the CA209901 substudy and previous nivolumab PK and E-R analyses demonstrating lack of clinically relevant covariate for PK and E-R, clinical equivalency for nivolumab 240 mg Q2W and 480 mg Q4W and lack of an impact of chemotherapy or line of therapy on nivolumab PK. Nivo + SOC demonstrated statistically significant improvements in OS and PFS (per BICR) compared with SOC chemotherapy, and was supported by an acceptable safety profile in subjects with previously untreated, unresectable or metastatic UC in the CA209901 substudy.

Posology Justification For Monotherapy Maintenance Dosing

Nivolumab dosing at 240 mg Q2W and/or 480 mg Q4W is approved for all monotherapy indications (including nivo monotherapy after nivo + chemotherapy combination) and tumour types, including advanced UC and adjuvant treatment of UC with demonstrated therapeutic equivalency (Opdivo SmPC). Previous E-R efficacy and safety analyses demonstrated a comparable benefit/risk profile for nivolumab monotherapy for adults for 240 mg Q2W or 480 Q4W in several tumour types, including adjuvant MIUC.

An alternative nivolumab dosing option of 240 mg Q2W in monotherapy maintenance after nivo + SOC in 1L UC provides patients and clinicians with dosing flexibility and is consistent with the current approved monotherapy dosing regimens of 240 mg Q2W or 480 mg Q4W for nivolumab monotherapy.

2.3.3. Discussion on clinical pharmacology

The nivolumab clinical pharmacology profile has been characterised in a large number of tumour types, including UC, with and without concomitant chemotherapy treatment with various dosing regimen i.e. 3 mg/kg Q2W, 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W as monotherapy and in combination with other treatments.

No new clinical pharmacology data were submitted in the current application as agreed with the Rapporteurs and EMA during the pre-submission meeting held on 25-Sep-2023.

2.3.4. Conclusions on clinical pharmacology

No new clinical pharmacology data have been submitted for this application which is considered acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies were performed. See section 2.2 'Pharmacokinetics' for the rationale for the selected dosing regimen.

2.4.2. Main study

CA209901, a randomised, open-label, Phase 3 study composed of 2 Phase 3 studies: a primary study (Arms A and B) and a substudy (Arms C and D)

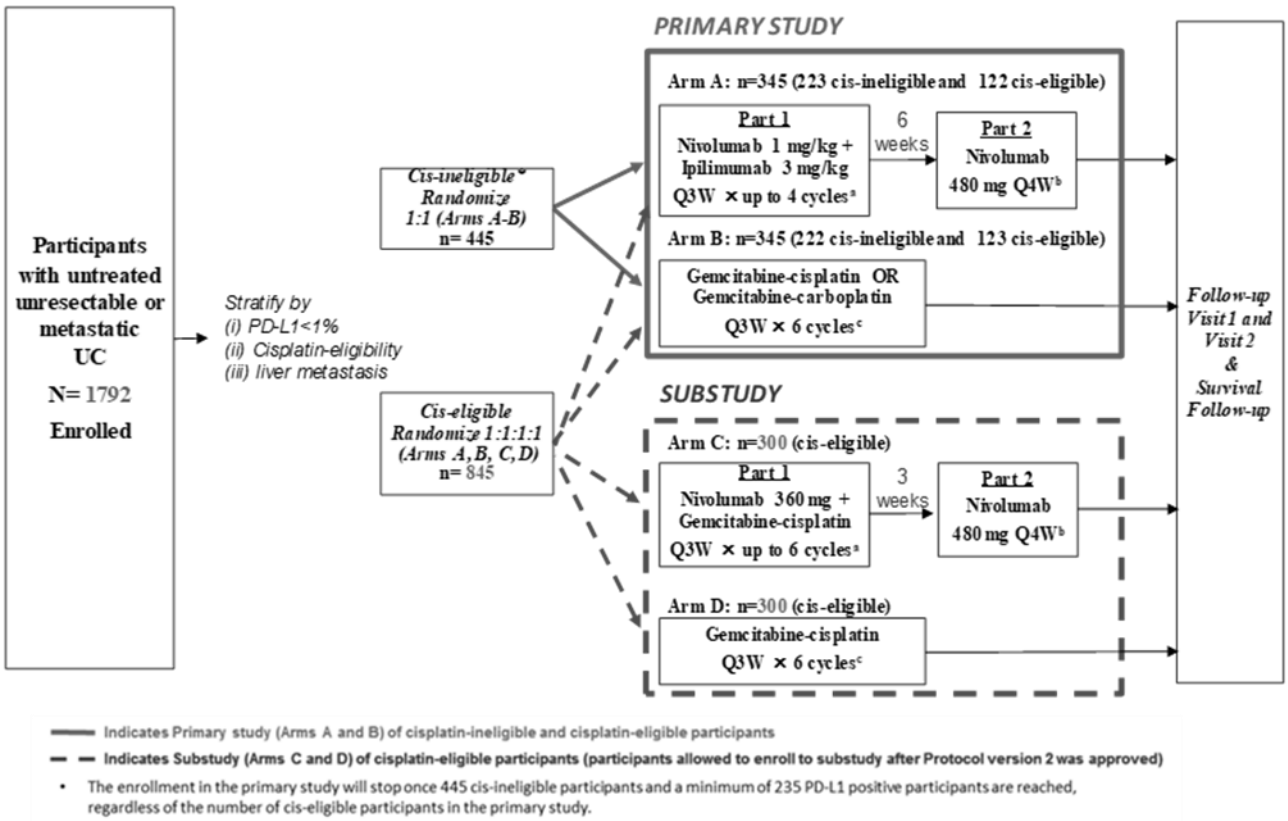
The study originally began only with the primary study, randomising 1:1 to arms A and B. After the substudy was opened, cisplatin-ineligible participants continued to be randomised 1:1 to arms A or B, while cisplatin-eligible participants were randomised 1:1:1:1 across arms A through D, and stratified by PD-L1 status [1% cut-off], cisplatin-eligibility (for primary study only), and presence of liver metastasis. Once the primary study met its enrolment target (approximately 445 cis-ineligible subjects and 235 PD-L1 TC ≥ 1% subjects were enrolled into Arms A and B), enrolment of the primary study stopped. Cis-eligible subjects continued to be randomised 1:1 into the substudy (Arms C and D) only.

In the CA209901 substudy (van der Heijden et al. N Engl J Med. 2023) which is the focus of this AR, only cisplatin-eligible subjects were randomised 1:1 to:

- Arm C: Nivolumab (360 mg) in combination with gemcitabine-cisplatin (nivo + SOC) every 3 weeks for up to 6 cycles, followed by nivolumab monotherapy (480 mg) every 4 weeks. Monotherapy began 3 weeks following the last dose of combination therapy and continued until confirmed disease progression, unacceptable toxicity, participant withdrawal of consent, or 24 months from first dose, whichever came first.
- Arm D: Gemcitabine-cisplatin for up to 6 cycles (additional cycles were permitted as per local guidelines).

The study design schematic is presented in Figure 1.

Figure 1. CA209901 Study design



a Arm A and Arm C: In Part 1, a minimum of 1 cycle of combination therapy is required before proceeding to nivolumab monotherapy dosing (Part 2). Subjects should be dosed no less than 19 days between combination treatment cycles for Arm A combination therapy.

b In Arm A, monotherapy should begin 6 weeks following the last combination dose. In Arm C, monotherapy will begin 3 weeks following the last combination therapy. During monotherapy subjects should be dosed no less than 26 days between monotherapy treatments. Subjects in Arms A and C will be treated until confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or up to 24 months of treatment, whichever occurs first.

c Arms B and D subjects will receive up to a maximum of 6 cycles per protocol. Additional optional cycles of SOC may be given per local guidelines. NOTES: All subjects will be randomised 1:1 to Arms A or B during the primary study, prior to substudy initiation. Following initiation of the substudy, cis-eligible patients will be randomised to Arms, A, B, C or D. Cis-ineligible patients are not eligible for Arms C and D treatment.

Methods

Study participants

Assuming a 28% screen failure rate, it was estimated that approximately 1792 participants with previously untreated unresectable or metastatic UC would be enrolled with approximately 1290 participants randomised to the primary study and substudy:

- 445 cisplatin-ineligible participants would be randomised in a 1:1 ratio to receive nivolumab plus ipilimumab vs SOC chemotherapy (primary study);
- 245 cisplatin-eligible participants would be randomised in a 1:1 ratio to receive nivolumab plus ipilimumab vs SOC chemotherapy (primary study);
    - Of these 690 primary study participants, 235 PD-L1 positive (≥ 1%) participants by IHC are expected to be randomised
- 600 cisplatin-eligible participants would be randomised in a 1:1 ratio to receive nivolumab plus SOC chemotherapy vs SOC chemotherapy (substudy).

The eligibility criteria are similar for the primary study and the substudy and the most important criteria are reflected here.

Inclusion Criteria

1) Target Population

a) Histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra. Minor histologic variants (< 50% overall) are acceptable (TCC must be the dominant histology).

b) All participants must have measurable disease by CT or MRI per RECIST 1.1 criteria.

c) Prior systemic chemotherapy for metastatic or surgically unresectable UC was not allowed. NOTE: (i) Prior intravesical therapy is permitted if completed at least 4 weeks prior to the initiation of study treatment. (ii) Prior neoadjuvant chemotherapy, radiation or prior adjuvant platinum-based chemotherapy or radiation following radical cystectomy with recurrence ≥ 12 months from completion of therapy is permitted.

d) Participants ineligible for cisplatin-based chemotherapy were defined by any one of the following criteria:

i. Impaired renal function (glomerular filtration rate [GFR] ≥ 30 but < 60 mL/min);

ii. Common Terminology Criteria for Adverse Events (CTCAE) version 4, ≥ Grade 2 hearing loss;

iii. CTCAE version 4, ≥ Grade 2 peripheral neuropathy.

Cisplatin-ineligible patients received gemcitabine-carboplatin treatment as chemotherapy (primary study).

e) Participants eligible for cisplatin-based chemotherapy had to exhibit adequate renal function as follows: GFR ≥ 60 mL/min (assessed by direct measurement (i.e. creatinine clearance) or, if not available, by calculation using the Cockcroft-Gault formula).

f) Participants had to provide a fresh tumour biopsy from the primary disease site or a metastatic site.

g) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.

h) Adequate hematologic and liver function (using CTCAE v4).

j) Prior palliative radiotherapy had to be completed at least 2 weeks prior to study drug administration.

Exclusion Criteria

1) Target Disease Exceptions

a) Had disease that is suitable for local therapy administered with curative intent.

b) Active brain metastases or leptomeningeal metastases. Participants with brain metastases were eligible if these were treated and there was no evidence of progression.

c) There had also to be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

2) Medical History and Concurrent Diseases

a) Prior malignancy active within the previous 3 years except for locally curable cancers that were apparently cured.

b) 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, impaired the ability of the participant to receive protocol therapy, or interfered with the interpretation of study results.

c) Participants had to have recovered from the effects of major surgery requiring general anaesthetic or significant traumatic injury at least 14 days before randomisation or treatment assignment.

d) Participants with active, known or suspected autoimmune disease, with some exceptions for mild cases.

e) Participants 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.

f) Uncontrolled adrenal insufficiency.

g) New York Heart Association (NYHA) Functional Classification of Heart Failure: Class III or Class IV.

h) ECOG PS ≥ 2.

k) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

l) Participants who had a history of acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation.

m) Participants with interstitial lung disease that was symptomatic or could interfere with the detection or management of suspected drug-related pulmonary toxicity.

5) Prior Investigational Agents

a) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

b) Use of an investigational agent within 4 weeks of Day 1 visit

Treatments

From here onward methods and results from the substudy are presented with additional information provided on the primary study only if considered relevant to the substudy.

The treatments administered in the CA209901 substudy are summarised in Table 1.

Table 1. Selection and Timing of Dose in the CA209901 Substudy (Arms C and D)

	Study Treatment	**Unit Dose Strength(s)/Dosage Level(s)**	**Dosage Formulation Frequency of Administration**	**Route of Administration**
Arm C	Nivolumab	360 mg in Part 1 480 mg in Part 2 monotherapy	Q3W (Part 1- 6 cycles) Q4W (Part 2)	Nivolumab 30 min IV infusion
Arm C+D	Gemcitabine + cisplatin	Gemcitabine (1000 mg/m^2) Cisplatin (70 mg/m^2)	Gemcitabine: Days 1 and 8 of each 3-week cycle Cisplatin: Day 1 of each 3-week for up to 6 cycles	Gemcitabine: 30 min IV infusion Cisplatin: 30-120 min IV infusion

Note: Treatments specified for Arm A (Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg) and Arm B (Gemcitabine 1000 mg/m2 plus Cisplatin 70 mg/m2 or Carboplatin AUC 4.5/5) are not shown in this table.

Starting 3 weeks following the last combination dose in Arm C Part 1, participants were administered a flat dose of 480 mg nivolumab on Day 1 of each treatment cycle given IV over approximately 30 minutes every 4 weeks (Q4W) until unacceptable toxicity, disease progression or up to 24 months of treatment.

Dose modifications

Dose delays of nivolumab were allowed for amongst others drug related events and chemistry laboratory abnormalities. Dose delays for platinum doublet chemotherapy regimen were allowed in case of hematologic events, skin events and chemistry laboratory abnormalities. Dose reduction for platinum doublet chemotherapy were also allowed (no clear criteria).

Discontinuation

Participants receiving cisplatin with gemcitabine had to discontinue cisplatin if the calculated creatinine clearance decreased to < 50 mL/min, but could be switched to carboplatin. Nivolumab had to be discontinued in case of certain Grade 2 AEs related to the eye, Grade 3 non skin, drug related AE lasting > 7 days except for certain immune related events, any Grade 4 drug-related adverse event or laboratory abnormality except for certain hematologic laboratory abnormalities and any event that led to delay in dosing lasting > 8 weeks, except for certain non-drug related events and periods for prolong steroid tapers. Platinum doublet chemotherapy had to be discontinued in case of Grade≥ 3 peripheral neuropathy, severe drug related liver function test, Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding, drug-related adverse event which recurred after two prior dose reductions, Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction, certain Grade 4 drug-related adverse event which could not be managed by dose modification, dosing delays lasting > 6 week for drug-related AEs. Participants could generally resume treatment with study drug when the drug-related AE(s) resolved to Grade ≤ 1 or baseline value.

Concomitant treatment

Recommended antiemetic treatments were dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid could be substituted) and a 5-HT3 receptor antagonist. Additional use of antiemetic pre-medications could be employed at the discretion of the investigator per local standards of care.

Any concurrent anti-neoplastic therapy was prohibited, as well as immunosuppressive agents (except to treat a drug-related AE), systemic corticosteroids > 10 mg daily prednisone equivalent, intravesical therapy lasting for >1 instillation, any live/attenuated vaccine and any botanical preparation.

Objectives

The study objectives were synonymous with the study endpoints, see Table 2.

Outcomes/endpoints

Table 2. Study CA209901 Substudy Objectives and Endpoints

Objective	Endpoint	Endpoint Description
Primary		
To compare OS of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	OS	OS was defined as the time from randomisation to the date of death from any cause. For subjects that are alive, their survival time was censored at the date of last contact (or "last known alive date"). OS was censored at the date of randomisation for subjects who were randomised but had no follow-up.

Objective	Endpoint	Endpoint Description
To compare PFS of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	PFS by BICR	PFS by BICR was defined as the time from randomisation to the date of documentation of disease progression or death from any cause, whichever occurred first. Subjects receiving subsequent anti-cancer therapy prior to documented disease progression or death were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy
Secondary		
To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (OS and PFS) of nivolumab combined with SOC chemotherapy as first-line therapy.	PFS by BICR and OS by PD-L1 expression at ≥ 1% by IHC	PFS by BICR using RECIST 1.1 in PD-L1 positive (≥ 1%) randomised subjects. OS in PD-L1 positive (≥ 1%) randomised subjects.
To evaluate changes from baseline in HRQoL of nivolumab combined with SOC chemotherapy.	EORTC QLQ-C30 Global Health Status score	The EORTC QLQC30 was collected in order to assess cancer specific health related quality of life.
Exploratory		
To estimate ORR of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	ORR by BICR	ORR is defined as the number of participants with a BOR of a confirmed CR or PR using the RECIST 1.1 criteria based on BICR assessments divided by the number of randomised participants for each treatment group.
To assess the safety and tolerability of nivolumab combined with SOC chemotherapy versus SOC chemotherapy.	AEs, clinical laboratory values, vital signs, or other safety biomarkers	The assessment of safety was based on the frequency of deaths, AEs, SAEs, AEs leading to discontinuation, and specific laboratory abnormalities. Analyses were conducted using the 30-day and 100-day safety window from day of last dose received. AEs were coded using MedDRA Version 26.0 and laboratory values were graded using the NCI CTCAE version 4.
To assess changes in reported global health outcomes based on EuroQol's EQ-5D-5L.	EQ-5D-5L index score, EQ-5D-5L dimensions, and EQ-5D-5L VAS	The EQ-5D-5L was collected in order to assess the impact of nivolumab on generic health related quality of life and the data was used for populating health economic models most notably, cost effectiveness analysis.
To evaluate HRQoL as assessed by EORTC QLQ-C30.	QLQ-C30 Functional scales; QLQ-C30 Symptom scales	The EORTC QLQ-C30 was collected in order to assess cancer specific health related quality of life.
To evaluate whether PD-L1 expression is a predictive biomarker of efficacy (ORR) of nivolumab combined with SOC chemotherapy as first-line therapy.	ORR by BICR PD-L1 expression at ≥ 1% by IHC	ORR is defined as the number of participants with a BOR of a confirmed CR or PR using the RECIST 1.1 criteria based on BICR assessments divided by the number of randomized participants for each treatment group.
To characterise the immunogenicity of nivolumab combined with SOC chemotherapy as first line therapy.	Incidence of anti-nivolumab antibody levels and their potential relationship with safety and efficacy endpoints.	Blood samples for immunogenicity analyses of nivolumab were collected according to the study schedule. Samples collected from subjects were evaluated for the development of ADA for nivolumab by validated immunoassays. Samples may also have been analysed for neutralising ADA response to nivolumab.

Sample size

In the CA209901 substudy a total of 600 cisplatin-eligible participants were planned to be randomised in a 1:1 ratio to receive nivolumab plus SOC chemotherapy vs SOC chemotherapy.

The sample size of the substudy accounted for the dual primary efficacy endpoints: PFS based on BICR assessments and OS, evaluated in subjects with previously untreated unresectable or metastatic UC. The overall alpha for the substudy was 0.05, which was split with 0.01 (two-sided) to evaluate PFS and 0.04 (two-sided) to evaluate OS. The number of events and power for PFS analysis were calculated assuming a non-proportional hazards model with a 3-month delayed treatment effect, a 0.20 cure fraction in nivo + SOC arm and a 0.15 cure fraction in SOC arm. 460 PFS events among the 600 cisplatin-eligible participants were planned to show a statistically significant difference between the treatment arms with 70% power under a two-sided experiment-wise alpha= 0.01 when the average HR of nivo + SOC arm to SOC arm is 0.7. It was projected that an observed HR of 0.786 or less would result in a statistically significant improvement in the final analysis of PFS.

The number of events and power for OS were calculated assuming a non-proportional hazards model with a 3-month delayed treatment effect, a 0.234 cure fraction in nivo + SOC arm and a 0.20 cure fraction in SOC arm. 356 OS events among the 600 randomised cisplatin-eligible participants were required to show a statistically significant difference in OS between the treatment arms with 85% power under a 2-sided experiment-wise alpha= 0.04 when the average HR of nivo + SOC arm to SOC arm is 0.7.

One interim analysis of OS was planned when 267 OS events (75% information fraction) were reached. The alpha allocation for the interim and final analyses was based on the Lan-DeMets alpha spending function approach using an O'Brien Fleming stopping boundary controlling for a 2-sided overall type 1 error of 4%. The stopping boundary depended on the actual number of OS events at the time of the interim analyses and the final analysis. It was projected that an observed HR of 0.74 and 0.8 or less would result in a statistically significant improvement in the interim and final analysis of OS, respectively.

The OS critical value for the final analysis was calculated (using Haybittle-Peto in EAST 6.3.1) considering the exact number of observed events at the interim and final analysis and the α-levels spent at interim analysis in order to achieve the planned cumulative alpha level (0.04 two-sided). The OS final analysis critical p-value was 0.0311 two-sided, before alpha recycling. This p-value cut-off of 0.0311 two-sided was used to assess the OS significance at the final analysis. After the alpha recycling (i.e., receiving 0.01 additional alpha when PFS was significant at the final analysis), the alpha available for OS testing became 0.0441 two-sided. This was used to derive the alpha adjusted (i.e., 95.59%) confidence interval of OS HR. The standard 95% CI was also reported, as planned.

Since no interim analysis on PFS was to be performed, the PFS critical value before alpha recycling was 0.01 two-sided. This p-value cut-off of 0.01 two-sided was used to assess the PFS significance at the final analysis. The alpha-adjusted confidence interval was 99%. The 95% CI was also reported.

Randomisation

Subjects who had met all eligibility criteria were centrally randomised using the Interactive Response Technology (IRT) prior to the start of study treatment administration for each participant. The site recorded the treatment assignment on the applicable case report form (CRF).

Blinding (masking)

Not applicable; this was an open-label study.

Statistical methods

Substudy

Dual Primary Endpoint

PFS and OS

OS was analysed in the substudy comparing subjects randomised to the nivo + SOC and SOC arms. OS was compared using a 2-sided 0.04 stratified log-rank test in subjects with the randomisation stratification factors recorded in the IRT. Median OS was estimated using the KM techniques. A two-sided 95% CI for median OS in each treatment group was computed using the log-log transformation method. OS rates at fixed time points (e.g., 6 months, depending on the minimum follow-up) is presented along with their associated 95% CIs. These estimates were derived from the KM estimate and corresponding CIs were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function. HR and corresponding two-sided (1 - α)*100% CI were estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by PD-L1 status ≥ 1 vs < 1% or indeterminate, and presence of liver metastasis, corresponding to the comparison of OS.

The following supplementary OS analyses were proposed in the SAP: A weighted log-rank test; presentation of HR estimates before and after 6 months ; the HR estimate derived from a multivariate model, in which prognostic baseline factors (age, sex, ECOG status, disease stage, prior systemic therapy) are included besides the stratification factors; stratification factors based on CRF information (instead of IRT (if concordance is observed for ≥ 10% of randomized subjects); an unstratified log-rank test, and an analysis for subjects with no relevant protocol deviations (if ≥ 10% of randomised subjects). Also, a statistical test to evaluate the assumption of proportional hazards was to be performed. Lastly, a supplementary analysis was performed in which subjects receiving subsequent Checkpoint Inhibitors before progression were censored.

PFS was also analysed in the substudy to compare the treatment groups in randomised subjects. PFS by BICR was defined as the time from randomisation to the date of documentation of disease progression or death from any cause, whichever occurred first. Subjects receiving subsequent anti-cancer therapy prior to documented disease progression or death were censored at the last evaluable tumour assessment on or prior to the date of subsequent therapy (PFS primary definition; Table 3). A sensitivity analysis of PFS by BICR not censoring by subsequent anti-cancer therapy before progression of disease or death was performed (PFS secondary definition; Table 4). In addition, several other sensitivity analyses for PFS were prespecified.

The PFS function for each treatment group was estimated using the KM product limit method and is displayed graphically. A two-sided 95% CI for median PFS in each treatment group was computed using the log-log transformation method. PFS rates at fixed time points (e.g., 6 months, depending on the minimum follow-up) is presented along with their associated 95% CIs. These estimates were derived from the Kaplan Meier estimate and corresponding CIs were derived based on Greenwood formula for variance derivation and on log-log transformation applied on survivor function.

For PFS (primary definition), the supportive analyses proposed in the SAP are analogous to the supportive analyses for OS, with the addition of an analysis of PFS based on investigator assessment

as opposed to BICR assessment (including a cross tabulation and listing of BICR vs. investigator assessment results).

The substudy final analysis was OS events driven and occurred with 365 OS events. The substudy PFS final analysis was conducted at the same time as the OS final analysis, which was earlier than the planned number of PFS events. 402 PFS events occurred at the time of final OS analysis.

Table 3. Censoring Scheme used in Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments*	Date of randomization	Censored
No on study tumor assessments and no death*	Date of randomization	Censored
Subsequent anti-cancer therapy started without death or progression per RECIST v1.1 reported prior or on the same day	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Documented progression per RECIST v1.1 and no new anti-cancer started before	Date of the first documented progression per RECIST v1.1 (excludes clinical progression)	Progressed
No progression and no death, and no new anti-cancer therapy started	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1 and no new anti-cancer started before	Date of death	Progressed

* Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.

Table 4. Censoring Scheme for Secondary Definition of PFS

Situation	Date of Progression of Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression per RECIST v1.1	Date of first documented progression per RECIST v1.1 criteria (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
Death without progression per RECIST v1.1	Date of death	Progressed

Secondary Endpoints

PD-L1 expression as a predictive biomarker of efficacy (OS and PFS)

PFS by BICR (using RECIST 1.1) and OS by PD-L1 expression at ≥ 1% by IHC.

Health-Related QoL

HRQoL assessments used in this study were the EORTC QLQ-C30 and EuroQol 5Q-5D-5L. Questionnaire completion rate, defined as the proportion of questionnaires received out of the expected number (based on the number of participants available for assessment), were calculated and summarised at each assessment time point. Descriptive statistics (i.e., N, mean with SD and 95% CI, median, first and third quartiles, minimum, maximum) were used to characterise scores and post-baseline changes in scores by treatment group as randomised for all subscales and assessment time points. Missing values were imputed for missing items by "assuming that the missing items had values equal to the average of those items which were present" for any scale in which at least half the items were completed. A scale in which less than half of the items were completed were treated as missing. This was the method proposed in the scoring manual. A questionnaire was considered as received if at least one of the 15 scales/items was non-missing (after imputation). Time points for QoL assessments were at baseline, week 4, 10 ,16, 20, 24 and thereafter every 12 weeks on study.

ORR and duration of response (DOR)

ORR was defined as the number of randomised subjects who achieved a best response of CR or confirmed PR based on BICR assessments (using RECIST v1.1 criteria) divided by the number of all randomised subjects. Confirmation of response was required at least 4 weeks after the initial response. DOR was defined as the time between the date of first confirmed documented response (CR or PR) to the date of the first documented tumour progression as determined by the BICR (per RECIST v1.1 criteria), or death due to any cause, whichever occured first. Subjects who started subsequent therapy without a prior reported progression were censored at the last evaluable tumour assessment prior to initiation of the subsequent anticancer therapy. Subjects who died without a reported prior progression were considered to have progressed on the date of their death. Subjects who neither progressed nor died, DOR was censored on the date of their last evaluable tumour assessment. DOR was evaluated for responders (confirmed CR or PR) only.

PD-L1 expression

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: Indeterminate: Tumour cell membrane staining hampered for reasons attributed to the biology of the tumour tissue sample and not because of improper sample preparation or handling, or Not evaluable: Tumour tissue sample was not optimally collected or prepared and PD-L1 expression was neither quantifiable nor indeterminate. Subjects with missing PD-L1 expression were subjects with no tumour tissue sample available for evaluation.

PD-L1 expression was to be collected in the IRT as well as in the clinical database. Statistical analysis using PD-L1 expression was to be solely based on PD-L1 expression data from clinical database.

Populations for analyses

- All Enrolled subjects: All subjects who signed the informed consent form and obtained a subject number.
- All Randomised subjects: All subjects who were randomised through the IRT.
- All Randomised PD-L1 ≥ 1% subjects: All Randomised subjects with baseline PD-L1 expression ≥ 1% (based on IRT).
- All Randomised PD-L1 < 1% subjects: All Randomised subjects with baseline PD-L1 expression < 1% (based on IRT).

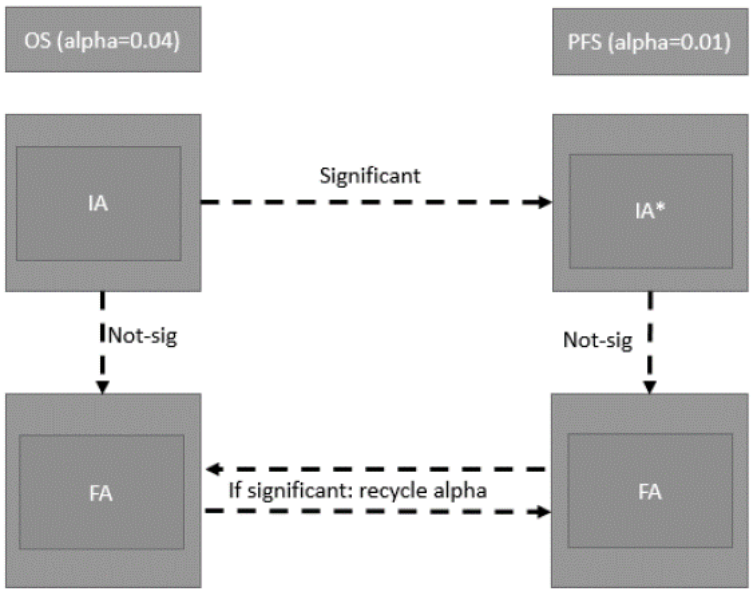
- All Cisplatin-eligible Randomised Subjects: All randomised subjects who were cisplatin eligible per IRT.
- All response evaluable subjects: All randomised subjects whose change in the sum of diameters of target lesions was assessed.
- All Treated subjects: All randomised subjects who received at least one dose of any study treatment.
- Immunogenicity subjects: All nivolumab or ipilimumab treated subjects with available ADA data.
- All Outcomes research subjects: All treated subjects who had an assessment at baseline (Visit 1 assessment prior to administration of drug) and at least 1 subsequent assessment (separately for each outcome research measure [EQ-5D-5L and QLQ-C30]).
- All Randomised Subjects Treated Beyond Progression: All participants who received at least one dose of study treatment after the date of initial progression based on investigator assessment.

Protection of Type I Error in the Substudy

OS in cisplatin-eligible subjects was to be tested at 4% type I error. PFS per BICR in cisplatin-eligible subjects was to be tested at 1% type I error. Alpha levels used in the OS interim and final analyses were derived using Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary. If OS superiority was demonstrated in interim analysis, formal testing of PFS was to be performed. The significance level of the PFS would depend on the number of PFS events which occurred at the time of the interim analysis. The hierarchical testing procedure under the group sequential testing setting as shown in

Figure 2 was to be employed to control the overall type 1 error. It was projected that there would be about 368 PFS events occurred (80% of total events). The significance level was to be adjusted according to the actual number of events occurred at the time of analysis.

Figure 2. Overall Hierarchical Testing Strategy Between OS Among Cis-eligible



* Analysis of PFS per BICR will be conducted only if OS is significant at IA, alpha assigned to OS gets recycled.

P-values in the final analyses for OS and PFS were compared against alpha levels of 0.0311 and 0.01 (before alpha recycling), which were derived based on the observed number of events using the Lan-DeMets alpha spending function with O'Brien and Fleming type boundary.

Interim analyses

One interim analysis of OS was planned and at the planning phase of study design. It was scheduled after approximately 267 OS events (approximately 75% of the targeted OS events in the substudy) had been observed among cisplatin-eligible randomised participants in the substudy based on above accrual rate and the non-proportional hazards model.

This formal comparison of OS would allow for early stopping for superiority, and the boundaries for declaring superiority at interim analysis would be derived based on the actual number of OS events using Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary in EAST (v 6.3.1). The boundary for declaring superiority in terms of statistical significance for the interim analysis after 267 events would be 0.74.

Information fraction for OS was based on total number of events of 356. Approximately 356 OS events in the cis-eligible randomised subjects in the substudy would provide approximately 85% power to detect an HR of 0.7 with an overall type I error of 4% (two-sided). This corresponds to a median increase from 16.0 months to 23.5 months.

If the study had exactly the planned number of events occurred at interim, the null hypothesis would be rejected when p-values from the log rank test was less than the prespecified alpha. If OS superiority was demonstrated in interim analysis, formal testing of PFS would be performed. The significance level of the PFS would depend on the number of PFS events occured at time of the interim analysis. It was projected that there would be about 368 PFS events occurred (80% of total events). The significance level was to be adjusted according to the actual number of events occurred at the time of interim analysis using Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary in EAST (v 6.3.1).

The DMC would review the safety and efficacy data from the informal interim analyses and would determine if the study should continue with or without changes or if accrual should be stopped. Subject enrolment would continue while waiting for the DMC's decisions.

Results

This report presents the results of the final analysis of the **substudy** (Arms C and D, hereinafter referred to as nivo + SOC and SOC, respectively) for the primary endpoints of OS and PFS of nivolumab plus cisplatin-based chemotherapy vs. cisplatin-based chemotherapy in subjects with previously untreated unresectable or metastatic UC. Additionally, results for secondary objectives and most of the exploratory objectives from the substudy are also presented.

Participant flow

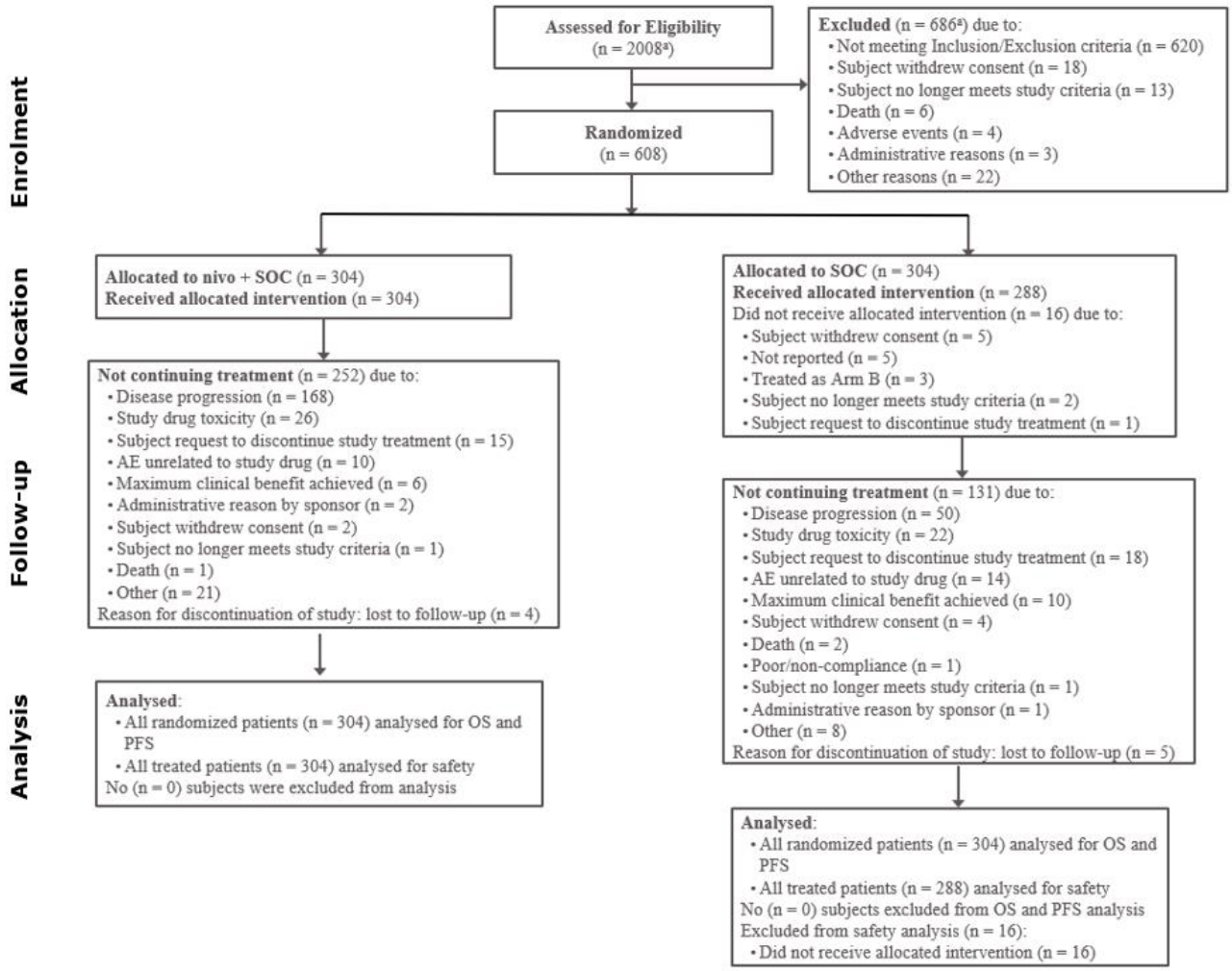
A total of 2008 subjects were assessed for eligibility for both the primary and substudy. Of the 2008 subjects, 686 subjects were excluded or not randomised. At the time of the substudy Final Analysis database lock (23-Jun-2023), 707 subjects were randomised to the primary study, and 608 subjects were randomised to the substudy (Figure 3).

In the nivo + SOC arm all randomised patients were treated. In the SOC arm 13/304 (4.3%) of the patients were not treated. The reasons were: N=5 patients withdrew consent, N=5 patients the reason

is not reported, N=2 patients no longer met study criteria and N=1 subject requested to discontinue study treatment. In addition, N=3 subjects did not receive the correct randomly allocated treatment. The 3 subjects were randomized as Arm D (SOC) in the substudy per IRT. However, per the clinical database, the site misplaced the subjects to Arm B (SOC) in the primary study. Two subjects received gemcitabine-cisplatin treatment and one subject received gemcitabine carboplatin treatment.

Fourty nine (49) of the 304 subjects in the nivo + SOC arm (16.1%) and 43 of the 288 subjects in the nivo arm (14.9%) received at least 1 dose of carboplatin.

Figure 3. Participant flow – Substudy



At the time of the 09-May-2023 data cut-off, the median follow-up (date of randomisation to the cut-off date) was 33.6 months in the nivo + SOC arm and 33.5 months in the SOC arm, and the minimum follow-up was 7.4 months in both arms.

Subject disposition

Subject disposition at end of treatment and end of study are shown in Table 5 and Table 6, respectively.

Table 5. End of Treatment Period Subject Status Summary - All Treated Subjects - Substudy

Status (%)	Nivo + SOC N = 304	SOC N = 288	Total N = 592
ONGOING TREATMENT	23 (7.6)	0	23 (3.9)
COMPLETED TREATMENT	29 (9.5)	157 (54.5)	186 (31.4)
NOT CONTINUING TREATMENT	252 (82.9)	131 (45.5)	383 (64.7)
REASON FOR NOT CONTINUING TREATMENT			
DISEASE PROGRESSION	168 (55.3)	50 (17.4)	218 (36.8)
STUDY DRUG TOXICITY	26 (8.6)	22 (7.6)	48 (8.1)
DEATH	1 (0.3)	2 (0.7)	3 (0.5)
ADVERSE EVENT UNRELATED TO STUDY DRUG	10 (3.3)	14 (4.9)	24 (4.1)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	15 (4.9)	18 (6.3)	33 (5.6)
SUBJECT WITHDREW CONSENT	2 (0.7)	4 (1.4)	6 (1.0)
MAXIMUM CLINICAL BENEFIT	6 (2.0)	10 (3.5)	16 (2.7)
POOR/NON-COMPLIANCE	0	1 (0.3)	1 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.3)	1 (0.3)	2 (0.3)
ADMINISTRATIVE REASON BY SPONSOR	2 (0.7)	1 (0.3)	3 (0.5)
OTHER	21 (6.9)	8 (2.8)	29 (4.9)
NOT CONTINUING TREATMENT DUE TO COVID-19	2 (0.7)	3 (1.0)	5 (0.8)
REASON FOR NOT CONTINUING TREATMENT DUE TO COVID-19			
ADVERSE EVENT UNRELATED TO STUDY DRUG	0	1 (0.3)	1 (0.2)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	2 (0.7)	1 (0.3)	3 (0.5)
OTHER	0	1 (0.3)	1 (0.2)
ONGOING STUDY	240 (78.9)	260 (90.3)	500 (84.5)
DISCONTINUED STUDY	41 (13.5)	28 (9.7)	69 (11.7)
REASON FOR DISCONTINUATION OF STUDY			
DEATH	32 (10.5)	18 (6.3)	50 (8.4)
SUBJECT WITHDREW CONSENT	3 (1.0)	5 (1.7)	8 (1.4)
OTHER	6 (2.0)	5 (1.7)	11 (1.9)
DISCONTINUED STUDY DUE TO COVID-19	0	1 (0.3)	1 (0.2)
REASON FOR DISCONTINUATION OF STUDY DUE TO COVID-19			
DEATH	0	1 (0.3)	1 (0.2)
NEXT EXPECTED STUDY PHASE			
FOLLOW-UP	210 (69.1)	234 (81.3)	444 (75.0)
SURVIVAL FOLLOW-UP	30 (9.9)	26 (9.0)	56 (9.5)

Percentages based on subjects entering period.

Disposition data for Nivolumab + SOC arm Part 1 and Part 2

At the time of the 23-Jun-2023 database lock, 225 (74.0%) subjects in the nivo + SOC arm completed Part 1, the planned 6 cycles of chemotherapy plus nivolumab (versus 157 (54.5%) in the SOC arm). Of the 244 subjects (87.7%) in the nivo + SOC arm who entered Part 2, 20 (8.2%) completed the subsequent nivolumab monotherapy (Part 2). The most frequent reason for study treatment discontinuation in Part 1 was disease progression: 6.6% in the nivo + SOC arm during chemotherapy (versus 17.4% in the SOC arm). The second most frequent reason for study treatment discontinuation was study drug toxicity: 7.6% in the nivo + SOC arm during chemotherapy part (and 7.6% in the SOC arm). In Part 2, 201 (82.4%) of the subjects discontinued treatment, the most important reasons were disease progression (59.8%) and study drug toxicity (7.0%).

Table 6. End of Study Subject Status Summary - All Randomised Subjects - Substudy

Status (%)	Nivo + SOC N = 304	SOC N = 304	Total N = 608
ONGOING STUDY	117 (38.5)	89 (29.3)	206 (33.9)
DISCONTINUED STUDY	187 (61.5)	215 (70.7)	402 (66.1)
REASON FOR DISCONTINUATION OF STUDY			
SUBJECT WITHDREW CONSENT	11 (3.6)	22 (7.2)	33 (5.4)
DEATH	164 (53.9)	178 (58.6)	342 (56.3)
LOST TO FOLLOW-UP	4 (1.3)	5 (1.6)	9 (1.5)
OTHER	8 (2.6)	10 (3.3)	18 (3.0)
DISCONTINUED STUDY DUE TO COVID-19	0	2 (0.7)	2 (0.3)
REASON FOR DISCONTINUATION OF STUDY DUE TO COVID-19			
DEATH	0	2 (0.7)	2 (0.3)

Recruitment

The key dates are presented in Table 7.

Table 7. Key Dates and Follow-up - Substudy

First Subject Randomisation Date	26-Feb-2018
Last Subject Randomisation Date	28-Sep-2022
Clinical Cut-off Date (LPLV for substudy)	09-May-2023
Database lock (Arms C and D)	23-Jun-2023

Conduct of the study

Amendments

The original protocol for this study was dated 14-Nov-2016. As of the 09-May-2023 data cut-off date, there were 3 global amendments/revisions that pertained to the substudy (Amendments 3, 4, and 5) and 8 global administrative letters (Table 8).

Table 8. Summary of Key Changes to Protocol CA209901 - Substudy

Document (Amendment)/Date	Summary of Key Changes	Planned Sample Size	Total number of subjects randomised into the study
Revised Protocol 02/ Amendment 03 21-Apr-2017	Added substudy (Arms C and D). Updated tumour tissue requirement. Updated treatment duration to 24 months. Section added regarding BICR assessments. Appendix 3, RECIST criteria updated.	300 cisplatin-eligible subjects	0
Revised Protocol 03 09-Apr-2019	Revised timing of the interim analysis for the substudy (from 2 to 1) to align with primary study. *Changes to the primary study were also made (at that time OS and PFS in cisplatin-ineligible patients were co-primary endpoints. PFS was removed as co-primary endpoint and OS analysis in PD-L1 pos. patients as primary population was added besides cisplatin-ineligible patients; addition of 100 cis-ineligible patients)*	300 cisplatin-eligible subjects	123
Revised Protocol 04 20-Mar-2020	• OS elevated to dual primary endpoint with PFS. • Increased number of cisplatin-eligible participants in the substudy from 300 to 600. • Removal of PFS interim analysis and addition of OS interim analysis. **Rationale:** Results of a randomised Phase 3 study (IMvigor 130), which assessed the addition of a PD-L1 inhibitor to cytotoxic, platinum-based doublet chemotherapy informed this protocol revision. In the cisplatin-based treated cohort (n = 273), adding the PD-L1 inhibitor to cisplatin/gemcitabine chemotherapy, led to a statistically significant PFS prolongation (HR = 0.73, 95% CI 0.55-0.97), corresponding to an absolute improvement of 2.4 months. The experimental regimen resulted in a numerically higher mOS (HR = 0.66, 95% CI 0.47 – 0.94), with an absolute OS prolongation that reached 8.4 months. Based on these results, OS was elevated to primary endpoint to capture the potential benefit of the addition of nivolumab, a PD-1 inhibitor, to cisplatin-gemcitabine chemotherapy for patients with newly diagnosed, previously untreated metastatic bladder cancer.	600 cisplatin-eligible subjects	262
Amendment 05 27-Apr-2023	This amendment updates the substudy final analysis strategy for PFS to coincide with the OS final analysis, regardless of the number of PFS events reached at this	600 cisplatin-eligible	608

Document (Amendment)/Date	Summary of Key Changes	Planned Sample Size	Total number of subjects randomised into the study
	time. This change is being made due to the actual substudy PFS event and added PFS power table corresponding to the expected number of PFS events at the time of final OS analysis. Corrected typos concerning inverted numbers of cure fraction for Arm C and Arm D from 0.20 to 0.234 and 0.234 to 0.20, respectively. Added description of substudy OS and PFS final analysis. **Rationale:** This change was made due to the actual substudy PFS event rate being lower than initially anticipated with a projected delay of approximately 3 years. This was mainly due to the high percentage of subjects censored for PFS. The reason for censoring was mainly due to subsequent anti-cancer therapy prior to progression. This high percentage of censoring was related to the treatment landscape change for this patient population during the conduct of this study with the introduction of avelumab maintenance therapy after initial platinum-based chemotherapy. Therefore, it was not possible for the originally planned number of PFS events to be reached simultaneously with the planned number of at least 356 OS events as previously specified for the final analysis in the protocol. Thus, this amendment allowed for the final analysis for OS and PFS to occur after only the required number of OS events had been reached in the substudy.	subjects	

Changes to Planned Analyses

The following ad-hoc analyses were performed that were not specified in the SAP:

- OS rates at fixed time points up to 24 months
- PFS rates (BICR) at fixed time points up to 24 months
- Percentage of subjects with progression per BICR at the end of Part 1 of treatment
- Duration of CR
- End of study subject disposition at data cut-off date

GCP Deviations and Serious Breach

There was one confirmed serious breach reported during this study. Unscheduled/additional PK/IMG samples were collected in clinical sites that were not specified in protocol. These unscheduled PK/IMG samples will be discarded following GxP guidance and will not be used for data analysis. PK/IMG data for this study are not impacted. No GCP deviations impacting the study were reported.

Important Protocol Deviations

Important Protocol Deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being (Table 9). After review of the IPDs, the MAH determined that there was no impact on the interpretability of the study results.

Table 9. Summary of Important Protocol Deviations - All Randomised Subjects - Substudy

PD Category	Nivo + SOC N = 304	SOC N = 304	Total N = 608
Subjects with at Least One Deviation, n (%)	160 (52.6)	168 (55.3)	328 (53.9)
Prohibited Concomitant Medication	21 (6.9)	49 (16.1)	70 (11.5)
Inclusion/Exclusion Criteria	25 (8.2)	19 (6.3)	44 (7.2)
Informed Consent and/or Ethics (IEC/IRB)	29 (9.5)	20 (6.6)	49 (8.1)
Safety Reporting	18 (5.9)	12 (3.9)	30 (4.9)
Trial Procedures	108 (35.5)	114 (37.5)	222 (36.5)
Study Intervention (Study Treatment)	33 (10.9)	25 (8.2)	58 (9.5)
Discontinuation	2 (0.7)	1 (0.3)	3 (0.5)
Other	1 (0.3)	2 (0.7)	3 (0.5)

The applicant did not systematically collect sub-categories for the IPDs; however, a review of the sub-categories of IPDs was performed to look for trends and assess the impact on patient safety and data integrity.

Most frequent sub-category deviations in each IPD:

- Prohibited Concomitant Medication
    - TCM/herbal Supplements taken
    - Subsequent therapy started prior to progression
- Inclusion/ Exclusion criteria
    - Laboratory tests not performed within screening window
- Safety Reporting
    - SAE not reported within 24 hour timeframe
- Trial Procedures
    - Certain laboratory tests not performed according to protocol
    - Tumor assessment not performed according to protocol
- Study Intervention (Study Treatment)
    - Incorrect study dosing/treatment compliance
    - Randomization error
    - Incorrect stratification

Relevant Protocol Deviations

Relevant Protocol Deviations (RPDs) are IPDs that could affect the interpretability of key study results, are programmable deviations from clinical database, and are protocol-specific (Table 10). The most frequently reported RPD in randomised subjects at study entrance was 'subjects with misclassified stratification level (IRT vs clinical database)', which was reported in 3.0% of subjects overall. The most frequently reported RPD reported in randomised subjects on-study was 'subjects receiving anti-cancer therapy other than study therapy while on study therapy', which was reported in 3.6% of subjects overall.

Table 10. Relevant protocol deviations - All Randomised Subjects - Substudy

	Number of Subjects (%)		
	Nivo + SOC N = 304	SOC N = 304	Total N = 608
SUBJECTS WITH AT LEAST ONE DEVIATION	25 (8.2)	19 (6.3)	44 (7.2)
AT ENTRANCE			
SUBJECTS WITH MISCLASSIFIED STRATIFICATION LEVEL (IRT VS CLINICAL DATABASE)	9 (3.0)	9 (3.0)	18 (3.0)
SUBJECTS WITHOUT MEASURABLE DISEASE AT BASELINE ASSESSED BY CT, MRI OR PET CT	0	1 (0.3)	1 (0.2)
SUBJECTS WITH BASELINE ECOG PERFORMANCE STATUS > 1	2 (0.7)	0	2 (0.3)
SUBJECTS WHO RECEIVED PRIOR INTRAVESICAL THERAPY WITHIN 4 WEEKS PRIOR TO INITIATION OF STUDY TREATMENT	0	0	0
ON-STUDY			
SUBJECTS RECEIVING ANTI-CANCER THERAPY OTHER THAN STUDY THERAPY WHILE ON STUDY THERAPY	15 (4.9)	7 (2.3)	22 (3.6)
SUBJECTS TREATED DIFFERENTLY AS RANDOMIZED	0	3 (1.0)	3 (0.5)

Discrepancies between IRT and Clinical Database in Stratification Factor:

For the stratification factor PD-L1 there were 2 subject (0.3%) with discrepancies, one in each arm; in the nivo + SOC arm one patient had a PD-L1 expression of < 1%/indeterminate in the IRT, which had a PD-L1 expression of ≥ 1% in the CRF. In the SOC arm one patient had a PD-L1 expression of ≥ 1% in the IRT while this patient had a PD-L1 expression of < 1%/indeterminate in the CRF.

For the stratification factor liver metastasis there were 8 subjects (1.3%) with discrepancies, 4 in each arm; in both the nivo + SOC arm and the SOC arm 3 patients that had a liver metastases in the IRT but did not have one in the CRF, and one patient that did have a liver metastasis in the CRF did not have one in the IRT.

Baseline data

The demographic and disease characteristics are shown in Table 11 and Table 12, respectively.

Table 11. Demographic Characteristics Summary - All Randomised Subjects - Substudy

	Nivo + SOC N = 304	SOC N = 304	Total N = 608
AGE (YEARS)			
N	304	304	608
MEDIAN	65.0	65.0	65.0
MIN , MAX	32 , 86	35 , 85	32 , 86
AGE CATEGORIZATION 3 (%)			
< 65	150 (49.3)	148 (48.7)	298 (49.0)
>= 65 AND < 75	120 (39.5)	116 (38.2)	236 (38.8)
>= 75 AND < 85	31 (10.2)	38 (12.5)	69 (11.3)
>= 85	3 (1.0)	2 (0.7)	5 (0.8)
SEX (%)			
MALE	236 (77.6)	234 (77.0)	470 (77.3)
FEMALE	68 (22.4)	70 (23.0)	138 (22.7)
RACE (%)			
WHITE	211 (69.4)	225 (74.0)	436 (71.7)
BLACK OR AFRICAN AMERICAN	0	2 (0.7)	2 (0.3)
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.3)	1 (0.3)	2 (0.3)
ASIAN	75 (24.7)	63 (20.7)	138 (22.7)
OTHER	17 (5.6)	13 (4.3)	30 (4.9)
ETHNICITY (%)			
HISPANIC OR LATINO	38 (12.5)	33 (10.9)	71 (11.7)
NOT HISPANIC OR LATINO	118 (38.8)	119 (39.1)	237 (39.0)
NOT REPORTED	148 (48.7)	152 (50.0)	300 (49.3)
COUNTRY BY GEOGRAPHIC REGION (%)			
ASIA	72 (23.7)	61 (20.1)	133 (21.9)
EUROPE	134 (44.1)	142 (46.7)	276 (45.4)
US	19 (6.3)	21 (6.9)	40 (6.6)
REST OF THE WORLD	79 (26.0)	80 (26.3)	159 (26.2)

Table 12. Baseline Disease Characteristics Summary - All Randomised Subjects - Substudy

	Number of Subjects (%)		
	Nivo + SOC N = 304	SOC N = 304	Total N = 608
TUMOR TYPE AT INITIAL DIAGNOSIS			
URINARY BLADDER	235 (77.3)	219 (72.0)	454 (74.7)
URETER	23 (7.6)	33 (10.9)	56 (9.2)
URETHRA	10 (3.3)	6 (2.0)	16 (2.6)
RENAL PELVIS	33 (10.9)	44 (14.5)	77 (12.7)
OTHER	3 (1.0)	2 (0.7)	5 (0.8)
TUMOR SUB-TYPE AT INITIAL DIAGNOSIS			
MUSCLE INVASIVE	133 (43.8)	114 (37.5)	247 (40.6)
NON-MUSCLE INVASIVE	66 (21.7)	47 (15.5)	113 (18.6)
METASTATIC OR ADVANCED, UNRESECTABLE	105 (34.5)	143 (47.0)	248 (40.8)
TIME FROM INITIAL DIAGNOSIS (YEARS)			
N	304	304	608
MEDIAN (MIN - MAX)	0.51 (0.0 - 27.8)	0.36 (0.0 - 23.9)	0.45 (0.0 - 27.8)
TIME FROM INITIAL DIAGNOSIS (%)			
< 1 YEAR	179 (58.9)	199 (65.5)	378 (62.2)
>= 1 YEAR	125 (41.1)	105 (34.5)	230 (37.8)
DISEASE STAGE AT STUDY ENTRY			
STAGE III	37 (12.2)	28 (9.2)	65 (10.7)
STAGE IV	265 (87.2)	274 (90.1)	539 (88.7)
NOT REPORTED	2 (0.7)	2 (0.7)	4 (0.7)
MINOR HISTOLOGICAL VARIANTS AT STUDY ENTRY			
ADENOCARCINOMA	53 (17.4)	50 (16.4)	103 (16.9)
SQUAMOUS CELL CARCINOMA	20 (6.6)	23 (7.6)	43 (7.1)

SMALL CELL CARCINOMA	4 (1.3)	3 (1.0)	7 (1.2)
MIROPAPILLARY	17 (5.6)	16 (5.3)	33 (5.4)
NESTED	0	2 (0.7)	2 (0.3)
PLASMACYTOID	1 (0.3)	2 (0.7)	3 (0.5)
SARCOMATOID	4 (1.3)	3 (1.0)	7 (1.2)
NONE	150 (49.3)	142 (46.7)	292 (48.0)
OTHER	53 (17.4)	61 (20.1)	114 (18.8)
NOT REPORTED	2 (0.7)	2 (0.7)	4 (0.7)
SUB-TYPE MINOR HISTOLOGY AT STUDY ENTRY			
METASTATIC	261 (85.9)	269 (88.5)	530 (87.2)
LOCALLY UNRESECT./NON-METASTATIC	41 (13.5)	33 (10.9)	74 (12.2)
NOT REPORTED	2 (0.7)	2 (0.7)	4 (0.7)
ECOG PERFORMANCE STATUS			
0	162 (53.3)	162 (53.3)	324 (53.3)
1	140 (46.1)	142 (46.7)	282 (46.4)
>1	2 (0.7)	0	2 (0.3)
PD-L1 STATUS (CLINICAL DATABASE)			
>=1%	112 (36.8)	109 (35.9)	221 (36.3)
<1%	192 (63.2)	195 (64.1)	387 (63.7)
INDETERMINATE	0	0	0
LIVER METASTASIS (CRF)			
YES	62 (20.4)	62 (20.4)	124 (20.4)
NO	242 (79.6)	242 (79.6)	484 (79.6)

Previous treatments

In all randomised subjects, 74.3% of subjects had not had prior systemic therapy and 28.9% of the patients in the nivo + SOC arm versus 22.4% of the SOC arm did receive prior therapy. Of those who had prior systemic therapy:

- 15.3 % had received adjuvant therapy - 17.8% in the nivo + SOC arm and 13.2% in the SOC arm
- 8.4% had received neo-adjuvant therapy - 9.5% in the nivo + SOC arm and 7.2% in the SOC arm
- 1.8% with no regimen reported - 1.6% in the nivo + SOC arm and 2.0% in the SOC arm.

Concomitant medications

Most treated subjects (99.3% in the nivo + SOC arm and 98.3% in the SOC arm) received concomitant medications on or after the first day of study therapy and within 100 days following the last dose of study therapy. Most of these medications considered anti-acids 64.5% versus 61.8%, blood and blood forming agents 85.5% versus 78.5%, plasma substitute and perfusion solution 65.8% versus 56.3%, cardiovascular drugs 63.8% versus 56.6%, systemic corticosteroid use 73.4% versus 70.5% respectively.

Subsequent anticancer therapy

In the nivo + SOC arm 127 (41.8%) of the patients received subsequent anticancer therapy and 171 (56.3%) of the patients in the SOC arm received subsequent anticancer therapy (Table 13).

Table 13. Summary of Subsequent Anticancer Therapy - All Randomised Subjects – Substudy

	Number of Subjects (%)	
	Nivo + SOC N = 304	SOC N = 304
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	127 (41.8)	171 (56.3)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	31 (10.2)	36 (11.8)
SUBJECTS RECEIVING SUBSEQUENT SURGERY (%)	26 (8.6)	22 (7.2)
SUBJECTS RECEIVING SUBSEQUENT SYSTEMIC THERAPY %)	108 (35.5)	156 (51.3)
ANTI-PD1	22 (7.2)	72 (23.7)
ANTI-PDL1	3 (1.0)	52 (17.1)
COMBO ANTI-CTLA4 + ANTI-PD1	1 (0.3)	0
OTHER IMMUNOTHERAPY	3 (1.0)	2 (0.7)
PLATINUM-BASED CHEMOTHERAPY	25 (8.2)	26 (8.6)
UNASSIGNED	91 (29.9)	81 (26.6)

Numbers analysed

The following analysis populations were used in the substudy:

Table 14. Analysis Populations in the CA209901 Substudy

Population (Definition)	Nivo + SOC	SOC	Total
All Randomised Subjects: All randomised subjects overall.	304	304	608
All Treated Subjects: All subjects who received any dose of study therapy. This is the primary dataset for drug exposure and safety analyses.	304	288	592
Immunogenicity Evaluable Subjects: All treated subjects with baseline and at least 1 post-baseline immunogenicity assessment.	252	0	252
All randomised subjects with PD-L1 expression at ≥ 1% expression by IHC in the substudy. This is the primary dataset for the secondary efficacy analysis in the PD-L1 expressing group in the substudy.	112	109	221

Outcomes and estimation

Primary endpoints

Overall Survival

Table 15. Overall survival in All Randomised Subjects – Substudy

	Nivo + SOC N = 304	SOC N = 304
Primary Endpoint		
OS		
Events, n (%)	172 (56.6)	193 (63.5)
Median[a] OS (95% CI), months	21.72 (18.63, 26.38)	18.86 (14.72, 22.44)
HR[b] (alpha-adjusted 95.59% CI) (95% CI)	0.78 (0.63, 0.96) (0.63, 0.96)	
p-value[c]	0.0171	
6-month OS Rates (95% CI), %	88.1 (83.8, 91.2)	83.9 (79.2, 87.7)
12-month OS Rates (95% CI), %	70.2 (64.6, 75.1)	62.7 (56.8, 68.1)
18-month OS Rates (95% CI), %	57.5 (51.5, 63.0)	51.7 (45.5, 57.4)
24-month OS Rates (95% CI), %	46.9 (40.7, 52.8)	40.7 (34.6, 46.7)

[a] Based on Kaplan-Meier Estimates

[b] Stratified Cox proportional hazard model.

[c] 2 sided p-value from stratified log-rank test.

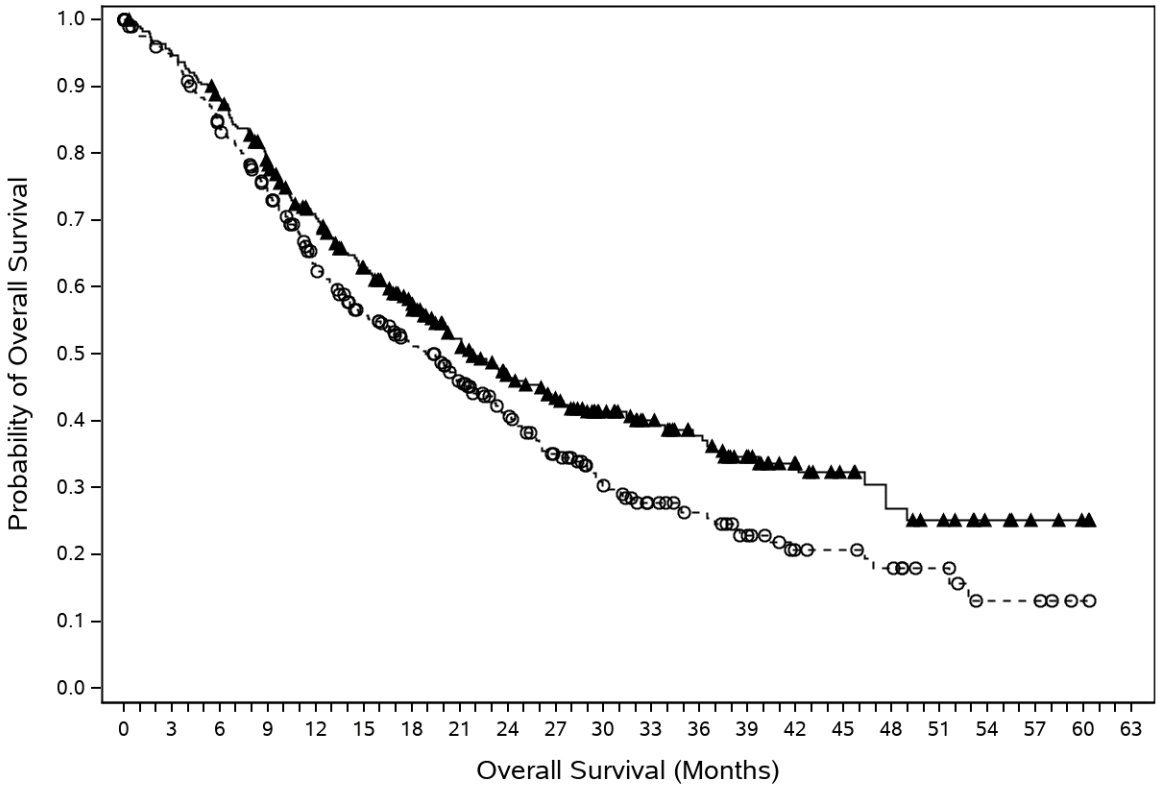
[d] Ad-hoc analysis.

Minimum follow-up for OS was 7.4 months.

Table 16. Status of Censored Subjects, Overall Survival – Substudy

	Number of Subjects (%)	
	Nivo + SOC N = 304	SOC N = 304
NUMBER OF DEATHS (%)	172 (56.6)	193 (63.5)
NUMBER OF SUBJECTS CENSORED (%)	132 (43.4)	111 (36.5)
STATUS OF CENSORED SUBJECTS (%)		
STILL ON-TREATMENT	23 (7.6)	0
NOT PROGRESSED	15 (4.9)	0
PROGRESSED (1)	8 (2.6)	0
IN FOLLOW-UP	94 (30.9)	89 (29.3)
OFF STUDY	15 (4.9)	22 (7.2)
LOST TO FOLLOW-UP	2 (0.7)	2 (0.7)
SUBJECT WITHDREW CONSENT	11 (3.6)	16 (5.3)
OTHER	2 (0.7)	4 (1.3)

Figure 4. Kaplan-Meier Plot of Overall Survival – All Randomised Subjects – Substudy



Number of Subjects at Risk

Nivo + SOC	304	286	264	228	196	167	142	119	97	84	69	58	48	36	25	20	15	12	7	4	2	0
SOC	304	277	242	208	166	140	122	102	82	65	49	39	33	24	17	16	13	9	4	4	1	0

Nivo + SOC (events: 172/304), median and 95% CI: 21.72 (18.63, 26.38)

SOC (events: 193/304), median and 95% CI: 18.86 (14.72, 22.44)

Nivo + SOC vs. SOC HR (95% CI): 0.78 (0.63, 0.96), (95.59% CI): (0.63, 0.96),
p-value: 0.0171

Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test.
Symbols represent censored observations.

Progression-free survival

Table 17. Progression-free Survival per BICR – All Randomised Subjects – Substudy

	Nivo + SOC **N = 304**	**SOC** **N = 304**
Primary endpoint		
PFS per BICR (Primary Definition)		
Events, n (%)	211 (69.4)	191 (62.8)
Median[a] PFS (95% CI), months	7.92 (7.62, 9.49)	7.56 (6.05, 7.75)
HR[b] (alpha-adjusted 99% CI) (95% CI)	0.72 (0.55, 0.94) (0.59, 0.88)	
p-value[c]	0.0012	
6-month PFS Rates (95% CI), %	65.5 (59.6, 70.7)	58.1 (51.6, 64.1)
12-month PFS Rates (95% CI), %	34.2 (28.6, 40.0)	21.8 (16.1, 27.9)
18-month PFS Rates (95% CI), %	27.6 (22.2, 33.2)	12.7 (8.1, 18.4)
24-month PFS Rates (95% CI), %	23.5 (18.3, 29.0)	9.6 (5.6, 15.0)
PFS per BICR (Secondary definition)		
Events, n (%)	229 (75.3)	248 (81.6)
Median[a] PFS (95% CI), months	7.92 (7.62, 9.46)	7.46 (6.05, 7.75)
HR[b] (95% CI)	0.74 (0.62, 0.89)	
p-value[c]		
6-month PFS Rates (95% CI), %	88.1 (83.8, 91.2)	83.9 (79.2, 87.7)
12-month PFS Rates (95% CI), %	70.2 (64.6, 75.1)	62.7 (56.8, 68.1)
18-month PFS Rates (95% CI), %	57.5 (51.5, 63.0)	51.7 (45.5, 57.4)
24-month PFS Rates (95% CI), %	46.9 (40.7, 52.8)	40.7 (34.6, 46.7)

[a] Based on Kaplan-Meier Estimates

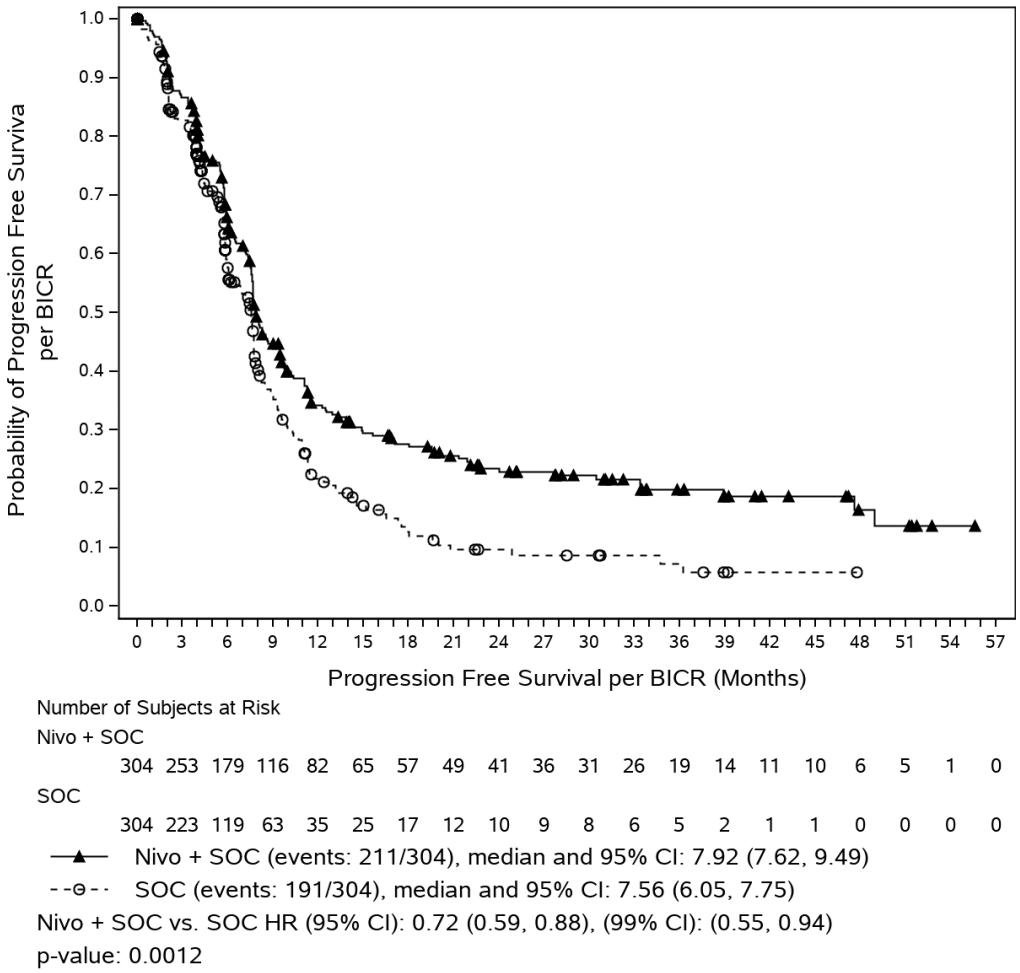
[b] Stratified Cox proportional hazard model.

[c] 2 sided p-value from stratified log-rank test.

[d] Ad-hoc analysis.

Minimum follow-up for OS was 7.4 months.

Figure 5. Kaplan-Meier Plot of Progression-free Survival per BICR, Primary Definition – All Randomised Subjects – Substudy



Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test. Symbols represent censored observations.

Figure 6. Kaplan-Meier Plot of Progression-free Survival per BICR, Secondary Definition – All Randomised Subjects – Substudy

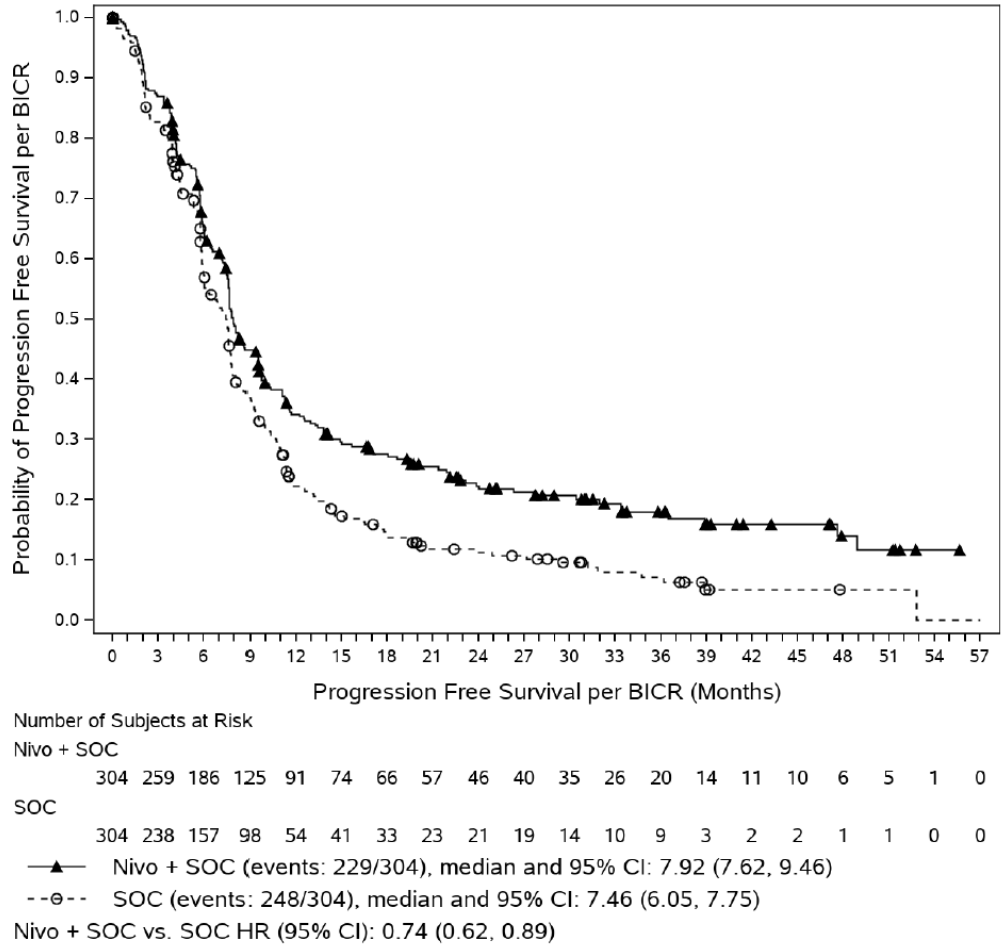


Table 18 and Table 19 show the reason for censoring for PFS per BICR (primary definition) and PFS per BICR (secondary definition).

Table 18. Reason for Censoring, PFS per BICR (Primary definition) – All Randomised Subjects – Substudy

	Nivo + SOC N = 304	SOC N = 304
NUMBER OF EVENTS (%)	211 (69.4)	191 (62.8)
TYPE OF EVENTS (%)		
PROGRESSION (1)	177 (58.2)	150 (49.3)
DEATH	34 (11.2)	41 (13.5)
NUMBER OF SUBJECTS CENSORED (%)	93 (30.6)	113 (37.2)
CENSORED ON DATE OF RANDOMIZATION	10 (3.3)	22 (7.2)
NO BASELINE TUMOR ASSESSMENT	3 (1.0)	1 (0.3)
NEVER TREATED	0	0
OTHER	3 (1.0)	1 (0.3)
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	7 (2.3)	21 (6.9)
NEVER TREATED	0	9 (3.0)
OTHER	7 (2.3)	12 (3.9)
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY	83 (27.3)	91 (29.9)
RECEIVED SUBSEQUENT ANTI-CANCER THERAPY (3)	24 (7.9)	74 (24.3)
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	16 (5.3)	60 (19.7)
RECEIVED SUBSEQUENT RADIOTHERAPY	1 (0.3)	7 (2.3)
RECEIVED SUBSEQUENT SURGERY	7 (2.3)	7 (2.3)
STILL ON-TREATMENT	16 (5.3)	0
IN FOLLOW-UP	39 (12.8)	13 (4.3)

	Nivo + SOC N = 304	SOC N = 304
OFF STUDY	4 (1.3)	4 (1.3)
LOST TO FOLLOW-UP	0	1 (0.3)
WITHDRAW CONSENT	4 (1.3)	3 (1.0)
OTHER	0	0

(1) RECIST 1.1 criteria
(2) Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered .
(3) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy without a prior reported PFS event. Those subjects were censored at the last evaluable tumor assessment prior to/on start date of subsequent anti-cancer therapy
Program Source: /opt/zfs001/prd/bms240818/stats/primary/prog/tables/rt-ef-pfs-reascens.sas 27JUL2023:04:08:00

Table 19. Reasons for Censoring, PFS per BICR (Secondary Definition) - All Randomised Subjects – Substudy

	Nivo + SOC N = 304	SOC N = 304
NUMBER OF EVENTS (%)	229 (75.3)	248 (81.6)
TYPE OF EVENTS (%)		
PROGRESSION (1)	188 (61.8)	189 (62.2)
DEATH	41 (13.5)	59 (19.4)
NUMBER OF SUBJECTS CENSORED (%)	75 (24.7)	56 (18.4)
CENSORED ON DATE OF RANDOMIZATION	6 (2.0)	14 (4.6)
NO BASELINE TUMOR ASSESSMENT	3 (1.0)	1 (0.3)
NEVER TREATED	0	0
OTHER	3 (1.0)	1 (0.3)
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	3 (1.0)	13 (4.3)
NEVER TREATED	0	9 (3.0)
OTHER	3 (1.0)	4 (1.3)
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY	69 (22.7)	42 (13.8)
STILL ON-TREATMENT	17 (5.6)	0
IN FOLLOW-UP	47 (15.5)	35 (11.5)
OFF STUDY	5 (1.6)	7 (2.3)
LOST TO FOLLOW-UP	0	1 (0.3)
WITHDRAW CONSENT	5 (1.6)	6 (2.0)
OTHER	0	0

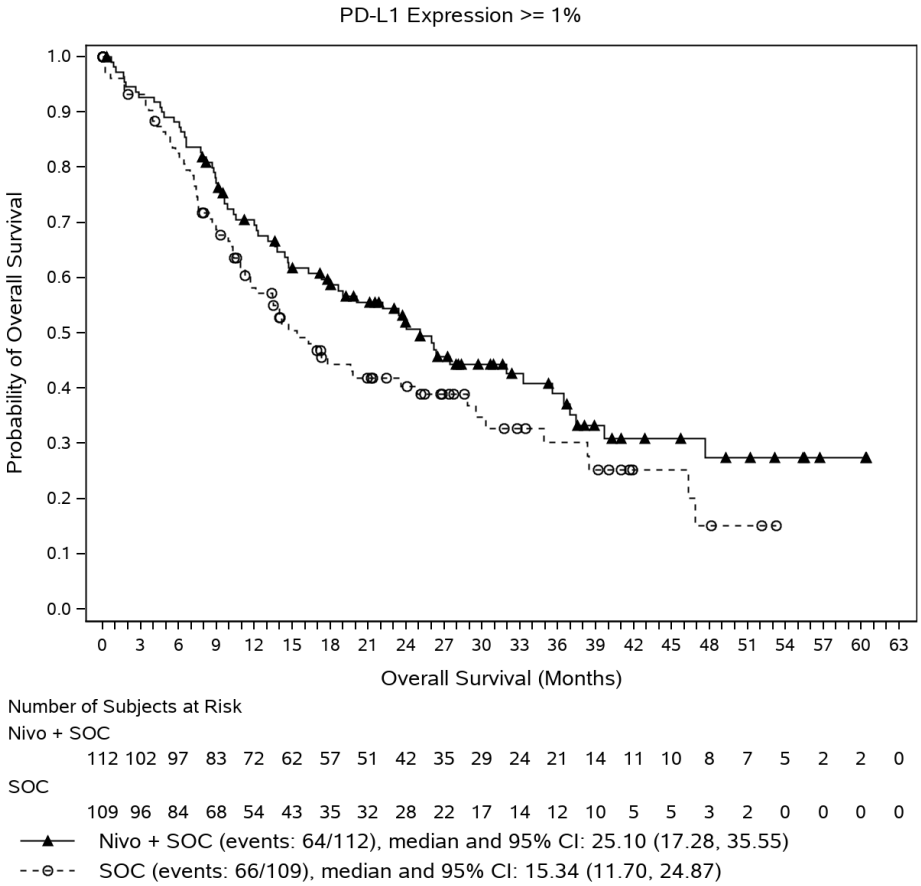
(1) RECIST 1.1 criteria
(2) Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are considered.
Secondary definition of PFS: the same as primary definition, but not accounting for subsequent therapy.

Secondary endpoints

Overall Survival by PD-L1 ≥ 1% by IHC

OS in subjects with PD-L1 expression ≥ 1% compared to SOC had a HR of 0.74 (95% CI: 0.52, 1.04) and the median (95% CI) OS was 25.10 (17.28, 35.55) and 15.34 (11.70, 24.87) months for the nivo + SOC and SOC arms, respectively (Figure 7). Subjects with PD-L1 expression ≥ 1% represented 36.3% (221 out of 608) of the study population (Table 12).

Figure 7. Kaplan-Meier Plot of Overall Survival – All Randomised PD-L1 ≥ 1% Subjects – Substudy

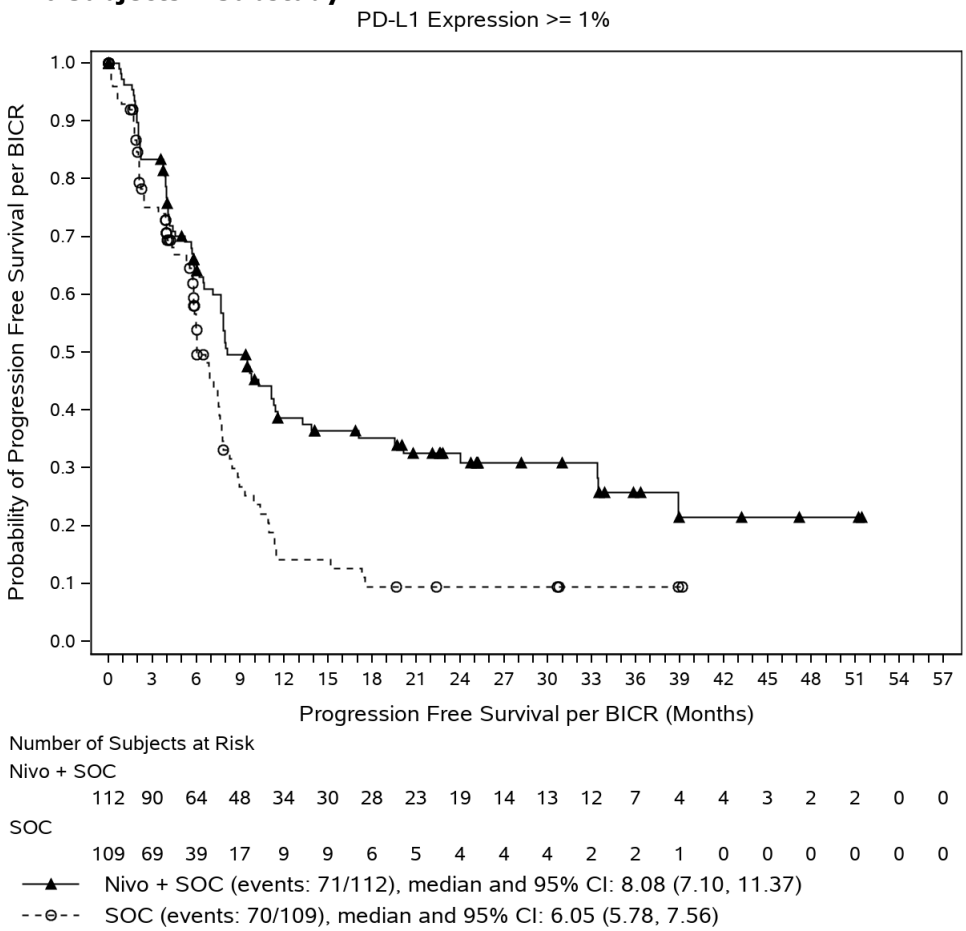


Symbols represent censored observations.

Progression-free Survival (per BICR) by PD-L1 ≥ 1% by IHC

PFS per BICR in subjects with PD-L1 expression ≥ 1% compared to SOC had a HR of 0.58 (95% CI: 0.41, 0.81) and the median PFS per BICR (95% CI) was 8.08 (7.10, 11.37) and 6.05 (5.78, 7.56) months, respectively in the nivo + SOC and SOC arm (Figure 8). PFS per Investigator in subjects with PD-L1 expression ≥ 1% had a HR of 0.53 (95% CI: 0.38, 0.74); of note, PFS per Investigator was not a secondary endpoint of the substudy.

Figure 8. Kaplan-Meier Plot of Progression Free Survival per BICR – All Randomised PD-L1 ≥ 1% Subjects – Substudy

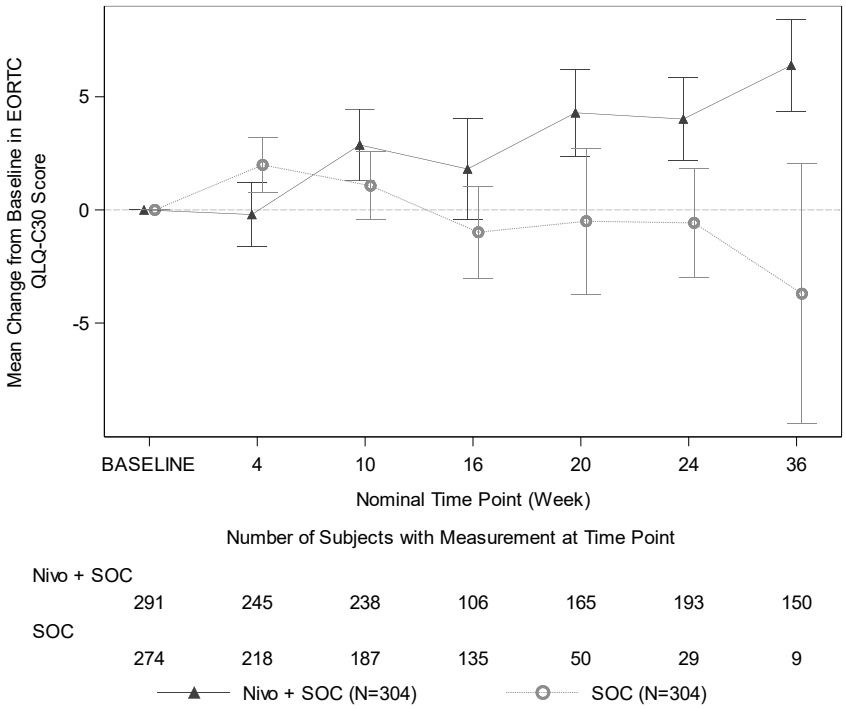


Symbols represent censored observations.

European Organization for Research and Treatment of Care (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30)

In all randomised subjects, questionnaire completion rates at baseline were 95.7% (291/304) in the nivo + SOC arm and 91.1% (277/304) in the SOC arm. At baseline, mean EORTC QLQ-global health status scores in all randomised subjects were comparable between treatment arms. After 24 weeks there were very few patients in the SOC arm (N≤43), thus comparisons are not reliable thereafter.

Figure 9. Mean Changes in EORTC QLQ-C30 Score from Baseline (Global Health Status) – All Randomised Subjects – Substudy



Error bars represent standard error for the mean.

Minimum important difference (MID) considered to be a change of ≥ 10 points from baseline.

Only time points where data available for ≥ 5 subjects in each treatment group are plotted.

Exploratory endpoints

ORR

The best ORR analysis is shown in Table 20. The median time to response and DOR are shown in Table 21, Table 22 and Figure 10.

Table 20. Best Overall Response per BICR – All Randomised Subjects – Substudy

	Nivo + SOC N = 304	SOC N = 304
BEST OVERALL RESPONSE		
COMPLETE RESPONSE (CR)	66 (21.7)	36 (11.8)
PARTIAL RESPONSE (PR)	109 (35.9)	95 (31.3)
STABLE DISEASE (SD)	77 (25.3)	86 (28.3)
PROGRESSIVE DISEASE (PD)	29 (9.5)	39 (12.8)
UNABLE TO DETERMINE (UTD)	23 (7.6)	48 (15.8)
OTHER	2 (0.7)	3 (1.0)
NOT REPORTED	21 (6.9)	45 (14.8)
OBJECTIVE RESPONSE RATE (1) (95% CI)	175/304 (57.6%) (51.8, 63.2)	131/304 (43.1%) (37.5, 48.9)
DIFFERENCE OF ORR (3, 4) (95% CI)	14.5% (6.7, 22.3)	
ESTIMATE OF ODDS RATIO (4, 5) (95% CI)	1.81 (1.31, 2.50)	

Per RECIST 1.1.
(1) CR+PR, confidence interval based on the Clopper and Pearson method.
(2) CR+PR+SD, confidence interval based on the Clopper and Pearson method.
(3) Strata adjusted difference in objective response rate based on DerSimonian and Laird method.
(4) Stratified by PD-L1(positive vs negative/indeterminate), Liver Metastasis (yes vs. no) as entered in the IRT.
(5) Strata adjusted odds ratio (Nivo + SOC over SOC) using Mantel-Haenszel method.

Table 21. Time to Objective Response and Duration of Response per BICR – All Responders – Substudy

	Nivo + SOC N=304	SOC N=304
Median TTR per BICR (Min, Max), months	2.10 (1.0, 21.0)	2.10 (1.2, 9.5)
Median DOR per BICR (95% CI), months	9.53 (7.59, 15.08)	7.26 (5.72, 8.90)

Figure 10. Kaplan-Meier Plot of Duration of Response per BICR – All Responders – Substudy

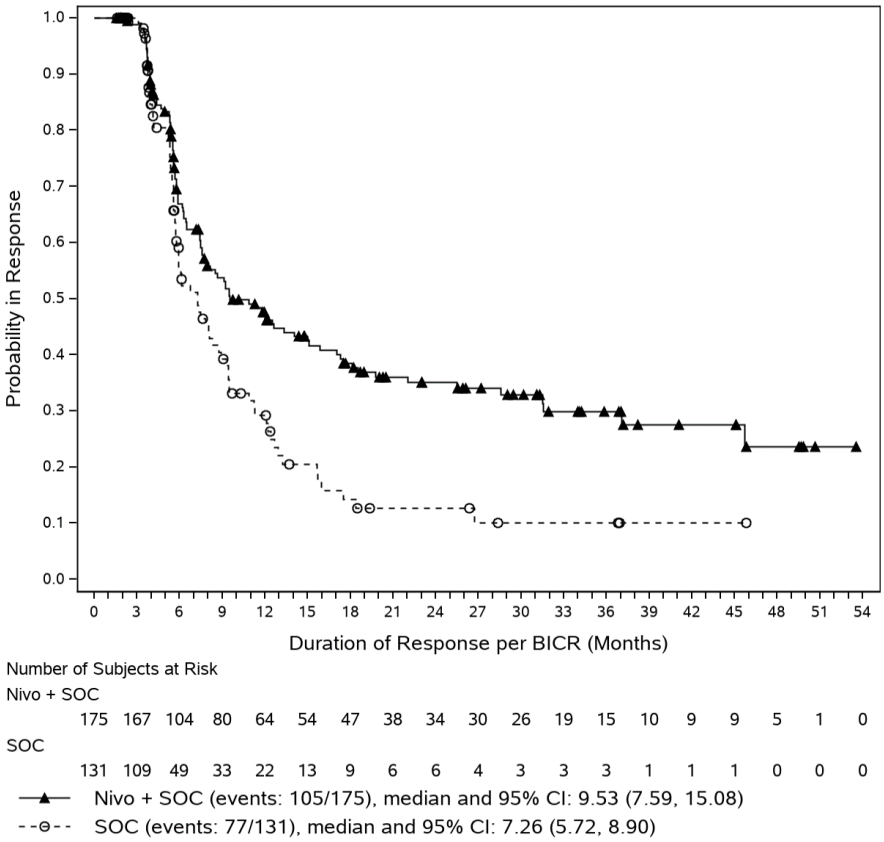


Table 22. Duration of Response per BICR, Reasons for Censoring

	Nivo + SOC N = 175	SOC N = 131
NUMBER OF EVENTS (%)	105 (60.0)	77 (58.8)
TYPE OF EVENTS (%)		
PROGRESSION (1)	96 (54.9)	73 (55.7)
DEATH	9 (5.1)	4 (3.1)
NUMBER OF SUBJECTS CENSORED (%)	70 (40.0)	54 (41.2)
RECEIVED SUBSEQUENT ANTI-CANCER THERAPY (2)	15 (8.6)	43 (32.8)
ONGOING FOLLOW-UP	51 (29.1)	11 (8.4)
CURRENT (3)	48 (27.4)	9 (6.9)
NOT CURRENT	3 (1.7)	2 (1.5)
OFF STUDY	4 (2.3)	0
SUBJECT WITHDREW CONSENT	4 (2.3)	0

HRQoL

QLQ-C30 Functional scales and Symptom scales were largely comparable between the study arms. Mean changes from baseline were not above or below the minimum important difference (MID;>= 10 points from baseline; Osoba et al. J Clin Oncol. 1998). After 24 weeks there were very few patients in the SOC arm (N ≤ 43), thus comparisons were not reliable thereafter.

EQ-5D-5L VAS Self-Rated Health Status and index scores were largely comparable between the two treatment arms. The EQ5D-5L-VAS Self-Rated Health Status mean changes did not reach a MID (defined at around 7); and neither did the EQ-5D-5L index score. After 24 weeks there were very few patients in the SOC arm (N ≤ 43), thus comparisons were not reliable thereafter.

Ancillary analyses

Overall survival

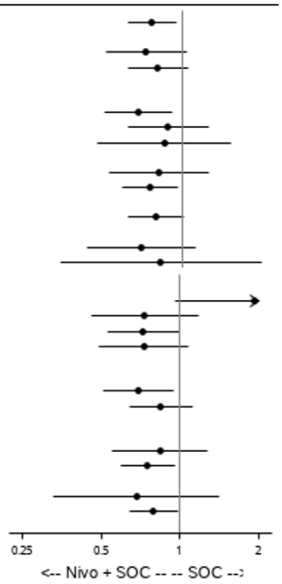
In an un-stratified analysis of OS the HR was 0.78 (95% CI: 0.63, 0.95 p-value = 0.0157). Analyses evaluating the potential impact of non-proportional hazards were performed and indicated that the assumption for proportional hazards is realistic (results not shown). Weighted log-rank test with presentation of HR estimates before and after 6 months are also not shown.

- Subgroup analyses for OS

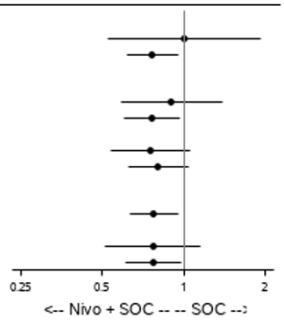
Subgroup analyses for OS in pre-defined subsets were performed (Figure 11).

Figure 11. Forest Plot of Treatment Effect on Overall Survival in Pre-Defined Subsets – All Randomised Subjects – Substudy

		Nivo + SOC		SOC		Unstratified
		N of Events	mOS	N of Events	mOS	Hazard Ratio
	N	(N of Subjects)	[95%CI]	(N of Subjects)	[95%CI]	[95%CI]
OVERALL	608	172 (304)	21.72 (18.63, 26.38)	193 (304)	18.86 (14.72, 22.44)	0.78 (0.63, 0.95)
PD-L1 STATUS						
>= 1%	221	64 (112)	25.10 (17.28, 35.55)	66 (109)	15.34 (11.70, 24.87)	0.74 (0.52, 1.04)
< 1%	387	108 (192)	21.06 (17.54, 26.71)	127 (195)	20.76 (16.07, 23.26)	0.82 (0.63, 1.05)
INDETERMINATE	0	0 (0)	N.A. (N.A., N.A.)	0 (0)	N.A. (N.A., N.A.)	N.M.E.
AGE CATEGORIZATION						
< 65	298	85 (150)	23.43 (17.97, 31.93)	100 (148)	17.58 (13.34, 21.78)	0.69 (0.51, 0.92)
>= 65 AND < 75	236	65 (120)	21.72 (15.21, 36.44)	66 (116)	21.68 (14.72, 28.19)	0.89 (0.63, 1.26)
>= 75	74	22 (34)	18.04 (10.94, 21.16)	27 (40)	13.34 (7.89, 26.12)	0.86 (0.49, 1.52)
SEX						
FEMALE	138	39 (68)	21.09 (14.39, 46.29)	46 (70)	18.86 (13.86, 24.87)	0.82 (0.54, 1.26)
MALE	470	133 (236)	23.13 (18.99, 27.47)	147 (234)	19.45 (14.13, 23.26)	0.76 (0.60, 0.97)
RACE						
WHITE	436	123 (211)	21.09 (16.30, 27.24)	145 (225)	20.21 (14.32, 23.46)	0.80 (0.63, 1.02)
BLACK OR AFRICAN AMERICAN	2	0 (0)	N.A. (N.A., N.A.)	2 (2)	7.49 (3.29, N.A.)	N.M.E.
ASIAN	138	38 (75)	26.02 (18.99, 28.91)	36 (63)	16.30 (11.76, 24.44)	0.71 (0.45, 1.12)
OTHER	32	11 (18)	19.35 (12.16, N.A.)	10 (14)	17.58 (10.61, 25.95)	0.84 (0.35, 1.97)
REGION						
US	40	18 (19)	11.99 (6.08, 21.72)	15 (21)	19.61 (11.70, 36.93)	1.92 (0.95, 3.88)
ASIA	133	36 (72)	24.02 (18.99, 28.91)	34 (61)	18.86 (11.99, 24.87)	0.73 (0.46, 1.17)
EUROPE	276	72 (134)	25.10 (17.94, 46.29)	90 (142)	20.76 (14.29, 25.49)	0.73 (0.53, 0.99)
REST OF THE WORLD	159	46 (79)	20.11 (14.39, 37.45)	54 (80)	14.72 (10.91, 20.80)	0.73 (0.49, 1.08)
BASELINE ECOG PERFORMANCE STATUS						
0	324	74 (162)	36.44 (26.18, 47.61)	87 (162)	25.95 (21.16, 30.29)	0.70 (0.51, 0.95)
1	282	96 (140)	14.39 (10.68, 17.97)	106 (142)	12.39 (9.23, 16.30)	0.85 (0.64, 1.11)
>1	2	2 (2)	10.46 (8.77, N.A.)	0 (0)	N.A. (N.A., N.A.)	N.M.E.
LIVER METASTASIS						
YES	124	45 (62)	10.15 (8.08, 18.04)	46 (62)	8.94 (5.75, 11.66)	0.84 (0.55, 1.27)
NO	484	127 (242)	26.02 (21.06, 35.55)	147 (242)	21.78 (17.28, 24.87)	0.75 (0.59, 0.96)
DISEASE STAGE AT STUDY ENTRY						
STAGE III	65	17 (37)	27.47 (16.30, N.A.)	13 (28)	18.04 (8.61, N.A.)	0.68 (0.33, 1.41)
STAGE IV	539	154 (265)	21.06 (17.97, 26.02)	179 (274)	19.61 (14.72, 22.44)	0.79 (0.64, 0.98)
NOT REPORTED	4	1 (2)	N.A. (10.94, N.A.)	1 (2)	N.A. (3.91, N.A.)	N.M.E.



		Nivo + SOC		SOC		Unstratified
		N of Events	mOS	N of Events	mOS	Hazard Ratio
	N	(N of Subjects)	[95%CI]	(N of Subjects)	[95%CI]	[95%CI]
PRIOR RADIOTHERAPY						
YES	50	18 (26)	12.45 (8.54, 16.10)	20 (24)	16.30 (7.56, 20.34)	1.00 (0.53, 1.92)
NO	558	154 (278)	23.43 (20.11, 27.73)	173 (280)	19.98 (14.72, 23.26)	0.76 (0.61, 0.95)
PRIOR SYSTEMIC CANCER THERAPY						
YES	156	44 (88)	25.10 (17.54, 33.84)	41 (68)	23.79 (19.75, 29.60)	0.90 (0.59, 1.38)
NO	452	128 (216)	21.09 (17.94, 27.47)	152 (236)	16.07 (13.34, 20.76)	0.76 (0.60, 0.96)
PD-L1 STATUS (IRT)						
>=1%	221	64 (111)	25.10 (17.28, 35.55)	67 (110)	15.34 (11.70, 24.87)	0.75 (0.53, 1.06)
<1%/INDETERMINATE	387	108 (193)	21.06 (17.54, 26.71)	126 (194)	20.76 (16.07, 23.26)	0.80 (0.62, 1.04)
CISPLATIN ELIGIBILITY (IRT)						
INELIGIBLE	0	0 (0)	N.A. (N.A., N.A.)	0 (0)	N.A. (N.A., N.A.)	N.M.E.
ELIGIBLE	608	172 (304)	21.72 (18.63, 26.38)	193 (304)	18.86 (14.72, 22.44)	0.78 (0.63, 0.95)
LIVER METASTASIS (IRT)						
YES	128	45 (64)	11.99 (8.64, 20.04)	48 (64)	8.94 (5.75, 12.88)	0.77 (0.51, 1.16)
NO	480	127 (240)	26.02 (21.06, 35.55)	145 (240)	22.44 (17.81, 25.49)	0.77 (0.61, 0.98)

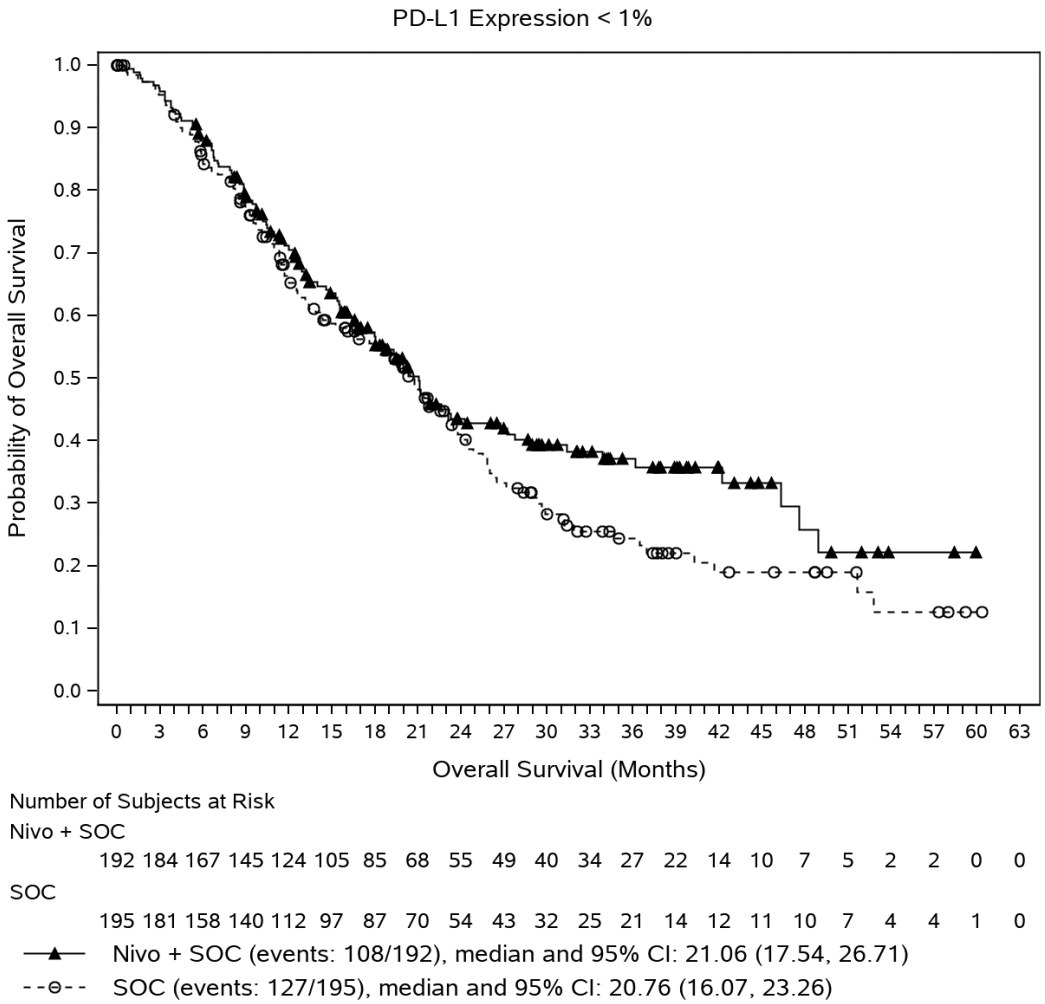


HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.

- OS in subjects with PD-L1 expression < 1%

OS in subjects with PD-L1 expression < 1% compared to SOC had a HR of 0.82 (95% CI: 0.63, 1.05). Median OS and 95% CI in both arms are shown in Figure 12.

Figure 12. Kaplan-Meier Plot of Overall Survival – All Randomised PD-L1 < 1% Subjects – Substudy



Symbols represent censored observations.

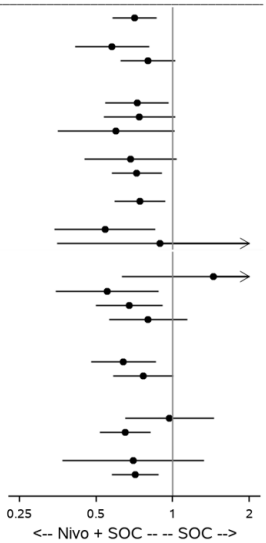
Progression-free survival

- Subgroup analyses for PFS

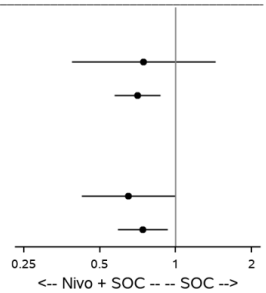
Subgroup analyses for all randomised subjects for PFS were performed (Figure 13).

Figure 13. Forest Plot of Treatment Effect on Progression-free Survival per BICR in Pre-Defined Subsets – All Randomised Subjects – Substudy

	N	Nivo + SOC N of Events (N of Subjects)	Nivo + SOC mPFS [95%CI]	SOC N of Events (N of Subjects)	SOC mPFS [95%CI]	Unstratified Hazard Ratio [95%CI]
OVERALL	608	211 (304)	7.92 (7.62, 9.49)	191 (304)	7.56 (6.05, 7.75)	0.71 (0.58, 0.86)
PD-L1 STATUS						
>= 1%	221	71 (112)	8.08 (7.10, 11.37)	70 (109)	6.05 (5.78, 7.56)	0.58 (0.41, 0.81)
< 1%	387	140 (192)	7.66 (7.49, 8.64)	121 (195)	7.72 (6.18, 8.18)	0.80 (0.62, 1.02)
INDETERMINATE	0	0 (0)	N.A. (N.A., N.A.)	0 (0)	N.A. (N.A., N.A.)	N.M.E.
AGE CATEGORIZATION						
< 65	298	102 (150)	7.69 (7.33, 11.27)	90 (148)	7.62 (6.60, 9.23)	0.72 (0.54, 0.96)
>= 65 AND < 75	236	81 (120)	8.08 (7.49, 9.53)	71 (116)	7.52 (5.82, 8.18)	0.74 (0.54, 1.02)
>= 75	74	28 (34)	7.66 (5.98, 9.66)	30 (40)	5.85 (3.94, 7.72)	0.60 (0.35, 1.01)
SEX						
FEMALE	138	48 (68)	7.49 (5.78, 9.56)	46 (70)	7.46 (5.55, 7.82)	0.68 (0.45, 1.03)
MALE	470	163 (236)	8.02 (7.66, 9.53)	145 (234)	7.59 (6.05, 8.18)	0.72 (0.57, 0.90)
RACE						
WHITE	436	153 (211)	7.82 (7.52, 9.49)	148 (225)	7.66 (6.05, 7.89)	0.74 (0.59, 0.94)
BLACK OR AFRICAN AMERICAN	2	0 (0)	N.A. (N.A., N.A.)	1 (2)	1.22 (N.A., N.A.)	N.M.E.
ASIAN	138	45 (75)	9.49 (7.59, 11.24)	35 (63)	7.20 (5.68, 7.75)	0.54 (0.34, 0.85)
OTHER	32	13 (18)	6.18 (5.62, 8.28)	7 (14)	5.88 (5.22, N.A.)	0.89 (0.35, 2.25)
REGION						
US	40	14 (19)	5.72 (3.88, 8.54)	10 (21)	8.18 (6.05, 10.94)	1.45 (0.63, 3.31)
ASIA	133	43 (72)	9.49 (7.59, 11.24)	33 (61)	7.20 (5.68, 7.82)	0.55 (0.35, 0.88)
EUROPE	276	94 (134)	7.92 (7.49, 11.27)	84 (142)	6.60 (5.82, 8.11)	0.67 (0.50, 0.91)
REST OF THE WORLD	159	60 (79)	7.66 (5.78, 9.49)	64 (80)	7.72 (5.72, 8.61)	0.80 (0.56, 1.14)
BASELINE ECOG PERFORMANCE STATUS						
0	324	97 (162)	11.10 (8.67, 16.82)	90 (162)	8.08 (7.62, 9.95)	0.64 (0.48, 0.86)
1	282	112 (140)	6.97 (5.78, 7.66)	101 (142)	5.85 (5.22, 7.52)	0.76 (0.58, 1.00)
>1	2	2 (2)	4.86 (4.11, N.A.)	0 (0)	N.A. (N.A., N.A.)	N.M.E.
LIVER METASTASIS						
YES	124	55 (62)	5.78 (3.94, 7.23)	44 (62)	5.36 (3.91, 5.88)	0.97 (0.65, 1.45)
NO	484	156 (242)	9.53 (7.85, 11.27)	147 (242)	7.72 (6.93, 8.18)	0.65 (0.52, 0.82)
DISEASE STAGE AT STUDY ENTRY						
STAGE III	65	24 (37)	7.85 (5.85, 19.55)	16 (28)	6.05 (4.44, 9.36)	0.70 (0.37, 1.33)
STAGE IV	539	185 (265)	7.92 (7.59, 9.49)	174 (274)	7.59 (6.05, 7.75)	0.71 (0.58, 0.88)
NOT REPORTED	4	2 (2)	17.64 (7.66, N.A.)	1 (2)	3.91 (N.A., N.A.)	N.M.E.



	N	Nivo + SOC N of Events (N of Subjects)	Nivo + SOC mPFS [95%CI]	SOC N of Events (N of Subjects)	SOC mPFS [95%CI]	Unstratified Hazard Ratio [95%CI]
PRIOR RADIOTHERAPY						
YES	50	19 (26)	6.01 (4.04, 8.54)	17 (24)	5.62 (4.14, 7.56)	0.75 (0.39, 1.44)
NO	558	192 (278)	8.08 (7.66, 9.53)	174 (280)	7.62 (6.60, 7.85)	0.70 (0.57, 0.87)
PRIOR SYSTEMIC CANCER THERAPY						
YES	156	55 (88)	9.66 (7.52, 13.24)	38 (68)	7.75 (6.05, 9.23)	0.65 (0.42, 1.00)
NO	452	156 (216)	7.75 (7.49, 8.51)	153 (236)	7.43 (5.88, 7.75)	0.74 (0.59, 0.93)



HR is not computed for subset (except age, race, region, and sex) category with less than 10 subjects per treatment group.
N.A.: not available; N.M.E.: not meaningful estimate.

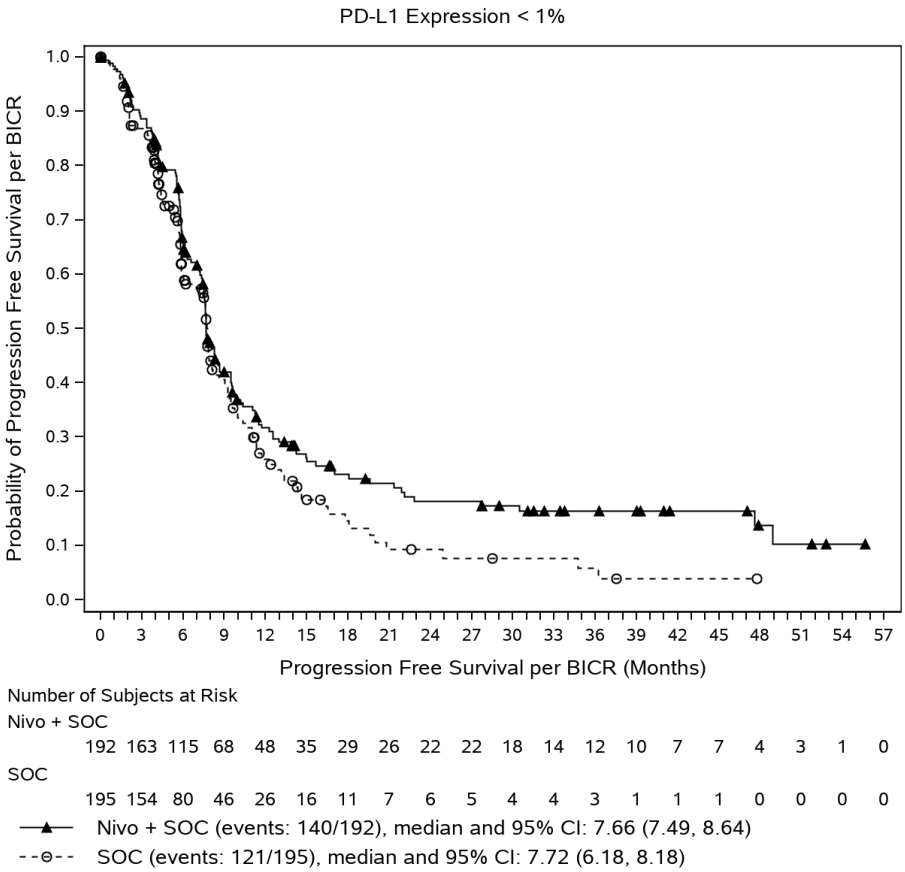
PFS per Investigator by primary definition (censoring by subsequent anticancer therapy before progression of disease) compared with SOC had a HR of 0.70 (95% CI: 0.57, 0.85). Median PFS (95% CI) per Investigator was 7.85 (7.66, 9.46) and 7.59 (6.34, 7.79) months in the nivo + SOC and SOC arms, respectively. PFS per Investigator by secondary definition (not censoring by subsequent anticancer therapy before progression of disease) had a HR of 0.72 (95% CI: 0.60, 0.86). Median PFS (95% CI) per Investigator was 7.85 (7.66, 9.43) and 7.59 (6.34, 7.79) months in the nivo + SOC and SOC arms, respectively. In a sensitivity analysis of PFS (unstratified PFS analysis) the HR was 0.71 (95%CI 0.58, 0.86), p-value 0.0006. Analyses evaluating the potential impact of non-proportional hazards were performed and indicated that the assumption for proportional hazards is realistic (results

not shown). Weighted log-rank test with presentation of HR estimates before and after 6 months are also not shown.

- PFS in subjects with PD-L1 expression < 1%

PFS per BICR in subjects with PD-L1 expression < 1% compared to SOC had a HR of 0.80 (95% CI: 0.62, 1.02) and the median (95% CI) PFS per BICR was 7.66 (7.49, 8.64) and 7.72 (6.18, 8.18) months for the nivo + SOC and SOC arms, respectively (Figure 11).

Figure 14. Kaplan-Meier Plot of Progression Free Survival per BICR – All Randomised PD-L1 < 1% Subjects – Substudy



Symbols represent censored observations.

Additional OS and PFS analyses

Pre-specified multivariate analyses for OS and PFS are shown below (Table 23). In addition, a supplementary OS analysis was performed in which subjects receiving subsequent Checkpoint Inhibitors before progression were censored: OS HR = 0.75 (95% CI: 0.61, 0.93).

Table 23. Overall Survival, Multivariate Analyses – All Randomised Subjects – Substudy

	HR (2) (95% CI)	P-Value (2)
TREATMENT NIVO + SOC VS SOC (1)	0.80 (0.65, 0.99)	0.0370
AGE < 65 VS >= 65	1.12 (0.91, 1.39)	0.2820
SEX MALE VS FEMALE	1.08 (0.84, 1.38)	0.5626
ECOG STATUS AT STUDY ENTRY 0 VS 1	0.49 (0.40, 0.61)	<0.0001
DISEASE STAGE AT STUDY ENTRY STAGE III VS STAGE IV	0.85 (0.58, 1.24)	0.3898
PRIOR SYSTEMIC CANCER THERAPY YES VS NO	0.79 (0.62, 1.01)	0.0621

(1) Effect of treatment adjusted for age (< 65, >= 65), sex (Male, Female), baseline ECOG Performance Status (0, 1), disease stage at study entry (III, IV), prior systemic anti-cancer therapy (yes, no).
(2) p-values and HRs from multivariate Cox Model stratified by PD-L1(positive vs negative/indeterminate), Liver Metastasis (yes vs. no) as entered in the IRT.
Source: Table S.5.29.1B.4

Table 24. Progression-free Survival per BICR, Multivariate Analysis – All Randomised Subjects – Substudy

	HR (2) (95% CI)	P-Value (2)
TREATMENT NIVO + SOC VS SOC (1)	0.74 (0.60, 0.90)	0.0035
AGE < 65 VS >= 65	0.94 (0.76, 1.15)	0.5202
SEX MALE VS FEMALE	0.98 (0.78, 1.24)	0.8931
ECOG STATUS AT STUDY ENTRY 0 VS 1	0.53 (0.43, 0.65)	<0.0001
DISEASE STAGE AT STUDY ENTRY STAGE III VS STAGE IV	0.98 (0.70, 1.37)	0.9099
PRIOR SYSTEMIC CANCER THERAPY YES VS NO	0.82 (0.65, 1.05)	0.1174

(1) Effect of treatment adjusted for age (< 65, >= 65), sex (Male, Female), baseline ECOG Performance Status (0, 1), disease stage at study entry (III, IV), prior systemic anti-cancer therapy (yes, no).
(2) p-values and HRs from multivariate Cox Model stratified by PD-L1(positive vs negative/indeterminate), Liver Metastasis (yes vs. no) as entered in the IRT.
Source: Table S.5.29.1A.1

Efficacy analyses by PD-L1 CPS

Efficacy analyses per PD-L1 CPS were not preplanned, but were provided by the applicant upon request. CPS was quantifiable in 491 (80.8%) of the patients; 79.9% of the patients in the nivo + SOC arm and 81.6% of the SOC arm. In patients with a missing PD-L1 CPS at baseline (13.7%), in total 5.6% was not evaluable. A box plot of PD-L1 CPS by response status per BICR among PD-L1 CPS Quantifiable Subjects was provided (not shown). The box plot indicates a higher median and 75th percentile of PD-L1 CPS in responders, compared to non-responders, however PD-L1 CPS between 0-

100 are observed in both groups and no distinction can be in terms of PD-L1 CPS between responders and non-responders.

Responses per different PD-L1 CPS cut-offs were provided (Table 25).

Table 25. Best ORR per BICR by PD-L1 CPS status at baseline – All Randomised Subjects – Substudy

N (%)/OBJECTIVE RESPONSE RATE % (95% CI)	**NIVO + SOC arm N=304**	**SOC Arm N=304**
BASELINE PD-L1 CPS >= 1 (95% CI)	N=199 (65.5%) ORR= 62.3% (55.2, 69.1)	N= 192 (63.2%) ORR=43.8% (36.6%, 51.1%)
BASELINE PD-L1 CPS < 1	N= 44 (14.5%) ORR=50.0% (34.6%, 65.4%)	N= 56 (18.4%) ORR=46.4% (33.0, 60.3%)
BASELINE PD-L1 CPS >= 10	N=114 (37.5%) ORR=81.6% (73.2, 88.2)	N=104 (34.2%) ORR=64.4% (54.4, 73.6)
BASELINE PD-L1 CPS N < 10	N=129 (42.4%) ORR=55.8% (46.8, 64.5)	N=144 (47.4%) ORR=46.5% (38.2, 55.0)
WITHOUT PD-L1 QUANTIFIABLE AT BASELINE	N= 61 (20.1%) ORR=47.5% (34.6, 60.7)	N=56 (18.4%) ORR=37.5% (24.9, 51.5)

Responses per PD-L1 expression status

Responses per different PD-L1 expression cut-offs were also provided (Table 26).

Table 26. Best ORR per BICR by PD-L1 expression status at baseline – All Randomised Subjects – Substudy

N (%)/OBJECTIVE RESPONSE RATE % (95% CI)	NIVO N=304	SOC N=304
BASELINE PD-L1 EXPRESSION >= 1% (95% CI)	N=112 (36.8) ORR=79.5% (70.8, 86.5)	N=109 (35.9) ORR=60.6% (50.7, 69.8)
BASELINE PD-L1 EXPRESSION < 1%	N= 192 (63.2) ORR=56.8% (49.4, 63.9)	N=195 (64.1) ORR=45.1% (38.0, 52.4)
BASELINE PD-L1 EXPRESSION >= 5%	N= 86 (28.3) ORR=60.5% (49.3, 70.8)	N=84 (27.6) ORR=38.1% (27.7, 49.3)
BASELINE PD-L1 EXPRESSION < 5%	N=218 (71.7) ORR=56.4% (49.6, 63.1)	N= 220 (72.4) ORR=45.0% (38.3, 51.8)
BASELINE PD-L1 EXPRESSION >= 10%	N= 71 (23.4) ORR=62.0% (49.7, 73.2)	N= 80 (26.3) ORR=37.5% (26.9, 49.0)
BASELINE PD-L1 EXPRESSION < 10%	N=233 (76.6) ORR=56.2% (49.6, 62.7)	N=224 (73.7) ORR=45.1% (49.6, 62.7)
WITHOUT PD-L1 QUANTIFIABLE AT BASELINE	0	0

Concordance between BICR and Investigator Assessments

In the nivo + SOC arm the overall concordance between BICR and investigator assessments was 83.9%. This is mainly due to the BICR reporting no response, while the investigator reported a response in 25 patients (8.2%) and the BICR reporting a response, while the investigator did not report a response in 21 patients (6.9%).

In the SOC arm the overall concordance between BICR and investigator assessments was 84.8%. This is mainly due to the BICR reporting no response, while the investigator reported a response in 24 patients (7.9%) and the BICR reporting a response, while the investigator did not report a response in 21 patients (7.0%).

In both arms there were small differences where the BICR reported a CR, while in the investigator reported a PR (8.9% vs 6.6%). When the BICR reported a PR stable disease by investigator 4.6% versus 5.6%).

Agreement for PFS between BICR and investigator assessments was 90.8% in the nivo + SOC arm and 86.5% in the SOC arm.

Efficacy analyses (i) using only data available up to 20-Mar-2020; and (ii) using only data from subjects randomised on or after 20-Mar-2020

Upon request of the CHMP, efficacy analyses prior to Revised Protocol 04 (dated 20-Mar-2020) were provided.

Table 27. Summary of OS, PFS by BICR, and PFS by BICR (Secondary definition) Analyses Prior to and On or After 20-Mar-2020 - All Randomised Subjects – Substudy

	Prior to 20-Mar-2020		**On or After 20-Mar-2020**	
	Nivo + SOC N = 131	SOC N = 131	Nivo + SOC N = 173	SOC N = 173
OS				
Events, n	92	99	80	94
Median[a] OS (95% CI), months	21.71 (17.28, 27.47)	18.37 (13.47, 23.46)	21.72, (17.97, NA)	19.75 (13.86, 23.59)
HR[b] (95% CI)	0.79 (0.60, 1.06)		0.77 (0.57, 1.03)	
p-value[c]	0.1154		0.0827	
PFS per BICR (Primary Definition)				
Events, n (%)	99	90	112	101
Median[a] PFS (95% CI), months	7.85 (7.33, 9.56)	6.83 (5.82, 7.85)	7.92 (7.49, 9.66)	7.62 (6.05, 7.89)
HR[b] (95% CI)	0.66 (0.49, 0.88)		0.78 (0.59, 1.02)	
p-value[c]	0.0047		0.0681	
PFS per BICR (Secondary Definition)				
Events, n (%)	108	113	121	135
Median[a] PFS (95% CI), months	7.84 (7.20, 8.67)	6.34 (5.82, 7.75)	8.11 (7.52, 9.66)	7.62 (6.18, 7.89)
HR[b] (95% CI)	0.70 (0.53, 0.91)		0.76 (0.59, 0.97)	

[d] Based on Kaplan-Meier Estimates
[e] Stratified Cox proportional hazard model
[f] 2-sided p-value from stratified long-rank test

Efficacy analyses using only data the first 300 subjects randomized; and (ii) using data from the 308 remaining subjects

Upon request of the CHMP, efficacy analyses using only data the first 300 subjects randomised; and (ii) using data from the 308 remaining subjects were provided (Table 28). Also analyses that would have been observed had revised protocol number 03 (09-Apr-2019) been followed i.e. based on the first 300 subjects randomised only, and with a data cut-off date corresponding to the 233rd PFS event were requested and provided (Table 29).

Table 28. Summary of OS, PFS by BICR, and PFS by BICR (Secondary definition) Analyses First 300 Subjects and Remaining 308 Subjects Randomised - All Randomised Subjects - Substudy

	First 300 Subjects Randomized		Remaining 308 Subjects Randomized	
	Nivo + SOC N = 151	SOC N = 149	Nivo + SOC N = 153	SOC N = 153
OS				
Events, n	103	113	69	80
Median[a] OS (95% CI), months	22.64 (17.28, 26.71)	18.40 (14.29, 23.06)	21.16 (17.97, NA)	20.21 (13.34, 26.02)
HR[b] (95% CI)	0.77 (0.59, 1.01)		0.79 (0.57, 1.09)	
p-value[c]	0.0594		0.1436	
PFS per BICR (Primary Definition)				
Events, n (%)	110	104	101	87
Median[a] PFS (95% CI), months	7.92 (7.49, 9.66)	7.52 (5.88, 7.85)	7.82 (7.46, 9.53)	7.62 (5.88, 7.89)
HR[b] (95% CI)	0.64 (0.49, 0.84)		0.80 (0.60, 1.08)	
p-value[c]	0.0014		0.1407	
PFS per BICR (Secondary Definition)				
Events, n (%)	121	129	108	119
Median[a] PFS (95% CI), months	7.89 (7.33, 9.46)	6.83 (5.88, 7.79)	7.92 (7.49, 9.66).	7.59 (5.98, 7.89)
HR[b] (95% CI)	0.69 (0.53, 0.89)		0.79 (0.61, 1.03)	

[a] Based on Kaplan-Meier Estimates
[b] Stratified Cox proportional hazard model
[c] 2-sided p-value from stratified long-rank test

Table 29. Efficacy Summary at Interim Analysis - All Randomised Subjects - Substudy

	Nivo + SOC N = 304	SOC N = 304
PFS IA		
Events, n/N	95/151	94/149
Median[a] PFS (95% CI), months	7.85 (7.49, 9.56)	7.52 (5.88, 8.11)
HR[b] (95% CI)	0.68 (0.51, 0.91)	
p-value[c]	0.0086	
OS IA		
Events, n/N	66/151	71/149
Median[a] PFS (95% CI), months	21.71 (17.54, NA)	19.45 (13.96, 23.79)
HR[b] (95% CI)	0.83 (0.59, 1.16)	
p-value[c]	0.2768	
OS FA		
Events, n/N (%)	96/151	102/149
Median OS (95% CI), months	22.64 (17.28, 26.71)	18.40 (14.29, 23.06)
HR (95% CI)	0.80 (0.60, 1.06)	
p-value	0.1187	

[a] Based on Kaplan-Meier Estimates
[b] Stratified Cox proportional hazard model.
[c] 2 sided p-value from stratified log-rank test.

In accordance with Revised Protocol 03 (dated April 09, 2019), A PFS IA was conducted on the planned 189 events (80% IF). The data cut-off for this analysis was the time of the 189th PFS event. Considering the planned number of PFS events at the IA (189) and FA (233), the adjusted alpha level at IA used to assess statistical significance was 0.026. At the time of PFS IA, there were 137 OS events. The data cut-off for this analysis was the time of the 189th PFS event. Considering the planned number of OS events at the FA (198) and the actual number of events at IA (137), the adjusted alpha level at IA used to assess significance was 0.014.

Summary of main study(ies)

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 30. Summary of Efficacy for trial: CA209901

Title: CA209901		
Study identifier	**CA209901**	
Design	randomised, open-label, Phase 3 study consisting of a primary study (arms A+B) and a substudy (Arms C+D)	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26-Feb-2018 – 09-May-2023 (DCO) Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Arm A: nivo+ipi	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, followed by nivolumab monotherapy (480 mg Q4W)
	Arm B: SOC platinum doublet chemotherapy	SOC platinum chemotherapy doublet (gemcitabine-cisplatin or gemcitabine-carboplatin), Q3W, up to 6 cycles

	Arm C: Nivo + SOC		Nivolumab (360 mg) in combination with gemcitabine-cisplatin (nivo + SOC) every 3 weeks for up to 6 cycles, followed by nivolumab monotherapy (480 mg) every 4 weeks. Monotherapy began 3 weeks following the last dose of combination therapy and continued until confirmed disease progression, unacceptable toxicity, participant withdrawal of consent, or 24 months from first dose, whichever came first.
	Arm D: SOC		Gemcitabine-cisplatin for up to 6 cycles (additional cycles may be permitted as per local guidelines).
Endpoints and definitions substudy	Primary endpoint	OS	Time from randomisation to the date of death from any cause
	Primary endpoint	PFS	PFS by BICR defined as the time from randomisation to the date of documentation of disease progression or death from any cause, whichever occurred first.
	Secondary endpoint	OS by PD-L1 $\geqslant$ 1% by IHC	OS in PD-L1 positive ($\geqslant$ 1%) randomised subjects
	Secondary endpoint	PFS by PD-L1 $\geqslant$ 1% by IHC	PFS by BICR using RECIST 1.1 in in PD-L1 positive ($\geqslant$ 1%) randomised subjects
	Secondary endpoint	EORTC QLQ-C30 Global Health Status score	The EORTC QLQ-C30 was collected in order to assess cancer specific health related quality of life. Descriptive statistics were used to characterise scores and post-baseline changes in scores by treatment group as randomised for all subscales and assessment time points.
Database lock (DBL)	23-Jun-2023		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Nivo + SOC	SOC
	Number of subjects	N=304	N=304
	OS, median	21.72	18.86
	95% CI	(18.63, 26.38)	(14.72, 22.44)
	PFS, median	7.92	7.56
	95% CI	(7.62, 9.49)	(6.05, 7.75)
	OS by PD-L1 $\geqslant$ 1% by IHC, median	25.10	15.34
	95% CI	(17.28, 35.55)	(11.70, 24.87)
	PFS (per BICR) by PD-L1 $\geqslant$ 1% by IHC, median	8.08	6.05
	95% CI	(7.10, 11.37)	(5.78, 7.56)
Effect estimate per comparison	OS	Comparison groups	Nivo + SOC vs SOC
		HR	0.78
		(alpha-adjusted 95.59% CI) (95% CI)	0.63, 0.96 0.63, 0.96
		P-value	0.0171
	PFS	Comparison groups	Nivo + SOC vs SOC
		HR	0.72
		(alpha-adjusted 99% CI) (95% CI)	0.55, 0.94 0.59, 0.88
		P-value	0.0012
	OS by PD-L1 $\geqslant$ 1% by IHC, median	Comparison groups	Nivo + SOC vs SOC
		HR	0.74
		95%CI	0.52, 1.04
		P-value	-

	PFS (per BICR) by PD-L1 ⩾ 1% by IHC, median	Comparison groups	Nivo + SOC vs SOC
		HR	0.58
		95%CI	0.41, 0.81
		P-value	-
Notes	Outcomes from the primary study are not available, not the subject of this variation and therefore not shown. Secondary endpoint mean changes in EORTC QLQ-C30 score from baseline do not reach above or below the minimum important difference.		

2.4.3. Discussion on clinical efficacy

The MAH applied for the following indication: "*Opdivo in combination with cisplatin -based chemotherapy is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma*."

The pivotal study is study CA209901 (NCT03036098), a randomised, open-label, Phase 3 study in patients who have not received prior systemic chemotherapy for unresectable or metastatic UC. The study is composed of two phase 3 studies: a primary study (Arms A and B) and a substudy (Arms C and D). The substudy is the focus of this application and in this substudy cisplatin-eligible patients were randomised to nivolumab (360 mg) in combination with gemcitabine-cisplatin (nivo + SOC) every 3 weeks for up to 6 cycles, followed by nivolumab monotherapy (480 mg) every 4 weeks (Arm C) or SOC of gemcitabine-cisplatin for up to 6 cycles (Arm D). In the primary study there was no requirement for cisplatin eligibility and patients were randomised between nivolumab + ipilimumab followed by nivolumab monotherapy (Arm A) or gemcitabine-cisplatin/carboplatin (Arm B).

Design and conduct of clinical studies

Design substudy and primary study – The primary study and substudy are separate and are independently powered and the substudy can be evaluated as an independent study. Starting from revised protocol 02/Amendment 3, cisplatin-eligible patients were randomised 1:1:1:1 over the substudy and primary study, until the primary study met its enrolment target after which inclusion in the substudy continued. The same control treatment as in arm D of the substudy was given to cisplatin-eligible patients included in the primary study (part of Arm B). However, as cisplatin-eligible patients were randomised 1:1 in the substudy, there are no concerns that the concurrent recruitment into the primary study influenced the substudy. The interim analysis of OS in the substudy was scheduled at the time of the cisplatin-ineligible final OS analysis in the primary study, however the final analyses for the results currently presented were triggered by OS events in the substudy only.

One pivotal study could be acceptable when data from this study are compelling (CPMP/EWP/2330/99). No supportive data have been submitted, however nivolumab has already been approved in urothelial carcinoma in other procedures establishing activity in this tumour type.

Study participants – The eligibility criteria are considered appropriate to select patients eligible for cisplatin who have not received prior systemic treatment for metastatic or surgically unresectable UC. As the indication explicitly reports a combination with cisplatin, it is not considered needed to report that patients should be cisplatin-eligible.

Treatments – Gemcitabine + cisplatin is the standard of care for first line treatment of UC (2020 ESMO guideline; 2023 EAU guideline). This regimen is usually given as gemcitabine 1 000 mg/m^2 on days 1, 8 and 15; cisplatin 70 mg/m^2 on day 2 every 28 days. Alternative three-week regimens are also given as they may reduce toxicity. The posology is gemcitabine (1 000-1 200 mg/m^2 on days 1 and 8) and cisplatin (70-75 mg/m^2 on day 2), repeated every 21 days for a median of six cycles (Als 2009, Parra 2002, Adamo 2005). Therefore, the control treatment is considered acceptable, however

due to the different regimens used in clinical practice, the gemcitabine-cisplatin posology used in the pivotal study is reported in section 5.1 of the SmPC. Of note, patients in the experimental arm were to continue with nivolumab monotherapy after up to 6 cycles of nivo + SOC treatment. Unfortunately, this study is not designed to allow conclusion on the benefit of the monotherapy phase or combination therapy phase alone.
The initially proposed indication states '*in combination with cisplatin-based chemotherapy',* however the only cisplatin-based chemotherapy studied is gemcitabine-cisplatin. Other cisplatin-based regimens such as MVAC (methotrexate, vinblastine, doxorubicin and cisplatin), dose-dense MVAC and PGC (paclitaxel, gemcitabine cisplatin) have not been studied and it is uncertain whether the efficacy and safety observed in the CA209901 substudy can be extrapolated to the other regimens. Due to differences in efficacy and/or safety between the possible cisplatin-based regimens, the B/R of adding nivolumab may differ with combinations other than the one studied in the pivotal study. The indication in combination with gemcitabine-cisplatin used in the pivotal study seems warranted (EMA/CHMP/483022/2019) and, upon request from the CHMP, the MAH amended the indication to specify the combination 'cisplatin and gemcitabine' only.

Objectives, endpoints – In general, the endpoints and objectives are considered to be acceptable, however, an HRQoL endpoint as a secondary endpoint in this study is questionable as this cannot be reliably assessed in an open label study. Plus, the statistical analysis methods for HRQoL endpoints are exploratory rather than confirmatory, as only descriptive statistics were pre-specified without predefining which outcomes were expected.

The MAH has committed to providing the biomarker analyses other than PD-L1 and CPS which have been provided, i.e. CD8, mutations/TMB, gene expression signature, MDSC and serum soluble factors by Q4 2024 (REC).

Sample size – The actual number of subjects included in the substudy (608) is close to the pre-specified target (600), as is the number of OS events (actual: 365, target: 356). The number of PFS events is lower than anticipated initially (actual: 402, target: 460). According to the Applicant, the reason for the PFS event rate being lower than anticipated was due to the changing treatment landscape, and reaching the target number of PFS events was expected to cause a delay of 3 years, which was the reason for protocol amendment 5. Overall, the sample size is considered acceptable, and the data is considered sufficiently mature.

Randomisation, blinding – Randomisation methods are considered acceptable, as well as the stratification factors, i.e., tumour PD-L1 expression using a 1% cut-off (negative/indeterminate vs. positive) and the presence of liver metastasis (yes vs. no). This was an open-label study.

Statistical methods - Methods to control type I error (alpha splitting across the dual primary outcomes and the use of O-Brien-Fleming type alpha spending function in the group-sequential interim analysis) are accepted.

The statistical analyses for OS and BICR-PFS are endorsed.

In the analysis, OS was censored at the date of randomisation for subjects who were randomised but had no follow-up. Similarly, PFS was censored at the randomisation date for subjects who were randomised but either had no evaluable baseline measurement or no on-study tumour assessments (and no death). In addition, subjects who did not experience the event and who withdrew their study consent are censored at the last date known to be event-free. However, these cases are reflective of 'premature censoring' which (as opposed to 'administrative censoring') are unlikely to be non-informative (EMA/CHMP/27994/2008/Rev.1), and treating them as non-informative may have introduced bias in the results (EMA/CPMP/EWP/1776/99 Rev. 1). The MAH has provided results from worst-case analyses for OS, PFS and PFS (secondary definition), where subjects who were prematurely

censored were either considered to have the event at the date of censoring (if in the experimental arm) or to not have the event up to DCO (if in the control arm). Even in this highly unlikely scenario, HR point estimates are still below 1 for OS and PFS (secondary definition). For PFS (primary definition), the worst-case HR exceeds 1 but only to a small extent (1.05). Overall, these findings are considered to support the main results. Analysis choices for the evaluation of secondary objectives (i.e. the assessment of whether PD-L1 expression is a predictive biomarker of efficacy (OS and PFS) of nivolumab combined with SOC chemotherapy as first-line therapy, and EORTC QLQ-C30 Global Health Status scores over time), which are not part of the formal testing strategy, are accepted.

Analysis choices for the evaluation of secondary objectives (i.e. the assessment of whether PD-L1 expression is a predictive biomarker of efficacy (OS and PFS) of nivolumab combined with SOC chemotherapy as first-line therapy, and EORTC QLQ-C30 Global Health Status scores over time), which are not part of the formal testing strategy, are accepted.

Conduct of the study – Many amendments were made to the CA209901 Primary and Substudy. With amendment 3 the substudy was added to the primary study. The primary endpoint was PFS and N=300 patients were planned to be randomised to the substudy. In the Revised Protocol 04 on 20-Mar-2020, OS was made a dual endpoint and the sample size of the substudy was increased from 300 to 600. According to the Applicant this was done after external data from a comparable product in a similar setting (Imvigor 130) were made publicly available. At that time N=262 patients were included in the substudy. This change in an ongoing open label study was not supported during scientific advice(EMEA/H/SA/2253/13/2020/II). With amendment 5 (N=608 patients included) it was decided that the PFS analysis should coincide with the OS final analysis due to the PFS event rate being lower than initially anticipated. The latter change is considered acceptable seeing the PFS outcomes.

Due to the open label design the amendments in an ongoing study are considered unfortunate. In general adjustments to an ongoing trial, particularly if open-label, bear the risk of increased type 1 error because the trial may be altered to increase the chance of a positive conclusion. It is uncertain whether internal data have not driven the proposed changes. It is however acknowledged that the IMvigor130 results were published on 30-Sep-2019 prior to the amendments of Revised Protocol 04 on 20-Mar-2020, which supports that external data was available. In addition, there were no changes to the study population for the substudy and thus it cannot be said that the most favourable population was selected. There are few concerns for multiplicity for the substudy (this may be different for the primary study, however the primary study is not under assessment in this application). While the timing of the amendment was unfortunate, the changes in sample size and adding OS as a primary endpoint are considered to have provided relevant information for decision making, which otherwise might not have been available from the study as originally planned with a smaller sample size and PFS as (sole) primary endpoint. The applicant has stated that they were not aware of study outcomes per treatment arm until the final analyses except for receiving the results of the interim analyses. In order to provide some reassurance that internal data have not driven decision making, efficacy results before (under revised protocol number 03 (09-Apr-2019) and after the protocol amendments and analyses for the first 300 patients randomised and the 308 remaining patients were provided to allow the evaluation of homogeneity of results. The provided data are considered reassuring, as the PFS primary endpoint would have been met under revised protocol number 03 even though OS would not. The PFS endpoint would also have been met in patients included prior to the amendment and in the first 300 patients. There is also homogeneity of PFS results between the earlier and the later included patients. In these analyses OS results were in line with the current OS results, but OS results were not statistically significant. The fact that OS was not met in the provided analyses/previous protocol analyses can be understood due to the reduced sample size and insufficient power to detect OS differences (e.g. under revised protocol number 03 OS was powered at 52%). Overall, the provided

data are considered reassuring and the type I error can be considered reasonably controlled in view of the positive PFS analysis according to protocol number 03.

Efficacy data and additional analyses

Participant disposition – The final results of the substudy have been presented (van der Heijden et al. N Engl J Med. 2023). In total, 608 subjects (304 in the nivo + SOC arm; 304 in the SOC arm) were randomised and 592 subjects (304 in the nivo + SOC; 288 in the SOC arm) were treated. The analysis population for efficacy consisted of all randomised subjects. At the time of the data cut-off (09-May-2023), the median follow-up (date of randomisation to the cut-off date) was 33.6 months in the nivo + SOC arm and 33.5 months in the SOC arm. Most patients discontinued treatment due to disease progression (36.8%). In total 13 patients in the SOC arm were not treated according to the Randomized Subject Status Summary and 3 subjects randomized as Arm D (SOC) in the substudy were treated as Arm B (SOC) in the primary study(two patients received gemcitabine-cisplatin and one gemcitabine carboplatin), but were included in the analyses. Overall, it is considered that these patients do not have a large influence on the outcomes.

Deviations – A large number of important protocol deviations were observed (in 53.9% of the total study patients).The number of deviations are generally comparable among the study arms. There was a small number of relevant protocol deviations (7.2%). Most deviations occurred in a small number of patients and the numbers are more or less comparable over the treatment arms. The deviations do not raise concern for interpretability of the data. In total, 3% of the patients was misclassified at stratification level. Since the total number of discrepancies is small and they were mostly comparable across the arms, this is considered not to have had a large impact on the results.

Baseline data – The baseline demographic and disease characteristics are comparable across the two study arms, with the exception that slightly more patients with muscle-invasive disease at initial diagnosis were assigned to the nivo + SOC arm and slightly more patients with metastatic, advanced or unresectable disease were assigned to the SOC arm. Also, a median longer time from initial diagnosis and a slightly higher number of patients that received prior (neo-) adjuvant therapy is observed for nivo + SOC patients compared to SOC patients. The consequences of these imbalances are unclear, but may be considered minor. In total, 74.7% of the patients had UC in the urinary bladder at diagnosis, this number is comparable in both arms (77.3% vs. 72% respectively), however literature reports frequency of bladder UC of 90%. Nevertheless, these numbers are not considered to have a large impact on efficacy. In total, 49 of the 304 subjects in the nivo + SOC arm (16.1%) and 43 of the 288 subjects in the SOC arm (14.9%) received at least 1 dose of carboplatin. These numbers are balanced between the two study arms (refer also to section 'Discussion on clinical safety').

Outcomes - The study met both the OS and PFS primary endpoints and demonstrated a statistically significant improvement in OS and PFS for nivo + SOC vs. SOC alone; OS HR = 0.78 (alpha-adjusted 95.59% CI: 0.63, 0.96), stratified log rank test p value = 0.0171 and PFS HR = 0.72 (alpha-adjusted 99% CI: 0.55, 0.94;), stratified log-rank test p-value = 0.0012. As shown in the OS KM-curves a moderate improvement in OS rate in the nivo + SOC over SOC appears to be maintained over time. Also, in the PFS KM-curves an improvement in PFS rate in the nivo + SOC over SOC appears to be maintained over time. Thus, the treatment effect is considered clinically relevant. The OS and PFS effect is consistent over pre-defined subgroups, except for the subgroup of patients from the region US (OS HR = 1.92, PFS HR = 1.45;). The reason for this inconsistency is unknown and may be related to the small sample size (N=40). The median OS reported for nivo + SOC is 21.7 months (95% CI: 18.6, 26.4) and 18.9 months (95% CI 14.7, 22.4) for SOC. The median OS in the SOC arm (18.9 months) is numerically higher compared to what is normally reported for gemcitabine-cisplatin patients (median OS 14-15 months). This may be because some patients, as a result of the change in treatment landscape, received a PD-(L)1 inhibitor as maintenance therapy (see above subsection 'Deviations').

Patients who receive such treatment are expected to have longer OS (median OS of 21 months; Bavencio II/18 EPAR).

The primary definition of PFS censored for any subsequent anticancer therapy prior to death or progression, while the secondary PFS definition did not censor/consider these patients progressed (in line with EMA guidance [EMA/CHMP/27994/2008/Rev.1]). Reassuringly, the results for the secondary definition are comparable to the primary definition, except that there is less censoring.

Results in patients with PD-L1 expression ≥ 1% support the primary endpoints (OS HR = 0.74 [95% CI: 0.52, 1.04] and PFS HR = 0.58 [95% CI: 0.41, 0.81]). In patients with PD-L1 expression < 1% results are somewhat less impressive (OS HR = 0.82 [95% CI: 0.63, 1.05] and PFS HR = 0.80 [95% CI: 0.62, 1.02]) compared to patients with PD-L1 expression ≥ 1%, however especially for OS results are considered similar. Thus, the results do not raise concerns that patients with PD-L1 expression < 1% do not benefit from the addition of nivolumab to SOC. See also the numerical benefit in ORR both in patients with PD-L1 expression ≥ 1% and < 1% (Table 26).

Analysis with different cut-offs for tumour PD-L1 expression and PD-L1 CPS do not indicate a cut-off at which responders and non-responders are clearly separated.

There were no large differences in mean changes in EORTC QLQ-C30 Global Health Status scores between treatment arms; however, over time few patients for whom results were available remained. Also, since this is an open-label trial HRQoL endpoints including EORTC QLQ C30 Global Health Status score and HRQoL exploratory endpoints cannot be adequately assessed.

Exploratory endpoints ORR (57.6% in the nivo + SOC arm vs. 43.1% in the SOC arm) and median DOR (9.53 vs. 7.26 months, respectively) support the primary endpoints.

Concordance BICR and investigator assessments was generally high and acceptable.

Wording of the indication - The wording "*in combination with cisplatin-based chemotherapy*" was not agreed, as the chemotherapy regimen used in the CA209901 substudy was gemcitabine-cisplatin. It was, therefore, uncertain whether the efficacy and safety observed in the CA209901 substudy could be extrapolated to other cisplatin-based regimens that were not studied, such as MVAC, dose dense MVAC and PGC. The Applicant was requested to justify why the indication could be extended to other cisplatin-containing regimens or revise the indication to reflect the treatment studied.

In response, the Applicant amended the wording of the indication to: "*Opdivo in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.*", which was accepted.

2.4.4. Conclusions on the clinical efficacy

The efficacy of nivolumab as add-on to gemcitabine-cisplatin chemotherapy followed by nivolumab monotherapy has been shown. Data from the pivotal CA209901 substudy indicate a statistically significant benefit of OS and PFS of nivo + SOC over SOC, that could be translated into a clinically relevant benefit. The efficacy is considered to be robust and consistent over almost all subgroups, including for patients with PD-L1 expression positive and negative tumours and thus results from the are considered compelling. The MAH has committed to submit biomarker analyses for the CA209901 substudy other than PD-L1 and CPS (which have already been provided), i.e., CD8, mutations/TMB, gene expression signature, MDSC and serum soluble factors by Q4 2024 (REC).

Amendments were made to this ongoing open label study though and this is considered to be unfortunate. While the changes in sample size and adding OS as a primary endpoint are considered to

have provided relevant information for decision making, the MAH may not be able to provide full reassurance that internal data have not driven decision making. On the other hand, it can be agreed that external data was available to support the changes. Further, as the primary endpoint of PFS would have been met under the protocol version prior to the amendments, , the type I error can be considered reasonably controlled.

2.5. Clinical safety

Introduction

The safety of nivolumab is well known, including for nivolumab treatment in combination with platinum-based (combination) chemotherapy in other tumour types.

For some indications Opdivo is approved for treatment in combination with other medicinal products, including platinum-based (combination) chemotherapy. The approvals for treatment in combination with chemotherapy are the following:

- OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% (see section 5.1 for selection criteria).
- OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2 negative advanced or metastatic gastric, gastro oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

Before the filing of this application, the safety information on nivolumab in combination with chemotherapy was based on a pooled dataset of 1268 patients across these other tumour types (gastric, GEJ or oesophageal adenocarcinoma, OSCC, or NSCLC), with a minimum follow-up ranging from 12.1 to 20 months.

For this variation application, the MAH provided safety data from the pivotal CA209901 substudy (see section 2.4.2 'Main study') on the all treated subjects population, i.e. all randomised subjects who received at least one dose of any study treatment (Table 14).

In the final analysis of the CA209901 substudy with a data cut-off (LPLV) of 09-May-2023 and a 23-Jun-2023 DBL, a total of 592 treated subjects had received at least one dose of study drug who were randomised to nivo + SOC (N = 304) and SOC (N = 288). At the time of the data cut off, the median follow-up was 33.6 months in the nivo + SOC arm and 33.5 months in the SOC arm, and the minimum follow-up was 7.4 months in both arms.

The assessment of safety was based on the incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, adverse events leading to dose modification, select adverse events (select AEs), immune-mediated AEs (IMAEs), other events of special interest (OESIs), and deaths. The use of immune modulating concomitant medication was also summarised. In addition, clinical laboratory tests and immunogenicity (i.e. development of anti-drug antibody [ADA]) were analysed.
Descriptive statistics of safety were presented using NCI CTCAE version 4 by treatment group. All AEs,

treatment-related AEs, SAEs, and treatment-related SAEs, IMAEs, and Select AEs were tabulated using worst grade per NCI CTCAE version 4.0 criteria by system organ class (SOC) and PT. Laboratory parameters including haematology, chemistry, liver function, and renal function were summarised using worst grade per NCI CTCAE version 4.0 criteria.

Safety reporting was primarily performed using a 30-day safety window, or a 100-day safety window for IMAEs and OESIs.

Patient exposure

Due to the different treatment durations between the two treatment arms (up to two years for nivo plus cisplatin-gemcitabine chemotherapy followed by nivo monotherapy [nivo + SOC] vs. approximately four months for cisplatin-gemcitabine alone [SOC]), the median duration of therapy was longer in the nivo + SOC arm (7.39 months; 95% CI: 7.06, 8.38) than in the SOC arm (3.75 months; 95% CI: 3.71, 3.84).

Subjects who discontinued cisplatin alone could, at the investigator's discretion, be switched to gemcitabine-carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total). During Part 1 of the treatment period, i.e., the nivo + chemo treatment period, most treated subjects in the nivo + SOC arm received ≥90% of the planned nivolumab, ≥70% to ≤110% gemcitabine, and ≥90% cisplatin dose intensity. For carboplatin, most treated subjects received 70% to <90% of the planned dose intensity. Generally similar rates were observed in the SOC arm. For the subjects in the nivo + SOC arm who proceeded to nivo monotherapy dosing (Part 2, n = 244), 87.7% of subjects received ≥90% of the planned nivolumab dose intensity (Table 31).

Table 31. Cumulative dose and relative dose intensity summary - All treated subjects - Substudy

Part 1				
	Nivo + SOC N = 304			
	Nivolumab N = 304	Gemcitabine N = 304	Cisplatin N = 301	Carboplatin N = 49
NUMBER OF DOSES RECEIVED				
MEAN (SD)	5.2 (1.5)	9.7 (3.2)	4.8 (1.9)	2.9 (1.6)
MEDIAN	6.0	11.0	6.0	3.0
(MIN - MAX)	(1 - 6)	(1 - 12)	(1 - 12)	(1 - 6)
CUMULATIVE DOSE (A)				
MEAN (SD)	1861.58 (557.67)	9239.1 (3153.4)	328.0 (152.8)	12.96 (6.81)
MEDIAN	2160.00	10300.8	391.5	12.45
(MIN - MAX)	(360.0 - 2160.0)	(971 - 12589)	(67 - 1336)	(3.3 - 25.8)
RELATIVE DOSE INTENSITY (%)				
>= 110%	0	1 (0.3)	4 (1.3)	0
90% TO < 110%	224 (73.7)	128 (42.1)	188 (62.5)	15 (30.6)
70% TO < 90%	72 (23.7)	125 (41.1)	97 (32.2)	22 (44.9)
50% TO < 70%	8 (2.6)	43 (14.1)	10 (3.3)	12 (24.5)
< 50%	0	6 (2.0)	1 (0.3)	0
NOT REPORTED	0	1 (0.3)	1 (0.3)	0

Part 1			
	SOC N = 288		
	Gemcitabine N = 288	Cisplatin N = 286	Carboplatin N = 43
NUMBER OF DOSES RECEIVED			
MEAN (SD)	9.6 (4.1)	4.5 (2.1)	3.2 (1.7)
MEDIAN	11.0	6.0	3.0
(MIN - MAX)	(1 - 30)	(1 - 12)	(1 - 8)
CUMULATIVE DOSE (A)			
MEAN (SD)	9109.2 (4195.3)	307.9 (161.7)	14.13 (7.96)
MEDIAN	9726.2	348.9	13.30
(MIN - MAX)	(691 - 30447)	(61 - 1363)	(0.7 - 36.4)

RELATIVE DOSE INTENSITY (%)			
>= 110%	4 (1.4)	3 (1.0)	1 (2.3)
90% TO < 110%	133 (46.2)	178 (62.2)	16 (37.2)
70% TO < 90%	92 (31.9)	83 (29.0)	12 (27.9)
50% TO < 70%	50 (17.4)	18 (6.3)	13 (30.2)
< 50%	7 (2.4)	2 (0.7)	1 (2.3)
NOT REPORTED	2 (0.7)	2 (0.7)	0

Part 2

	Nivo + SOC N = 304
	Nivolumab N = 244
NUMBER OF DOSES RECEIVED	
MEAN (SD)	8.8 (7.1)
MEDIAN	6.0
(MIN - MAX)	(1 - 28)
CUMULATIVE DOSE (A)	
MEAN (SD)	4223.6 (3422.1)
MEDIAN	2880.0
(MIN - MAX)	(480 - 13440)
RELATIVE DOSE INTENSITY (%)	
>= 110%	0
90% TO < 110%	214 (87.7)
70% TO < 90%	23 (9.4)
50% TO < 70%	6 (2.5)
< 50%	1 (0.4)

(A) Dose units: Nivolumab in mg; Gemcitabine and Cisplatin in mg/m^2, Carboplatin in AUC.

Study therapy (dose) modifications

Dose delays - The proportions of subjects with at least 1 dose delay during Part 1 were as follows:

- Nivo + SOC arm (N = 304): 55.6% for nivolumab (N = 304), 65.5% for gemcitabine (N = 304), 48.5% for cisplatin (N = 301), and 49.0% for carboplatin (N = 49).
- SOC arm (N = 288): 63.2% for gemcitabine (N = 288), 46.9% for cisplatin (N = 286), and 46.5% for carboplatin (N = 43).

The most common reason for dose delays for each treatment in each treatment arm was AE; however, no reason was reported for many subjects.

Dose reductions - Dose reductions of nivolumab were not permitted. The proportions of subjects with at least 1 dose reduction were as follows:

- Nivo + SOC arm (N = 304): 31.3% for gemcitabine (N = 304), 19.9% for cisplatin (N = 301), and 61.2% for carboplatin (N = 49).
- SOC arm (N = 288): 30.6% for gemcitabine (N = 288), 23.8% for cisplatin (N = 286), and 60.5% for carboplatin (N = 43).

The most common reason for dose reductions for each treatment in each treatment arm was AE; however, no reason was reported for many subjects.

Chemotherapy dose discontinuation - The proportions of subjects with at least 1 chemotherapy dose discontinuation were as follows:

- Nivo + SOC arm (N = 304): 8.9% for gemcitabine (N = 304), 18.3% for cisplatin (N = 301), and 4.1% for carboplatin (N = 49).
- SOC arm (N = 288): 7.6% for gemcitabine (N = 288), 14.7% for cisplatin (N = 286), and 7.0% for carboplatin (N = 43).

The most common reason for dose discontinuation for each treatment in each treatment arm was AE.

Switch from cisplatin to carboplatin - 49 of the 304 subjects in the nivo + SOC arm (16.1%) and 43 of the 288 subjects in the SOC arm (14.9%) switched from cisplatin to carboplatin and received at least 1

dose of the latter (Table 31). The median number of carboplatin doses received was 3.0 in each study arm.

Adverse events

Table 32. Overall safety summary - Substudy

	No. of Subjects (%)	
	Nivo + SOC N = 304	**SOC N = 288**
Deaths	172 (56.6)	186 (64.6)
Primary reason for death		
Disease	141 (46.3)[b]	162 (56.3)[c]
Study drug toxicity	7 (2.3)[b]	2 (0.7)[c]
Unknown	7 (2.3)	8 (2.8)
Other[c]	17 (5.6)[b]	14 (4.9)

	Adverse Event Grades			
Safety Parameter	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	142 (46.7)	113 (37.2)	105 (36.5)	79 (27.4)
Drug-related SAEs	75 (24.7)	61 (20.1)	48 (16.7)	37 (12.8)
All-causality AEs leading to DC	90 (29.6)	50 (16.4)	69 (24.0)	38 (13.2)
Drug-related AEs leading to DC	64 (21.1)	33 (10.9)	50 (17.4)	22 (7.6)
All-causality AEs	303 (99.7)	220 (72.4)	284 (98.6)	187 (64.9)
Drug-related AEs	296 (97.4)	187 (61.5)	267 (92.7)	148 (51.4)
≥ 15% Drug-related AEs in Any Treatment				
Anaemia	174 (57.2)	67 (22.0)	137 (47.6)	51 (17.7)
Nausea	142 (46.7)	1 (0.3)	138 (47.9)	3 (1.0)
Neutropenia	93 (30.6)	57 (18.8)	86 (29.9)	44 (15.3)
Neutrophil count decreased	75 (24.7)	44 (14.5)	60 (20.8)	32 (11.1)
Fatigue	74 (24.3)	6 (2.0)	69 (24.0)	4 (1.4)
Decreased appetite	68 (22.4)	4 (1.3)	45 (15.6)	1 (0.3)
Platelet count decreased	66 (21.7)	23 (7.6)	43 (14.9)	14 (4.9)
White blood cell count decreased	64 (21.1)	30 (9.9)	40 (13.9)	11 (3.8)
Vomiting	55 (18.1)	4 (1.3)	48 (16.7)	6 (2.1)
Asthenia	47 (15.5)	3 (1.0)	46 (16.0)	5 (1.7)
All-causality select AEs, by category				
Endocrine	66 (21.7)	4 (1.3)	3 (1.0)	1 (0.3)
Gastrointestinal	59 (19.4)	7 (2.3)	41 (14.2)	0
Hepatic	54 (17.8)	15 (4.9)	31 (10.8)	3 (1.0)
Pulmonary	7 (2.3)	2 (0.7)	1 (0.3)	1 (0.3)
Renal	88 (28.9)	17 (5.6)	73 (25.3)	5 (1.7)
Skin	114 (37.5)	8 (2.6)	28 (9.7)	1 (0.3)
Hypersensitivity/infusion reactions	14 (4.6)	0	10 (3.5)	0
Drug-related select AEs, by category				
Endocrine	64 (21.1)	4 (1.3)	0	0
Gastrointestinal	42 (13.8)	6 (2.0)	25 (8.7)	0

	No. of Subjects (%)			
	Nivo + SOC N = 304		SOC N = 288	
Hepatic	40 (13.2)	8 (2.6)	24 (8.3)	2 (0.7)
Pulmonary	6 (2.0)	1 (0.3)	0	0
Renal	58 (19.1)	11 (3.6)	54 (18.8)	3 (1.0)
Skin	96 (31.6)	8 (2.6)	19 (6.6)	1 (0.3)
Hypersensitivity/infusion reactions	10 (3.3)	0	9 (3.1)	0
All-causality IMAEs within 100 days of last dose				
Treated with immune-modulating medication, by category				
Diarrhoea/Colitis	4 (1.3)	4 (1.3)	0	0
Hepatitis	4 (1.3)	4 (1.3)	0	0
Pneumonitis	5 (1.6)	2 (0.7)	0	0
Nephritis/Renal Dysfunction	4 (1.3)	2 (0.7)	0	0
Rash	26 (8.6)	4 (1.3)	2 (0.7)	0
Hypersensitivity/Infusion Reactions	1 (0.3)	0	0	0
All-causality endocrine IMAEs within 100 days of last dose				
With or without immune-modulating medication, by category				
Adrenal Insufficiency	3 (1.0)	1 (0.3)	0	0
Hypophysitis	3 (1.0)	2 (0.7)	0	0
Hypothyroidism/Thyroiditis	40 (13.2)	0	0	0
Hyperthyroidism	22 (7.2)	1 (0.3)	0	0
Diabetes Mellitus	1 (0.3)	0	0	0
All-causality OESI within 100 days of last dose				
With or without immune-modulating medication, by category				
Pancreatitis	3 (1.0)	3 (1.0)	0	0
Encephalitis	1 (0.3)	1 (0.3)	0	0
Myositis/Rhabdomyolysis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Guillain-Barre Syndrome	0	0	0	0
Uveitis	0	0	0	0
Myocarditis	3 (1.0)	2 (0.7)	0	0
Graft Versus Host Disease	0	0	0	0
Autoimmune cytopenia	1 (0.3)	1 (0.3)	0	0
Autoimmune eye disorder	0	0	0	0
Immune-mediated arthritis	0	0	0	0

[a] Includes all deaths for any reason that occurred at any time.
[b] Of the 141 deaths classified as due to disease, 2 deaths of malignant neoplasm progression were originally attributed to other reasons by the investigator and were then reclassified as disease progression deaths. An additional death originally attributed to disease progression by the investigator was reclassified as study drug toxicity death. Of the7 deaths classified as due to study toxicity death, 4 were originally attributed to other reasons and 1 death was originally attributed to disease progression by the investigator and then reclassified as deaths due to study drug toxicity. 11 PTs were reported in 7 subjects and included abdominal sepsis, thrombocytopenia, hypovolemic shock, multiple organ dysfunction syndrome, multiple organ failure, myocarditis, acute kidney injury, small intestinal obstruction, adrenal insufficiency (one each) and sepsis (2 subjects).
[c] Of the 2 study drug toxicity deaths in the SOC arm, 1 death was originally attributed to disease progression by investigator and then reclassified as study drug toxicity death. The reported PTs were acute kidney failure and septic shock.
[d] The verbatim terms reported for the 'other' reasons for death are provided in Table 35. None were considered related to study drug (per the investigator).
MedDRA Version 26.0. CTCAE Version 4.

Note: Includes events reported between first treatment and 30 days after last treatment of study therapy, unless otherwise indicated.

AEs regardless of causality (Table 33; Figure 15) SOC: anaemia (20.8%), neutropenia (15.3%), neutrophil count decreased (11.5%).

Figure 15 is a tornado plot displaying all-causality AEs occurring at any Grade in ≥10% of treated subjects in either study arm.

Drug-related AEs (Table 32; Figure 16) Figure 16 is a tornado plot displaying drug-related AEs occurring at any Grade in ≥10% of treated subjects in either study arm.

Exposure-adjusted AEs - When incidence rates of AEs were adjusted for exposure, the AE (all causality) rate per 100 person years was 1765.0 in the nivo + SOC arm and 2958.0 in the SOC arm.

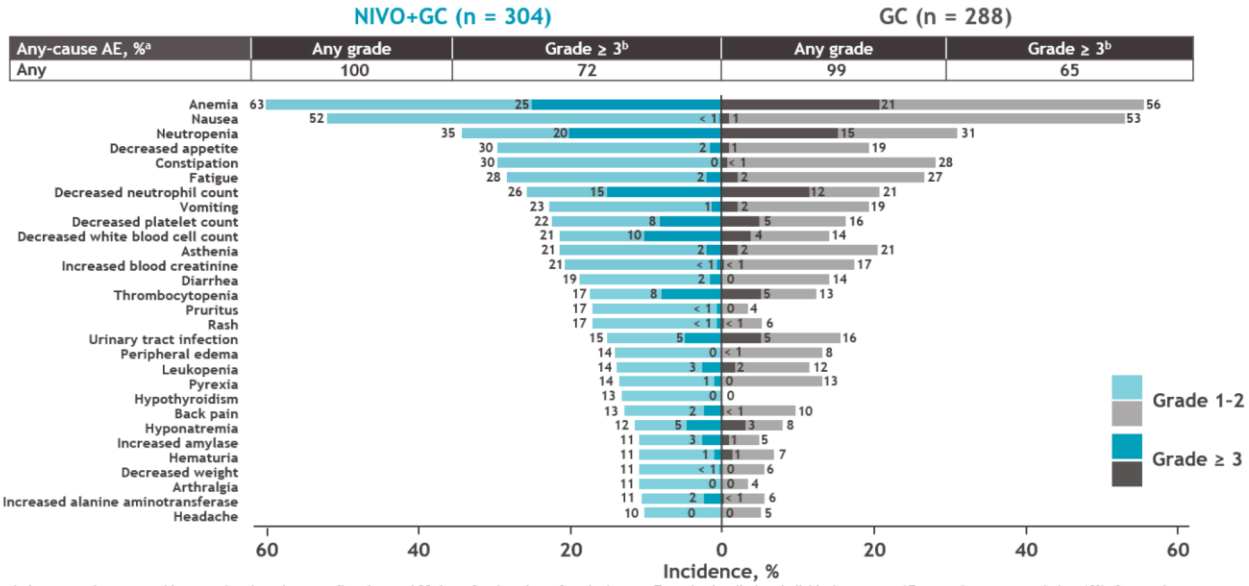
Table 33. Adverse events by worst CTC Grade in ≥ 5% for any grade - All treated subjects - Substudy

System Organ Class (%)	Nivo + SOC N = 304			SOC N = 288		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	303 (99.7)	220 (72.4)	13 (4.3)	284 (98.6)	187 (64.9)	8 (2.8)
Blood and lymphatic system disorders	237 (78.0)	121 (39.8)	0	205 (71.2)	107 (37.2)	0
Anaemia	192 (63.2)	76 (25.0)	0	160 (55.6)	60 (20.8)	0
Neutropenia	105 (34.5)	61 (20.1)	0	89 (30.9)	44 (15.3)	0
Thrombocytopenia	53 (17.4)	24 (7.9)	0	36 (12.5)	15 (5.2)	0
Leukopenia	42 (13.8)	8 (2.6)	0	33 (11.5)	5 (1.7)	0
Gastrointestinal disorders	236 (77.6)	28 (9.2)	0	207 (71.9)	15 (5.2)	1 (0.3)
Nausea	158 (52.0)	1 (0.3)	0	153 (53.1)	3 (1.0)	0
Constipation	90 (29.6)	0	0	81 (28.1)	2 (0.7)	0
Vomiting	69 (22.7)	4 (1.3)	0	56 (19.4)	6 (2.1)	0
Diarrhoea	57 (18.8)	5 (1.6)	0	41 (14.2)	0	0
Abdominal pain	25 (8.2)	1 (0.3)	0	15 (5.2)	1 (0.3)	0
General disorders and administration site conditions	205 (67.4)	25 (8.2)	0	167 (58.0)	17 (5.9)	2 (0.7)
Fatigue	86 (28.3)	6 (2.0)	0	77 (26.7)	6 (2.1)	0
Asthenia	65 (21.4)	6 (2.0)	0	59 (20.5)	6 (2.1)	0
Oedema peripheral	43 (14.1)	0	0	23 (8.0)	1 (0.3)	0
Pyrexia	41 (13.5)	3 (1.0)	0	38 (13.2)	0	0
Malaise	19 (6.3)	1 (0.3)	0	12 (4.2)	0	0
Investigations	201 (66.1)	88 (28.9)	0	155 (53.8)	58 (20.1)	0
Neutrophil count decreased	78 (25.7)	46 (15.1)	0	60 (20.8)	33 (11.5)	0
Platelet count decreased	68 (22.4)	25 (8.2)	0	47 (16.3)	14 (4.9)	0
White blood cell count decreased	65 (21.4)	31 (10.2)	0	41 (14.2)	11 (3.8)	0
Blood creatinine increased	63 (20.7)	2 (0.7)	0	50 (17.4)	1 (0.3)	0
Amylase increased	33 (10.9)	8 (2.6)	0	14 (4.9)	3 (1.0)	0
Weight decreased	33 (10.9)	1 (0.3)	0	16 (5.6)	0	0
Alanine aminotransferase increased	32 (10.5)	7 (2.3)	0	16 (5.6)	1 (0.3)	0
Lipase increased	30 (9.9)	10 (3.3)	0	13 (4.5)	4 (1.4)	0
Aspartate aminotransferase increased	29 (9.5)	5 (1.6)	0	14 (4.9)	1 (0.3)	0
Lymphocyte count decreased	16 (5.3)	9 (3.0)	0	11 (3.8)	3 (1.0)	0
Metabolism and nutrition disorders	159 (52.3)	42 (13.8)	0	114 (39.6)	23 (8.0)	0
Decreased appetite	90 (29.6)	5 (1.6)	0	56 (19.4)	3 (1.0)	0
Hyponatraemia	35 (11.5)	14 (4.6)	0	23 (8.0)	9 (3.1)	0
Hypomagnesaemia	21 (6.9)	4 (1.3)	0	33 (11.5)	1 (0.3)	0
Hypokalaemia	19 (6.3)	2 (0.7)	0	16 (5.6)	5 (1.7)	0
Hyperglycaemia	18 (5.9)	3 (1.0)	0	13 (4.5)	5 (1.7)	0
Infections and infestations	143 (47.0)	49 (16.1)	2 (0.7)	88 (30.6)	43 (14.9)	0
Urinary tract infection	46 (15.1)	15 (4.9)	0	45 (15.6)	15 (5.2)	0
COVID-19	24 (7.9)	1 (0.3)	0	6 (2.1)	1 (0.3)	0
Skin and subcutaneous tissue disorders	136 (44.7)	8 (2.6)	0	58 (20.1)	1 (0.3)	0
Pruritus	52 (17.1)	2 (0.7)	0	10 (3.5)	0	0
Rash	52 (17.1)	2 (0.7)	0	16 (5.6)	1 (0.3)	0
Alopecia	20 (6.6)	0	0	26 (9.0)	0	0
Nervous system disorders	120 (39.5)	10 (3.3)	0	76 (26.4)	7 (2.4)	0
Headache	31 (10.2)	0	0	15 (5.2)	0	0
Dizziness	23 (7.6)	0	0	17 (5.9)	2 (0.7)	0
Neuropathy peripheral	22 (7.2)	1 (0.3)	0	14 (4.9)	0	0
Dysgeusia	21 (6.9)	0	0	12 (4.2)	0	0
Paraesthesia	16 (5.3)	0	0	16 (5.6)	0	0
Musculoskeletal and connective tissue disorders	107 (35.2)	9 (3.0)	0	64 (22.2)	4 (1.4)	0
Back pain	39 (12.8)	7 (2.3)	0	28 (9.7)	1 (0.3)	0
Arthralgia	33 (10.9)	0	0	10 (3.5)	0	0
Myalgia	17 (5.6)	0	0	5 (1.7)	0	0
Renal and urinary disorders	101 (33.2)	27 (8.9)	0	67 (23.3)	14 (4.9)	1 (0.3)
Haematuria	33 (10.9)	3 (1.0)	0	20 (6.9)	4 (1.4)	0
Acute kidney injury	23 (7.6)	15 (4.9)	0	17 (5.9)	3 (1.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	97 (31.9)	23 (7.6)	0	60 (20.8)	10 (3.5)	0

System Organ Class (%) Preferred Term (%)	Nivo + SOC N = 304 Any Grade	Grade 3-4	Grade 5	SOC N = 288 Any Grade	Grade 3-4	Grade 5
Cough	25 (8.2)	0	0	12 (4.2)	0	0
Dyspnoea	21 (6.9)	4 (1.3)	0	12 (4.2)	0	0
Hiccups	18 (5.9)	2 (0.7)	0	8 (2.8)	0	0
Pulmonary embolism	18 (5.9)	11 (3.6)	0	18 (6.3)	8 (2.8)	0
Vascular disorders	82 (27.0)	21 (6.9)	0	51 (17.7)	10 (3.5)	0
Hypertension	25 (8.2)	9 (3.0)	0	10 (3.5)	4 (1.4)	0
Hypotension	19 (6.3)	5 (1.6)	0	6 (2.1)	2 (0.7)	0
Endocrine disorders	56 (18.4)	5 (1.6)	0	0	0	0
Hypothyroidism	40 (13.2)	0	0	0	0	0
Hyperthyroidism	21 (6.9)	1 (0.3)	0	0	0	0
Psychiatric disorders	38 (12.5)	1 (0.3)	0	24 (8.3)	0	0
Insomnia	19 (6.3)	0	0	13 (4.5)	0	0
Ear and labyrinth disorders	34 (11.2)	1 (0.3)	0	30 (10.4)	1 (0.3)	0
Tinnitus	19 (6.3)	0	0	20 (6.9)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	32 (10.5)	12 (3.9)	11 (3.6)	13 (4.5)	6 (2.1)	3 (1.0)
Malignant neoplasm progression	18 (5.9)	6 (2.0)	11 (3.6)	9 (3.1)	6 (2.1)	3 (1.0)

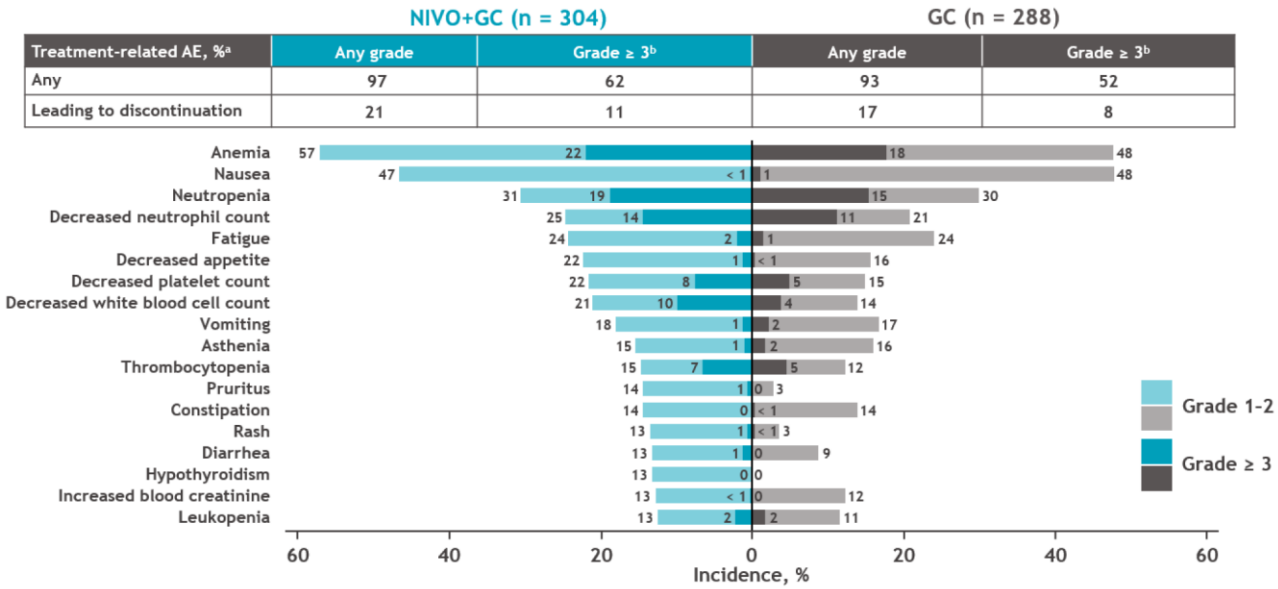
MedDRA Version: 26.0. CTC Version 4.
Note: Includes events reported between first dose and 30 days after last dose of study therapy.

Figure 15. All-causality AEs occurring at any Grade in ⩾10% of treated subjects in either study arm - All treated subjects - Substudy



aIncludes events that occurred in treated patients between first dose and 30 days after last dose of study therapy. Tornado plot displays individual any-cause AEs occurring at any grade in ≥ 10% of treated patients in either arm. bGrade 5 events occurred in a total of 13 (4%) patients treated with NIVO+GC (malignant neoplasm progression, n = 11 [4%]) and 8 (3%) patients treated with GC (malignant neoplasm progression, n = 3 [1%]; acute kidney injury, n = 1 [< 1%]).
AE, adverse event; GC, gemcitabine-cisplatin; NIVO, nivolumab.

Figure 16. Drug-related AEs occurring at any Grade in ⩾10% of treated subjects in either study arm - All treated subjects - Substudy



[a]Includes events that occurred in treated patients between first dose and 30 days after last dose of study therapy. Tornado plot displays individual treatment-related AEs occurring at any grade in ≥ 10% of treated patients in either arm. [b]One grade 5 event occurred in each arm (sepsis in the NIVO+GC arm and acute kidney injury in the GC arm).
AE, adverse event.

Discontinuation due to adverse events

The overall frequencies of all-causality and drug-related AEs leading to discontinuation of study drug are shown in Table 32.

Table 34. Adverse events leading to discontinuation by worst CTC Grade in ≥ 1% for any Grade - All treated subjects - Substudy

System Organ Class (%) Preferred Term (%)	Nivo + SOC N = 304			SOC N = 288		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	90 (29.6)	50 (16.4)	1 (0.3)	69 (24.0)	38 (13.2)	1 (0.3)
Renal and urinary disorders	18 (5.9)	7 (2.3)	0	10 (3.5)	3 (1.0)	0
Acute kidney injury	9 (3.0)	6 (2.0)	0	5 (1.7)	1 (0.3)	0
Renal impairment	4 (1.3)	0	0	1 (0.3)	0	0
Renal failure	3 (1.0)	1 (0.3)	0	3 (1.0)	1 (0.3)	0
Investigations	15 (4.9)	3 (1.0)	0	13 (4.5)	2 (0.7)	0
Blood creatinine increased	8 (2.6)	0	0	6 (2.1)	0	0
Blood and lymphatic system disorders	12 (3.9)	12 (3.9)	0	17 (5.9)	10 (3.5)	0
Thrombocytopenia	6 (2.0)	5 (1.6)	0	2 (0.7)	1 (0.3)	0
Anaemia	4 (1.3)	3 (1.0)	0	8 (2.8)	4 (1.4)	0
Febrile neutropenia	4 (1.3)	4 (1.3)	0	0	0	0
Neutropenia	4 (1.3)	3 (1.0)	0	6 (2.1)	4 (1.4)	0
Infections and infestations	11 (3.6)	9 (3.0)	1 (0.3)	8 (2.8)	6 (2.1)	0
Sepsis	4 (1.3)	3 (1.0)	1 (0.3)	1 (0.3)	1 (0.3)	0
General disorders and administration site conditions	8 (2.6)	3 (1.0)	0	7 (2.4)	2 (0.7)	0
Fatigue	5 (1.6)	2 (0.7)	0	1 (0.3)	0	0
Gastrointestinal disorders	7 (2.3)	7 (2.3)	0	5 (1.7)	3 (1.0)	0
Intestinal obstruction	3 (1.0)	3 (1.0)	0	0	0	0
Ear and labyrinth disorders	6 (2.0)	0	0	8 (2.8)	1 (0.3)	0
Tinnitus	4 (1.3)	0	0	4 (1.4)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.3)	3 (1.0)	0	5 (1.7)	5 (1.7)	0
Malignant neoplasm progression	4 (1.3)	3 (1.0)	0	5 (1.7)	5 (1.7)	0

MedDRA Version: 26.0. CTC Version 4. Note: Includes events reported between first dose and 30 days after last dose of study therapy.

Deaths

Number of deaths in each arm of the substudy (nivo + SOC arm and SOC arm) is shown in Table 32.

The verbatim terms for the 'other' reasons for death are shown in Table 35. None were considered related to study drug (per the investigator).

Table 35. Verbatim terms for deaths attributed to 'other' reasons

Nivo + SOC		SOC	
Reported event(s)	**Days since last dose[a]**	**Reported event(s)**	**Days since last dose[a]**
Ascites	34	Hypokalaemia	5
Sepsis	32	Cardiopulmonary arrest	498
Sepsis	31	Non-traumatic intracerebral haemorrhage	346
Hypovolemic shock	54	COVID-19 pneumonia	224
Cardiac failure	1051	Thrombotic stroke	30
Cerebral ischemia	42	Hepatic cirrhosis, multiple organ dysfunction syndrome, pneumonitis, sepsis	43
Septic shock	35	COVID-19	10
Syncope	29	Septic shock	58
Acute hepatic failure, multiple organ dysfunction syndrome	98	Gastrointestinal haemorrhage	4
Physician-assisted death	185	Pneumonia bacterial	57
Considered death from various diseases	227	Cardio-respiratory arrest	13
Intestinal obstruction	28	Acute myocardial infarction	915
Cardiac arrest	138	Electrolyte imbalance, multiple organ dysfunction syndrome	34
Septic shock	33	Sepsis	10
Nicotine-induced emphysema	731		
Stroke	440		
Adrenal insufficiency, autoimmune enteritis due to side effects of pembrolizumab[b]	187		

Note: Table 8.3.2-1 of the CA209901 substudy Interim CSR included 6 additional cases in nivo + SOC arm (2 malignant neoplasm progression, 1 myocarditis, 1 sepsis, 1 acute kidney injury, 1 adrenal insufficiency) for deaths attributed to 'other' reasons which have been reclassified as disease progression or study drug toxicity.
[a] Defined as days between last dose and death.
[b] Pembrolizumab was administered as second-line treatment.

Other serious adverse events (SAEs)

The overall frequencies of SAEs (both all-causality and drug-related) are shown in Table 32.

The most frequently reported all causality SAEs (any grade) reported in ≥1% of subjects are shown in Table 36.

Table 36. Serious adverse events by worst CTC Grade in ≥ 1% for any Grade - All treated subjects - Substudy

System Organ Class (%) Preferred Term (%)	Nivo + SOC N = 304			SOC N = 288		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	142 (46.7)	113 (37.2)	13 (4.3)	105 (36.5)	79 (27.4)	8 (2.8)
Infections and infestations	52 (17.1)	43 (14.1)	2 (0.7)	42 (14.6)	35 (12.2)	0
Urinary tract infection	13 (4.3)	11 (3.6)	0	16 (5.6)	12 (4.2)	0
COVID-19	6 (2.0)	1 (0.3)	0	3 (1.0)	1 (0.3)	0
Sepsis	6 (2.0)	4 (1.3)	2 (0.7)	4 (1.4)	4 (1.4)	0
Pneumonia	4 (1.3)	4 (1.3)	0	6 (2.1)	5 (1.7)	0
Urosepsis	4 (1.3)	4 (1.3)	0	3 (1.0)	2 (0.7)	0
Infection	3 (1.0)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
Pyelonephritis	3 (1.0)	3 (1.0)	0	1 (0.3)	1 (0.3)	0
Septic shock	3 (1.0)	3 (1.0)	0	1 (0.3)	1 (0.3)	0

System Organ Class (%) Preferred Term (%)	Nivo + SOC N = 304			SOC N = 288		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (7.9)	12 (3.9)	11 (3.6)	7 (2.4)	4 (1.4)	3 (1.0)
Malignant neoplasm progression	18 (5.9)	6 (2.0)	11 (3.6)	7 (2.4)	4 (1.4)	3 (1.0)
Renal and urinary disorders	24 (7.9)	20 (6.6)	0	16 (5.6)	12 (4.2)	1 (0.3)
Acute kidney injury	13 (4.3)	12 (3.9)	0	4 (1.4)	3 (1.0)	1 (0.3)
Haematuria	3 (1.0)	3 (1.0)	0	5 (1.7)	4 (1.4)	0
Gastrointestinal disorders	23 (7.6)	20 (6.6)	0	13 (4.5)	8 (2.8)	1 (0.3)
Intestinal obstruction	5 (1.6)	5 (1.6)	0	1 (0.3)	1 (0.3)	0
Vomiting	3 (1.0)	2 (0.7)	0	3 (1.0)	3 (1.0)	0
Blood and lymphatic system disorders	18 (5.9)	17 (5.6)	0	13 (4.5)	12 (4.2)	0
Anaemia	8 (2.6)	7 (2.3)	0	7 (2.4)	7 (2.4)	0
Thrombocytopenia	6 (2.0)	6 (2.0)	0	3 (1.0)	3 (1.0)	0
Febrile neutropenia	4 (1.3)	4 (1.3)	0	2 (0.7)	2 (0.7)	0
General disorders and administration site conditions	14 (4.6)	10 (3.3)	0	13 (4.5)	5 (1.7)	2 (0.7)
Pyrexia	6 (2.0)	2 (0.7)	0	4 (1.4)	0	0
General physical health deterioration	4 (1.3)	4 (1.3)	0	2 (0.7)	2 (0.7)	0
Respiratory, thoracic and mediastinal disorders	14 (4.6)	12 (3.9)	0	9 (3.1)	7 (2.4)	0
Pulmonary embolism	8 (2.6)	7 (2.3)	0	6 (2.1)	5 (1.7)	0
Dyspnoea	3 (1.0)	3 (1.0)	0	0	0	0
Investigations	9 (3.0)	9 (3.0)	0	5 (1.7)	3 (1.0)	0
Platelet count decreased	6 (2.0)	6 (2.0)	0	1 (0.3)	1 (0.3)	0
Musculoskeletal and connective tissue disorders	5 (1.6)	4 (1.3)	0	4 (1.4)	3 (1.0)	0
Back pain	3 (1.0)	2 (0.7)	0	1 (0.3)	0	0

MedDRA Version: 26.0. CTC Version 4. Note: Includes events reported between first dose and 30 days after last dose of study therapy.

Selected adverse events

The most frequently reported drug-related select AEs by preferred term (any grade) reported in ≥10% of subjects were:

- Nivo + SOC: pruritis (14.5%), rash (13.5%), hypothyroidism and diarrhoea (13.2% each), and blood creatinine increased (12.8%).
- SOC: blood creatinine increased (12.2%).

Drug-related serious select AEs were infrequent; only the following events (any grade) were reported in >1 subject, by treatment arm:

- Nivo + SOC: acute kidney injury (8 subjects, 2.6%), rash maculo-papular (2 subjects, 0.7%), and hypopituitarism (2 subjects, 0.7%).
- SOC: acute kidney injury (4 subjects, 1.4%) and renal failure (2 subjects, 0.7%).

Across select AE categories, the majority of events in the nivo + SOC arm were manageable using the established IMAE management algorithms, with resolution reported when immune-modulating medication (IMM; mainly systemic corticosteroids) were administered (Table 34). Except for endocrine events, most drug-related select AEs were reported to have resolved (range, 67.2% to 100% across categories). Certain endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

Table 37. Onset, management, and resolution of drug-related select AEs in all treated subjects in the nivo + SOC Arm (n = 304)

Category	N (%) Treated subjects with any Grade / Grade 3-4 drug-related select AE	Median time to onset of drug-related select AE (range), wks	% Treated subjects with drug-related select AE leading to DC	% Subjects with drug-related select AE treated with IMM / high-dose corticosteroids[a]	Median time[b] to resolution of drug-related select AE (range), wks[c,d,e]	% Subjects with drug-related select AE that resolved[d,e]
Endocrine	64 (21.1) / 4 (1.3)	17.93 (1.1 – 62.7)	1.3	7.8 / 4.7	NA (2.1 – 233.6+)	28.1

Category	N (%) Treated subjects with any Grade / Grade 3-4 drug-related select AE	Median time to onset of drug-related select AE (range), wks	% Treated subjects with drug-related select AE leading to DC	% Subjects with drug-related select AE treated with IMM / high-dose corticosteroids[a]	Median time[b] to resolution of drug-related select AE (range), wks[c,d,e]	% Subjects with drug-related select AE that resolved[d,e]
Gastrointestinal	42 (13.8) / 6 (2.0)	6.64 (0.1 – 48.3)	0.7	9.5 / 9.5	2.64 (0.1 – 212.3+)	85.7
Hepatic	40 (13.2) / 8 (2.6)	14.79 (0.4 – 99.0)	0	10.0 / 7.5	5.29 (0.6 – 240.0+)	72.5
Pulmonary	6 (2.0) / 1 (0.3)	28.21 (24.3 – 46.1)	0.7	66.7 / 50.0	11.64 (0.9 – 62.1)	100
Renal	58 (19.1) / 11 (3.6)	4.14 (0.1 – 38.3)	4.6	6.9 / 3.4	18.29 (0.6 – 226.0+)	67.2
Skin	96 (31.6) / 8 (2.6)	8.86 (0.1 – 77.7)	0.3	33.3 / 6.3	10.29 (0.3 – 258.7+)	71.6
Hypersensitivity/ Infusion reaction	10 (3.3) / 0	8.00 (0.1 – 29.1)	0	30.0 / 20.0	0.57 (0.1 – 22.9+)	90.0

[a] Denominator is based on the number of subjects who experienced the event
[b] From Kaplan-Meier estimation.
[c] Symbol + indicates a censored value.
[d] Subjects who experienced Select AE without worsening from baseline grade were excluded from time to resolution analysis.
[e] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.
MedDRA Version: 26.0, CTC Version 4.0
Includes events reported between first treatment and 30 days after last treatment of study therapy.

Immune-mediated adverse events (IMAEs)

IMAEs frequencies are shown in Table 32.

Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution reported when IMMs (mostly systemic corticosteroids) were administered (Table 38). Certain endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

Table 38. Onset, management, and resolution of all-causality IMAEs within 100 days of last dose in all treated subjects in the nivo + SOC Arm (n = 304)

IMAE Category	N (%) Subj. with any Grade / Grade 3-4 IMAEs	Median time to IMAE onset (range), wks	% Subj. with IMAE leading to DC / dose delay	% Subj. with IMAEs receiving IMM / high-dose corticosteroids[a]	Median duration IMM (range), wks	% Subj. with resolution of IMAE[b,c]	Median[dt]Time to resolution (range), wks[b,c,e]
Pneumonitis	5 (1.6) / 2 (0.7)	26.43 (24.3 - 108.7)	0.7 / 0.3	100 / 80.0	3.86 (0.7 - 57.9)	100	4.57 (0.6 - 62.1)
Diarrhea/Colitis	4 (1.3) / 4 (1.3)	36.14 (31.3 - 48.3)	0.7 / 0.3	100 / 100	5.50 (4.3 - 8.1)	100	4.43 (1.6 - 9.0)
Hepatitis	4 (1.3) / 4 (1.3)	29.43 (2.9 - 56.4)	0 / 1.0	100 / 75.0	8.93 (1.1 - 23.3)	100	3.86 (0.6 - 5.3)
Nephritis/Renal Dysfunction	4 (1.3) / 2 (0.7)	23.64 (1.9 - 38.3)	1.0 / 0	100 / 75.0	6.57 (1.7 - 11.3)	50.0	NA (4.1 - 53.7+)
Rash	26 (8.6) / 4 (1.3)	23.07 (0.7 - 208.0)	0.3 / 1.3	100 / 19.2	7.14 (0.3 - 123.1)	65.4	14.00 (0.4 - 258.7+)
Hypersensitivity	1 (0.3) / 0	20.14 (20.1 - 20.1)	0 / 0	100 / 0	22.86 (22.9 - 22.9)	0	NA (22.9+ - 22.9+)
Adrenal Insufficiency	3 (1.0) / 1 (0.3)	47.86 (36.1 - 84.9)	0.7 / 0	100 / 33.3	87.57 (0.7 - 171.0)	0	NA (20.0+ - 171.0+)
Hypothyroidism/ Thyroiditis	40 (13.2) / 0	22.07 (1.1 - 62.7)	0.7 / 0.7	0 / 0	NA	27.5	NA (2.1 - 233.6+)
Diabetes Mellitus	1 (0.3) / 0	59.86 (59.9 - 59.9)	0 / 0.3	0 / 0	NA	0	NA (44.4+ - 44.4+)
Hyperthyroidism	22 (7.2) / 1 (0.3)	15.29 (2.7 - 36.1)	0 / 0.3	0 / 0	NA	72.7	9.64 (2.4 - 144.1+)

IMAE Category	N (%) Subj. with any Grade / Grade 3-4 IMAEs	Median time to IMAE onset (range), wks	% Subj. with IMAE leading to DC / dose delay	% Subj. with IMAEs receiving IMM / high-dose corticosteroids[a]	Median duration IMM (range), wks	% Subj. with resolution of IMAE[b,c]	Median[dt]Time to resolution (range), wks[b,c,e]
Hypophysitis	3 (1.0) / 2 (0.7)	29.00 (24.4 - 38.9)	0 / 1.0	100 / 66.7	14.43 (11.9 - 64.6)	0	NA (11.9+ - 86.9+)

[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] From Kaplan-Meier estimation. Note that the number of events was very low for most categories.
[e] Symbol + indicates a censored value.
MedDRA Version: 26.0, CTC Version 4.0

Other events of special interest (OESIs)

All-causality OESIs were reported in 9/304 (3.0%) subjects in the nivo + SOC arm and 1/288 (0.3%) subjects in the SOC arm (Table 32).

Grade 3-4 drug-related OESIs by treatment arm were:

- Nivo + SOC: pancreatitis (0.7%); and myocarditis, immune-mediated cytopenia, immune-mediated myocarditis, and encephalitis autoimmune (0.3% each).
- SOC: none.

Laboratory findings

Laboratory abnormalities (haematology; liver, thyroid, and kidney function tests) were primarily Grade 1-2 in severity.

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1-2. Grade 3-4 hematologic abnormalities reported in ≥5% of subjects with on-treatment laboratory results included:

- Nivo + SOC: absolute neutrophil count (26.2% Grade 3 and 9.3% Grade 4), haemoglobin (21.2% Grade 3), lymphocytes (16.1% Grade 3), leukocytes (15.2% Grade 3), and platelet count (7.9% Grade 3 and 5.3% Grade 4)
- SOC: absolute neutrophil count (20.7% Grade 3 and 6.8% Grade 4), haemoglobin (20.6% Grade 3), leukocytes (11.8% Grade 3), and lymphocytes (11.8% Grade 3)

Abnormalities in hepatic parameters/liver tests (all increases from baseline) were primarily Grade 1-2 in severity across treatment arms. Grade 3-4 abnormalities in hepatic parameters reported in ≥2% of subjects with on-treatment laboratory results included:

- Nivo + SOC: alkaline phosphatase increased (2.7% Grade 3); AST increased (2.4% Grade 3); ALT increased (2.4% Grade 3)
- SOC: N/A

Five subjects in the nivo + SOC arm had concurrent ALT or AST > 3 × ULN with total bilirubin > 2 × ULN within 1 day of last dose of study therapy (thus meeting *Hy's Law*) vs. 0 subjects in the SOC arm.

Regarding thyroid tests, the majority of subjects were reported to have normal TSH levels at baseline and throughout the treatment period. TSH increases (> ULN) from a baseline level ≤ ULN were reported in 24.7% of subjects in the nivo + SOC arm and 2.4% of subjects in the SOC arm. Decreases

to < LLN from a baseline level ≥ LLN were reported in 27.1% of subjects in the nivo + SOC arm and 7.3% of subjects in the SOC arm.

Regarding kidney function tests, most subjects with at least 1 on-treatment measurement were reported to have normal creatinine values. Reported creatinine abnormalities were primarily Grade 1-2. Grade 3-4 increased creatinine levels were reported in 7 subjects (2.3% all Grade 3) in the nivo + SOC arm and 3 subjects (0.7% Grade 3 and 0.4% Grade 4) in the SOC arm.

Safety to support the product information

Pooling methodology

To facilitate the comparison of the CA209901 substudy results to nivo + chemo in a similar population, a *pooled nivolumab + chemotherapy excluding CA209901 substudy dataset* used the data from all treated subjects in the nivo + chemo arms in the studies:

- **CA209648** (Opdivo II/107 EPAR): all treated subjects in the nivolumab 240mg Q2W + FOLFOX treatment group; 04-Oct-2021 DBL
- **CA209649** (Opdivo II/96 EPAR): all treated subjects in the nivolumab 240mg Q3W + XELOX treatment group; 10-Jul-2020 DBL
- **CA209816** (Opdivo II/117 EPAR): all treated subjects in the nivolumab 360mg Q3W + Chemotherapy (investigator's choice) treatment group; 14-Oct-2022 DBL

To support the SmPC outputs, the above pool (n=1268) with the addition of all treated subjects in the CA209901 substudy nivolumab 360 mg + chemotherapy/nivolumab 480 mg treatment group during the overall treatment period dataset (n=304; 23-Jun-2023 DBL) was generated (*pooled nivolumab + chemotherapy including CA209901 substudy* [n=1572]).

Side-by-side comparisons were made between the CA209901 substudy safety data alone and pooled nivo + chemo safety data excluding the CA209901 substudy (i.e., data approved in SmPC section 4.8 prior to the submission of this application, n=1268) to identify any potential differential safety profile of clinical relevance between the CA209901 substudy and the pool data of the other studies in different tumour types (Table 39).

Table 39. Summary of any adverse events (re-mapped terms) by worst CTC Grade (Any Grade, Grade 3-4) occurring in at least 20% of the subjects treated with nivolumab + chemotherapy in any grade across tumour types all treated subjects with nivolumab + chemotherapy

	CA209901 Nivo + Chemo N = 304		CA209901 Chemo N = 288	
Preferred Term (%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	303 (99.7)	220 (72.4)	284 (98.6)	187 (64.9)
Nausea	158 (52.0)	1 (0.3)	153 (53.1)	3 (1.0)
Anaemia	193 (63.5)	76 (25.0)	160 (55.6)	60 (20.8)
Neutropenia	175 (57.6)	107 (35.2)	141 (49.0)	74 (25.7)
Fatigue	147 (48.4)	12 (3.9)	123 (42.7)	12 (4.2)
Neuropathy peripheral	45 (14.8)	2 (0.7)	26 (9.0)	0
Decreased appetite	90 (29.6)	5 (1.6)	56 (19.4)	3 (1.0)
Thrombocytopenia	112 (36.8)	48 (15.8)	81 (28.1)	29 (10.1)
Constipation	90 (29.6)	0	81 (28.1)	2 (0.7)
Diarrhoea	57 (18.8)	5 (1.6)	41 (14.2)	0
Vomiting	69 (22.7)	4 (1.3)	56 (19.4)	6 (2.1)

Preferred Term (%)	Pooled Nivo + Chemo Including CA209901 Sub-study N = 1572		Pooled Nivo + Chemo Excluding CA209901 Sub-study N = 1268	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	1552 (98.7)	1062 (67.6)	1249 (98.5)	842 (66.4)
Nausea	801 (51.0)	40 (2.5)	643 (50.7)	39 (3.1)
Anaemia	712 (45.3)	226 (14.4)	519 (40.9)	150 (11.8)
Neutropenia	693 (44.1)	401 (25.5)	518 (40.9)	294 (23.2)
Fatigue	636 (40.5)	84 (5.3)	489 (38.6)	72 (5.7)
Neuropathy peripheral	536 (34.1)	60 (3.8)	491 (38.7)	58 (4.6)
Decreased appetite	510 (32.4)	56 (3.6)	420 (33.1)	51 (4.0)
Thrombocytopenia	498 (31.7)	101 (6.4)	386 (30.4)	53 (4.2)
Constipation	479 (30.5)	8 (0.5)	389 (30.7)	8 (0.6)
Diarrhoea	473 (30.1)	56 (3.6)	416 (32.8)	51 (4.0)
Vomiting	406 (25.8)	46 (2.9)	337 (26.6)	42 (3.3)

MedDRA version: 26.0, CTC version: 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Pooled Nivolumab + Chemotherapy Including CA209901 sub-study treatment group consists of Nivolumab + Chemotherapy treatment group from studies CA209648, CA209649, CA209816 and CA209901 Substudy.
Pooled Nivolumab + Chemotherapy Excluding CA209901 sub-study treatment group consists of Nivolumab + Chemotherapy treatment group from studies CA209648, CA209649, CA209816.
Grade 3-4 by worst CTC grade
Some preferred terms are re-mapped based on BMS medical review.

Pooled safety data from CA209901 substudy with studies CA209648, CA209649, and CA209816 were used to summarise the safety profile of nivo + chemo for section 4.8 of SmPC, i.e., the tabulated summary of adverse reactions (nivo + chemo column) as well as the description of select immune-related adverse reactions (irARs).

Adverse drug reactions (section 4.8 of the SmPC)

Tabulated summary of adverse drug reactions (ADRs) for pooled nivo + chemo studies

Per the EU SmPC guideline and EMA guidance (EMA/CHMP/205/95 Rev.5), and in line with the pooling strategy previously agreed upon with the CHMP, the following methodology was used to summarise the adverse reactions for Section 4.8 of the Opdivo SmPC:

1) Pool all-causality AE data from CA209648, CA209649, CA209816, and CA209901 substudy for the nivo + chemo regimen (see above).

2) Programmatically remap MedDRA PTs representing the same or similar clinical conditions and generate summary tables using the MedDRA version for the most recent study.
Frequencies of adverse reactions included in Section 4.8 of the SmPC are based on all-causality AEs (30 days follow-up) with remapped (grouped) PTs from the pooled nivo + chemo dataset (CA209648, CA209649, CA209816 and CA209901 substudy, n=1572 treated subjects).

3) Identify clinically relevant events based on the MAH's medical review of the all-causality re-mapped AE summary table.
PTs that met 1 or more of the following criteria were excluded from section 4.8: overly general/non-specific, no suspected causal relationship to nivolumab, single case events with limited data, and medical concept captured under a different term.

4) Present resulting clinically relevant re-mapped events by system organ class (SOC) and all-causality frequency in the updated nivo + chemo column of the adverse reaction table in section 4.8 of the nivolumab SmPC.
Adverse reactions are presented by SOC and by frequency grouping (e.g., common, uncommon, rare, or very rare). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000).

5) To calculate the frequencies of laboratory adverse reactions, the laboratory abnormality change from baseline tables for CA209901 substudy pooled with CA209648 + CA209649 + CA209816 were used.
   The denominator used to compute frequency was the number of subjects for whom laboratory data were available, as opposed to all treated subjects. Hence, there is variability in the denominator for each individual laboratory abnormality and the respective reported frequency.

Frequencies of adverse reactions included in section 4.8 of the SmPC are based on all-causality AEs (30-day follow-up) with remapped (grouped) PTs from the pooled nivo + chemo dataset (CA209648 + CA209649 + CA209816 + CA209901 substudy; n=1572 treated subjects).

- The overall frequencies of any-grade and Grade 3-4 all-causality AEs (remapped terms) were numerically higher in nivo + chemo-treated subjects in the CA209901 substudy (99.7% any-grade; 72.4% Grade 3-4) vs. CA209648, CA209649 and CA209816 pooled studies (98.5% any-grade; 66.4% Grade 3-4) (Table 39).
- The frequencies of any-grade all-causality AEs were numerically higher (>5% absolute difference) in nivo + chemo-treated subjects in the CA209901 substudy vs. the CA209648 + CA209649 + CA209816 pooled studies for urinary tract infection (UTI) (15.1% vs. 3.0%; 4.9 vs. 0.7% Grade 3-4), fatigue (48.4% vs. 38.6%; 3.9% vs. 5.7% Grade 3-4), musculoskeletal pain (25.3% vs. 15.7%; 2.6% vs. 0.9% Grade 3-4), haematuria (10.9% vs. 1.0%; 1.0% vs. 0 Grade 3-4), pruritus (17.4% vs. 9.0%; 0.7% vs. <0.1% Grade 3-4), renal failure (10.5% vs. 3.0%; 5.3% vs. 1.3% Grade 3-4), rash (23.4% vs. 17.6%; 2.3% vs. 1.5% Grade 3-4), and hypothyroidism (13.2% vs. 8.0%; no Grade 3-4).

Table 40. Frequency of adverse drug reactions with nivolumab in combination with chemotherapy (safety pool)

Infections and infestations	
Common	upper respiratory tract infection, pneumonia[a]
Blood and lymphatic system disorders	
Very common	neutropaenia[b], anaemia[b,d], leucopoenia[b], lymphopaenia[b], thrombocytopaenia[b]
Common	febrile neutropaenia[a]
Uncommon	eosinophilia
Immune system disorders	
Common	hypersensitivity, infusion related reaction (including cytokine release syndrome)
Endocrine disorders	
Common	hypothyroidism, hyperthyroidism, diabetes mellitus
Uncommon	adrenal insufficiency, thyroiditis, hypopituitarism, hypophysitis
Metabolism and nutrition disorders	
Very common	decreased appetite, hypoalbuminaemia, hyperglycaemia[b], hypoglycaemia[b]
Common	hypophosphataemia
Rare	tumour lysis syndrome
Nervous system disorders	
Very common	peripheral neuropathy
Common	paraesthesia, dizziness, headache
Rare	Guillain Barré syndrome, encephalitis
Eye disorders	

Infections and infestations	
Common	dry eye, blurred vision
Uncommon	uveitis
Cardiac disorders	
Common	tachycardia, atrial fibrillation
Uncommon	myocarditis
Vascular disorders	
Common	thrombosis[a,e], hypertension, vasculitis
Respiratory, thoracic and mediastinal disorders	
Very common	cough
Common	pneumonitis[a], dyspnoea
Gastrointestinal disorders	
Very common	diarrhoea[a], stomatitis, vomiting, nausea, abdominal pain, constipation
Common	colitis, dry mouth
Uncommon	pancreatitis
Uncommon	hepatitis
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus
Common	palmar-plantar erythrodysaesthesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[e]
Common	arthralgia, muscular weakness
Renal and urinary disorders	
Common	renal failure[a]
Uncommon	cystitis noninfective, nephritis
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema (including peripheral oedema)
Common	malaise
Investigations	
Very common	hypocalcaemia[b], increased AST [b], increased ALT [b], hyponatraemia[b], increased amylase[b], hypomagnesaemia[b], increased alkaline phosphatase[b], hypokalaemia[b,], increased creatinine[b], increased lipase[b], hyperkalaemia[b], increased total bilirubin[b]
Common	hypernatraemia[b], hypercalcaemia[b], hypermagnesaemia[b]

[a] Fatal cases have been reported in completed or ongoing clinical studies.
[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements.
[c] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, nodular rash, and pemphigoid.
[d] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased.
[e] Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, limb venous thrombosis.

Select immune-related adverse reactions (irARs) in section 4.8 of the SmPC

Of note, the reported frequencies of irARs in section 4.8 of the SmPC are based on all drug-related irARs (i.e., drug-related select AEs, as reported by investigators) in all treated subjects in the nivo + chemo arms in the pooled nivolumab + chemotherapy including CA209901 substudy dataset. This is in contrast to frequencies provided in other parts of section 4.8, where frequencies are provided based on all reported adverse reactions, regardless of the investigator assessment of causality, as requested per EMA guidelines.

The following outputs summarising the onset, management and resolution of select irARs (drug-related select AEs) in all nivo + chemo treated subjects in the pooled nivolumab + chemotherapy studies (CA209648 + CA209649 + CA209816 + CA209901 substudy) were used to support section 4.8 the SmPC:

- drug-related select adverse events by worst CTC grade;
- time to onset of drug-related select AEs; and
- time to resolution of drug-related select AEs.

Overall, any-grade drug-related select AEs (by category) were numerically lower in nivo + chemo treated subjects in the CA209901 substudy relative to the pooled nivolumab + chemotherapy studies (CA209648 + CA209649 + CA209816), except for renal, skin and endocrine select AEs.

Any-grade drug-related renal select AEs were >10% (absolute difference) higher on the CA209901 substudy (CA209901 substudy: 58/304; 19.1% vs. pooled excluding CA209901 substudy: 112/1268; 8.8%), which was mainly due to cases of increased blood creatinine (CA209901 substudy: 39/304; 12.8% vs. pooled excluding CA209901 substudy: 69/1268; 5.4%) and acute kidney injury (CA209901 substudy: 15/304; 4.9% vs. pooled excluding CA209901 substudy: 11/1268; 0.9%).
The rates of Grade 3-4 drug-related renal select AEs were comparable in the CA209901 substudy (11/304; 3.6%) and the pooled excluding CA209901 substudy (15/1268; 1.2%). Moreover, renal select AEs were comparable between nivo + SOC and SOC arm in the CA209901 substudy (Table 32).
Most drug related renal select AEs resolved, with comparable rates between CA209901 substudy (67.2%) and pooled excluding CA209901 substudy (64.3%).

Any-grade drug-related skin select AEs were higher on the CA209901 substudy (CA209901 substudy: 96/304; 31.6% vs. pooled excluding CA209901 substudy: 306/1268; 24.1%), which was mainly due to cases of rash (CA209901 substudy: 41/304; 13.5% vs. pooled excluding CA209901 substudy: 120/1268; 9.5%) and pruritus (CA209901 substudy: 44/304; 14.5% vs. pooled excluding CA209901 substudy: 82/1268; 6.5%).
The rates of Grade 3-4 drug-related renal select AEs were similar in the CA209901 substudy (8/304; 2.6%) and the pooled excluding CA209901 substudy (31/1268; 2.4%).
Most drug-related skin select AEs in both the CA209901 substudy (71.6%) and pooled excluding CA209901 substudy (67.0%) studies resolved.

Any-grade drug-related endocrine select AEs were higher on the CA209901 substudy (CA209901: 64/304; 21.1% vs. pooled excluding CA209901 substudy: 155/1268; 12.2%), which was mainly due to cases of (Grade 1-2) hypothyroidism (CA209901 substudy: 62/304; 20.4% vs. pooled excluding CA209901 substudy: 92/1268; 7.3%) and hyperthyroidism (CA209901 substudy: 20/304; 6.6% vs. pooled excluding CA209901 substudy: 37/1268; 2.9%).
The rates of Grade 3-4 drug-related endocrine select AEs were low in both the CA209901 substudy (4/304; 1.3%) and the pooled excluding CA209901 substudy (10/1268; 0.8%).
Certain drug-related endocrine select AEs in both CA209901 substudy (28.1%) and pooled excluding CA209901 substudy (40.9.0%) studies were not resolved.

The following outputs summarising the proportion of subjects with irARs (drug-related select AEs) leading to permanent discontinuation or requiring high-dose corticosteroids in all nivo + chemo treated subjects in the pooled dataset of studies CA209648, CA209649, CA209816 and CA209901 substudy) were used to support Table 8 in the proposed SmPC:

- drug-related select AEs leading to discontinuation; and
- duration of IMM for drug-related select AE management (including the proportion of subjects treated with high-dose corticosteroids).

Table 41. Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab in combination with chemotherapy) (%)

Immune-related adverse reaction leading to permanent discontinuation – Frequency (%)	
Pneumonitis	1.8
Colitis	1.8
Hepatitis	0.8
Nephritis and renal dysfunction	3.3
Endocrinopathies	0.6
Skin	1.0
Hypersensitivity/Infusion reaction	1.8
Immune-related adverse reaction requiring high-dose corticosteroids[a,b] – Frequency (%)	
Pneumonitis	58
Colitis	8
Hepatitis	8
Nephritis and renal dysfunction	7
Endocrinopathies	5
Skin	6
Hypersensitivity/Infusion reaction	22

[a] at least 40 mg daily prednisone equivalents
[b] frequency is based on the number of patients who experienced the immune-related adverse reaction

Safety in special populations

Within each treatment arm, the frequencies of all-causality (Table 42) and drug-related (data not shown) AEs for subgroups of sex, race, age, and geographic region were generally similar to the AE frequencies reported for the overall population, with the following exceptions:

- The frequencies of Grade 3-4 all-causality and drug-related AEs in the nivo + SOC arm were numerically higher for subjects aged ≥75 years compared to the overall substudy population (88.2% vs. 72.4%; and 79.4% vs. 61.5%, respectively).

- The frequencies of Grade 3-4 all-causality and drug-related AEs in the nivo + SOC arm were numerically higher in females compared to in males/the overall substudy population (77.9% vs. 70.8%/72.4%; and 66.2% vs. 60.2%/61.5%, respectively).
- The frequencies of Grade 3-4 all-causality AEs in the nivo + SOC arm were numerically higher for subjects in the US compared to the overall substudy population, but Grade 3-4 drug-related AEs were numerically lower (78.9% vs. 72.4%; and 47.4% vs. 61.5%, respectively).

Table 42. Adverse events summary by worst CTC Grade and by age, sex, race, and region - All treated subjects – Substudy

	All-Causality AEs (n [%])							
	Nivo + SOC				SOC			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	304	303 (99.7)	220 (72.4)	13 (4.3)	288	284 (98.6)	187 (64.9)	8 (2.8)
By Age (yrs)								
<65	150	149 (99.3)	105 (70.0)	3 (2.0)	140	137 (97.9)	89 (63.6)	1 (0.7)
≥65	154	154 (100.0)	115 (74.7)	10 (6.5)	148	147 (99.3)	98 (66.2)	7 (4.7)
≥65 and <75	120	120 (100.0)	85 (70.8)	8 (6.7)	111	110 (99.1)	73 (65.8)	5 (4.5)
≥75	34	34 (100.0)	30 (88.2)	2 (5.9)	37	37 (100.0)	25 (67.6)	2 (5.4)
≥75 and <85	31	31 (100.0)	27 (87.1)	2 (6.5)	35	35 (100.0)	23 (65.7)	2 (5.7)
≥85	3	3 (100.0)	3 (100.0)	0	2	2 (100.0)	2 (100.0)	0
By Sex								
Male	236	235 (99.6)	167 (70.8)	11 (4.7)	223	219 (98.2)	146 (65.5)	6 (2.7)
Female	68	68 (100.0)	53 (77.9)	2 (2.9)	65	65 (100.0)	41 (63.1)	2 (3.1)
By Race								
White	211	211 (100.0)	155 (73.5)	12 (5.7)	214	212 (99.1)	135 (63.1)	8 (3.7)
Black or African American	0	0	0	0	2	1 (50.0)	0	0
Asian	75	74 (98.7)	52 (69.3)	1 (1.3)	59	58 (98.3)	42 (71.2)	0
American Indian or Alaska Native	1	1 (100.0)	0	0	1	1 (100.0)	1 (100.0)	0
Other	17	17 (100.0)	13 (76.5)	0	12	12 (100.0)	9 (75.0)	0
By Region								
US	19	19 (100.0)	15 (78.9)	1 (5.3)	20	19 (95.0)	13 (65.0)	0
Europe	134	134 (100.0)	96 (71.6)	8 (6.0)	134	132 (98.5)	82 (61.2)	4 (3.0)
Asia	72	71 (98.6)	49 (68.1)	1 (1.4)	57	56 (98.2)	40 (70.2)	0
Rest of the World	79	79 (100.0)	60 (75.9)	3 (3.8)	77	77 (100.0)	52 (67.5)	4 (5.2)

MedDRA version 26.0; CTC version 4.0.
Includes events reported between first dose and 30 days after last dose of study therapy.

The frequencies of total AEs, SAEs, AEs leading to discontinuation, and AEs by MedDRA High level Group Term (HLGT)/SMQs/SOC by age group are presented for all treated subjects in the nivo + SOC (N = 304) and SOC (N = 288) arms (Table 43).

Table 43. Summary of on-treatment adverse events by age group - Treated subjects - CA209901 Substudy

Treatment Group: Nivolumab + Chemotherapy N = 304

MedDRA Terms (%)	Age Group (Years) < 65 N = 150	65–74 N = 120	75–84 N = 31	>= 85 N = 3	Total N = 304
TOTAL SUBJECTS WITH AN EVENT	149 (99.3)	120 (100.0)	31 (100.0)	3 (100.0)	303 (99.7)
SERIOUS AE - TOTAL	64 (42.7)	55 (45.8)	21 (67.7)	2 (66.7)	142 (46.7)
FATAL (DEATH)	9 (6.0)	17 (14.2)	3 (9.7)	0	29 (9.5)
HOSPITALIZATION/PROLONGATION	60 (40.0)	48 (40.0)	19 (61.3)	2 (66.7)	129 (42.4)
LIFE THREATENING	2 (1.3)	6 (5.0)	1 (3.2)	0	9 (3.0)
CANCER	0	0	0	0	0
DISABILITY/INCAPACITY	0	2 (1.7)	0	0	2 (0.7)
IMPORTANT MEDICAL EVENT	4 (2.7)	4 (3.3)	0	0	8 (2.6)
AE LEADING TO DISCONTINUATION	38 (25.3)	40 (33.3)	11 (35.5)	1 (33.3)	90 (29.6)
PSYCHIATRIC DISORDERS	18 (12.0)	19 (15.8)	1 (3.2)	0	38 (12.5)
NERVOUS SYSTEM DISORDERS	64 (42.7)	47 (39.2)	9 (29.0)	0	120 (39.5)
ACCIDENT AND INJURIES	10 (6.7)	8 (6.7)	4 (12.9)	0	22 (7.2)
CARDIAC DISORDERS	8 (5.3)	11 (9.2)	4 (12.9)	0	23 (7.6)
VASCULAR DISORDERS	36 (24.0)	37 (30.8)	8 (25.8)	1 (33.3)	82 (27.0)
CEREBROVASCULAR DISORDERS	4 (2.7)	2 (1.7)	0	0	6 (2.0)
INFECTIONS AND INFESTATIONS	70 (46.7)	53 (44.2)	17 (54.8)	3 (100.0)	143 (47.0)
ANTICHOLINERGIC SYNDROME	38 (25.3)	29 (24.2)	6 (19.4)	0	73 (24.0)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	16 (10.7)	17 (14.2)	3 (9.7)	0	36 (11.8)

Treatment Group: Chemotherapy N = 288

MedDRA Terms (%)	Age Group (Years) < 65 N = 140	65–74 N = 111	75–84 N = 35	>= 85 N = 2	Total N = 288
TOTAL SUBJECTS WITH AN EVENT	137 (97.9)	110 (99.1)	35 (100.0)	2 (100.0)	284 (98.6)
SERIOUS AE - TOTAL	45 (32.1)	40 (36.0)	18 (51.4)	2 (100.0)	105 (36.5)
FATAL (DEATH)	2 (1.4)	10 (9.0)	3 (8.6)	1 (50.0)	16 (5.6)
HOSPITALIZATION/PROLONGATION	40 (28.6)	36 (32.4)	17 (48.6)	2 (100.0)	95 (33.0)
LIFE THREATENING	2 (1.4)	1 (0.9)	0	0	3 (1.0)
CANCER	0	1 (0.9)	0	0	1 (0.3)
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	2 (1.4)	2 (1.8)	1 (2.9)	0	5 (1.7)
AE LEADING TO DISCONTINUATION	27 (19.3)	29 (26.1)	12 (34.3)	1 (50.0)	69 (24.0)
PSYCHIATRIC DISORDERS	7 (5.0)	12 (10.8)	4 (11.4)	1 (50.0)	24 (8.3)
NERVOUS SYSTEM DISORDERS	42 (30.0)	25 (22.5)	8 (22.9)	1 (50.0)	76 (26.4)
ACCIDENT AND INJURIES	2 (1.4)	1 (0.9)	1 (2.9)	0	4 (1.4)
CARDIAC DISORDERS	6 (4.3)	5 (4.5)	1 (2.9)	0	12 (4.2)
VASCULAR DISORDERS	25 (17.9)	22 (19.8)	4 (11.4)	0	51 (17.7)
CEREBROVASCULAR DISORDERS	2 (1.4)	0	0	1 (50.0)	3 (1.0)
INFECTIONS AND INFESTATIONS	37 (26.4)	31 (27.9)	18 (51.4)	2 (100.0)	88 (30.6)
ANTICHOLINERGIC SYNDROME	31 (22.1)	25 (22.5)	11 (31.4)	2 (100.0)	69 (24.0)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA,	11 (7.9)	9 (8.1)	5 (14.3)	1 (50.0)	26 (9.0)

CTC version: 4.0; MedDRA version: 26.0
Includes events reported between first dose and 30 days after last dose of study therapy.

A summary of on-treatment AEs by age group for all nivo + chemo-treated subjects in the pooled CA209901 substudy+ CA209816 + CA209649 + CA209648 dataset is provided in Table 44.

Table 44. Summary of on-treatment adverse events by age group - Treated subjects – Pooled nivolumab + chemotherapy including CA209901 Sub-study

Treatment Group: Pooled Nivo + Chemo Including CA209901 Sub-study N = 1572

	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 875	65-74 N = 547	75-84 N = 142	>= 85 N = 8	Total N = 1572
TOTAL SUBJECTS WITH AN EVENT	865 (98.9)	541 (98.9)	138 (97.2)	8 (100.0)	1552 (98.7)
SERIOUS AE - TOTAL	434 (49.6)	272 (49.7)	70 (49.3)	5 (62.5)	781 (49.7)
FATAL (DEATH)	102 (11.7)	76 (13.9)	21 (14.8)	0	199 (12.7)
HOSPITALIZATION/PROLONGATION	391 (44.7)	239 (43.7)	61 (43.0)	5 (62.5)	696 (44.3)
LIFE THREATENING	28 (3.2)	24 (4.4)	4 (2.8)	0	56 (3.6)
CANCER	21 (2.4)	8 (1.5)	2 (1.4)	0	31 (2.0)
DISABILITY/INCAPACITY	5 (0.6)	6 (1.1)	1 (0.7)	0	12 (0.8)
IMPORTANT MEDICAL EVENT	39 (4.5)	30 (5.5)	5 (3.5)	0	74 (4.7)
AE LEADING TO DISCONTINUATION	318 (36.3)	224 (41.0)	63 (44.4)	4 (50.0)	609 (38.7)
PSYCHIATRIC DISORDERS	132 (15.1)	84 (15.4)	15 (10.6)	1 (12.5)	232 (14.8)
NERVOUS SYSTEM DISORDERS	456 (52.1)	260 (47.5)	76 (53.5)	1 (12.5)	793 (50.4)
ACCIDENT AND INJURIES	50 (5.7)	42 (7.7)	16 (11.3)	1 (12.5)	109 (6.9)
CARDIAC DISORDERS	46 (5.3)	41 (7.5)	14 (9.9)	0	101 (6.4)
VASCULAR DISORDERS	143 (16.3)	121 (22.1)	35 (24.6)	3 (37.5)	302 (19.2)
CEREBROVASCULAR DISORDERS	13 (1.5)	13 (2.4)	4 (2.8)	0	30 (1.9)
INFECTIONS AND INFESTATIONS	301 (34.4)	225 (41.1)	54 (38.0)	4 (50.0)	584 (37.2)
ANTICHOLINERGIC SYNDROME	292 (33.4)	178 (32.5)	35 (24.6)	1 (12.5)	506 (32.2)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	77 (8.8)	68 (12.4)	15 (10.6)	1 (12.5)	161 (10.2)

CTC version: 4.0; MedDRA version: 26.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Immunogenicity

Immunogenicity was analysed in the population of immunogenicity evaluable subjects, i.e., all treated subjects with a baseline and at least one post-baseline immunogenicity assessment (Table 14). Of the 252 immunogenicity evaluable subjects in the nivo + SOC arm, 8 (3.2%) subjects were nivolumab ADA positive at baseline and 6 (2.4%) subjects were nivolumab ADA positive after the start of treatment. No subject was considered persistent positive. One (0.4%) subject was neutralising antibody positive.

Regarding the effects of immunogenicity on efficacy, subjects with nivolumab ADA continued treatment and there was no trend for the presence of ADA to be associated with a reduction in efficacy (data not shown).

Regarding the effects of immunogenicity on safety, of all nivolumab treated subjects who were evaluable for immunogenicity, hypersensitivity/infusion reaction select AEs were reported in 13 (5.3%) nivolumab ADA-negative subjects, and in no nivolumab ADA-positive subjects.

Safety related to drug-drug interactions and other interactions

No formal pharmacokinetic drug interaction studies have been conducted with nivolumab, as it is a human monoclonal antibody. This is reflected in section 4.5 of the Opdivo SmPC and no new information has been generated in support of this application.

Post marketing experience

Nivolumab as monotherapy or in combination with other agents (e.g., chemotherapy, ipilimumab, cabozantinib) is approved in multiple countries, including US and EU, for multiple indications. Post-marketing data for nivolumab are subject to continued active pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements, as well as periodically to global health authorities. The nivolumab risk management plan (RMP) should be consulted for risk management actions for nivolumab (see summary of RMP at EMA website).

Based on pharmacovigilance activities conducted by the MAH's Worldwide Patient Safety, review of post-marketing safety data is consistent with the clinical trial safety data for nivolumab. No new post-marketing concerns have been identified. The safety profile of nivolumab in the post-marketing setting supports the favourable benefit-risk profile of nivolumab established during clinical trials.

2.5.1. Discussion on clinical safety

Introduction - The analysis population used for the safety profile of nivolumab in combination with chemotherapy followed by nivolumab monotherapy in patients with unresectable or metastatic UC is the population of all treated subjects (n=592) who had received at least one dose of study drug who were randomized to nivo + SOC (n=304) and SOC (n=288). At the time of the 09-May-2023 data cut-off (23-Jun-2023 DBL), the minimum follow-up was 7.4 months in both arms and the median follow-up was approximately 33.5 months.

Patient exposure - Due to the different treatment durations between the two treatment arms (up to two years for nivo plus cisplatin-gemcitabine followed by nivo monotherapy [nivo + SOC] vs. approximately four months for cisplatin-based chemotherapy alone [SOC]), the median duration of therapy was longer in the nivo + SOC arm (7.39 months) than in the SOC arm (3.75 months).

Most treated subjects in the nivo + SOC arm received ≥90% of the planned nivolumab. Moreover, the addition of nivolumab to SOC chemotherapy did not (negatively) impact the tolerability of the chemotherapy, as the received cumulative chemotherapy dose and relative dose intensity were similar in both study arms.

Subjects who discontinued cisplatin alone could, at the investigator's discretion, be switched to gemcitabine/carboplatin for the remainder of the platinum doublet cycles (up to 6 cycles in total). A similar percentage of patients in both study arms switched from cisplatin to carboplatin and the median number of carboplatin doses received was the same. The addition of nivolumab to SOC chemotherapy thus did not make it more likely for a subject to switch from cisplatin to carboplatin.

The addition of nivolumab to SOC chemotherapy did not (negatively) impact chemotherapy dose delays or dose reductions. The rate of chemotherapy dose discontinuations were numerically higher in the nivo + SOC arm vs. the SOC arm for gemcitabine (8.9% vs. 7.6%) and cisplatin (18.3% vs. 14.7%), but not for carboplatin (4.1% vs. 7.0%).

Adverse events (AEs) – Similar to as observed in other tumour types, the addition of nivolumab to chemotherapy in unresectable or metastatic UC resulted in increased toxicity, combining the toxicities

of both nivolumab and chemotherapy. This is among other things reflected by a numerical increase in the frequencies of Grade 3-4 AEs. There were no major differences between study arms, and no new ADR and/or other safety concern was identified. Also, it should be taken into account that the median duration of therapy was approximately twice as long in the nivo + SOC arm than in the SOC arm (see above), and that when incidence rates of AEs were adjusted for exposure, the rate per 100 person years was lower in the nivo + SOC arm than in the SOC arm (1765.0 and 2958.0, respectively).

Discontinuation due to adverse events - The overall frequencies of all-causality and drug-related AEs leading to discontinuation were numerically higher in the nivo + SOC arm compared with the SOC arm (Table 32). This difference seems to be due to the longer duration of therapy in the nivo + SOC arm vs. the SOC arm. Upon request, the MAH provided information on AEs leading to discontinuation (both all causality and drug related) for Part 1 and Part 2 of the study separately. The frequencies of all-causality and drug-related AEs leading to discontinuation were numerically lower in the nivo + SOC arm compared to SOC arm in Part 1, and the frequencies of all causality and drug-related AEs leading to discontinuation were numerically higher in Part 1 compared to Part 2 in the nivo + SOC arm, as anticipated (data not shown). The most frequently reported all-causality AEs leading to discontinuation (any grade) reported in ≥2% of subjects in the nivo + SOC arm were acute kidney injury (3.0%), blood creatinine increased (2.6%), and thrombocytopenia (2.0%) (Table 34).

Deaths - A lower proportion of treated subjects in the nivo + SOC arm died compared with the SOC arm and disease progression was the most frequently reported cause of death in both arms (Table 32).

Deaths due to drug-related study drug toxicity were reported in 7 subjects (2.3%) in the nivo + SOC arm (11 PTs were reported in these 7 subjects, i.e., abdominal sepsis, thrombocytopenia, hypovolemic shock, multiple organ dysfunction syndrome, multiple organ failure, myocarditis, acute kidney injury, small intestinal obstruction, adrenal insufficiency [one each] and sepsis [two subjects]) and in two subjects (0.7%) in the SOC (death due to acute kidney failure and septic shock [one each]).

Deaths attributed to 'other' reasons per the investigator were reported in 5.6% and 4.9% of subjects treated in the nivo + SOC and SOC arms, respectively (Table 32). Most of the verbatim terms for the 'other' reasons for death are considered consistent with events expected in the population under study. None were considered related to study drug (per the investigator).

Other serious adverse events (SAEs) - The overall frequencies of SAEs (both all-causality and drug-related) were numerically higher with nivo + SOC than with SOC alone (Table 32). The most frequently reported all causality SAEs (any grade, excluding malignant neoplasm progression) reported in ≥3% of subjects in the nivo + SOC arm were urinary tract infection and acute kidney injury (4.3% each) (Table 36).

Selected adverse events - The overall frequencies of all-causality select AEs by category were similar between nivo + SOC and SOC alone with the exception of the endocrine, gastrointestinal, hepatic, and skin categories where there was >5% difference between the arms (Table 32).The overall frequencies of drug-related select AEs by category were similar between nivo + SOC and SOC arms (Table 32), with the exception of the endocrine, gastrointestinal, and skin categories, where the frequencies were 5% higher in nivo + SOC arm compared to SOC arm. The majority of the select AEs in all categories were Grade 1-2 and most select AEs were considered drug-related by the investigator (Table 32).
The most frequently reported drug-related select AEs by preferred term (any grade) reported in ≥10% of subjects in the nivo + SOC arm were pruritis (14.5%), rash (13.5%), hypothyroidism and diarrhoea (13.2% each), and blood creatinine increased (12.8%).
Across select AE categories, the majority of events in the nivo + SOC arm were manageable using the established IMAE management algorithms, with resolution reported when immune-modulating

medication (IMM; mainly systemic corticosteroids) were administered (Table 34). Except for endocrine events, most drug-related select AEs were reported to have resolved.

Immune-mediated adverse events (IMAEs) - Across IMAE categories, the majority of events were manageable using the established management algorithms, with resolution reported when IMMs (mostly systemic corticosteroids) were administered (Table 38). Certain endocrine IMAEs were not considered resolved due to the continuing need for hormone replacement therapy.

Safety to support the product information - The safety profile of nivo + chemo from the CA209901 substudy was compared with pooled safety data for nivo + chemo from studies CA209648 (Opdivo II/107 EPAR), CA209649 (Opdivo II/96 EPAR), and CA209816 (Opdivo II/117 EPAR).
No new ADR and/or other safety concern was identified in the CA209901 substudy.
The overall frequencies of any-grade and Grade 3-4 all-causality AEs were numerically higher in nivo + chemo-treated subjects in the CA209901 substudy (99.7% any-grade; 72.4% Grade 3-4) vs. CA209648, CA209649 and CA209816 pooled studies (98.5% any-grade; 66.4% Grade 3-4).
The frequencies of any-grade all-causality AEs were numerically higher (>5% absolute difference) in nivo + chemo-treated subjects in the CA209901 substudy vs. the CA209648 + CA209649 + CA209816 pooled studies for UTI (15.1% vs. 3.0%), fatigue (48.4% vs. 38.6%), musculoskeletal pain (25.3% vs. 15.7%), haematuria (10.9% vs. 1.0%), pruritus (17.4% vs. 9.0%), renal failure (10.5% vs. 3.0%), rash (23.4% vs. 17.6%), and hypothyroidism (13.2% vs. 8.0%).

Firstly, the study populations, study treatments (including chemotherapy backbone), sample size of the nivo + chemo arms, and duration of study treatments differ between studies CA209901, CA209648, CA209649 and CA209816, limiting the cross-trial comparisons.
Nonetheless, the safety profile of nivo + chemo from the CA209901 substudy is in general considered similar to the pooled safety data for nivo + chemo from studies CA209648, CA209649, and CA209816. The numerical differences in the overall frequencies of any-grade and Grade 3-4 all-causality AEs are considered relatively small. Plus, several of the above-mentioned PTs with numerically higher frequencies in nivo + chemo-treated subjects in the CA209901 substudy vs. the CA209648 + CA209649 + CA209816 pooled studies are considered to reflect the underlying pathology (UC) with its associated comorbidities, rather than nivolumab-related toxicity. This is illustrated by the fact that in the CA209901 substudy the frequency of UTI was very similar in the nivo + SOC arm (15.1%) and the SOC arm (15.6%), and so was the frequency of haematuria (10.9% and 6.9, respectively). Regarding the remapped (grouped) PT renal failure, the frequency of renal select AEs (all causality, any Grade) was also very similar in the nivo + SOC arm (28.9%) and the SOC arm (25.3%) (Table 32), and so was the frequency of acute kidney injury (7.6% and 5.9%, respectively) (Table 33).

The MAH has updated the information in section 4.8 of the SmPC with the ADR frequencies based on all-causality AEs with remapped (grouped) PTs from the overall pooled nivo + chemo dataset (CA209648 + CA209649 + CA209816 + CA209901 substudy; n=1572 treated subjects).

Overall, the update is acknowledged and the changes are considered rather minor, e.g. small numerical changes in ADR and irAR frequencies, and for a few ADRs upgrading of the frequency category in the ADR table of nivo+chemo in section 4.8 of the SmPC. Among the most relevant changes in the subsection on irARs are the following:
- +1 case of immune-related nephritis or renal dysfunction with fatal outcome; and
- +1 case of immune-related adrenal insufficiency with fatal outcome.

Safety in special populations - The frequencies of Grade 3-4 all-causality and drug-related AEs in the nivo + SOC arm were numerically higher for subjects aged ≥75 years compared to the overall substudy population, whereas this was not the case in the SOC arm (88.2% vs. 72.4%; and 79.4% vs. 61.5%, respectively). The number of patients ≥75 years of age (n=34 in the nivo + SOC arm) is,

however, considered too limited to draw conclusions on this population. Plus, it is noted that the frequency of SAEs was higher in subjects aged ≥75 years compared to the overall substudy population in both study arms and not just in the nivo +SOC arm (Table 43). The frequencies of AEs for all subgroups were close to 100% in all age groups. Only three subjects in the nivo + SOC arm and two subjects in the SOC arm were aged ≥85 years, and a small number of subjects were in the 75 to 84 years group (nivo + SOC: n =31; SOC: n =35).

The frequencies of Grade 3-4 all-causality (Table 42) and drug-related (data not shown) AEs in the nivo + SOC arm were numerically higher in females compared to in males/the overall substudy population, whereas this was not the case in the SOC arm. Of the overall substudy population 77% were male subjects and 23% were female. The more limited sample size of the female subpopulation thus may have been of influence. Also, no such trend was observed in studies CA209648 (Opdivo II/107 EPAR), CA209649 (Opdivo II/96 EPAR), and CA209816 (Opdivo II/117 EPAR). Lastly, there is no clear rationale for increased toxicity of adding nivolumab to chemotherapy in females when compared to males. Therefore, this issue will not be pursued further.

Immunogenicity - The incidence of nivolumab ADA in the CA209901 substudy was low and did not appear to have an effect on the efficacy or safety of the nivo + SOC regimen. The nivolumab ADA and NAb incidences in the CA209901 substudy are lower than that of the current ADA pooled incidence reported in section 4.8 of the SmPC for nivolumab in combination with chemotherapy, and since the current ADA pooled incidence in the SmPC already includes a large number of subjects and there has been no clinically significant impact of ADA on nivolumab (either as monotherapy or in combination with chemotherapy) across many indications, the MAH proposed to not update the ADA pooled incidence in the SmPC. This was agreed.

2.5.2. Conclusions on clinical safety

The safety of nivolumab is well known, including for nivolumab treatment in combination with platinum-based (combination) chemotherapy in other tumour types. See the approved Opdivo SmPC that includes safety information on nivolumab in combination with chemotherapy in a pooled dataset of patients across these other tumour types (gastric, GEJ or oesophageal adenocarcinoma, OSCC, or NSCLC).

For the assessment of the safety profile of nivolumab in combination with chemotherapy in patients with unresectable or metastatic UC the MAH has provided comprehensive data from the pivotal CA209901 substudy that included n=304 subject treated with nivo + SOC.

Similar to what was observed in other tumour types, the addition of nivolumab to chemotherapy in unresectable or metastatic UC resulted in increased toxicity, combining the toxicities of both nivolumab and chemotherapy. This is among other things reflected by a numerical increase in the frequencies of Grade 3-4 AEs, SAEs, and AEs leading to discontinuation (both all causality and drug related) in the nivo + SOC arm over the SOC arm. There were no major differences between study arms, and no new ADR and/or other safety concern was identified.
It should be taken into account that the nivolumab monotherapy phase increased the duration of therapy.

The safety profile of nivo + chemo from the CA209901 substudy was compared with pooled safety data for nivo + chemo from studies CA209648, CA209649, and CA209816 (n=1268), and it is in general considered similar. The MAH has updated the information in section 4.8 of the SmPC with safety data from the overall pooled nivo + chemo dataset (CA209648 + CA209649 + CA209816 + CA209901

substudy; n=1572). Overall, the update is acknowledged and the changes are considered rather minor.

Altogether, the toxicity of nivolumab in combination with chemotherapy in unresectable or metastatic UC is considerable. Nevertheless, there were no major differences between the nivo + SOC arm and the SOC arm in the CA209901 substudy. Plus, the toxicity of nivo + chemo in unresectable or metastatic UC is in general similar to for the nivo + chemo approved indications across other tumour types. Moreover, the safety profile can be acceptable in the context of the observed clinical activity, i.e., a benefit in OS (and PFS).

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 35.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 35.1 with the following content:

Safety concerns

Table 45. Summary of Safety Concerns

Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs) Severe infusion reactions
Important potential risks	Embryofoetal toxicity Immunogenicity 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 Long-term safety in adolescent patients ≥ 12 years of age

Pharmacovigilance plan

Table 46. 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 authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation 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 ARs (including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other irARs [uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and Vogt-Koyanagi-Harada disease]), and severe infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually Q4 2024
Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557)a Voluntary PASS Planned	To assess safety and long-term outcomes in children and adolescents.	Long-term safety in adolescent patients ⩾ 12 years of age	1. Submission of protocol[a] 2. Interim Study Report 3. Final report of study results	Q4 2023 Q4 2026 Q4 2033

[a] The protocol, CA184557, which includes patients treated with ipilimumab monotherapy, will be amended to include patients who received nivolumab monotherapy or nivolumab in combination with ipilimumab (including those receiving therapy prior to the start of data collection). The study milestones presented are specific to the protocol extension for nivolumab or nivolumab in combination with ipilimumab treated patients.

Risk minimisation measures

Table 47. Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8 Additional risk minimisation 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 minimisation measures: SmPC Sections 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofoetal toxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimisation measures: SmPC Section 4.4 and 4.8 Additional risk minimisation 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 minimisation measures: SmPC Sections 4.2 and 5.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in adolescent patients ⩾ 12 years of age	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: Long-term follow-up of ipilimumab, nivolumab, and

		nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been 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 readability of the PL (QRD template Version 9.0) of OPDIVO (nivolumab), in English, was assessed during the review of the initial Marketing Authorisation Application (MAA) according to the methods outlined in the European Commission's guideline titled: *A guideline on the readability of the label and package leaflet of medicinal products for human use, Revision 1, 12 January 2009*. The final report was then submitted to the EMA on 02 September 2014 as part of the initial MAA dossier (EMEA/H/C/3985, MAA approved on 19 June 2015).
- The new indication in adults that is hereby applied for, concerns the same route of administration and has a similar safety profile as the previously approved indications (i.e., key safety messages for the existing and new applied for indication are essentially the same).
- Administration of OPDIVO (nivolumab) is done by a health care professional. The instructions for dose calculation, preparation, administration, storage and disposal that are currently reflected in the approved PL were also successfully tested as part of the user consultation performed for the initial MAA and remain unchanged.
- The general design and layout of the proposed PL have not changed compared to the tested one.
- Overall, the proposed leaflet shares large text sections with the reference one. The modifications now proposed in the PL (i.e., those relevant to the new indication) do not represent major changes.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication is: "Opdivo in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma."

UC is a common cancer type in the European Union and the age-standardised incidence rate (per 100,000 person/years) is 20 for men and 4.6 for women[16]. UC is characterised by multiple non-muscle

[16] International Agency for Research on Cancer. (2020). GLOBOCAN 2020: Estimated cancer incidence, mortality and prevalence worldwide. IARC. https://gco.iarc.fr/today

invasive recurrences, however approximately 15% to 25% of UCs either present with or eventually progress to muscle-invasive or metastatic disease[17]. For patients with muscle-invasive disease more than 50% of patients with MIBC will eventually develop metastases. The prognosis for patients with unresectable or metastatic UC is dismal.

3.1.2. Available therapies and unmet medical need

Gemcitabine plus cisplatin has been established as the preferred regimen in first-line treatment of locally advanced unresectable or metastatic UC patients eligible for cisplatin (2020 ESMO guideline; 2023 EAU guideline). Studies have shown a median OS of 14-15 months and median PFS of approximately 7 months[18]. For patients who are unable to receive cisplatin, carboplatin-based chemotherapy provides an alternative treatment option[19]. Also atezolizumab or pembrolizumab may be considered in patients with PD-L1 positive tumours[20,21]. In 2020 (after the start of the pivotal CA209901 substudy) avelumab maintenance treatment has been approved for patients who are progression-free after platinum-based chemotherapy (median OS of 21 months; Bavencio II/18 EPAR). Nevertheless, there is an unmet medical need for treatments which prolong survival and progression free survival and a reduced toxicity in patients with unresectable or metastatic UC.

3.1.3. Main clinical studies

The pivotal study is study CA209901 (NCT03036098), a randomised, open-label, Phase 3 study in patients who have not received prior systemic chemotherapy for unresectable or metastatic UC. The study is composed of two phase 3 studies: a primary study (Arms A and B) and a substudy (Arms C and D). The substudy is the focus of this variation application. In this substudy cisplatin-eligible patients were randomised to nivolumab (360 mg) in combination with gemcitabine-cisplatin chemotherapy (nivo + SOC) every 3 weeks for up to 6 cycles, followed by nivolumab monotherapy (480 mg) every 4 weeks (Arm C) or SOC of gemcitabine-cisplatin every 3 weeks for up to 6 cycles (Arm D). Stratification factors were tumour PD-L1 expression using a 1% cut-off (negative/indeterminate vs. positive) and the presence of liver metastasis (yes vs. no). The analysis population for efficacy consisted of all randomised subjects; N=304 in the nivo + SOC arm and N=304 in the SOC arm. At the time of the 09-May-2023 data cut-off (23-Jun-2023 DBL) the minimum follow-up was 7.4 months in both arms and the median follow-up was 33.6 months in the nivo + SOC arm and 33.5 months in the SOC arm. No supportive study was submitted.

3.2. Favourable effects

The pivotal study met both dual primary endpoints of OS and PFS.
Nivo + SOC demonstrated a statistically significant improvement in OS compared with SOC alone: HR = 0.78 (alpha-adjusted 95.59% CI: 0.63, 0.96), stratified log rank test p value = 0.0171. The median OS was 21.7 (95% CI 18.6, 26.4) months in the nivo + SOC and 18.9 (95% CI 14.7, 22.4) months in the SOC arm, respectively.

[17] Balasubramanian, A., et al. (2022). Adjuvant therapies for non-muscle-invasive bladder cancer: Advances during BCG shortage. World Journal of Urology, 40, 1111–1124. https://doi.org/10.1007/s00345-021-03908-x
[18] NCCN Clinical Practice guidelines in Oncology. Bladder Cancer Version 4.2019. www.nccn.org.
[19] De Santis, M., et al. (2012). Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. Journal of Clinical Oncology, 30(2), 191-199. https://doi.org/10.1200/JCO.2011.37.3571
[20] European Medicines Agency. Tecentriq: EPAR - Product Information
[21] European Medicines Agency. Keytruda: EPAR - Product Information

Also, a statistically significant improvement in PFS per BICR was observed with nivo + SOC compared to SOC alone: HR = 0.72 (alpha-adjusted 99% CI: 0.55, 0.94), stratified log-rank test p-value = 0.0012. The median PFS was 7.92 (95%CI 7.62, 9.49) and 7.56 (95%CI 6.05, 7.75) months, respectively.

Analysis with the primary definition of PFS which censored for subsequent anticancer therapy without death or progression is comparable to the secondary PFS definition that did not censor/consider these patients as progressed (HR = 0.74 [95% CI: 0.62, 0.89]).
The OS and PFS effect is consistent over predefined subgroups, except for the subgroup of patients from the region US (OS HR = 1.92 [95%CI:0.95, 3.88], PFS HR = 1.45 [95%CI: 0.63, 3.31]). The reason for this inconsistency is unknown and may be related to the small sample size (N=40).

Secondary endpoints OS and PFS in patients with PD-L1 expression ≥ 1% support the primary endpoints (OS HR = 0.74 [95% CI: 0.52, 1.04] and PFS HR = 0.58 [95% CI: 0.41, 0.81]).
Subgroup analysis of OS and PFS in patients with PD-L1 expression < 1% do not raise concerns that patients with PD-L1 expression < 1% do not benefit from the addition of nivolumab to SOC (OS HR = 0.82 [95% CI: 0.63, 1.05] and PFS HR = 0.80 [95% CI: 0.62, 1.02]).

There were no large differences in mean changes in EORTC QLQ-C30 Global Health Status scores between treatment arms and differences did not reach an MID.

3.3. Uncertainties and limitations about favourable effects

Amendments were made to the ongoing CA209901 substudy that were not supported in scientific advice (EMEA/H/SA/2253/13/2020/II). While N=262 patients had been included in the substudy, OS was upgraded to a dual primary endpoint and the sample size of the substudy was increased from 300 to 600 patients. These changes were informed by external data from the IMvigor130 study (published on 30-Sep-2019) available prior to the amendments (20-Mar-2020). Plus, it is considered reassuring that the PFS primary endpoint would have been met under the protocol version prior to these amendments (revised protocol number 03 09-Apr-2019).

3.4. Unfavourable effects

The analysis population used for the safety profile of nivolumab in combination with chemotherapy in patients with unresectable or metastatic UC is the population of all treated subjects (n=592) who had received at least one dose of study drug who were randomized to nivo + SOC (n=304) and SOC (n=288).

In the nivo + SOC arm 16.1% of subjects switched from cisplatin to carboplatin (allowed per protocol) vs. 14.9% in the SOC arm, with a median number of carboplatin doses received of 3.0 in each study arm.

The rate of all-causality (drug-related) any-Grade AEs in the nivo + SOC arm vs. the SOC arm, respectively, was 99.7% vs. 98.6% (97.4% vs. 92.7%), the rate of Grade 3-4 AEs was 72.4% vs. 64.9% (61.5% vs. 51.4%), the rate of SAEs was 46.7% vs. 36.5% (24.7% vs. 16.7%), the rate of AEs leading to discontinuation was 29.6% vs. 24.0% (21.1% vs. 17.4%), and the rate of death due to study drug toxicity (all drug-related) was 2.3% (11 PTs were reported in these 7 subjects, i.e., abdominal sepsis, thrombocytopenia, hypovolemic shock, multiple organ dysfunction syndrome, multiple organ failure, myocarditis, acute kidney injury, small intestinal obstruction, adrenal insufficiency [one each] and sepsis [two subjects]) vs. 0.7% (death due to acute kidney failure and septic shock [one each]).

The most frequently reported all-causality any-Grade AEs reported in ≥25% of subjects in the nivo + SOC arm were anaemia (63.2%), nausea (52.0%), neutropenia (34.5%), constipation (29.6%), decreased appetite (29.6%), fatigue (28.3%), and neutrophil count decreased (25.7%).
The most frequently reported all-causality Grade 3-4 AEs reported in ≥10% of subjects in the nivo + SOC arm were anaemia (25.0%), neutropenia (20.1%), neutrophil count decreased (15.1%), and white blood cell count decreased (10.2%).

The overall frequencies of drug-related selected AEs by category were similar between nivo + SOC and SOC arms, with the exception of the endocrine (21.1% vs. 0%), gastrointestinal (13.8% vs. 8.7%), and skin categories (31.6% vs. 6.6%), where the frequencies were 5% higher in nivo + SOC arm compared to SOC arm, respectively.

All-causality IMAEs were reported more frequently in the nivo + SOC arm than in the SOC arm. Overall, the majority of IMAEs were Grade 1-2. The most frequently (reported in ≥5% of subjects) reported IMAEs (any grade) by category in the nivo + SOC arm were hypothyroidism/thyroiditis (13.2%), rash (8.6%), and hyperthyroidism (7.2%).

All-causality OESIs were reported in 3.0% of subjects in the nivo + SOC arm vs. 0.3% in the SOC arm. Grade 3-4 drug-related OESIs reported in the nivo + SOC arm were pancreatitis (0.7%); and myocarditis, immune-mediated cytopenia, immune mediated myocarditis, and encephalitis autoimmune (0.3% each).

The safety profile of nivo + chemo from the CA209901 substudy was compared with pooled safety data for nivo + chemo from studies CA209648, CA209649, and CA209816.
The overall frequencies of any-grade and Grade 3-4 all-causality AEs were numerically higher in nivo + chemo-treated subjects in the CA209901 substudy (99.7% any-grade; 72.4% Grade 3-4) vs. the pooled studies (98.5% any-grade; 66.4% Grade 3-4).
The frequencies of any-grade all-causality AEs were numerically higher (>5% absolute difference) in nivo + chemo-treated subjects in the CA209901 substudy vs. the pooled studies for e.g., urinary tract infection (15.1% vs. 3.0%), haematuria (10.9% vs. 1.0%), and renal failure (10.5% vs. 3.0%).

Nonetheless, the safety profile of nivo + chemo from the CA209901 substudy is in general considered similar to the pooled safety data for nivo + chemo from studies CA209648, CA209649, and CA209816.

3.5. Uncertainties and limitations about unfavourable effects

The MAH has committed to submit biomarker analyses for the CA209901 substudy other than PD-L1 and CPS (which have already been provided), i.e., CD8, mutations/TMB, gene expression signature, MDSC and serum soluble factors by Q4 2024 (REC).

3.6. Effects Table

Table 48. Effects Table for Opdivo (nivolumab) in combination with cisplatin and gemcitabine in the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma (data cut-off: 09-May-2023)

Effect	Short description	Unit	Treatment Nivo + SOC	Control SOC	Uncertainties / Strength of evidence	References
Favourable Effects						
All randomised subjects			N=304	N=304		
OS	Overall	Median	21.7	18.9	Strengths:	Section

Effect	Short description	Unit	Treatment Nivo + SOC	Control SOC	Uncertainties / Strength of evidence	References
	survival	(95%CI) in months	(18.6, 26.4) HR = 0.78 (alpha-adjusted 95.59% CI: 0.63, 0.96), stratified log rank test p-value = 0.0171.	(14.7, 22.4)	- Derived from a Phase 3, randomised study with SOC control arm. -Effect consistent in most subgroups (including patients with PD-L1 expression <1%). - OS and PFS analyses were adjusted for multiplicity. Uncertainty: - Amendments to the primary endpoints and sample size were made in an ongoing study.	2.4
Unfavourable Effects						
All treated subjects			N=304	N=288		
Grade 3-4 AEs	All causality (drug-related)	%	72.4 (61.5)	64.9 (51.4)	Strength: - Phase 3, randomised study with SOC control arm Uncertainties: - Open-label study - Limited data in patients ⩾ 75 years of age	Table 32
SAEs	All causality (drug-related)	%	46.7 (24.7)	36.5 (16.7)		
AEs leading to DC	All causality (drug-related)	%	29.6 (21.1)	24.0 (17.4)		
Drug-related select AEs (any grade) (by category)						
Endocrine		%	21.1	0		
Gastrointestinal		%	13.8	8.7		
Skin		%	31.6	6.6		

Abbreviations: AEs: adverse events; BICR: blinded independent central review; CI: confidence interval; DC: discontinuation; HR: hazard ratio; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; RECIST 1.1: Response Evaluation Criteria In Solid Tumours version 1.1; SOC: standard of care; SAEs: serious adverse events.
Note: In patients with PD-L1 expression ≥1% OS HR = 0.74 (95% CI: 0.52, 1.04). In patients with PD-L1 expression <1% OS HR = 0.82 (95% CI: 0.63, 1.05).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The prognosis of patients with unresectable or metastatic UC is dismal and there is an unmet medical need for treatments which prolong survival, progression free survival and reduced toxicity. Addition of nivolumab to SOC 1L chemotherapy treatment resulted in a statistically significant improvement in OS and PFS. The improvement in OS and PFS rates is small but appears to be maintained over time and is consistent over the majority of subgroups. Particularly, the results from subgroup analyses do not raise concerns that patients with PD-L1 expression < 1% do not benefit from the addition of nivolumab to SOC chemotherapy, especially as the OS HRs for patients with PD-L1 expression ≥ 1% and patients with PD-L1 expression < 1% are similar. Therefore, the treatment effect is considered compelling and clinically relevant.

The MAH has committed to submit biomarker analyses for the CA209901 substudy other than PD-L1 and CPS (which have already been provided), i.e., CD8, mutations/TMB, gene expression signature, MDSC and serum soluble factors by Q4 2024 (REC).

The protocol amendments made are considered to be unfortunate. The change in sample size and adding OS as a primary endpoint are considered to have provided relevant information for decision making and are likely informed by external data publicly available prior to the amendments. Results that would have been observed had the trial followed the initial design, and results to assess

homogeneity of results before and after the design adjustments were provided by the applicant during the procedure and are considered reassuring. The PFS primary endpoint would have been met under the protocol version prior to these amendments and there is homogeneity of PFS results before and after the amendments. Overall, the provided data are considered reassuring and the type I error can be considered reasonably controlled in view of the positive PFS analysis according to protocol number 03.

The safety of nivolumab is well known, including for nivolumab treatment in combination with platinum-based (combination) chemotherapy in other tumour types (see Opdivo SmPC).

Similar to, and as observed in other tumour types, the addition of nivolumab to chemotherapy in unresectable or metastatic UC resulted in increased toxicity, combining the toxicities of both nivolumab and chemotherapy. This is among other things reflected by numerical increases in the frequencies of Grade 3-4 AEs, SAEs, and AEs leading to discontinuation (both all causality and drug related) in the nivo + SOC arm over the SOC arm. There were no major differences between study arms though, and no new ADR and/or other safety concern was identified.

When compared with pooled safety data for nivo + chemo in other tumour types, the safety profile of nivo + chemo from the CA209901 substudy is in general considered similar. The minor changes to section 4.8 of the SmPC are acceptable.

3.7.2. Balance of benefits and risks

Nivolumab has demonstrated a statistically significant and clinically relevant improvement in OS and PFS when added to gemcitabine-cisplatin for the treatment of patients with unresectable or metastatic UC. While the effect on PFS may be less pronounced, the primary outcomes are robust and compelling. Amendments to this ongoing open-label study included adjustments to the sample size and endpoints, which is considered to be unfortunate. However, external data supporting these changes were available at the time the amendments were made and the PFS primary endpoint would have been met under the protocol version prior to these amendments. Considering this, the type I error can be considered reasonably controlled.

The toxicity of nivolumab in combination with chemotherapy in unresectable or metastatic UC is considerable. Nevertheless, there were no major differences between the nivo + SOC arm and the SOC arm in the CA209901 substudy. In addition, the toxicity of nivo + chemo in unresectable or metastatic UC is in general similar to that observed in the other indications across other tumour types with nivo + chemo. Moreover, the safety profile can be acceptable in the context of the observed clinical activity, i.e., a benefit in OS (and PFS).

3.7.3. Additional considerations on the benefit-risk balance

The MAH has committed to submit biomarker analyses for the CA209901 substudy other than PD-L1 and CPS (which have already been provided), i.e., CD8, mutations/TMB, gene expression signature, MDSC and serum soluble factors by Q4 2024 (REC).

3.8. Conclusions

The overall B/R of Opdivo (nivolumab) in combination with cisplatin and gemcitabine for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include OPDIVO in combination with cisplatin and gemcitabine for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma, based on interim results from study CA209901 (CheckMate901). This is a Phase 3, open-label, randomised study of nivolumab combined with ipilimumab, or with standard of care chemotherapy, versus standard of care chemotherapy in participants with previously untreated unresectable or metastatic urothelial cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 35.1 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics 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 Annex(es) I and IIIB and to the Risk Management Plan are recommended.