27 March 2025
EMA/CHMP/142870/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Opdivo

International non-proprietary name: Nivolumab

Procedure No. EMEA/H/C/003985/X/0144

Note

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

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List of abbreviations

1L	first line
2L	second line
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE(s)	adverse event(s)
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AS	Active Substance
AST	aspartate aminotransferase
AUC	area under the curve
AUC(TAU)	area under the curve (AUC) for the defined interval between doses (TAU).
BICR	Blinded Independent Central Review
BMS	Bristol Myers Squibb Company
BOR	best overall response
Cavg1	time-averaged concentration after the 1st dose
Cavgd28	average serum concentration over 28 days
Cavgss	time-averaged serum concentration at steady state
ccRCC	clear cell renal cell carcinoma
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CHMP	Committee for Medicinal Products for Human Use
cHL	classical Hodgkin lymphoma
CI(s)	confidence interval(s)
Cmax	maximum serum concentration
Cmax1	maximum serum concentration after the first dose
Cmaxss	peak serum concentration at steady state
CMH	Cochran-Mantel-Haenszel
Cmin1	the trough concentration after the 1st dose
Cmind28	trough serum concentration at Day 28
Cminss	trough serum concentration at steady state
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
Ctau	concentration at end of dosing interval
CTC	Common Terminology Criteria

Ctrough	trough serum concentration
DBL	database lock
DC	discontinue
DCR	disease control rate
dMMR	mismatch repair deficient
DOR	duration of response
EMA	European Medicines Agency (formerly EMEA)
EQ-5D-5L	5-level version of the EuroQol Group's EQ-5D questionnaire
EU	European Union
FDA	Food and Drug Administration
FKSI	Functional Assessment of Cancer Therapy-Kidney Symptom Index
FKSI-19	FKSI-19 Item Version
FP	Finished Product
GEJ	gastro-oesophageal junction
GEJC	gastro-oesophageal junction cancer
GCP	Good Clinical Practice
GMR	Geometric means ratio
HCC	hepatocellular carcinoma
HCP	Healthcare provider
HR(s)	hazard ratio(s)
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IMAE(s)	immune-mediated adverse event(s)
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
irAR	immune-related adverse reaction
IRT	Interactive Response Technology
IV	intravenous(ly)
LPLV	last patient, last visit
MAX	maximum
MCB	medium cycle bioreactor
MedDRA	Medical Dictionary for Regulatory Activities
MIN	minimum
MPM	malignant pleural mesothelioma
MSI-H	high microsatellite instability
mUC	metastatic urothelial carcinoma
N	number
N.A or n/a	not available
Nivo, nivo	nivolumab
NSCLC	non-small cell lung cancer
NSQ	non-squamous

OC	oesophageal adenocarcinoma
OESI(s)	other event(s) of special interest
ORR	objective response rate
OSCC	oesophageal squamous cell carcinoma
OS	overall survival
PD	progressive disease
PD-1	programmed death-1
PD-L1, PDL1	programmed death ligand-1
PD-L2	programmed death ligand-2
PFS	progression-free survival
PK	pharmacokinetic(s)
PI	Product Information
popPK	population pharmacokinetic(s)
PR	partial response
PT	preferred term
Q1, Q3	quartile 1, quartile 3
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RCC	renal cell carcinoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
rHuPH20	recombinant human hyaluronidase PH20
RO	receptor occupancy
RFS	refractory free survival
RMP	Risk Management Plan
RR	relative risk
SAE(s)	serious adverse event(s)
SC	subcutaneous(ly)
SCCHN	squamous cell cancer of the head and neck
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	System Organ Class
SQ	squamous
T cells	T lymphocyte(s) (thymocyte-derived)
T half	apparent terminal phase half-life
Tmax	time to maximum serum concentration (Cmax)
TTR	time to objective response

UC	urothelial carcinoma
UF/DF	ultrafiltration/diafiltration
US, USA	United States; United States of America
UTD	unable to determine
VAS	visual analog scale(s)
vs, vs.	versus

1. Background information on the procedure

1.1. Submission of the dossier

Bristol-Myers Squibb Pharma EEIG submitted on 31 May 2024 extensions of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (solution for injection), a new strength (600 mg) and a new route of administration (subcutaneous use).
Version 40.0 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) (d) (e) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0280/2020 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. 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 indications.

1.5. Scientific advice

The MAH received scientific advice from the CHMP on 31 May 2018 (EMEA/H/SA/2253/7/2018/III), 30 January 2020 (EMEA/H/SA/2253/7/FU/1/2019/II), 10 December 2020 (EMEA/H/SA/2253/14/2020/II), 24 February 2022 (EMA/SA/0000074196) and 11 May 2022 (EMA/SA/0000087715). The scientific advice pertained to *quality, non-clinical, and clinical* aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Antonio Gomez-Outes

The application was received by the EMA on	31 May 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	17 October 2024
The MAH submitted the responses to the CHMP consolidated List of Questions on	27 November 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 January 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2025
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	30 January 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 February 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 March 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to OPDIVO on	27 March 2025

2. Scientific discussion

2.1. Problem statement

The Applicant is currently seeking approval for the use of a subcutaneous formulation of nivolumab, co-formulated with a permeation enhancer rHuPH20, as an alternative to the use of the currently approved IV formulation for solid tumour indications in adults (excluding paediatric indications, cHL, when nivo is administered as Q3W (neoadjuvant & metastatic NSCLC, MPM), OSCC as 1L treatment PD-L1 ê 1% (nivo+ipi) combination treatment without monotherapy maintenance phase).

The indications included in the current application are:

Melanoma

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression.

Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Non-small cell lung cancer (NSCLC)

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

Renal cell carcinoma (RCC)

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma.

Squamous cell cancer of the head and neck (SCCHN)

OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.

Urothelial carcinoma

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

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.

Adjuvant treatment of urothelial carcinoma

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.

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings:

- First-line treatment of unresectable or metastatic colorectal cancer;
- Treatment of metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Oesophageal squamous cell carcinoma (OSCC)

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

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC)

OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

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.

2.2. About the product

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

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).

The recommended posology for the subcutaneous administration is either nivolumab 600 mg every 2 weeks or 1200 mg every 4 weeks (for more details see section 4.2 of the SmPC) administered into the subcutaneous tissue of the abdomen or thigh over a period of 3 to 5 minutes.

If patients need to be switched from the 600 mg every 2 weeks schedule to the 1200 mg every 4 weeks schedule, the first 1200 mg dose should be administered two weeks after the last 600 mg dose. Conversely, if patients need to be switched from the 1200 mg every 4 weeks schedule to the 600 mg every 2 weeks schedule, the first 600 mg dose should be administered four weeks after the last 1200 mg dose.

2.3. Type of Application and aspects on development

This application is primarily based on pivotal study CA20967T, evaluating non-inferiority of nivolumab SC co-formulated with rHuPH20 versus nivolumab IV monotherapy in 2L RCC subjects, together with

data from CA2098KX (supportive PK/safety and dose-finding study conducted across multiple tumour types), and a simulation-based PK bridging strategy.

Of note, in clinical studies CA20967T and CA2098KX for both nivolumab IV and SC formulations, active substance (AS) manufacturing Process C was used. For manufacturing of the commercial formulation of nivolumab SC, use of an optimized AS manufacturing Process D (D-His.2 is formulated for SC use) is proposed.

The introduction of nivolumab AS manufacturing Process D as a commercial manufacturing process for OPDIVO IV formulation along with CA2098FC clinical study results demonstrating the biocomparability between Process C and Process D were already assessed with the EMEA/H/C/003985/X/0132 procedure for which a CHMP positive opinion was adopted on 25 January 2024 and the EC Decision was granted on 25 March 2024

2.4. Quality aspects

2.4.1. Introduction

The finished product Nivolumab subcutaneous (SC) is presented as a solution containing 600 mg/vial of nivolumab (120 mg/mL) as active substance for subcutaneous injection.

Other ingredients are: recombinant human hyaluronidase (rHuPH20), histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, methionine and water for injection.

The product is available in Type I glass vial with a butyl rubber stopper and an aluminium seal with a plastic orange flip-off cap containing 5 mL of solution for injection. Pack of one vial.

2.4.2. Active Substance

2.4.2.1. General Information

The INN of the active substance (AS) is nivolumab. Nivolumab is a fully human monoclonal antibody (mAb) of the IgG4 class consisting of four polypeptide chains; two identical heavy chains of 440 amino acids and two identical kappa light chains of 214 amino acids, which are linked through inter-chain disulfide bonds. The heavy chain includes a S221P mutation, which is known to impart increased stability to IgG4 antibodies.

Nivolumab binds to the programmed death-1 (PD-1) receptor and potentiates in vitro T-cell responses through dual ligand blockade of PD-L1 and PD-L2. The Anti-PD-1 Human Monoclonal Antibody uses the laboratory codes BMS-936558-01 (also referred to as BMS-936558), histidine formulation for nivolumab subcutaneous injection.

The nivolumab subcutaneous formulation is manufactured with the new recombinant CHO host cell line approved in procedure EMEA/H/C/003985/X/0132, utilizing a high concentration active substance manufacturing process with a histidine buffer to produce nivolumab Process D-Histidine.2 (Process D-His.2) active substance.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturer

Process D-His.2 active substance is manufactured at the currently approved active substance manufacturing site, located in Cruiserath, Dublin, Ireland (BMS-Cruiserath). Valid GMP certificates, QP declarations of GMP compliance, and screen shots of drug establishments for the US FDA website are provided for the manufacturing and testing sites of Nivolumab in the EU, UK and USA.

Description of manufacturing process and process controls

Detailed information on the active substance manufacture is provided. Information on cell banking was already provided for Process D. The manufacturing process for nivolumab Process D and Process D-His.2 are identical up to and including viral filtration (VF). After the VF step, an ultrafiltration/diafiltration (UF/DF) step is utilized to concentrate and diafilter the viral filtered pool to formulate the purified active substance with addition of polysorbate 80 and 5-mM diethylene triamine pentaacetic acid (DTPA). The nivolumab active substance is stored protected from light, into bioprocess containers.

Control of materials

No materials of animal or human origin are used in the nivolumab active substance manufacturing process. Compendial and non-compendial materials used in the manufacturing process are purchased from qualified vendors. Raw material quality is assessed as defined in the testing specification for each raw material.

The cell banking system, characterisation, and testing for the nivolumab Process D-His.2 active substance is the same as the nivolumab Process D since the same cell line is used for both processes. The new Working Cell Bank (WCB) qualification consists of a tiered approach that includes biosafety and identity testing, process performance evaluation and active substance release specification evaluation.

Control of critical steps and intermediates

An in-process control (IPC) strategy was defined for the nivolumab active substance manufacturing process that is not site-specific but does differentiate with regards to site-specific equipment or procedures. Critical process parameters (CPPs) and critical performance attribute (CPAs) were determined.

Process validation

The Process D His.2 process performance qualification (PPQ) campaign qualified the downstream steps specific to the active substance formulation. Supporting studies were completed during the nivolumab Process D PPQ campaign for the media preparation, upstream, downstream, buffer preparation, and active substance handling at the approved manufacturing site. The active substance manufacturing process has been validated adequately.

Manufacturing process development

A comprehensive analytical comparability study was performed comparing analytical data collected from the active substances produced from Process C-Histidine.1 (active substance used to manufacture clinical nivolumab SC injection), Process D-citrate (active substance used to manufacture commercial nivolumab IV injection), and Process D-His.2 (active substance used to manufacture commercial nivolumab SC injection) at BMS-Cruiserath.

The results demonstrated that the active substance obtained from each process are comparable. Small differences were found that are explained by the different manufacturing processes are not regarded inconsistent with considering the three processes comparable.

Characterisation

Documentation for "Elucidation of structure and other characteristics" corresponding to Process D-His.2 is cross-referenced to Process D-citrate, previously authorised for the IV finished product.

Regarding impurities, due to the similarities in the manufacturing processes (C, D and D-His.2) and the active substance obtained (nivolumab), the expected impurity profile and impurity control strategy are aligned between Process D and D-His.2.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The specifications for release and stability testing of nivolumab active substance are largely in line with the previous process. Specification for release and stability testing of nivolumab active substance include tests for appearance, quantity, pH, purity, identity, potency, host cell protein, bacterial endotoxins, and bioburden.

In addition, a "Nitrosamine Risk Assessment Summary - Active Substance" is included in the dossier. A theoretical risk was identified from one of the excipients, pentetic acid (DTPA); however, the level of nitrosamine impurities is too low and below a level of concern. The conclusion was that the risk level is negligible and that there are no actionable risks identified for the presence of nitrosamines in the active substance.

Analytical procedures and reference standards

Most validation of the analytical methods has been leveraged from previous active substance manufacturing process. Only some supplemental validation work was performed for some methods to support the higher concentration of the nivolumab Process D-His.2 active substance.

For the reference standards there are no changes, and a cross-reference is given to Process D-citrate.

Batch analysis

Batch analysis data are provided with satisfactory results.

Container closure

The active substance is filled into single-use, pre-sterilized bioprocess containers. Details are provided of the bioprocess container configurations used. They have the same materials with bags of the same shape, clamshell and clamps. They comply with European regulation for bacterial endotoxins, particulates and sterility and they are declared as free from Bovine Spongiform Encephalopathy (BSE)/ Transmissible Spongiform Encephalopathy (TSE).

Suitable studies have been performed for extractable and leachables from the container closure as expected.

2.4.2.4. Stability

An initial shelf-life of 48 months is proposed for nivolumab D-His.2 active substance when stored at ≤-35° C.

The authorised shelf-life for nivolumab active substance manufactured using Processes C and D (citrate formulation in both) is 36 months at 2°C to 8°C and protected from light is based on the real-time stability data provided.

Data is provided from stability studies with batches of nivolumab active substance manufactured at the intended commercial manufacturing facility, BMS-Cruiserath, at the intended commercial manufacturing-scale. Real-time stability data at the long-term storage condition of -40ºC are available for the Process D-His.2 active substance batches. All results meet the proposed acceptance criteria. The study is ongoing up to the intended 60 months. Supplemental data through 48 months is also provided from additional batches manufactured using Process C-Histidine.1.

Stability studies have been conducted for batches at the accelerated condition of 5°C and the stress condition of 25ºC/40%RH for 6 months. The studies at stress conditions of 40ºC/75%RH are complete with 3 months of data. While at the accelerated 5°C condition the data show no changes over time for all quality attributes and all batches, there are changes at the 25°C/40%RH condition, which are expected based on previous data from Process C and D. Changes are also found at the 40ºC/75%RH stress condition.

Based on the real-time stability data provided for nivolumab D-His.2 and comparabilities to the Process D-citrate and Process C-His.1, the proposed shelf-life of 48 months is proposed for nivolumab D-His.2 active substance when stored at ≤-35° C, and protected from light, is considered acceptable.

Bristol Myers Squibb Company (BMS) commits to complete all on-going long-term stability studies on batches from the first campaign of nivolumab Process D-His.2 manufactured at commercial scale at the BMS-Cruiserath facility according to the defined stability protocol. Upon request, the MAH submitted additional real-time active substance stability results collected during the evaluation of this extension application which are satisfactory.

In addition, BMS commits to place annually thereafter into the post-approval stability program one batch of nivolumab Process D-His.2 manufactured for commercial distribution at the BMS-Cruiserath facility each year that commercial production occurs according to the stability protocol for all future annual stability enrolments.

2.4.3. Finished Medicinal Product

2 . 4 . 3 . 1 . Description of the product and Pharmaceutical Development

Description of the product

Nivolumab and Hyaluronidase (rHuPH20) SC Injection, 600 mg and 10,000 Units/5 mL (120 mg and 2,000 Units/mL), is a sterile, non-pyrogenic, single-use, preservative-free, isotonic aqueous solution for subcutaneous (SC) administration. Recombinant human hyaluronidase PH20 is also referred to as rHuPH20 throughout the dossier. The other excipients include histidine, histidine hydrochloride monohydrate, pentetic acid, sucrose, polysorbate 80, methionine and water for injections. There are no novel excipients.

There are no excipients of human or animal origin used in the manufacturing of nivolumab. The manufacture of the excipient recombinant human hyaluronidase PH20 (rHuPH20) bulk enzyme from Chinese hamster ovary (CHO) cells is also free of materials of animal or human origin and it is not considered a novel excipient because it is already used as a permeation enhancer in other authorised products.

Pharmaceutical development

Formulation development studies were focused on the use of a histidine-based buffer as several SC marketed products use this buffer for SC administration, without the SC injection issues associated to citrate-based buffer.

The development studies were conducted as expected to support the final commercial finished product and utilized both the final Process D-His.2 sourced active substance and the Process C-Histidine.1 active substance available earlier in development.

In all cases the same active nivolumab molecule is used and the change in formulation does not affect the physical or chemical properties of the nivolumab molecule. A comprehensive analytical comparability study confirms that nivolumab-citrate active substance and nivolumab Process D-His.2 active substance have comparable release and stability profiles, as well as degradation rates.

Suitable studies are provided to support the coformulation of nivolumab and rHuPH20 enzyme indicating no adverse impact on the critical quality attributes of nivolumab or rHuPH20 enzyme.

Two manufacturing sites have been used to manufacture nivolumab SC injection, clinical manufacturing site, and for commercial manufacturing site. Material compatibility studies with manufacturing components showed that the components used during commercial manufacture are compatible with the nivolumab SC injection solution. The leachables/extractables risk assessment was also satisfactory. Studies were undertaken for technology transfer with commercial scale batches manufactured at the commercial site. The results indicated the suitability of the manufacturing process, including the process hold-times, which were studied in parallel. Finally, the ranges for PPs and CPPs for the nivolumab SC injection manufacturing process based on prior knowledge were supported from these studies.

Comparability has been shown between nivolumab SC injection finished product.

Other development studies produced satisfactory results.

2.4.3.2. Manufacture of the product and process controls

Manufacturers, manufacturing process and process controls

Detailed information on manufacturers has been provided as well as the batch formula. The manufacturing process is well described and includes the following steps: thaw-formulate-fill-finish process. At the secondary packaging and labelling facility, the bulk vials are labelled, packaged and the finished product is released at Swords Laboratories Unlimited (Dublin, Ireland). The manufacturers of the finished product are appropriately authorised and GMP compliant.

The documentation provides a flow diagram for the finished product manufacturing process with the in-process tests (IPTs) for each step. Information is included on process parameters (PPs), critical process parameters (CPPs) and hold times.

Process validation / verification

The process validation strategy for the nivolumab SC injection is based on a life-cycle management approach that includes the process design stage, process qualification stage, and continued process verification stage. The process design is described, while the process qualification stage was carried out by producing PPQ batches at the commercial manufacturing site, which results confirmed the manufacturing process proposed. For the process verification stage, manufacturing will be monitored for continued assurance of process control.

Validation of the sterilization and aseptic manufacturing of the nivolumab subcutaneous (SC) injection finished product has been provided.

2.4.3.3. Product specification, analytical procedures, batch analysis

Specifications

The acceptance criteria for release and stability testing of the nivolumab SC injection finished product is presented. Specification for release and stability testing of the nivolumab SC injection finished product include tests for appearance, quantity/identity, pH, polysorbate 80, osmolality, particulate matter, extractable volume in container, purity, identity, potency, activity, bacterial endotoxins, sterility and container closure integrity testing.

The justification of the specifications includes a comparison of the acceptance criteria for the commercially approved nivolumab-citrate IV finished product and the nivolumab SC injection finished product. When appropriate, the acceptance criteria have been aligned.

The provided specifications and acceptance criteria for release and stability testing of nivolumab SC injection finished product are acceptable, showing an adequate control of this product.

In addition, it should be noted that a "Nitrosamine Risk Assessment Summary - Finished Product" has been provided. The conclusion was that the risk level is negligible and that there are no actionable risks identified for the presence of nitrosamines in the finished product. This risk assessment considers that the nitrosamine risk assessments supplied by Halozyme, Inc. for rHuPH20 bulk enzyme reported that there is no risk of formation or contamination with nitrosamines.

Analytical procedures and reference standards

The analytical procedures used are indicated and information on validation is provided. Most non-compendial methods for this finished product are also used to test the active substance. Particular attention is given to the potential impact of the rHuPH20 on the methods used to control nivolumab, which is considered irrelevant as the rHuPH20 concentration in the finished product.

Batch analysis

Batch analysis was undertaken with batches of finished product. Satisfactory data is obtained from all these batches and is provided in individual tables and a summary.

Container closure

Nivolumab subcutaneous (SC) injection is packaged in a Type I clear tubing glass vial, closed with a chlorobutyl rubber stopper and an aluminum crimp seal with an orange polypropylene flip-off button. The vial presentation is packaged in a paperboard folding carton to protect the product from light.

2.4.3.4. Stability of the product

A shelf-life of 3 years is proposed for nivolumab SC injection, stored at the recommended storage condition of 2°C to 8°C, protected from light.

The MAH has conducted stability studies in accordance with ICH stability guidelines, with registrational batches.

Real-time stability data at 5°C are available. The stability profiles are similar meeting the proposed acceptance criteria throughout the study period, and all test results show little to no change over time.

Accelerated stability studies up to 6 months at 25°C/60%RH are available. Under the stress condition of 40°C/75%RH, as expected, similar but greater changes are observed. These results confirm that appropriate stability-indicating assays are used.

Data from photostability studies show that the nivolumab SC injection is sensitive to high-intensity fluorescent visible light and ultraviolet-A irradiation (HIL/UVA) and that paperboard carton provides sufficient protection from light.

Additional freeze-thaw cycling stress-store studies and light exposure studies were undertaken to demonstrate that the excursions tested did not adversely affect the long-term stability of finished product.

Based on the real-time data the claimed shelf-life of 3 years for nivolumab SC injection when stored at the recommended storage condition of 2°C to 8°C and protected from light, is considered acceptable.

Finally, Bristol Myers Squibb Company (BMS) commits to the completion of all on-going long-term stability studies on nivolumab SC injection batches according to their defined protocol. Upon request, the MAH submitted additional real-time active substance stability results collected during the evaluation of this line extension which are satisfactory. The MAH also commits to place annually, thereafter into the post-approval stability program, one batch of nivolumab SC injection manufactured for commercial distribution each calendar year that commercial production occurs.

2.4.3.5. Post approval change management protocol(s)

N/A

2.4.3.6. Adventitious agents

2.4.3.6.1. Adventitious agents safety evaluation (nivolumab) – Process D-His.2

Non-viral adventitious agents information is adequate, justifying that the raw materials are non-animal derived. Information has been provided to justify that they comply with the TSE regulation (EMA/410/01 Rev.03).

Viral clearance studies have been updated.

2.4.3.6.2. Adventitious agents safety evaluation - rHuPH20 bulk enzyme - Subcutaneous

An additional adventitious agents safety evaluation is provided for the excipient rHuPH20 bulk enzyme and upon request the MAH confirmed that MVM is tested at harvest step for each lot. Compliance with TSE regulation (EMA/410/01 Rev.03) is also indicated for raw materials involved in the manufacture of rHuPH20 bulk enzyme, which are also animal component-free. Information on the characterization and qualification of the cell banks, together with information on cell banks stability and qualification protocol for new WCBs is provided.

2.4.3.7. Recombinant human hyaluronidase PH20 (rHuPH20) enzyme (Excipient)

Although recombinant human hyaluronidase PH20 (rHuPH20) enzyme is not a novel excipient, because it has been already used as a permeation enhancer in other commercially approved products, information on its manufacture, characterization and stability has been provided.

Halozyme, Inc. is responsible for the oversight of the contract manufacturing and testing sites and release of rHuPH20 excipient. Upon request, the MAH included the information related to the manufacturing sites of rHuPH20 excipient in the documentation.

The manufacturing process is overall sufficiently described. The production system is derived from the parental cell line and information is provided regarding the rHuPH20 expression construct. The MAH was requested to provide more information on the generation of the production system, including the demonstration of single-clone origin of the MCB as well as information on the characterization and qualification of the cell banks as well as information on cell banks stability and qualification protocol for new WCBs. The MAH has submitted all that requested information, which is satisfactory.

The documentation explains that validation was conducted at each commercial scale that met the pre-determined acceptance criteria for CPPs and QAs. Information on the current manufacturing scales to produce the commercial excipient was requested as well as a summary of the data demonstrating comparability. Detailed information on comparability is also now included in the dossier. The MAH has also confirmed that process validation included process transfer activities so that the manufacturing process is stablished in both manufacturing facilities.

Comprehensive characterization studies have been included in the documentation. Therefore, the rHuPH20 is considered to be sufficiently characterized. However, no information on rHuPH20 reference standard was originally presented. Since release testing is conducted by comparison to the reference standard, the MAH was requested to update the rHuPH20 documentation by including information on the current reference standard material (qualification and stability), as well as the qualification protocol for establishing a new reference standard. The MAH has included information on the two reference standards used, and the qualification protocols for establishing new reference standards.

Several product-related and process-related impurities are routinely monitored as part of batch release. Stability of rHuPH20 in the standard formulation has been assessed. Stability protocols have been presented and are considered to cover relevant quality attributes and storage temperature conditions for the proposed shelf life.

2.4.3.8. GMO

N/A

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Nivolumab and hyaluronidase Injection, 600 mg and 10,000 Units/5 mL (120 mg and 2,000 Units/mL), is a sterile, non-pyrogenic, single-use, preservative-free, isotonic aqueous solution for subcutaneous (SC) administration provided in glass vials. While nivolumab is the active ingredient (it is a fully human IgG4 monoclonal antibody against PD-1), recombinant hyaluronidase (rHuPH20) is used as a permeation enhancer and it is considered as a known excipient, as it is used in other authorised products.

The active molecule in the nivolumab Process D-His.2 active substance is the same as in the nivolumab active substance formulated in citrate-based buffer (nivolumab Process D) that is used commercially to manufacture intravenous (IV) nivolumab finished product. Process D-His.2 active substance is manufacturer at the currently approved active substance manufacturing site, located in Cruiserath, Dublin, Ireland (BMS-Cruiserath).

A comprehensive analytical comparability study was performed with release, stress stability and extended characterization data of the active substances produced at commercial scale. The results demonstrated that the active substance obtained from each process are comparable.

Specifications and acceptance criteria for nivolumab Process D-His.2 D active substance are considered in general adequate. The proposed storage period at the recommended storage condition is considered acceptable.

Two manufacturing sites have been used to manufacture nivolumab SC injection finished product: clinical manufacturing site, and for commercial manufacturing site. Comparability has been shown between nivolumab SC injection finished product. The results showed the comparability of all the manufacturing process with the expected differences due to their different processes.

As for the active substance, the nivolumab SC injection finished product has appropriate specifications for release and stability control. A shelf-life of 3 years is proposed for nivolumab SC injection stored at the recommended storage condition of 2°C to 8°C, protected from light, and is considered acceptable.

Although the recombinant human hyaluronidase PH20 (rHuPH20) enzyme is not a novel excipient, detailed information on its manufacture, characterization and stability has been provided.

The dossier presented in support of the extension application for nivolumab subcutaneous (SC) is of good quality and provides comprehensive information regarding the new development of manufacturing Process D-His.2 active substance and the new subcutaneous finished product. After the assessment of the information available, it is concluded that, from a quality point of view, nivolumab subcutaneous (SC) is approvable.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

n/a

2.5. Non-clinical aspects

2.5.1. Introduction

A complete nonclinical information package was included in the original submission for nivolumab (see OPDIVO EPAR). Nivolumab is being developed for SC administration co-formulated with the excipient recombinant human hyaluronidase PH20 (rHuPH20), which main role is increasing the dispersion and absorption of co-formulated substances when administered subcutaneously and is not considered a novel excipient as it has been previously registered as a permeation enhancer in other commercially approved products. The applicant considers that the systemic safety profile of nivolumab SC has been well demonstrated from the non-clinical toxicological testing conducted for the IV formulation. The applicant provided additional pharmacology, pharmacokinetics and toxicology data with the objective to characterize the tolerability and PK of the novel formulation. As the existing non-clinical toxicology package was conducted with nivolumab administered intravenously, a GLP local tolerance and PK study in monkeys has been performed to additionally support the proposed clinical development of nivolumab administered by subcutaneous injection. A single-dose IV and repeat-dose (Q3Wx2) SC, with and without the excipient rHuPH20, pharmacokinetic, pharmacodynamic and local tolerance study

in monkeys has been provided. In addition, a single-dose comparability evaluation was conducted in monkeys to support a proposed change in the nivolumab active substance manufacturing process from Process C-citrate (a previously approved commercial process) to Process D-citrate (an improved manufacturing process).

One CHMP SA (EMEA/H/SA/2253/7/2018/III) was previously received for nivolumab SC regarding the non-clinical study design. In principle, a combined local tolerance and PK study in Cynomolgus monkeys with a single dose level of nivolumab in presence and in absence of the excipient rHuPH20 was considered adequate to assess the tolerability of the novel formulation and to evaluate PK.

2.5.2. Pharmacology

No additional studies have been submitted.

2.5.3. Pharmacokinetics

No additional studies have been submitted.

2.5.4. Toxicology

2.5.4.1. Repeat dose toxicity

In support of the clinical development of nivolumab SC, a study was conducted to determine systemic exposures to nivolumab BMS-936558 when administered as a single intravenous injection followed by a 3-week post-dose observation period and, to evaluate local tolerance and systemic exposures to nivolumab BMS-986298 when administered twice (3 weeks apart) as a subcutaneous formulation with or without recombinant human hyaluronidase PH20 (rHuPH20). In addition, an active substance process change bridging/comparability assessment was conducted with nivolumab IV (BMS-936558) to determine systemic exposures to nivolumab manufacturing Process C-citrate and Process D-citrate (current commercial material and next generation process respectively) in monkeys. Nivolumab SC (BMS-986298) was manufactured with Process C-citrate.

BMS-986298 was administered by SC injection at doses of 0 (control) or 50 mg/kg (with or without rHuPH20 [at a target concentration of 2000 U/mL]) and BMS-936558 (current commercial material and next generation process) was administered as a single IV injection at a dose of 50 mg/kg.

Criteria for evaluation included survival, pharmacokinetics, clinical observations, body weights, feeding behaviour, anti-drug antibodies, subset and activated T-cell immunophenotyping, ex vivo recall response to keyhole limpet hemocyanin (KLH) (immunized with KLH on Day 1 prior to dose administration), T-cell-dependent antibody response (TDAR) to KLH, spleen weight, and gross and microscopic pathology analyses.

There were no deaths and no BMS-936558- or BMS-986298-related clinical observations, body weight changes, effects on feeding behaviour, spleen weight changes, or gross or microscopic pathology findings. BMS-986298 and BMS-936558 had no pharmacological effects on TDAR to KLH, the percentages of CD25+ CD8+ cells and naive and memory T cell subtypes or the percentages of CD107a+ helper and cytotoxic T cells. However, BMS-986298- and BMS-936558-related increases were observed in other pharmacodynamic biomarkers, including the percentages of CD4 regulatory T cells (up to 2.10x control), CD25+ CD4 T cells (up to 3.97x), HLA-DR+ CD4 T cells (up to 3.11x), and HLA-DR+ CD8 T cells (up to 3.52x), Ki67+ helper T cells and Ki67+ cytotoxic T cells (up to 5.75x).

BMS-936558 and BMS-986298 enhanced ex vivo recall responses to KLH relative to vehicle control, as demonstrated by increases in the percentages of T-helper cells expressing interferon (IFN), CD69, and/or tumour necrosis factor.

2.5.4.2. Toxicokinetic data

Newly submitted studies evaluated the toxicocokinetics of nivolumab following IV and/or SC administration in monkeys. Following subcutaneous dosing 1, mean nivolumab systemic exposures AUC(0-T) at 50 mg/kg with and without rHuPH20 were 182.000 and 166.000 µg*h/mL respectively. Cmax (µg/mL) was 647 in presence of rHuPH20 and 454 in absence of excipient. Mean Tmax was 32 hours post dose with rHuPH20 and 68 hours post dose without rHuPH20. Following IV injection on Day 1, mean nivolumab systemic exposures AUC(0-T) at 50 mg/kg nivolumab using the Process C-citrate material were generally similar to those at 50 mg/kg of nivolumab using the Process D-citrate process with no substantial sex differences noted.

2.5.4.3. Local tolerance

The local tolerance of nivolumab with or without the excipient rHuPH20 was assessed as part of the repeat-dose (Q3W×2) SC toxicity study. At the subcutaneous and/or intravenous injection sites, findings considered to be related to the subcutaneous and/or intravenous dosing procedures (minimal haemorrhage that correlated with dark discoloration observed grossly at necropsy, and/or minimal to mild mixed-cell inflammation) were observed in control and treated monkeys to a similar extent and were considered incidental and not BMS-936558 or BMS-986298 related. Localized minimal degeneration/regeneration of the panniculus muscle was noted in a few control or treated monkeys and was considered to represent physical damage due to needle tract injury at subcutaneous injection sites. Furthermore, no changes related to either intravenous formulation of BMS-936558 (commercial material or next generation process), or of BMS-986298 administered subcutaneously with or without rHuPH20 were noted in this study, suggesting that the formulations were well tolerated locally.

2.5.4.4. Other toxicity studies

Following SC treatment, ADAs were detected in 1 of 6 and 2 of 6 monkeys on and/or after Day 8 at 50 mg/kg of nivolumab with and without rHuPH20, respectively. Following IV treatment, ADAs were detected in 4 of 6 and 3 of 6 monkeys on and/or after Day 8 at 50 mg/kg of nivolumab using the Process C-citrate material or the Process D-citrate material, respectively.

2.5.5. Ecotoxicity/environmental risk assessment

According to the CHMP guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) with effective date of December 2006, proteins are exempted of environmental risk assessment. Since nivolumab is a monoclonal antibody, and thus a protein, no Environmental Risk Assessment is required.

2.5.6. Discussion on non-clinical aspects

The non-clinical systemic toxicity studies with the IV formulation are directly applicable to nivolumab SC. Moreover, non-clinical efficacy from pharmacology studies can be extrapolated to the new route of administration. The potential risk of nivolumab SC from a toxicological point of view concerns local tolerance and immunogenicity, which has been addressed in a local tolerance study using SC

administration in monkeys. Toxicokinetics has been addressed in the same study.

A single dose level of nivolumab, 50mg/Kg, in presence and in absence of the excipient rHuPH20 (2000 U/mL) was considered adequate to assess the tolerability of the novel formulation according to a previous scientific advice (EMA/CHMP/SAWP/302616/2018).

The dose of nivolumab (50 mg/kg) was selected as it was well tolerated when administered intravenously in repeated dose pivotal toxicity studies. A NOAEL of 50mg/Kg IV in a 3 months repeated dose study in monkeys was established in the original dossier (see Opdivo EPAR).

There were no differences in pharmacodynamic endpoints between nivolumab administered IV or SC in presence or absence of rHuPH20, indicating that nivolumab retains its primary pharmacodynamic effect and there was not any detrimental effect of formulating the product with rHuPH20 or altering the administration route. Moreover, no differences between manufacturing process were found.

No new additional toxicities were observed following SC injection of nivolumab formulation containing 2000 IU/mL rHuPH20, when compared to the IV administration (both manufacturing process). There were no local tolerance issues observed at the SC injection sites.

Dedicated studies with rHuPH20 alone have not been provided, and no data regarding systemic exposure of rHuPH20 are available. This is acceptable as rHuPH20 is not considered a novel excipient as it has been previously registered as a permeation enhancer in other commercially approved products.

Regarding the PK, the data demonstrate an earlier Tmax with rHuPH20 SC co-administration, indicating that rHuPH20 indeed did facilitate faster absorption of nivolumab without no substantial impact on the overall nivolumab systemic exposures when administered SC without excipient. Moreover, following IV injection on Day 1, mean nivolumab systemic exposures AUC(0-T) at 50 mg/kg of BMS-936558 using the current commercial material were generally similar to those at 50 mg/kg of BMS-936558 using the next generation process. As could be expected, Cmax decreases when SC administration is used compared with IV administration, nevertheless this lower exposure does not seem to impact in the PD effect.

Overall, the presence of treatment-emergent ADAs appears to have no substantial or meaningful impact on the individual and mean nivolumab exposure. ADA formation following SC administration has been studied in humans.

The nivolumab exposure (AUC[0-T]) when administered with rHuPH20 was 182,000 µg*h/mL, which is approximately 7.6× and 1.9× the nivolumab exposure in humans at the proposed dose of 600 mg nivolumab Q2W SC and 1200 mg nivolumab Q4W SC, respectively. Moreover, the applicant provided safety margins regarding the mean exposures following IV administration in the 3-months pivotal toxicity study in monkeys (NOAEL 50mg/kg) and mean exposures following subcutaneous administration in humans at 600mg Q2W and 1200mg Q4W. Based on Cmax a safety margin of 63 and 16 were calculated and, based on AUC, a safety margin of 67 and 17 has been established respectively for the human doses.

The lack of reproductive and developmental studies with the nivolumab SC formulation is considered to be justified. It is not expected that nivolumab given SC will give rise to any additional reproductive findings not already observed following IV administration, and the excipient rHuPH20 has been studied previously. Reproductive organs were examined as part of the repeat-dose SC toxicity study with nivolumab SC in Cynomolgus monkey and no adverse findings were noted. In line with other medicinal products SC formulations approved in the EU, information related to the reproductive toxicity of the excipient has been included in the SmPC section 5.3 where it states that hyaluronidase is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no

special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. Reproductive toxicology studies with rHuPH20 revealed embryofoetal toxicity in mice at high systemic exposure but did not show teratogenic potential.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, nivolumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

In conclusion, the toxicity data provided for this application support the expectation of safety with rHuPH20 in the formulation and for the product to be given subcutaneously. BMS-986298, with and without rHuPH20 (administered SC, two doses three weeks apart), and BMS-936558, commercial material or next generation process (administered IV as a single dose), at 50 mg/kg, were well tolerated. There were no local tolerance issues observed at the SC injection sites. There were no differences in exposure or pharmacodynamic endpoints to nivolumab, when administered SC, in the presence or absence of rHuPH20. In addition, the process change for nivolumab (current commercial material or next generation process), when administered IV, did not lead to any exposure or pharmacodynamic differences. New information related to the subcutaneous formulation is included in the SmPC section 5.3.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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.

To support the use of an SC formulation of nivolumab co-formulated with rHuPH20 as an alternative route of administration to nivolumab IV for solid tumour indications in adults, the MAH conducted two clinical studies: CA20967T and CA2098KX (below table).

Table 1. Tabular Listing of Clinical Studies Supporting Nivolumab Subcutaneous Formulation Application for RCC and Multiple Solid Tumour Therapeutic Indications.

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective	Study Design	Test Product(s); Dosage Regimen; Route of Administration	No. Subjects Randomised/ Treated	Study Population	Study Status; Type of Report
PK/Efficacy/ Safety (Pivotal study)	Study Identifier: CA20967T Report location: Module 5.3.5.1	Primary Objective: *To demonstrate PK noninferiority of nivolumab SC vs nivolumab IV administration*	Phase 3, multicenter, randomised, open-label study evaluating PK and efficacy (ORR) noninferiority of nivo SC vs nivo IV and safety and tolerability of nivo SC in adult subjects with advanced or metastatic clear cell RCC after receiving no more than 2 prior treatments	Arm A: nivo SC 1200 mg coformulated[a] with rHuPH20 20,000 units Q4W Arm B: nivo IV 3 mg/kg Q2W	Total: 495 subjects randomised/492 subjects treated Arm A: N = 248/247 Arm B: N = 247/245	Adults (≥ 18 years) with advanced or metastatic clear cell RCC who are naive to immuno-oncology treatment, and have evidence of progression after having received no more than 2 prior systemic treatment regimens	Study Status: ongoing Type of Report: Primary CSR: DBL 21-Aug-2023 (DCN: 930214780)

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective	Study Design	Test Product(s); Dosage Regimen; Route of Administration	No. Subjects Randomised/ Treated	Study Population	Study Status; Type of Report
PK/Safety/ Exploratory efficacy (Supportive study)	Study Identifier: CA2098KX Report location: Module 5.3.3.2	Primary Objective: *Parts A-D: PK of nivo SC with or without rHuPH20* *Part E: PK of nivo SC 600 mg Q2W coformulated with rHuPH20*	Phase 1/2, randomised[b], open-label, multicenter study of nivo SC administered with and without rHuPH20 SC in adult subjects with advanced (metastatic and/or unresectable) solid tumours	**Parts A and B:** 1. Single nivo SC dose (ie, 1 cycle): • Part A (Group 1): nivo SC 720 mg + rHuPH20 • Part B (Group 2): nivo SC 720 mg • Part B (Group 3): nivo SC 960 mg + rHuPH20 • Part B (Group 4): nivo SC 960 mg 2. Four weeks after above mentioned single nivo SC dosing, subjects in Parts A and B received nivo IV 480 mg Q4W. 3. Four weeks after last nivo IV dose subjects in Parts A and B switch to Part C. **Part C**[d]: nivo SC 1200 mg + rHuPH20 Q4W **Part D**[d] (Group 5): nivo SC 1200 mg + rHuPH20 Q4W **Part E** (Group 6): nivo SC 600 mg coformulated[a] with rHuPH20 Q2W	Total: 139 subjects treated Parts A-B: 67 Part C: 28 (switched from Parts A-B) Part D: 36 Part E: 36	Parts A-D[c]: Adult subjects with 1 of the following tumour types: metastatic NSCLC; advanced or metastatic RCC; unresectable or metastatic melanoma; HCC; or metastatic CRC (MSI-H or dMMR) Part E: Adult subjects with mUC in addition to the tumour types listed for Parts A-D above	Study Status: ongoing Type of Report: Primary CSR: DBL 18-Nov-2022 (DCN: 930209252)

Abbreviations: CRC: colorectal cancer; CSR: clinical study report; CTD: common technical document; DBL: database lock; DCN: Document Control Number; dMMR: deficient mismatch repair; HCC: hepatocellular carcinoma; IV: intravenous; MSI-H: microsatellite instability - high; mUC: metastatic urothelial

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Bioanalytical methods

Methods to quantitate nivolumab concentrations (method ICD 416), detect anti-nivolumab antibodies(method ICDIM 140), and characterise anti-nivolumab neutralizing (method VSDCBA 68) in human serum were submitted in previous procedures and methods to detect anti- rHuPH20 antibodies (method ECL 0346) and to characterize positive anti-rHuPH20 antibodies for neutralizing activity (method ENZYMATIC-0005) in human plasma were submitted.

Sample analysis

Study CA20967T

Nivolumab concentrations

Nivolumab concentrations were analysed in multiple samples from Study CA20967T

Overall, a few pre-dose samples produced results within the range of quantitation. Several samples were reassayed due to the following reasons: Result above upper limit of quantitation, confirmatory reanalysis due to quantitating pre-dose sample, result outside the limit of quantitation that was adjusted due to deletion of calibration standard, diluted sample quantitated below limit of quantitation, no recorded result, replicate analysis coefficient of variation unacceptable, data not used due to unacceptable dilution QCs.

Incurred sample reanalysis was performed in some samples and the percent difference in more than 67% of the samples were within ±30%.

Anti-nivolumab antibodies determination

Human serum samples from Study CA20967T were analysed for anti-nivolumab antibodies . A total of 169 runs were performed, and 156 of them were accepted (92.3%). .

Multiple samples were received, analysed and reported. Some samples were not analysed per protocol/SOP, and one sample was pending analysis when the report was issued. During ADA analysis, a few samples had insufficient volume for the titer assay and additionally, the report described a few samples as grossly hemolysed (≥500 mg/dL) and 1 sample as hemolysed (≥ 140 mg/dL).

Reasons for sample reassay were the following: Deactivated due to lack of pellet formation, no recorded result and reassayed inadvertently.

Anti-nivolumab neutralizing antibodies determination

Multiple samples from Study CA20967T were received. Of those, only the some samples that confirmed positive for ADA were analysed for Nab. A total of 15 runs were performed and 12 were acceptable according to pre-defined criteria.

Overall, a few samples were reanalysed due to no recorded result.

Regarding neutralising activity results, a few samples were reported as “positive”.

Anti-rHuPH20 antibodies determination and anti-rHuPH20 neutralizing antibodies determination

A total of 1048 samples were received

for ADA determination.

Out of samples analysed, some samples screened positive, and 109 samples confirmed positive for ADA analysis.

Overall, 3 samples were reanalysed due to high %CV or anomalous result.

For NAb determination, some samples were analysed in 6 accepted runs.

Regarding neutralising activity results, 7 samples were screened positive.

Study CA2098KX

Nivolumab concentrations

Multiple samples from Study CA2098KX were received. Overall, Nivolumab concentrations were analysed in samples from Study CA2098KX. Results of 1597 samples were finally reported (results of a few samples were not reported due to different reasons, one sample was pending analysis and a few samples were not analysed per protocol/SOP).

Overall, 1 pre-dose sample produced results within the range of quantitation. Several samples were reassayed due to the following reasons: Result above upper limit of quantitation, confirmatory reanalysis due to quantitating predose sample, diluted sample quantitated below limit of quantitation, data not used due to unacceptable dilution QCs.

Incurred sample reanalysis was performed in some samples and the percent difference in more than 67% of the samples were within ±30%.

Anti-nivolumab antibodies determination

Human serum samples from Study CA2098KX were analysed for anti-nivolumab antibodies. A total of 106 runs were performed, and 101 of them were accepted (95.3%).

Multiple samples were received, analysed and reported.

During ADA analysis, a few samples had insufficient volume for the titer assay.

From all samples, the report described a few samples as grossly hemolysed (≥500 mg/dL).

Reasons for sample reassay were the following: Deactivated due to incorrectly performed confirmatory control inhibition, data not used due to unacceptable confirmatory controls and no recorded result and reassayed inadvertently.

Anti-nivolumab neutralizing antibodies determination

Multiple samples from Study CA2098KX were received. Of those, only some samples that were confirmed positive for ADA and were analysed for Nab..

Overall, a few samples were reanalysed due to no recorded result.

Regarding neutralising activity results, no samples were reported as “positive”.

Absorption

Study CA2098KX (see section “Pharmacokinetics in the target population”)

Maximum concentrations were observed 5 to 7 days after dosing, which is reflective of absorption processes following SC administration.

Table 2. Summary Statistics for PK Parameters - Evaluable PK Subjects - CA2098KX

Parameter Statistic	Treatment					
	PART A (GRP 1)	PART B (GRP 2)	PART B (GRP 3)	PART B (GRP 4)	PART D	PART E
CMAX (ug/mL)						
GEO.MEAN [N]	54.8 [22]	56.6 [18]	81.4 [10]	63.9 [17]	106 [34]	57.8 [36]
(GEO.%CV)	(51)	(34)	(41)	(30)	(46)	(31)
TMAX (h)						
MEDIAN [N]	167 [22]	167 [18]	141 [10]	168 [17]	130 [34]	130 [36]
(MIN-MAX)	(47.0 - 357)	(50.1 - 339)	(47.2 - 333)	(139 - 355)	(44.5 - 317)	(45.2 - 337)
AUC(TAU) (h*ug/mL)						
GEO.MEAN [N]	24908 [20]	27909 [16]	40264 [10]	32702 [13]	53561 [33]	15857 [35]
(GEO.%CV)	(53)	(36)	(45)	(31)	(40)	(30)
CTAU (ug/mL)						
GEO.MEAN [N]	22.2 [20]	26.9 [16]	39.2 [10]	34.8 [13]	54.4 [33]	43.6 [35]
(GEO.%CV)	(86)	(65)	(67)	(41)	(49)	(36)

Source: Table 9.2-1 of the CA2098KX Primary CSR[3]
Note: The PK values for only Nivolumab (SC) - Cycle 1 are presented.
PART A - GRP 1: nivolumab SC 720 mg + rHuPH20 2,000 units/mL
PART B - GRP 2: nivolumab SC 720 mg
PART B - GRP 3: nivolumab SC 960 mg + rHuPH20 2,000 units/mL
PART B - GRP 4: nivolumab SC 960 mg
PART D: nivolumab SC 1200 mg + rHuPH20 2,000 units/mL
PART E: nivolumab SC 600 mg coformulated with rHuPH20 2,000 units/mL

Final Population PK analysis (see section "Pharmacokinetics in the target population")

The final popPK analysis conducted to support the CA2098KX CSR and the CA20967T popPK analysis estimated the typical value (95% CI) bioavailability to be 81.5% (75.8% to 87.2%) and first-order rate of absorption to be 0.310 (95% CI: 0.281 to 0.338) day-1 when nivolumab SC was co-administered with rHuPH20.

Distribution

Not Applicable

Elimination

Not Applicable

Dose proportionality and time dependencies

Results of the non-compartmental PK analysis of CA2098KX suggest that nivolumab SC exposures increased proportionally to dose (see above table).

Pharmacokinetics in the target population

For this submission, two separate popPK analyses were conducted. One analysis was conducted to characterize the PK and evaluate covariates impacting the PK of nivolumab co-formulated with rHuPH20 following SC administration in multiple solid tumour types. The analysis included concentration-time data from the Phase 1/2 multi-tumour Study CA2098KX of nivolumab SC monotherapy, where 4 dosages of nivolumab SC (single dose of 720 mg with or without rHuPH20, single dose of 960 mg with or without rHuPH20, and 1200 mg with rHuPH20 Q4W) including an alternative SC dosing regimen of 600 mg with rHuPH20 Q2W were administered to subjects with NSCLC, RCC, HCC, CRC, or mUC. The second popPK analysis was conducted to support the benefit-risk assessment of nivolumab SC 1200 mg co-formulated with rHuPH20 Q4W with nivolumab SC and IV concentration-time data from 2L RCC subjects in the Phase 3 Study CA20967T.

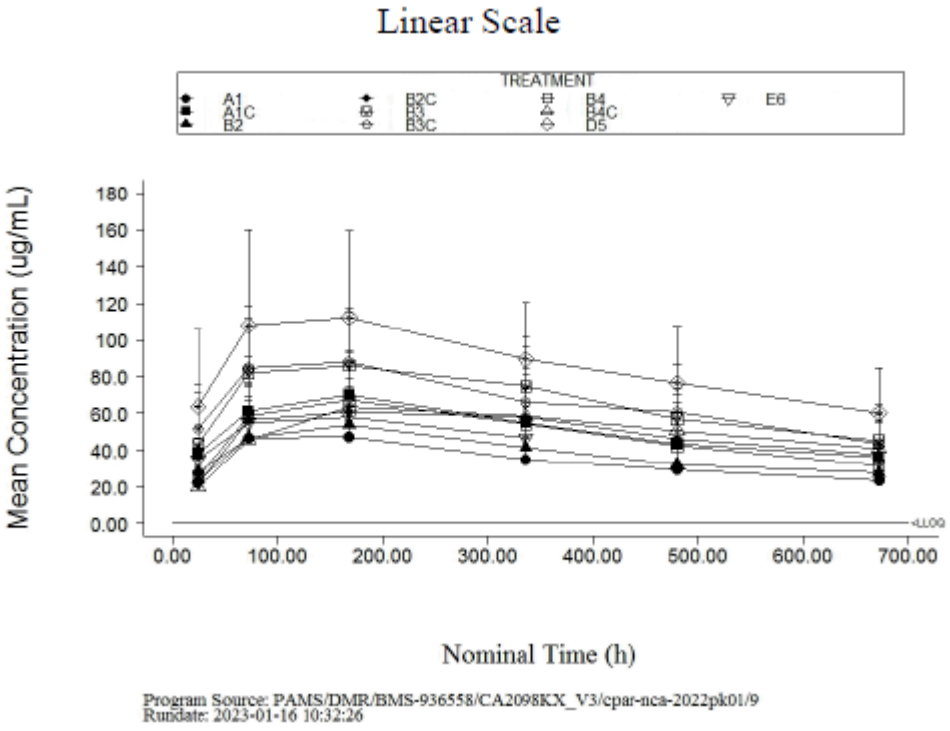
Phase 1 / 2 multi-tumour Study CA2098KX

See section 2.6.5.6 for study details.

The primary objective of this study was to describe the PK of nivolumab administered subcutaneously, with or without rHuPH20, for parts A-E.

Non-compartmental PK analysis using actual sample collection times was used to determine the primary PK endpoints of the study. Summary statistics for PK parameters by treatment group for Cycle 1 of nivolumab SC are presented in the below table. Geometric mean nivolumab exposures increased with increasing SC doses in Parts A-D. The exposures during Cycle 1 in Part E had similar overall exposure to the 1200 mg Q4W dosing regimen (Part D) when comparing both treatments over four weeks. The median time to Cmax ranged from 117 to 168 hours (~ 5 to 7 days). Plots of mean (+SD) nivolumab serum concentration vs time profile by treatment group following nivolumab SC administration on after first dose are presented in Figure 1. Subjects in Part C transitioned from Parts A and B. Ctrough was characterized during Part C, as the NCA only captured Cycle 1 following the first dose.

Figure 1. Mean (+SD) BMS-936558 (Nivolumab) Serum Concentration vs Time Profile by Treatment Group Following Nivolumab SC (BMS-986298) Administration on Cycle 1 Day 1



Program Source: PAMS/DMR/BMS-936558/CA2098KX_V3/cpar-nca-2022pk01/9
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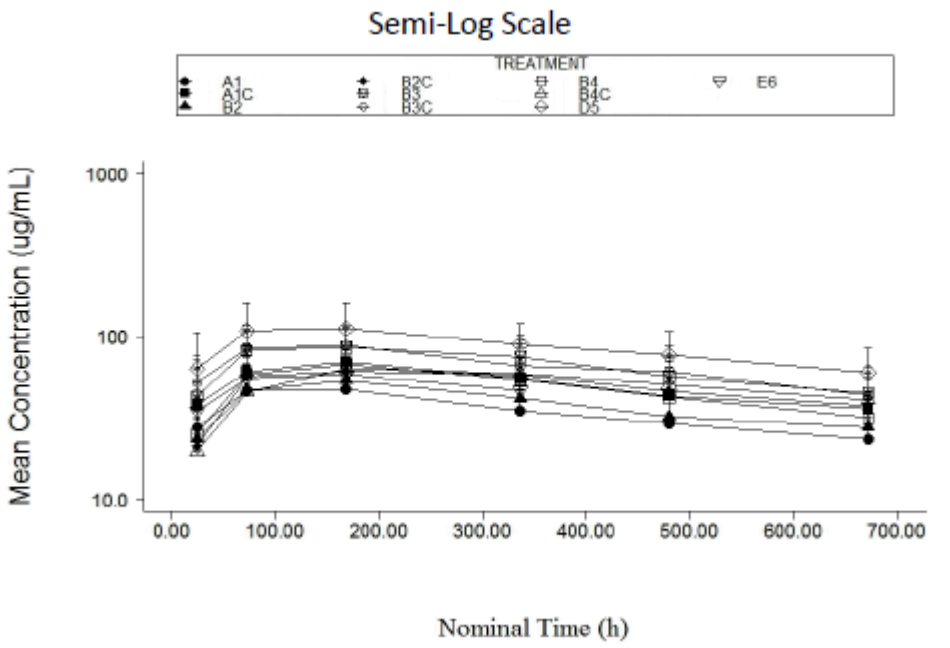

Treatment
A1 = NIVOLUMAB SC 720MG+RHUPH20
A1C = NIVOLUMAB SC 720MG+RHUPH20 - NIVOLUMAB SC 1200MG+RHUPH20
B2 = NIVOLUMAB SC 720MG
B2C = NIVOLUMAB SC 720MG - NIVOLUMAB SC 1200MG+RHUPH20
B3 = NIVOLUMAB SC 960MG+RHUPH20
B3C = NIVOLUMAB SC 960MG+RHUPH20 - NIVOLUMAB SC 1200MG+RHUPH20
B4 = NIVOLUMAB SC 960MG
B4C = NIVOLUMAB SC 960MG - NIVOLUMAB SC 1200MG+RHUPH20
D5 = NIVOLUMAB SC 1200MG+RHUPH20
E6 = NIVOLUMAB SC 600MG+RHUPH20

<LLOQ=Less than lower limit of quantitation; LLOQ = 0.200 ug/mL
Source: Figure S.9.1

Phase 3 Study CA20967T

See section 2.6.5 for study details.

Table 3: Primary Statistical Analyses of Nivolumab SC and Nivolumab IV Pharmacokinetic Co-primary Endpoints - Stratification Factors from CRF - PK Evaluable Subjects

PK parameter = Cavgd28 (µg/mL)

		On Natural Logarithmic Scale				On Original Scale		
TREATMENT AND COMPARISON	N	ADJUSTED MEAN	ADJUSTED MEAN DIF	STANDARD ERROR	90% CI	ADJUSTED GEO MEAN	ADJUSTED GMR	90% CI
SC	242	4.349		0.0225	(4.312, 4.386)	77.373		(74.555, 80.297)
IV	245	3.608		0.0220	(3.571, 3.644)	36.875		(35.565, 38.235)
SC vs. IV			0.741	0.0288	(0.694, 0.789)		2.098	(2.001, 2.200)

PK parameter = Cminss (µg/mL)

		On Natural Logarithmic Scale				On Original Scale		
TREATMENT AND COMPARISON	N	ADJUSTED MEAN	ADJUSTED MEAN DIF	STANDARD ERROR	90% CI	ADJUSTED GEO MEAN	ADJUSTED GMR	90% CI
SC	242	4.806		0.0394	(4.741, 4.871)	122.227		(114.552, 130.416)
IV	245	4.233		0.0384	(4.169, 4.296)	68.901		(64.676, 73.402)
SC vs. IV			0.573	0.0504	(0.490, 0.656)		1.774	(1.633, 1.927)

MODEL INFORMATION

Estimation Method	- REML
Residual Variance Method	- Profile
Fixed Effects SE Method	- Model-Based
Degrees of Freedom Method	- Residual
Fixed Effects	- Weight categorization (CRF), IMDC risk group (CRF) and treatment

Source: Table S.8.2.3

Note: Nivolumab exposure measures were determined from the popPK analysis.

A linear fixed effect model with treatment and stratification factors as fixed effects was fitted to the log transformed Cavgd28 and Cminss for use in estimation of effects and construction of CIs.

To assess non-inferiority of nivolumab SC to nivolumab IV, point estimates and the 2-sided 90% CIs for treatment differences on the log scale were exponentiated to obtain estimates for the ratio of geometric means and respective 90% CIs for Cavgd28 and Cminss on the original scale.

Non-inferiority of nivolumab SC to nivolumab IV was concluded if the lower limit of the 2-sided 90% CIs for the ratio of geometric means for both nivolumab Cavgd28 and Cminss were not lower than 0.8.

Nivolumab Exposures Following Administration of Nivolumab SC and Nivolumab IV (All PK Endpoints)

All PK endpoints determined for nivolumab are summarized by treatment arm in the table below. As expected, all nivolumab exposure measures were higher for nivo SC relative to nivo IV. This is consistent with model-predicted exposures for nivo SC and nivo IV that were used to support dosing regimen selection.

Table 4. Summary Statistics for All PK Endpoints - PK Evaluable Subjects

PARAMETER STATISTIC	Nivolumab SC	Nivolumab IV
CMAX1 (ug/mL)		
GEO.MEAN [N]	108 [242]	91.7 [245]
CV (%)	(33)	(35)
CMIND28 (ug/mL)		
GEO.MEAN [N]	50.8 [242]	31.9 [245]
CV (%)	(44)	(30)
CAVGD28 (ug/mL)		
GEO.MEAN [N]	78.8 [242]	37.7 [245]
CV (%)	(36)	(25)
CMAXSS (ug/mL)		
GEO.MEAN [N]	230 [242]	160 [245]
CV (%)	(39)	(28)
CMINSS (ug/mL)		
GEO.MEAN [N]	126 [242]	71.5 [245]
CV (%)	(51)	(40)
CAVGSS (ug/mL)		
GEO.MEAN [N]	182 [242]	92.5 [245]
CV (%)	(44)	(34)
CTROUGH AT WEEK 17 (ug/mL)		
GEO.MEAN [N]	123 [154]	66.3 [148]
CV (%)	(46)	(33)

Source: Table 9.1

Note: All nivolumab exposure measures with the exception of Ctrough at Week 17 (observed) were determined from the popPK analysis. Values below LLOQ (0.200 µg/mL) were set to 1/2×LLOQ (0.100 µg/mL) for computation of Ctrough at Week 17 summary statistics.

Population PK model-Phase 1/2 clinical study CA2098KX

The popPK analysis was performed using data from all subjects enrolled in the studies listed in Table 5 who received nivolumab monotherapy administered either IV or SC with rHuPH20, and for whom nivolumab concentration-time data were available. These studies were selected to enable a robust characterization of nivolumab PK in the following tumour types: NSCLC, SCLC, melanoma, RCC, SCCHN, UC, and GC and across different lines of therapy.

Phase 1/2 study CA2098KX provided nivolumab PK data to evaluate absorption after SC administration. All the other selected studies provided nivolumab PK data when administered IV across multiple tumour types, including some Phase 1 studies with intense PK sampling. These studies enabled sufficient characterization of the distribution and elimination of nivolumab.

Table 5. Description of Clinical Studies Included in the Nivolumab popPK Analyses

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Assessments
CA209001 (MDX1106-01): Phase 1, open-label, dose escalation, safety, and pharmacokinetic study of MDX-1106 in patients with selected refractory or relapsed malignancies *Multiple refractory or relapsed tumor types including melanoma, RCC, and NSCLC*	Single-dose Phase (Cycle 1): Nivo 0.3, 1, 3, or 10 mg/kg, 60 min IV infusion Re-treatment Phase (Cycle 2): Nivo 0.3, 1, 3, or 10 mg/kg, 60 min IV infusion, on D1 and D29; eligible subjects were treated with the same dose level as in the single-dose phase and could receive additional re-treatment cycles	39	Single-dose Phase: Pre-dose, 30 mins into dosing, immediately post-infusion, and 30 mins, 1, 2, 4, 6, 8, 24, 48, and 72 hrs post-infusion end time; on D8, D15, D22, D29, D43, D57, D71, and D85 Re-treatment Phase: Pre-dose and peak on treatment D1 and D29; single samples on D8, D15, D36, D43, D57, D85, and D113
CA209003 (MDX1106-03): Phase 1, open-label, multicenter, multidose, dose escalation study of BMS-936558 (MDX1106) in subjects with selected advanced or recurrent malignancies *Pathologically verified and advanced or recurrent and progressing colorectal adenocarcinoma, melanoma, NSCLC, metastatic CRPC, and RCC*	Nivo 0.1, 0.3, 1, 3, or 10 mg/kg Q2W depending upon tumor type, 60 min IV infusion for up to twelve 8-week cycles	450 (290 + 160 from amendment)	Pre-Amendment: C1: EOI and pre-infusion levels on infusion days: D1, D15, D29, and D43 and C2-C12: EOI and pre-infusion on D1 Follow-up visit 1 and visit 2: Single samples were collected Post-Amendment: Serial PK samples were collected from all subjects enrolled in 0.1, 0.3 and 1 mg/kg melanoma cohorts and first 16 subjects each from 3 and 10 mg/kg NSCLC cohorts. C1: D1 (after 60-min infusion, 4hr, 8hr), D2, D3, D5, D8, D15 (pre-infusion), C2: D1 (pre-infusion), C3: D1 (pre-infusion, after 60-min infusion), and D2, D3, D5, D8, D15 (pre-infusion) Limited PK samples were collected from subjects enrolled in 1 mg/kg RCC cohort, 1 mg/kg NSCLC and remaining 16 subjects each from 3 and 10 mg/kg NSCLC. C1: D1 (pre-infusion and after 60-min infusion), D3, D8, D15(pre-infusion), C2D1 (pre-infusion), C3: D1 (pre-infusion, after 60-min infusion), and D3, D8, D15 (pre-infusion) Follow-up visit 1 to 6: Single samples were collected Each treatment cycle is comprised of 4 doses administered on D1, D15, D29, and D43 of the cycle
CA209005 (ONO-4538-01): Phase 1 single dose study to evaluate of safety, tolerability, and pharmacokinetics in subjects with progressive or recurrent solid tumors *Melanoma and NSCLC*	Nivo 1, 3, 10, and 20 mg/kg Q3W for 1st dose then Q2W (60 min IV infusion)	24 (up to 6 subjects at each dose level)	Single-dose Phase: D1: 1 hour after the start and 2 and 8 hours after EOI, Pre-D2, pre-D3; pre-D4; D8, D15, and D22 or study discontinuation Multiple-dose Phase: Before administration on D1; before administration and immediately after the end of administration on D15; and D29 or study discontinuation Extended-treatment phase: Before administration on D1; before administration on D15 and D29; before administration and immediately after the end of administration on D43 and D57
CA209009: An Exploratory Study to Investigate the Immunomodulatory Activity of Various Dose Levels of Anti-Programmed-Death-1 (PD-1) Antibody (BMS-936558) in Subjects with Metastatic Clear Cell Renal Cell Carcinoma (RCC) *Metastatic clear cell RCC*	Nivo 0.3, 2, and 10 mg/kg Q3W, 60 min IV infusion	80	C1: predose, EOI(1h), 3h, 7h, 24h, 72h, 168h C2: predose, 168h C3, 4, 8: predose C7: predose and EOI (1h) C8: predose and 2 follow samples Cycle defined as 3 weeks
CA209010: Phase 2, randomized, blinded, dose-ranging study of BMS-936558 (MDX-1106) in subjects with progressive advanced/metastatic clear cell RCC who have received prior antiangiogenic therapy *Advanced/metastatic clear cell RCC*	Nivo 0.3, 2, or 10 mg/kg Q3W, 60 min IV infusion	167	C1: D1 EOI and 3 hours after infusion, D3 - 5 (48 - 96 hours), D7 - 15 (144 - 336 hours) C2 and 4: D1 predose C7: D1 predose, 1 and 3 hours after infusion, D3 - 5 (48 - 96 hours), D7 - 15 (144 - 336 hours) C8: D1 predose Follow-up visit 1 and 2 Cycle defined as 3 weeks
CA209017: An Open-Label, Randomized Phase 3 Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer (NSCLC) *Advanced/metastatic SQ NSCLC*	Nivo 3 mg/kg Q2W, 60 min IV infusion	132	D1 (C1) and D99 (C8), pre-infusion, after 60-minute infusion and pre-infusion at C2 and 3 and every 8th Cycle after C8D1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle

Protocol #: Title *Study Population*	Treatment	Planned Sample Size*	Assessments
CA209025: A randomized , open-label, phase 3 study of nivolumab (BMS-936558) vs everolimus in subjects with advanced or metastatic clear-cell RCC who have received prior antiangiogenic therapy. *Advanced/metastatic clear cell RCC.*	Nivo 3 mg/kg Q2W, 30 or 60 min IV infusion	403 (nivolumab treated)	Nivolumab 3 mg/kg: C1D1: predose and EOI (1 hour), Dose 2 predose C2D1: predose C3D1: predose C4D1: predose and EOI (1 hour) Every fourth cycle Day 1 predose and Follow-up visit 1 and 2
CA209026: An open-label, randomized, phase 3 trial of nivolumab versus investigator's choice chemotherapy as first-line therapy for stage IV or recurrent PD-L1+ non-small cell lung cancer *Advanced/recurrent PD-L1+ SQ and non-SQ NSCLC*	Nivo 3 mg/kg Q2W, 60 min IV infusion	330	Arm A: D1 at C1, C3, C8 and D1 every 8 cycle, and 2 follow samples Arm B: (crossover subjects for nivo treatment): D1 at C1, C3, C8 and D1 every 8th cycle after C8D1 until discontinuation of study treatment or completion of 2 years of study treatment
CA209032: Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab in patients with advanced or metastatic solid tumors *Advanced UC from a multi-tumor study*	Nivo 3 mg/kg Q2W, 60 min IV infusion	78	Pre-dose at Weeks 1, 3, 5, and 13, then every 16 weeks
CA209037: A randomized, open label Phase 3 trial of BMS-936558 (nivolumab) versus Investigators choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA4 therapy *Advanced/metastatic melanoma who progressed post anti-CTLA4 therapy*	Nivo 3 mg/kg Q2W, 60 min IV infusion	268	D1 (C1) and D99 (C8), preinfusion, after 60-min infusion and preinfusion at C2 and 3 and every 8th Cycle after C8D1 until discontinuation of study treatment Each 14 day dosing period is considered a cycle. D1 (C1) and D99 (C8), preinfusion, after 60-min infusion and preinfusion at C2 and 3 and every 8th Cycle after C8D1 until discontinuation of study treatment, and two follow up samples up to 100 days from last dose Each 14-day dosing period is considered a cycle.
CA209051 (ONO-4538-02): A multicenter, open-label uncontrolled study to evaluate the efficacy and safety of ONO-4538 in subjects with unresectable, advanced (Stage III or IV) or recurrent malignant melanoma in a multicenter, open-label uncontrolled trial. *Unresectable (stage III or IV) or recurrent malignant stage 3/4 melanoma*	Nivo 2 mg/kg Q3W, 60 min IV infusion	35	Treatment phase: Between initiation of the study and pre dose, post-dose, and 3 hours after start of infusion on D1; on D3 (48 to 96 hours after start of infusion) and D10 (144 to 336 hours after start of infusion); pre-dose and just before the end of infusion on D22; and on D43 or at the end of the treatment Follow-up Phase: 28 days (4 weeks) after the final dose of ONO-4538 or at the time of discontinuation within 4 weeks after the final dose and between 6 and 12 weeks after the final dose
CA209057: An Open-Label, Randomized Phase 3 Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Non-Squamous Cell Non-Small Cell Lung Cancer (NSCLC) Advanced/metastatic *NSQ NSCLC*	Nivo 3 mg/kg Q2W, 60 min IV infusion	287	D1 (C1) and D99 (C8), pre-infusion, after 60-min infusion and pre-infusion at C2 and 3 and every 8th Cycle after C8D1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle
CA209063: A single-arm Phase 2 study of BMS-936558 in subjects with advanced or metastatic squamous cell non-small cell lung cancer who have received at least two prior systemic regimens Advanced/metastatic *SQ NSCLC*	Nivo 3 mg/kg Q2W, 60 min IV infusion	100	D1 (C1) and D99 (C8), pre-infusion, after 60-min infusion and pre-infusion at C2 and 3 and every 8th Cycle after C8D1 until discontinuation of study treatment Each 14-day dosing period is considered a cycle
CA209066: Phase 3, randomized, double-blind study of BMS-936558 (nivolumab) vs dacarbazine in subjects with previously untreated, unresectable, or metastatic melanoma *Previously untreated unresectable or metastatic melanoma*	Nivo 3 mg/kg Q2W, 60 min IV infusion	206 (nivolumab treated)	C1: D1 predose and EOI (1 hr), D15 and D29 (Predose) C3: D15 predose and EOI (1hr) Cycle defined as 6 weeks.

Protocol #: Title *Study Population*	Treatment	Planned Sample Size[a]	Assessments
CA209067: Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma. *Previously untreated, unresectable or metastatic melanoma*	A: Nivo 3 mg/kg Q2W B: Nivo 1 mg/kg + ipi 3 mg/kg Q3W for 4 doses then nivo 3 mg/kg Q2W C: Ipi 3 mg/kg Q3W for a total of 4 doses + Nivo-placebo on Weeks 1, 3, 4 and 5 for cycles 1 and 2 then Q2W Nivo: 60 min IV infusion Ipi: 90 min IV infusion	915	Pre-dose sample at D1, Week 3 and 4 C1, D1 C2, D1 C3 and C4, and first 2 follow-up visits (approximately up to 100 days from the discontinuation study drug) End of infusion samples at D1 C1, 2 and 4.
CA209141: An open-label, randomized Phase 3 clinical trial of nivolumab vs therapy of investigator's choice in recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN) *Recurrent or metastatic platinum-refractory SCCHN*	Nivo 3 mg/kg Q2W, 60 min IV infusion	240	Week 1, 5, and 13 Day 1: predose D1 of every 16th week until discontinuation of study treatment: predose Follow-up visits 1 and 2
CA209275: A Phase 2 single arm clinical trial of nivolumab (BMS-936558) in subjects with metastatic or unresectable urothelial cancer who have progressed or recurred following treatment with a platinum agent *Metastatic or unresectable UC*	Nivo 3 mg/kg Q2W, 60 min IV infusion	242	Pre-dose on D1 of C1, 2, 4, and 7; D1 of every 8 cycles until discontinuation of study treatment and first 2 follow-up visits FU1 and 2
CA2098KX: Phase 1/2 pharmacokinetic multi-tumor study of subcutaneous formulation of nivolumab monotherapy *NSCLC, RCC, unresectable or*	Part A: Group 1: 720 mg nivo SC with rHuPH20, manually by syringe (single dose only) Part B: Group 2: 720 mg nivo SC, manually by syringe pump (single dose only)	179	Parts A and B: C1D1 predose, C1D2, C1D4 (±1 day), C1D8 (±2 days), C1D15 (±5 days), and C1D21 (±5 days) C2D1 predose and EOI, C2D15 (±5 days) C3D1 predose, C5D1 predose, C9D1 predose Predose every 6 cycles starting with C13D1 and first 2 follow-up visits FU1 and 2
metastatic melanoma, HCC, MSI-H or dMMR CRC, mUC	Group 3: 960 mg nivo SC with rHuPH20, manually by syringe Group 4: 960 mg nivolumab SC, manually by syringe pump Part C: 1200 mg nivo SC with rHuPH20 Q4W, manually by syringe Part D: 1200 mg nivo SC with rHuPH20 Q4W, manually by syringe Part E: 600 mg nivo SC co-formulated with rHuPH20 Q2W, manually by syringe		Part C: C1D1, C2D1, C3D1, C5D1, and C9D1 predose Predose every 6 cycles starting with C13D1 and first 2 follow-up visits FU1 and 2 Part D: C1D1 predose, C1D2, C1D4 (±1 day), C1D8 (±2 days), C1D15 (±5 days), and C1D21 (±5 days) C2D1 predose, C2D15 (±5 days) C3D1 predose, C5D1 predose, C9D1 predose Predose every 6 cycles starting with C13D1 and first 2 follow-up visits FU1 and 2 Part E: C1D1 predose, C1D2, C1D4 (±1 day), C1D8 (±2 days), C1D15 predose C2D1 and C2D15 predose C3D1 predose, C3D2, C3D4 (±1 day), C3D8 (±2 days), C3D15 C5D1, C9D1 Predose every 6 cycles starting with C13D1 and first 2 follow-up visits FU1 and 2

[a] As per protocol

Analysis dataset

The popPK analysis dataset was representative of the included studies. As the current analysis serves as a prespecified model for the analysis of nivolumab PK and exposures in Study CA20967T, in which nivolumab SC is co-administered with rHuPH20, the focus is on characterizing the PK of nivolumab SC co-administered with rHuPH20 only. Accordingly, about 25% of subjects in Study CA2098KX receiving nivolumab SC without co-administration with rHuPH20 were excluded from the analysis (table below).

Table 6. Subjects Included in the Population Pharmacokinetic Analysis Dataset by Study

Study	Nivolumab Treated	PK Database[a]	Flagged for Exclusion	Included in the PopPK Analysis (% of subjects in PK Database)
MDX1106-01 (CA209001)	39	39	0	39 (100)
MDX1106-03 (CA209003)	306	310	6	304 (98.1)
ONO-4538-01 (CA209005)	17	17	0	17 (100)
CA209009	91	91	1	90 (98.9)
CA209010	167	171	4	167 (97.7)
CA209017	132	127	2	125 (98.4)
CA209025	406	404	1	403 (99.8)
CA209026	393	393	52	341 (86.8)
CA209032	266	266	0	266 (100)
CA209037	268	239	7	232 (97.1)
ONO-4538 (CA209051)	35	35	0	35 (100)
CA209057	287	282	2	280 (99.3)
CA209063	117	118	3	115 (97.5)
CA209066	206	192	14	178 (92.7)
CA209067	312	312	2	310 (99.4)
CA209141	236	213	41	172 (80.8)
CA209275	270	252	23	229 (90.9)
CA2098KX	139	139	35	104 (74.8)
Total	**3687**	3600	193	3407 (94.6)

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
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Table 7. Summary of Covariates in the Population Pharmacokinetic Analysis Dataset by Administration Route

	IV (N = 3303)	SC (N = 104)	Overall (N = 3407)
Age (years)			
Mean (SD)	61.2 (11.2)	64.9 (11.4)	61.3 (11.2)
Median [Min, Max]	62 (18, 90)	66.5 (24, 93)	62 (18, 93)
Missing, n (%)	40 (1.21)	0 (0)	40 (1.17)
Baseline body weight (kg)			
Mean (SD)	78.3 (19.1)	77.5 (18.2)	78.3 (19)
Median [Min, Max]	76.8 (34.1, 180)	77.3 (42, 133)	76.8 (34.1, 180)
Missing, n (%)	1 (0.0303)	0 (0)	1 (0.0294)
Baseline albumin (g/dL)			
Mean (SD)	3.89 (0.504)	3.63 (0.542)	3.87 (0.509)

Median [Min, Max]	3.9 (1.4, 5.3)	3.66 (2.3, 4.7)	3.9 (1.4, 5.3)
Missing, n (%)	1351 (40.9)	0 (0)	1351 (39.7)
Baseline EGFR (mL/min/1.73 m^2)			
Mean (SD)	80.4 (22)	79.1 (22)	80.3 (22)
Median [Min, Max]	82.6 (18.1, 191)	80.8 (32.4, 143)	82.6 (18.1, 191)
Missing, n (%)	48 (1.45)	0 (0)	48 (1.41)
Sex, n (%)			
Female	2237 (67.7)	67 (64.4)	2304 (67.6)
Male	1066 (32.3)	37 (35.6)	1103 (32.4)
Race, n (%)			
Missing	6 (0.2)	0 (0)	6 (0.2)
White	2930 (88.7)	91 (87.5)	3021 (88.7)
Black/African American	92 (2.8)	3 (2.9)	95 (2.8)
Asian	218 (6.6)	2 (1.9)	220 (6.5)
Other	57 (1.7)	8 (7.7)	65 (1.9)
PS, n (%)			
0	1413 (42.8)	38 (36.5)	1451 (42.6)
1	1826 (55.3)	66 (63.5)	1892 (55.5)
2	61 (1.8)	0 (0)	61 (1.8)
Missing	3 (0.1)	0 (0)	3 (0.1)
Tumor type, n (%)			
NSCLC	1000 (30.3)	31 (29.8)	1031 (30.3)
MEL	875 (26.5)	5 (4.8)	880 (25.8)
Others[a]	102 (3.1)	35 (33.7)	137 (4.0)
RCC	695 (21.0)	23 (22.1)	718 (21.1)
SCLC	95 (2.9)	0 (0)	95 (2.8)
Bladder	306 (9.3)	9 (8.7)	315 (9.2)
Gastric	58 (1.8)	0 (0)	58 (1.7)
SCCHN	172 (5.2)	1 (1.0)	173 (5.1)
Dose regimen			
600 mg Q2W	0 (0)	36 (34.6)	36 (1.1)
1200 mg Q4W	0 (0)	50 (48.1)	50 (1.5)
Other	3303 (100.0)	18 (17.3)	3321 (97.5)
Coadministration with rHuPH20			
Yes	0 (0)	104 (100.0)	104 (3.1)
No	3303 (100.0)	0 (0)	3303 (96.9)

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
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Source: Analysis-Directory/reports/Table3.3.5.2-1.rtf

[a] Others includes: Colorectal Cancer, Pancreatic Cancer, Prostate cancer, Triple Negative Breast Cancer and Other. Other is 4 subjects from study CA209-005.

Base model

A combined IV/SC popPK model was previously derived by modifying an established nivolumab IV popPK model13 to determine the KA and F of nivolumab SC administered with and without rHuPH2014. The available nivolumab SC concentration data from CA2098KX study were pooled with the existing nivolumab IV concentration data from an additional 19 historical nivolumab IV studies to extend the combined IV/SC popPK model. An extravascular absorption compartment was added to the established nivolumab IV popPK model and the absorption PK parameters KA and F were estimated.

The structural model consisted of two compartments, with zero-order IV infusion when nivolumab was administered by the IV route and first order absorption when nivolumab was administered by the SC route, and time-varying clearance with proportional residual error model and random effects on CL, VC, VP, EMAX, KA, and F.

Base model development consisted of re-estimating parameters for the previously developed full model. Various IIV and RUV models were evaluated. The addition of additive error did not improve the BIC. Model base had a lower BIC however the condition number was higher, indicating the model was over-parameterized.

The condition number of the final base model (base1new) was found to be 81.78, indicating that the model is stable.

Final model

The final model is to provide the best parsimonious description of the data. The final model was developed from the base model by further excluding covariate-parameter relationships that are not statistically significant. In addition, the regimen effect (600 mg Q2W vs 1200 mg Q4W) was evaluated as a covariate on F.

The final model was derived by removing all non-significant covariates (defined as the 95% CI including the null value) from the base model. Each of the covariates removed were added back one at a time to evaluate the significance of the covariate. Bayesian information criterion was used to ensure a parsimonious model.

The final model and additional covariate steps along with the respective BIC values are presented below. Based on parameter precision, condition number, and BIC, full1 model was selected as the final model and represents a parsimonious model

To evaluate the potential difference in bioavailability between the two SC dosing regimens of interest (600 mg Q2W and 1200 mg Q4W), a regimen effect was added on F (evaluated in full1-REGM2). The BIC was higher than for the final model and the covariate effect of regimen was not statistically significant (95% CI included the null value), indicating there was no dosing regimen effect on F.

Table 8. Parameter Estimates of the Final Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL [L/h]	θ_1	0.0108	1.75E0-4 (1.63)	0.0104 - 0.0111
VC [L]	θ_2	4.29	0.0334 (0.777)	4.23 - 4.36
Q [L/h]	θ_3	0.0312	0.00108 (3.46)	0.0291 - 0.0333
VP [L]	θ_4	2.73	0.0623 (2.29)	2.60 - 2.85
CL_{EMAX}	θ_5	-0.263	0.0204 (7.78)	-0.303 - -0.223
CL_{T50}	θ_6	1.53E+03	72.8 (4.76)	1.39E+03 - 1.67E+03
CL_{HILL}	θ_7	3.84	0.813 (21.2)	2.24 - 5.43
KA	θ_8	0.0129	6.15E-04 (4.77)	0.0117 - 0.0141
F1	θ_9	0.815	0.0291 (3.58)	0.758 - 0.872
CL_{WTB}	θ_{12}	0.607	0.0306 (5.04)	0.547 - 0.666
CL_{GFR}	θ_{13}	0.166	0.0210 (12.7)	0.125 - 0.207
CL_{SEX}	θ_{14}	-0.169	0.0165 (9.72)	-0.202 - -0.137
CL_{PS}	θ_{15}	0.169	0.0135 (7.98)	0.143 - 0.196
VC_{WTB}	θ_{17}	0.621	0.0297 (4.78)	0.563 - 0.680
VC_{SEX}	θ_{18}	-0.136	0.0147 (10.9)	-0.165 - -0.107
$F1_{SEX}$	θ_{26}	0.895	0.0574 (6.41)	0.783 - 1.01
$F1_{PS}$[f]	θ_{27}	1.00		

Random Effects				
ZCL [-]	$\omega_{1,1}$	0.122 (0.349)	0.00579 (4.76)	0.110 - 0.133
ZVC [-]	$\omega_{2,2}$	0.0853 (0.292)	0.00711 (8.33)	0.0714 - 0.0993
ZVP [-]	$\omega_{3,3}$	0.212 (0.461)	0.0322 (15.2)	0.149 - 0.276
ZEMAX [h]	$\omega_{4,4}$	0.0537 (0.232)	0.00759 (14.1)	0.0388 - 0.0685
ZKA	$\omega_{5,5}$	0.132 (0.364)	0.0232 (17.5)	0.0869 - 0.178
F1	$\omega_{6,6}$	0.807 (0.898)	0.213 (26.4)	0.390 - 1.22
ZCL:ZVC	$\omega_{1,2}$	0.0402 (0.395)	0.00332 (8.24)	0.0337 - 0.0467
ZKA:F1	$\omega_{5,6}$	0.180 (0.551)	0.0588 (32.6)	0.0650 - 0.295
Residual Error				
Proportional [-]	θ_{10}	0.188	0.00281 (1.49)	0.183 - 0.194

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Program Source/nm/full1/reports/full1_RTF.rtf

Note: $CL0_{REF}$ is the typical value in a reference subject weighing 80 kg, EGFR of 90 mL/min/1.73 m^2, 65 year old male with PS = 0. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.
Note1 : ETA shrinkage (%): ETA_CL: 12.3; ETA_VC: 22.3; ETA_VP: 44.3; ETA_EMAX: 51.2; ETA_KA: 20.1; ETA_F: 24.2; EPS shrinkage (%): 17.2.
Note 2: Between-subject variability in Q and VP and the covariance between Q and VP were fixed to the corresponding values as CL0 and VC.

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

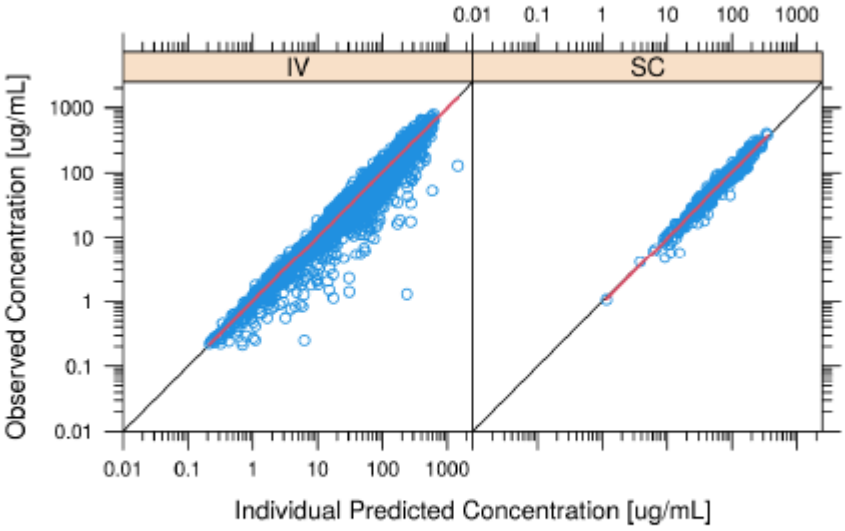
[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters.

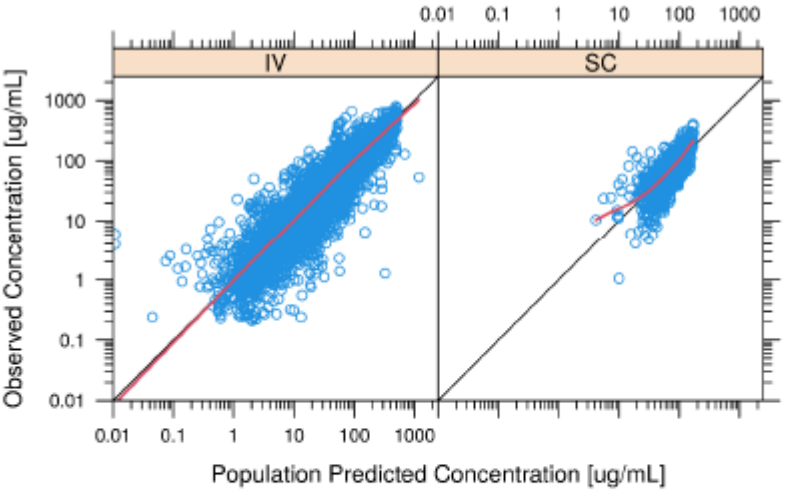
[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$).

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

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

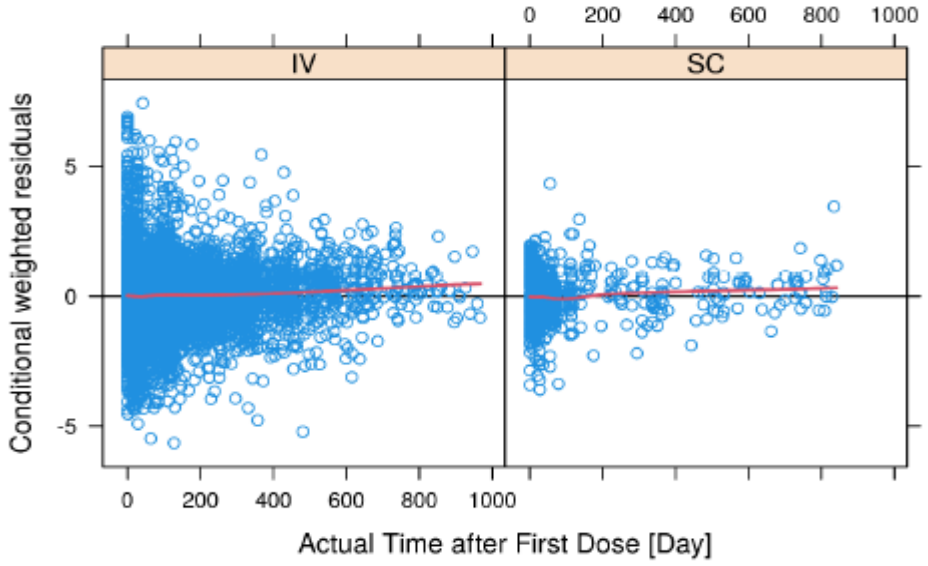
Figure 2. Observed Versus Predicted Population Average and Individual Concentration in the Final Population Pharmacokinetic Model by Administration Route





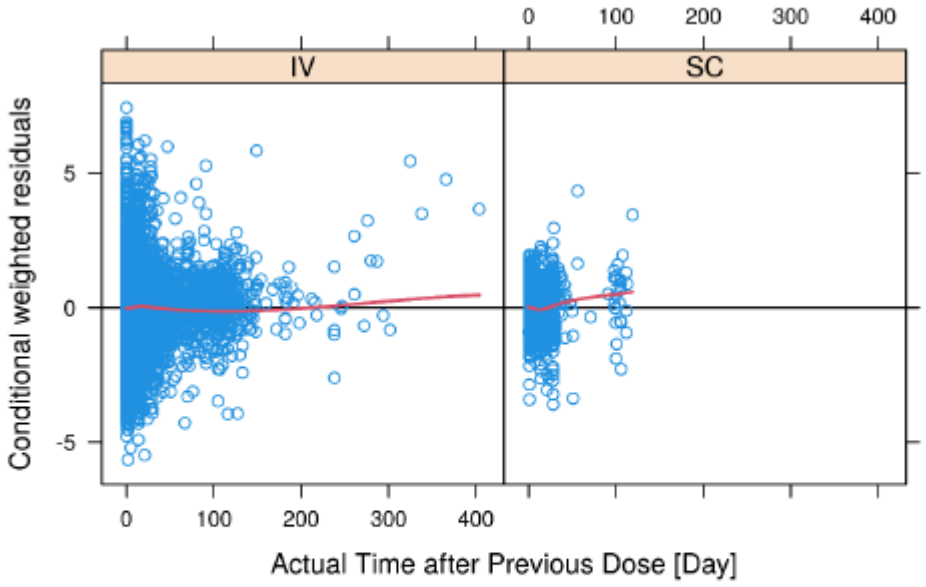
Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx
Note 1: Solid red line represents linear regression line. Solid black line represents line of identity

Figure 3. CWRES versus Time after First Dose in the Final Population Pharmacokinetic Model by Administration Route



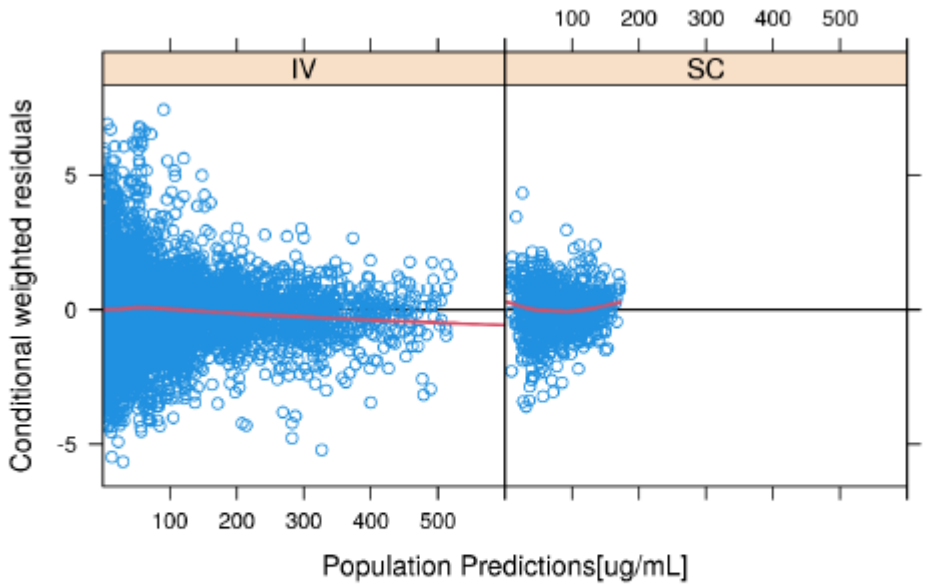
Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx
Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Figure 4. CWRES versus Time after Previous Dose in the Final Population Pharmacokinetic Model by Administration Route



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx
Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Figure 5. CWRES versus Population Predicted Concentration in the Final Population Pharmacokinetic Model by Administration Route

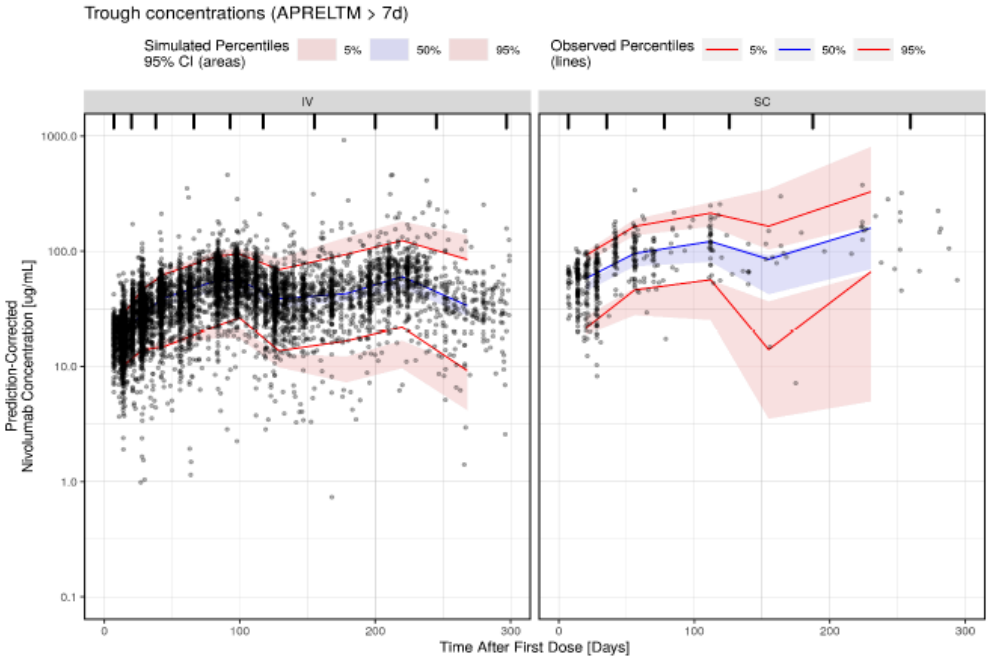


Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx
Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Model evaluation

The final popPK model of nivolumab was also evaluated using pcVPC with 1000 simulations (below figures).

Figure 6. Prediction-Corrected Visual Predictive Check of Trough Nivolumab Concentrations versus Actual Time after First Dose by Administration Route in the Final Population Pharmacokinetic Model

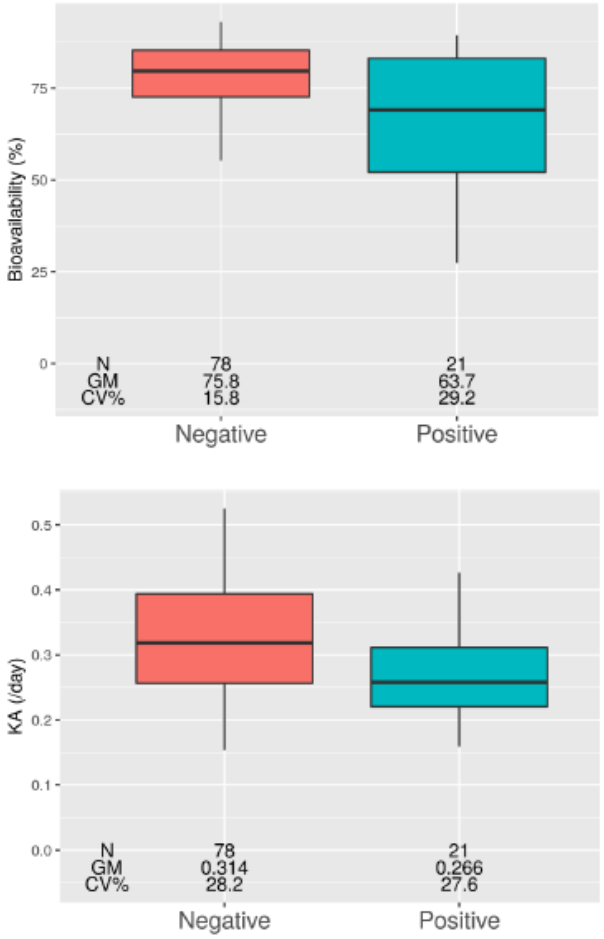


Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx

Model Application

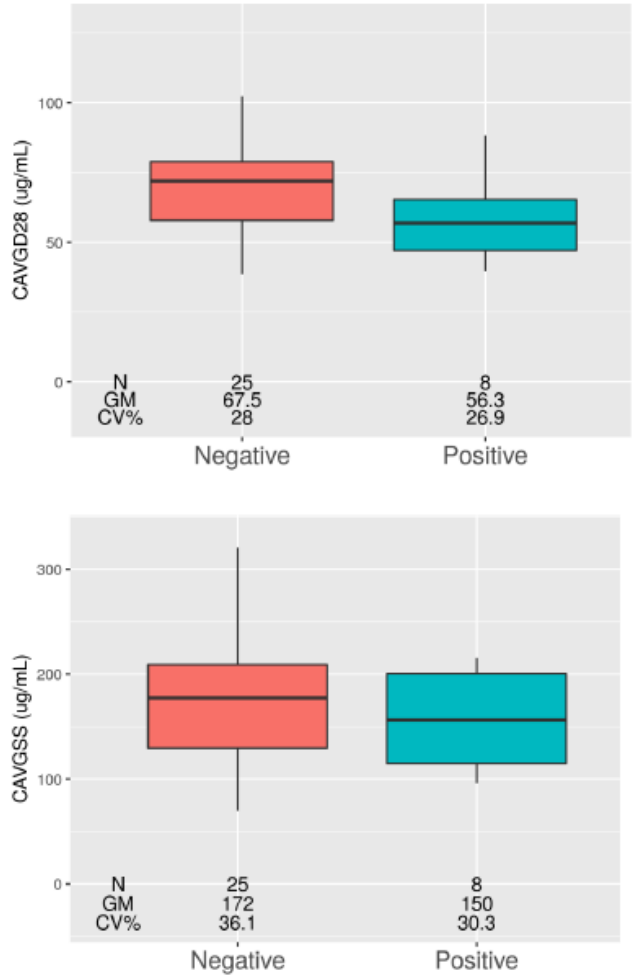
Comparison of Nivolumab SC PK Parameters and Exposures by ADA Status (Anti-nivolumab Antibodies)

Figure 7. Comparison of Nivolumab SC PK parameters (Bioavailability and Absorption Rate) in Nivolumab ADA+ and ADA- Subjects in Study CA2098KX



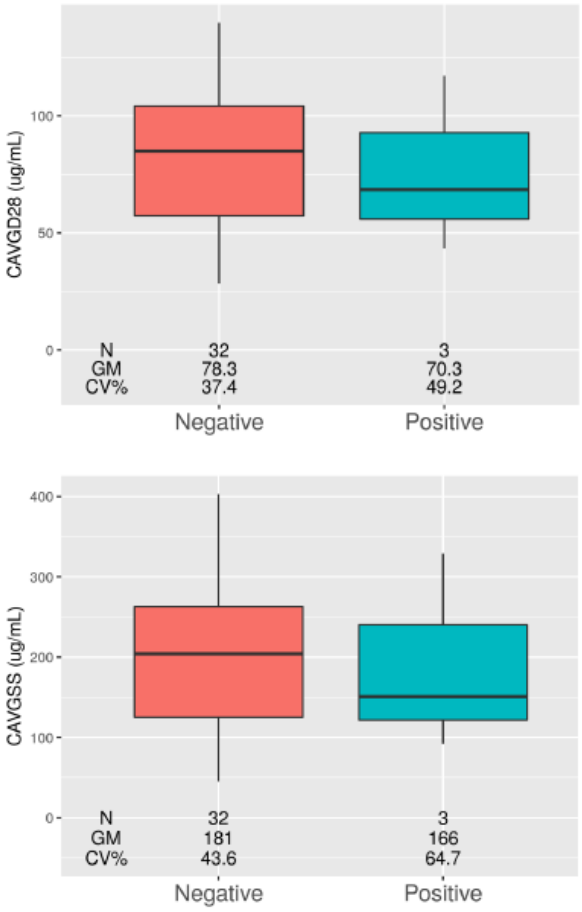
Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.
Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx

Figure 8. Comparison of Nivolumab SC Exposures (Cavgd28 and Cavgss) in ADA+ and ADA- Subjects in Study CA2098KX Part E Receiving 600 mg SC Q2W



Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.
Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx

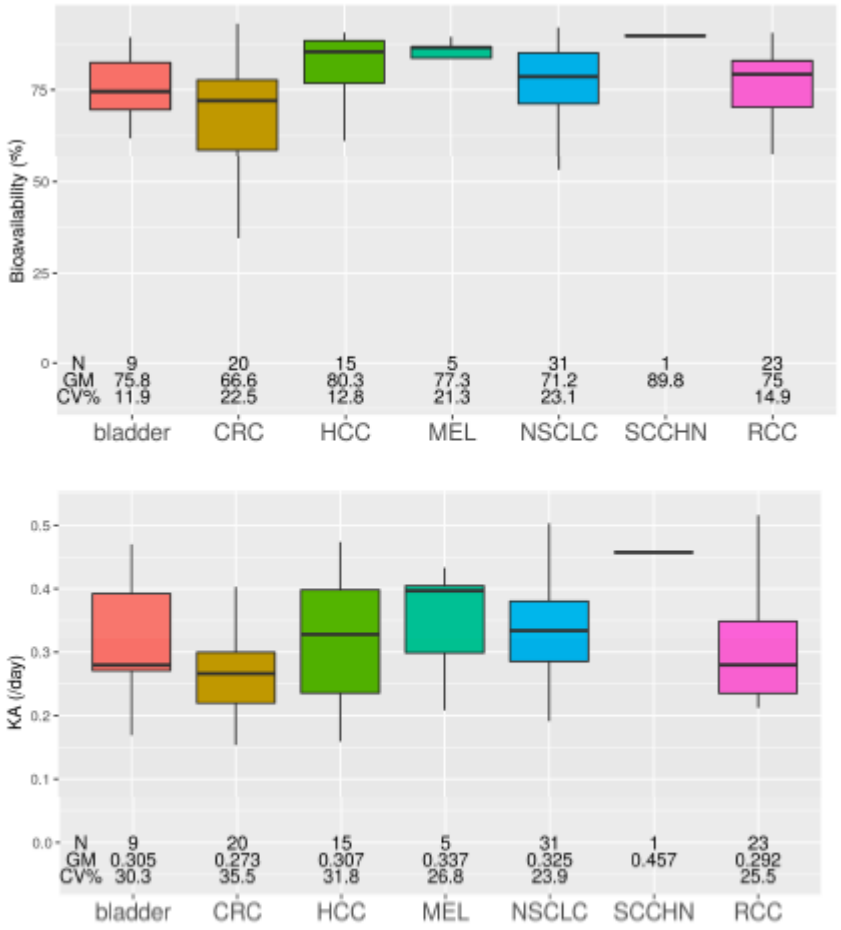
Figure 9. Comparison of Nivolumab SC Exposures (Cavgd28 and Cavgss) in ADA+ and ADA- Subjects in Study CA2098KX Part D Receiving 1200 mg SC Q4W



Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.
Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx

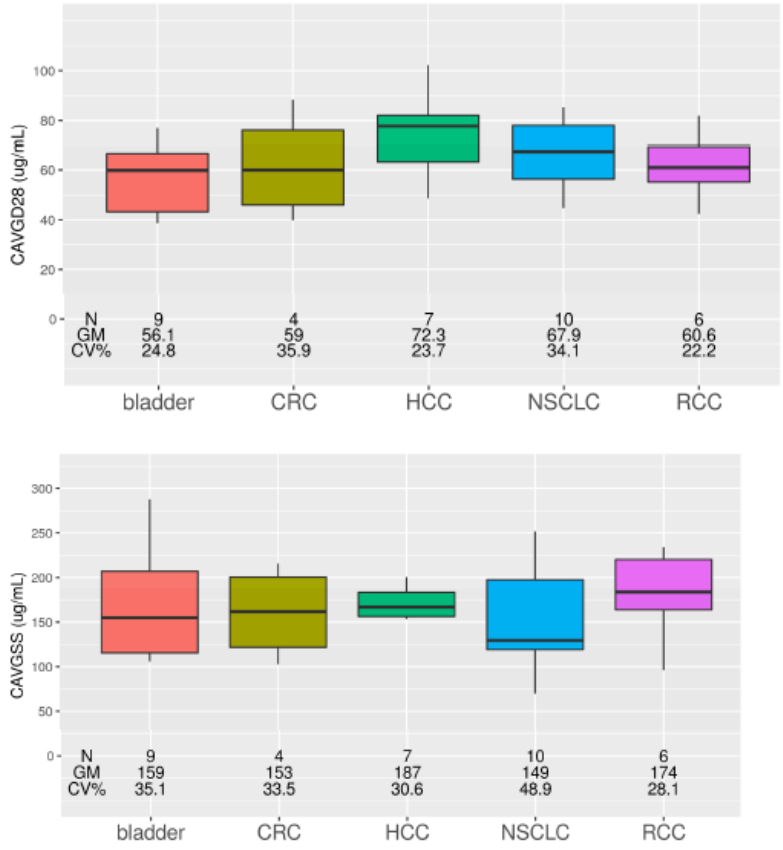
Comparison of Nivolumab SC PK Parameters and Exposures by Tumor Type

Figure 10. Comparison of Nivolumab SC PK parameters (Bioavailability and absorption Rate) of Subjects in Study CA2098KX by Tumor Type



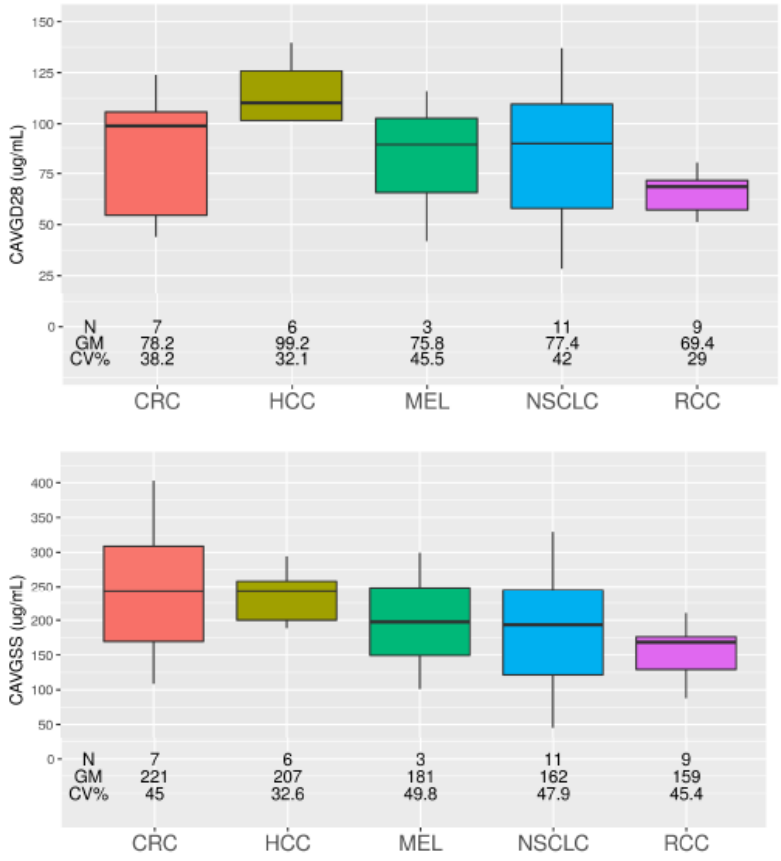
Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx

Figure 11. Comparison of Nivolumab SC Exposures (Cavgd28 and Cavgss) of Subjects in Study CA2098KX Part E Receiving 600 mg SC Q2W by Tumor Type



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx

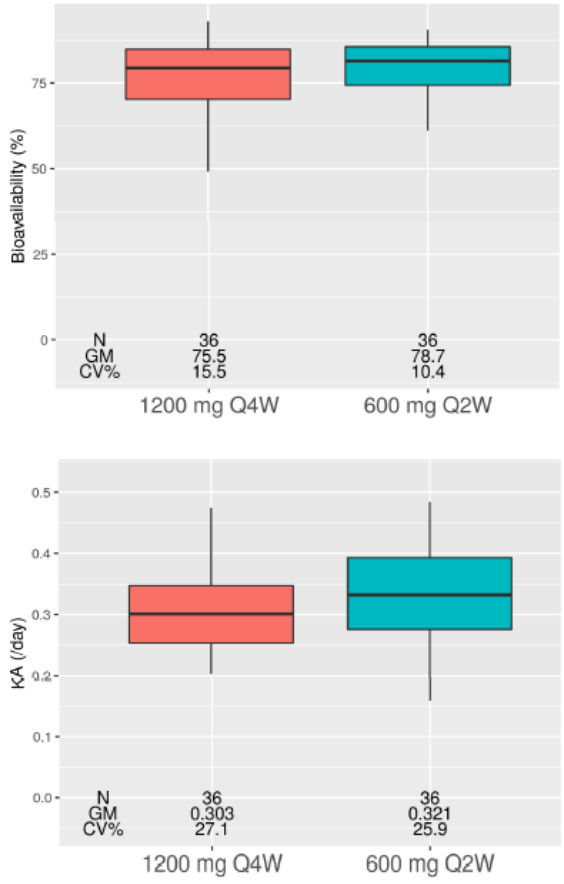
Figure 12. Comparison of Nivolumab SC Exposures (Cavgd28 and Cavgss) of Subjects in Study CA2098KX Part D Receiving 1200 mg SC Q4W by Tumor Type



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx

Comparison of Nivolumab SC PK Parameters by SC Dosing Regimen

Figure 13. Comparison of Nivolumab SC PK parameters (Bioavailability and Absorption Rate Constant) of Subjects in Study CA2098KX Part D and E by Dosing Regimen



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.docx

Table 9. Comparison of Nivolumab SC Exposures for 1200 mg Q4W and 600 mg Q2W

Exposure (µg/mL)	1200 mg Q4W Geo.Mean (%CV) N=36	600 mg Q2W Geo.Mean (%CV) N=36	% Diff GM[a]
CAVG1	78.5 (37.4)	47.3 (28.9)	-39.7
CMAX1	109 (39.7)	58.2 (29)	-46.6
CMIN1	51.6 (41.6)	41 (30.8)	-20.5
CAVGD28	78.5 (37.4)	63.3 (29)	-19.4
CMINSS	126 (51.3)	136 (39.4)	7.94
CMAXSS	228 (42.2)	183 (33.9)	-19.7
CAVGSS	180 (43.9)	163 (35.7)	-9.44

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc/prd/scppk-2023/final/
Program Source: Analysis-Directory/R/scripts/PPK_report-nivo-sc.Rmd
Source: Analysis-Directory/R/export/exp.stats.600.1200.csv

[a] Percent difference calculated relative to the reference exposure for 1200 mg Q4W

The purpose of the pharmacometric analysis is to support the benefit-risk assessment of nivolumab SC (BMS-986298) 1200 mg co-formulated with rHuPH20 20,000 units Q4W, relative to nivolumab IV (BMS-936558) 3 mg/kg Q2W for the treatment of previously treated advanced or metastatic cc RCC.

The previous characterization included intensive PK data collected for nivolumab SC in Phase 1/2 Study CA2098KX, and PK data from 17 historical nivolumab IV monotherapy clinical studies. The prior characterization serves as the pre-specified analysis that was used to supply prior information for the $PRIOR subroutine being implemented in this analysis.

The popPK analysis was performed using all available nivolumab SC and IV PK data from subjects in the Phase 3 Study CA20967T to ensure a robust characterization of nivolumab PK for each administration route. The popPK analysis included all subjects in Study CA20967T who received at least 1 dose of nivolumab IV or SC, and who had at least 1 evaluable nivolumab concentration value (below table).

Table 10. Description of Clinical Study Included in the Nivolumab Population Pharmacokinetic Analyses

Protocol #: Title *Study Population*	Treatment	Planned Sample Size	PK Sampling Schedule
CA20967T: A Phase 3 open-label, randomized, noninferiority trial of subcutaneous formulation of nivolumab versus intravenous nivolumab in participants with advanced or metastatic clear cell renal cell carcinoma who have received prior systemic therapy	Arm A: Nivolumab SC 1200 mg Q4W co-formulated with rHuPH20 Arm B: Nivolumab IV 3 mg/kg Q2W	454 (1:1 randomized to SC and IV arms)	Cycle = 28 days for SC and 14 days for IV SC Arm: Cycle 1 pre-dose, 72, 168, 336 and 504 hours. Predose at cycles 2, 3, 4, 5, 9, 13, 17, 21 and 25. follow up visits 1 and 2. IV Arm: Cycle 1 and 2 predose, EOI, and 168 hours. Pre-dose at cycles 3, 5, 7, 9, 17, 25, 33, 41 and 49. follow-up visits 1 and 2.

Analysis datasets

Table 11. Subjects Included in the Population Pharmacokinetic Analysis Dataset

Study	Nivolumab Treated	PK Database[a]	Flagged for Exclusion[b]	Included (% of subjects in PK Database)
CA20967T	492	489	2	487 (99.6)

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/Table3.3.1-1.rtf

[a] eToolbox or PAMS included subjects with at least 1 PK sample collected, including pre-dose samples (before nivolumab treatment) and samples collected after nivolumab treatment

[b] Exclusion criteria are provided in Table 3.3.2-1.

Table 12. Summary of Samples Included and Excluded in the Population Pharmacokinetic Analysis Dataset

Study	PK Database[a]	Day 1 Pre-dose[b]	Missing Dose or Sample Information	Below LLOQ[c]	Subsequent Therapy	Samples Included in Analysis, N (%)[d]
CA20967T	4438	447	173	19	65	3734 (93.6)

Analysis-Directory:/global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/sas/samples_ie.sas
Source: Analysis-Directory/reports/Table3.3.2-1.rtf
a eToolbox or PAMS included subjects with at least 1 PK sample collected, including pre-dose samples (before nivolumab treatment) and samples collected after nivolumab treatment.
b Day 1 pre-dose samples were excluded from the calculation of the percentage of samples in the analysis c LLOQ: Post dose nivolumab serum concentration values below the lower limit of quantification.
d Percentages based on number of samples in PK database (Samples included in analysis / (PK DB - Day 1 Pre-Dose) =%)

Table 13. Summary of Covariates in the Population Pharmacokinetic Analysis Dataset by Administration Route (IV and SC)

	IV (N =245)	SC (N =242)	Overall (N =487)
Age (years)			
Mean (SD)	64.1 (10.1)	63.7 (10.5)	63.9 (10.3)
Median [Min, Max]	66 (20, 87)	64 (35, 93)	65 (20, 93)
Missing, n (%)	0 (0)	0 (0)	0 (0)
Baseline body weight (kg)			
Mean (SD)	77.7 (16.4)	77.7 (18.2)	77.7 (17.3)
Median [Min, Max]	76.6 (47.5, 157)	76.5 (35, 153)	76.5 (35, 157)
Missing, n (%)	0 (0)	0 (0)	0 (0)
Baseline serum albumin (g/dL)			
Mean (SD)	3.93 (0.498)	3.89 (0.551)	3.91 (0.525)
Median [Min, Max]	4 (2.36, 4.91)	3.97 (2.1, 5.1)	4 (2.1, 5.1)
Missing, n (%)	4 (1.63)	3 (1.24)	7 (1.44)
Baseline EGFR (mL/min/1.73 m²)			
Mean (SD)	62.4 (19.8)	64.9 (19.9)	63.7 (19.9)
Median [Min, Max]	60.6 (20.7, 118)	63 (24.4, 124)	61.2 (20.7, 124)
Missing, n (%)	0 (0)	0 (0)	0 (0)
Sex, N (%)			
Female	74 (30.2)	84 (34.7)	158 (32.4)
Male	171 (69.8)	158 (65.3)	329 (67.6)
Missing	0 (0)	0 (0)	0 (0)
Race, N (%)			
American Indian/Alaska Native	3 (1.2)	2 (0.8)	5 (1.0)
Asian	1 (0.4)	3 (1.2)	4 (0.8)
Black/African American	2 (0.8)	0 (0)	2 (0.4)
Others	23 (9.4)	38 (15.7)	61 (12.5)
White	215 (87.8)	199 (82.2)	414 (85.0)
Missing	1 (0.4)	0 (0)	1 (0.2)
PS, N (%)			
0	91 (37.1)	100 (41.3)	191 (39.2)

1	137 (55.9)	126 (52.1)	263 (54.0)
2	17 (6.9)	16 (6.6)	33 (6.8)
3	0 (0)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	0 (0)
ADA Nivo , N (%)			
Negative	200 (81.6)	155 (64.0)	355 (72.9)
Persistent Positive	0 (0)	2 (0.8)	2 (0.4)
Only The Last Sample Positive	6 (2.4)	17 (7.0)	23 (4.7)
Other Positive	9 (3.7)	27 (11.2)	36 (7.4)
Missing	30 (12.2)	41 (16.9)	71 (14.6)
ADA rHuPH20 , N (%) [a]			
Negative	NA	196 (81.0)	NA
Persistent Positive	NA	7 (2.9)	NA
Only The Last Sample Positive	NA	11 (4.5)	NA
Other Positive	NA	1 (0.4)	NA
Missing	NA	27 (11.2)	NA

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/sas/Table3.3.5.2-1.sas
Source: Analysis-Directory/reports/Table3.3.5.2-1.rtf

a: ADA rHuPH20 is only applicable to the SC route and not applicable to the IV route or the total study population.

The pre-specified analysis provided a robust characterization of nivolumab IV/SC PK; therefore, the current analysis only included data from Study CA20967T and utilized the $PRIOR subroutine in NONMEM to support characterization of nivolumab IV and SC PK parameters in ccRCC patients. The $PRIOR subroutine was implemented for a subset of PK parameters along with the FOCE-I estimation method. Model development and covariate inclusion was based on the final model from the previous pooled analysis.

Results

Model development

Final model development consisted of re-estimating parameters of the fully pre-specified model.

The condition number of the final model was found to be 11.01, indicating the model was stable. The parameter estimates of the final model are presented below. The model-estimated typical values of KA and F were 0.0123 hr-1 (or 0.295 Day-1) and 0.788, respectively.

Table 14: Parameter Estimates of the Final Population Pharmacokinetic Model

Parameter [Units][a,b]	Symbol	Estimate[c]	Standard Error (%RSE)[d]	95% CI[e,BS]
Fixed Effects				
$CL0_{REF}$ [L/h]	θ_1	0.0108	1.63E-04 (1.51)	0.0107 - 0.0110
VC_{REF} [L]	θ_2	4.25	0.0318 (0.748)	4.23 - 4.26
Q_{REF} [L/h]	θ_3	0.0312	0.00101 (3.25)	0.0301 - 0.0318
VP_{REF} [L]	θ_4	2.67	0.0531 (1.99)	2.62 - 2.73
CL_{EMAX}	θ_5	-0.260	0.0148 (5.69)	-0.280 - -0.240
CL_{T50}	θ_6	1.41E+03	52.5 (3.73)	1.29E+03 - 1.52E+03
CL_{HILL}	θ_7	3.39	0.372 (11.0)	2.62 - 4.03
KA[/hr]	θ_8	0.0123	4.47E-04 (3.62)	0.0118 - 0.0129
F1	θ_9	0.788	0.0171 (2.17)	0.761 - 0.815
CL_{WTB}	θ_{11}	0.644	0.0975 (15.1)	0.439 - 0.834
CL_{GFR}	θ_{12}	0.306	0.0483 (15.8)	0.213 - 0.400

CL_{SEX}	θ_{13}	-0.149	0.0467 (31.3)	-0.234 - -0.0632
CL_{PS}	θ_{14}	0.122	0.0322 (26.3)	0.0618 - 0.184
VC_{WTB}	θ_{15}	0.525	0.0936 (17.8)	0.354 - 0.687
VC_{SEX}	θ_{16}	-0.228	0.0406 (17.8)	-0.298 - -0.165
$F1_{SEX}$	θ_{19}	0.942	0.0419 (4.44)	0.861 - 1.02
$F1_{PS}$[f]	θ_{20}	1.00		1.00 - 1.00
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.135 (0.367)	0.00830 (6.16)	0.114 - 0.160
ZVC [-]	$\omega_{2,2}$	0.0827 (0.288)	0.00546 (6.60)	0.0729 - 0.0956
ZVP [-]	$\omega_{3,3}$	0.211 (0.459)	0.0225 (10.7)	0.168 - 0.331
ZEMAX [h]	$\omega_{4,4}$	0.0572 (0.239)	0.00602 (10.5)	0.0448 - 0.0711
ZKA	$\omega_{5,5}$	0.211 (0.459)	0.0400 (19.0)	0.116 - 0.331
F1	$\omega_{6,6}$	0.615 (0.784)	0.144 (23.4)	0.333 - 0.898
ZCL:ZVC	$\omega_{1,2}$	0.0395 (0.374)	0.00522 (13.2)	0.0324 - 0.0487
ZKA:F1	$\omega_{5,6}$	0.0744 (0.207)	0.0574 (77.2)	-0.0595 - 0.210
Residual Error				
Proportional [-]	θ_{10}	0.157	0.00241 (1.53)	0.145 - 0.169

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final

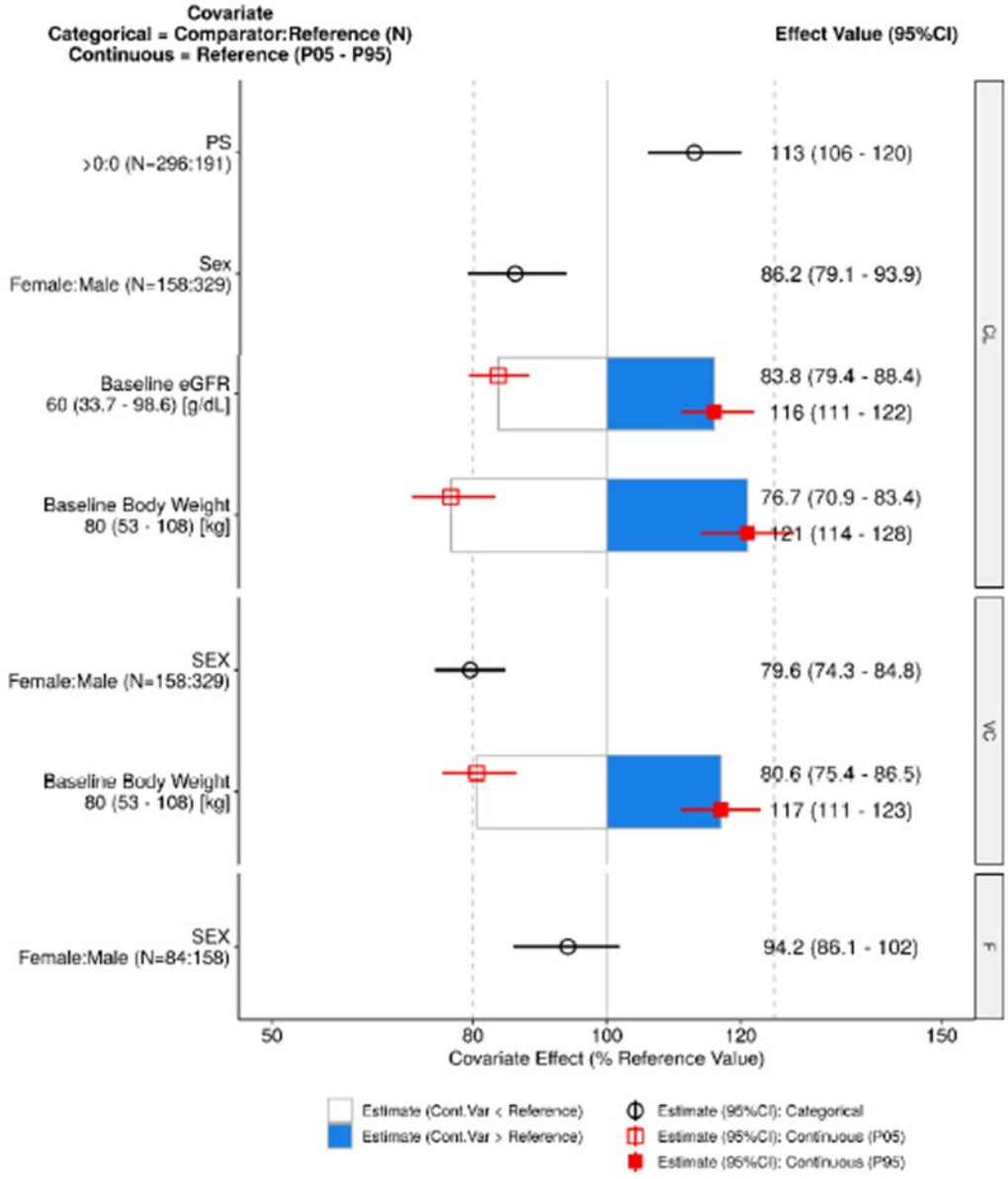
Program Source: Analysis-Directory/R/scripts/1-prep-data-mod-dev.Rmd

Source: Program: Analysis-Directory/nm/base/reports/base_RTF.rtf

Note 1: $CL0_{REF}$ is the typical value in a reference subject weighing 80 kg, EGFR of 90 mL/min/1.73 m^2, 65 year old male with PS = 0. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the popPK analysis dataset used to establish the pre-specified model and also represent the approximate median values in the current popPK analysis dataset except for EGFR.
Note 2: ETA shrinkage (%): ETA_CL: 9.37; ETA_VC: 30.4; ETA_VP: 35.5; ETA_EMAX: 34.5; ETA_KA: 32.4; ETA_F: 36.6; EPS shrinkage (%): 17.0.
Note 3: Condition no: 11.01

[a] Parameters with fixed values (not estimated) are denoted with a superscript '*f*' after the names, with the fixed value given in the Estimate column
[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters
[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)
[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)
[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*
[BS] Confidence Interval values are taken from bootstrap calculations (992 successful out of a total of 1000)

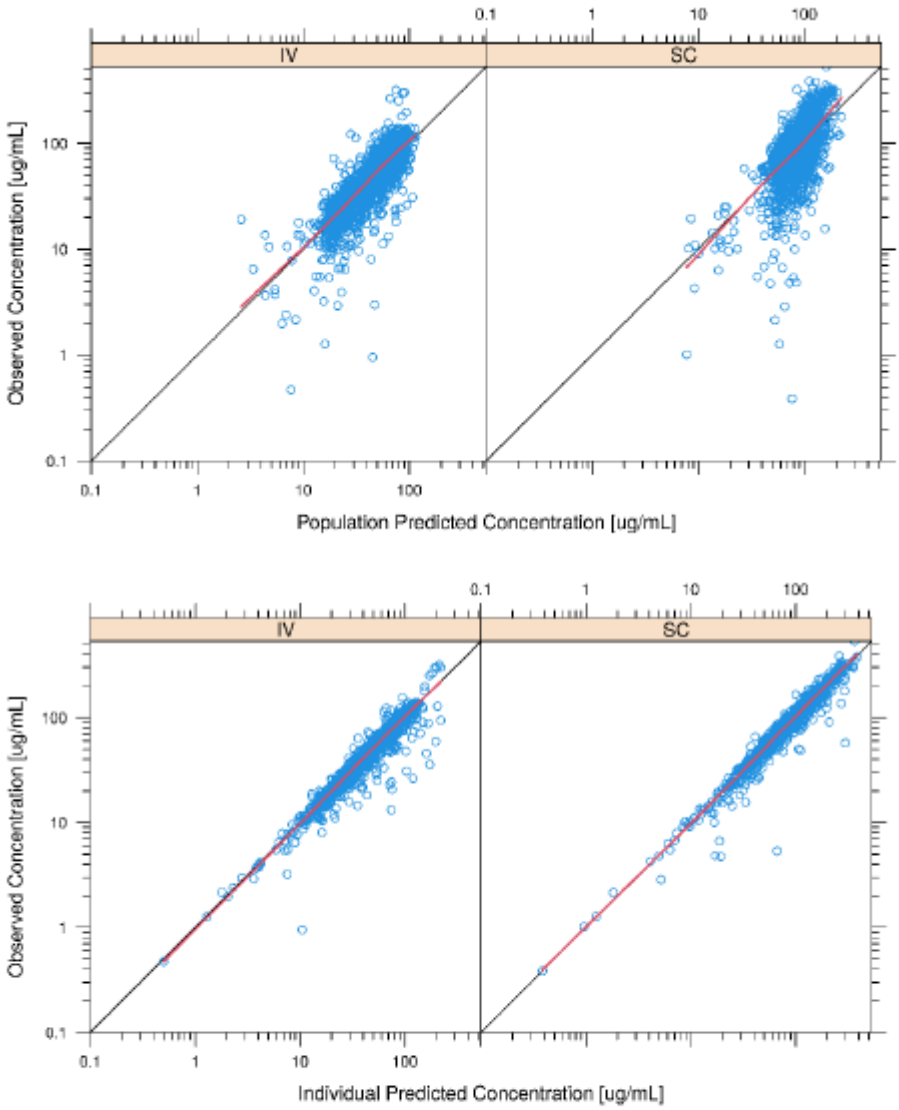
Figure 14: Covariate Effects on Final Nivolumab Population Pharmacokinetic Model



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html

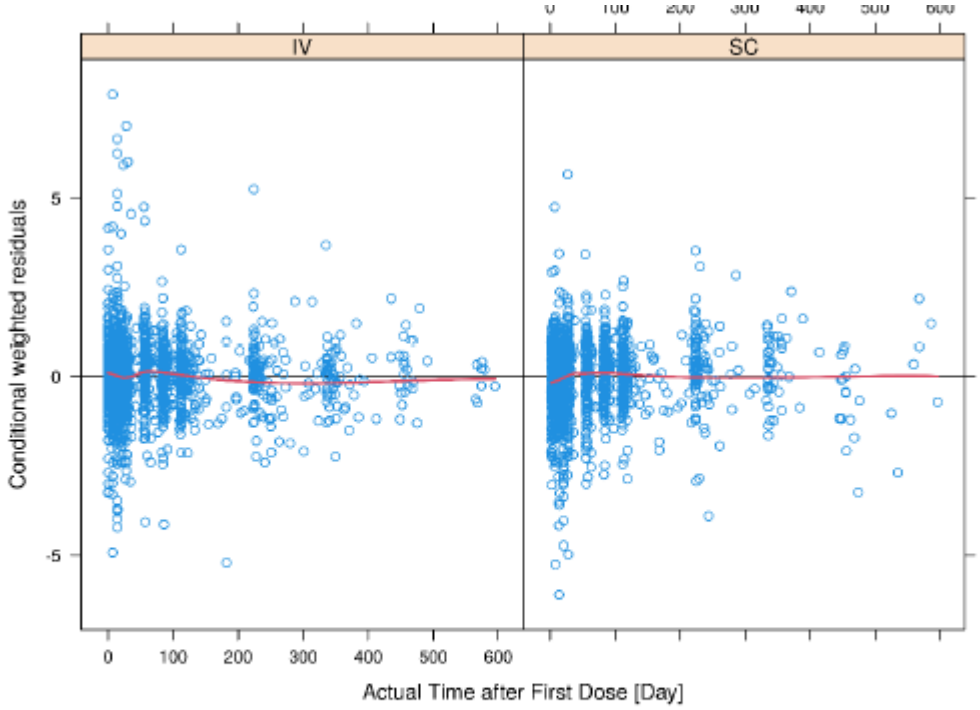
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is a 65-year-old male, weighing 80 kg, with a normal PS status (PS = 0). Baseline eGFR of 60 mL/min/1.73 m^2 was used in this plot as a median to represent the study distribution. VC_{REF} is typical value in a reference male subject weighing 80 kg. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 125% of this value.

Figure 15: Observed Versus Predicted Population Average and Individual Concentrations in the Final Population Pharmacokinetic Model by Administration Route (IV and SC)



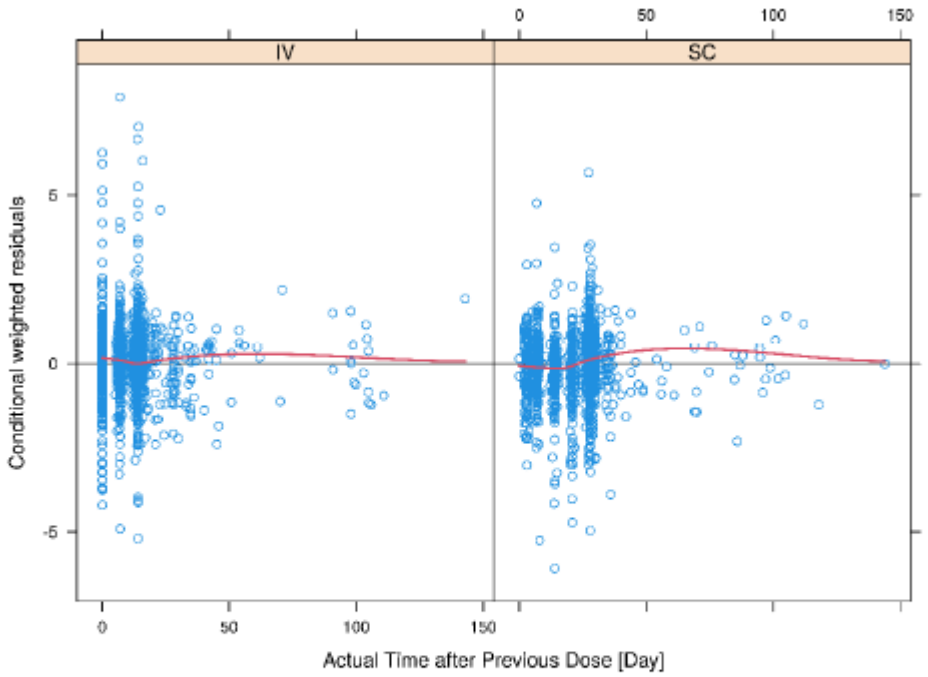
Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note 1: Solid red line represents linear regression line. Solid black line represents line of identity

Figure 16: CWRES versus Time after First Dose in the Final Population Pharmacokinetic Model by Administration Route (IV and SC)



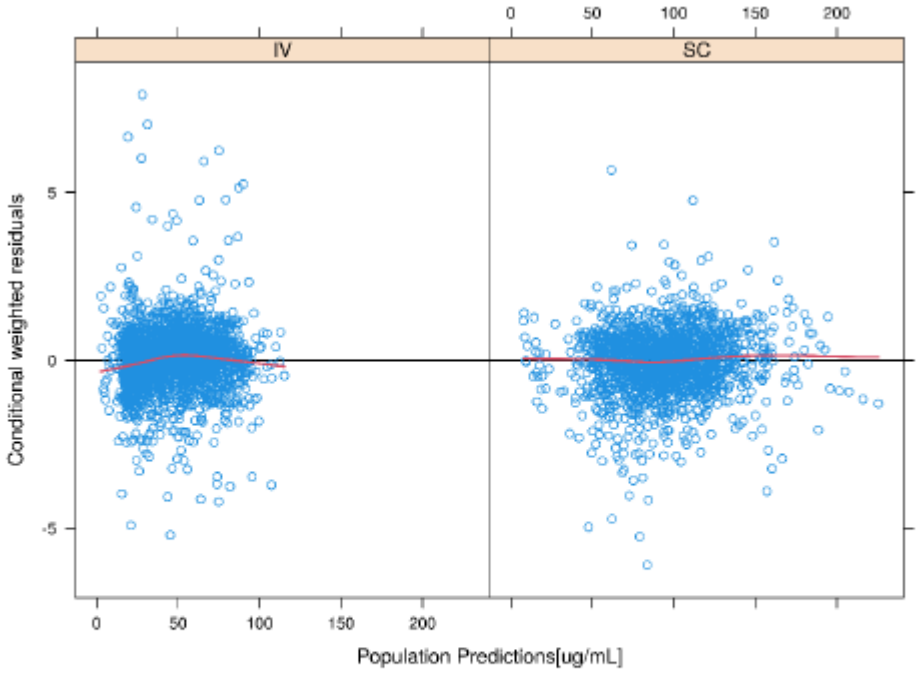
Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Figure 17: CWRES versus Time after Previous Dose in the Final Population Pharmacokinetic Model by Administration Route (IV and SC)



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

Figure 18: CWRES versus Population Predicted Concentration in the Final Population Pharmacokinetic Model by Administration Route (IV and SC)



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: Solid red line represents locally weighted smooth line; solid black line represents line of identity.

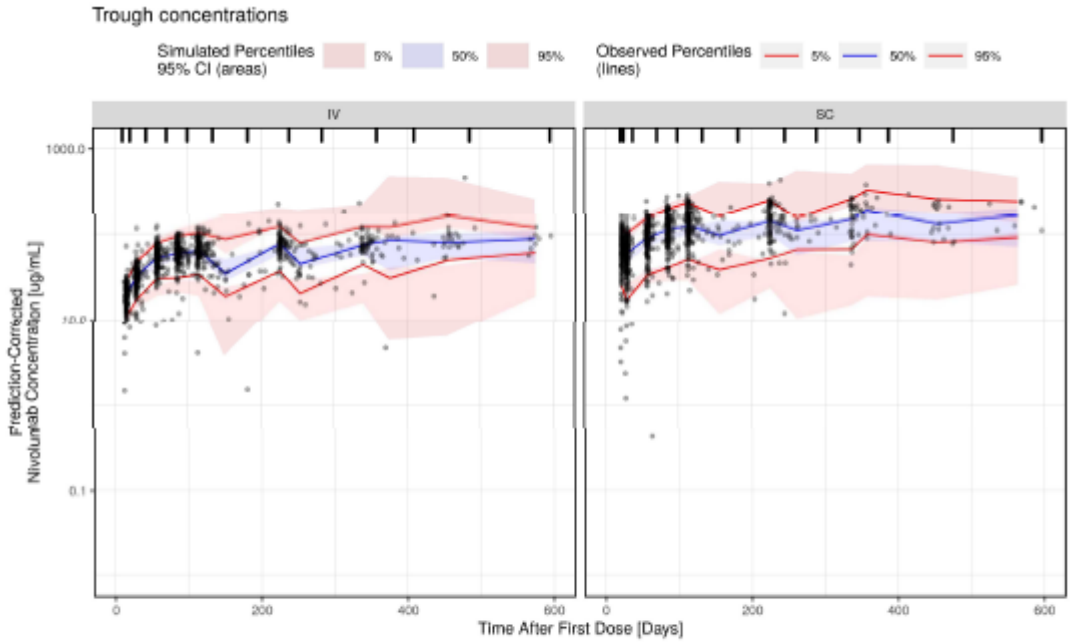
Sensitivity Analysis ($PRIOR vs Pooled Approach)

A comparison of the parameter estimates between the final model using $PRIOR and the sensitivity analysis using the pooled dataset approach was performed. Differences in the primary PK parameters were small (<10%). There were some differences in covariate effect estimates observed, possibly due to differences in subject disposition in the pooled dataset vs the CA20967T population.

Model evaluation

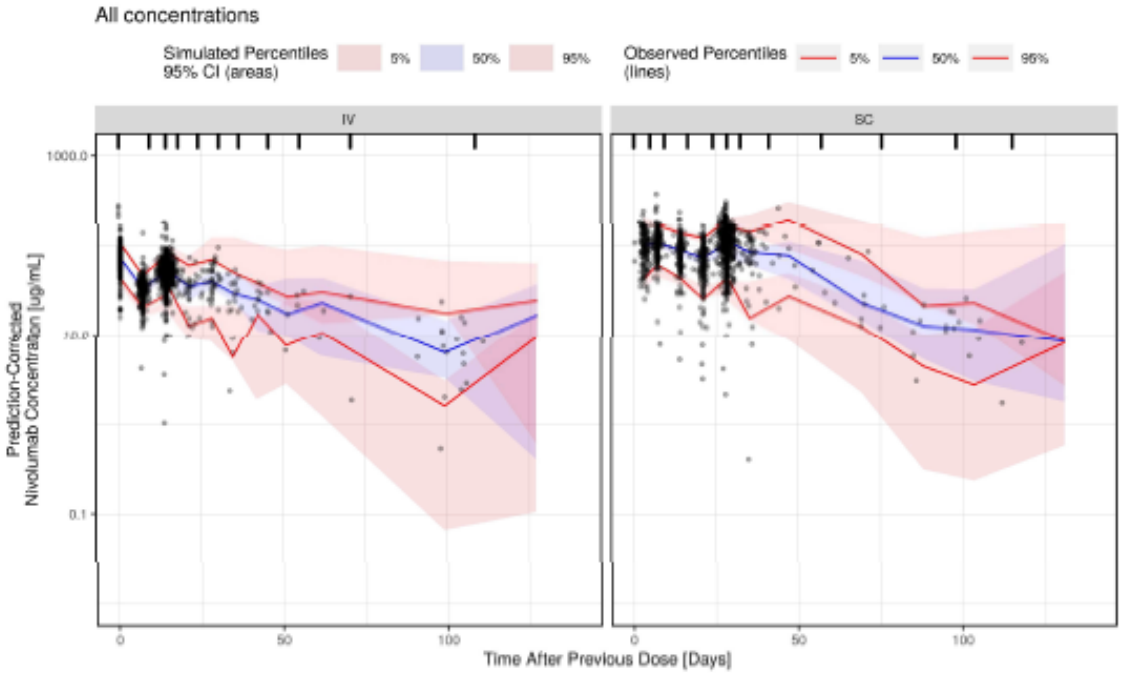
Visual predictive checks were performed for the final model stratified by administration route (IV and SC) (below figures).

Figure 19: Prediction-Corrected Visual Predictive Check of Trough Nivolumab Concentrations versus Actual Time after First Dose by Administration Route in the Final Population Pharmacokinetic Model (IV and SC)



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/2-vpc.Rmd
Source: Analysis-Directory/R/plots/base-trough-vpc.PNG

Figure 20: Prediction-Corrected Visual Predictive Check of Nivolumab Concentrations versus Actual Time after Previous Dose by Administration Route in the Final Population Pharmacokinetic Model (IV and SC)

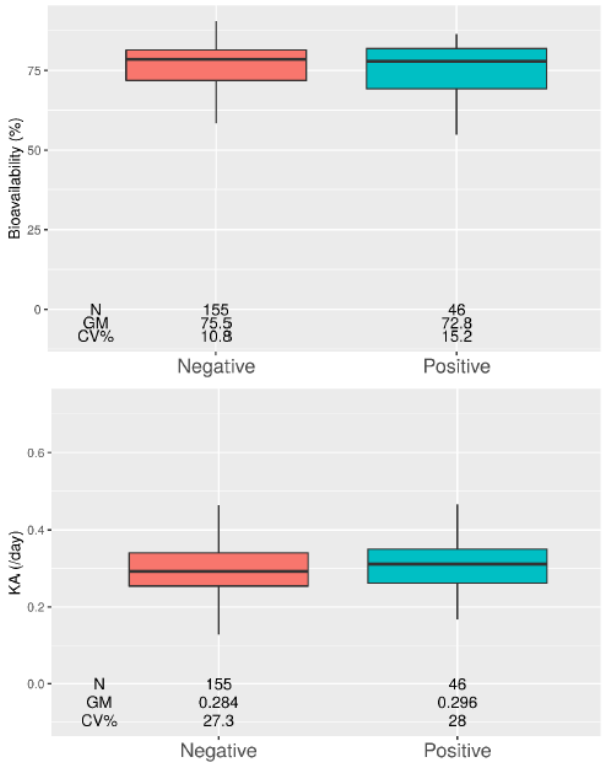


Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/2-vpc.Rmd
Source: Analysis-Directory/R/plots/base-all-vpc.PNG

Model Application

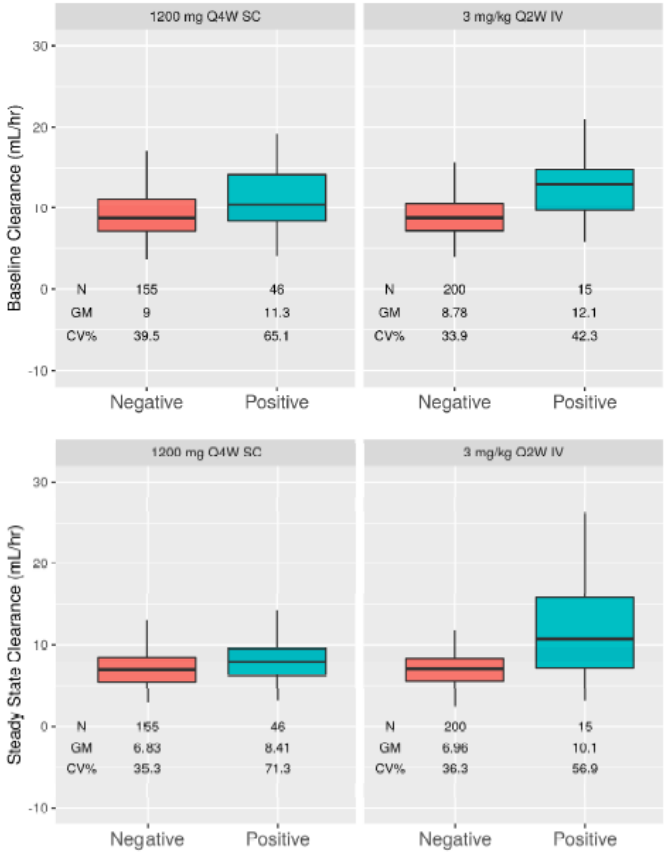
Comparison of Nivolumab SC PK Parameters and Exposure Measures by Nivolumab ADA Status

Figure 21: Comparison of Nivolumab SC PK Parameters (Bioavailability and Absorption Rate) by Nivolumab ADA Status



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.

Figure 22: Comparison of Baseline and Steady State CL by Nivolumab ADA Status (SC and IV)



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.

Figure 23: Comparison of Nivolumab Exposures (Cavgd28, Cavgss, and Cminss) by Nivolumab ADA Status (SC and IV)

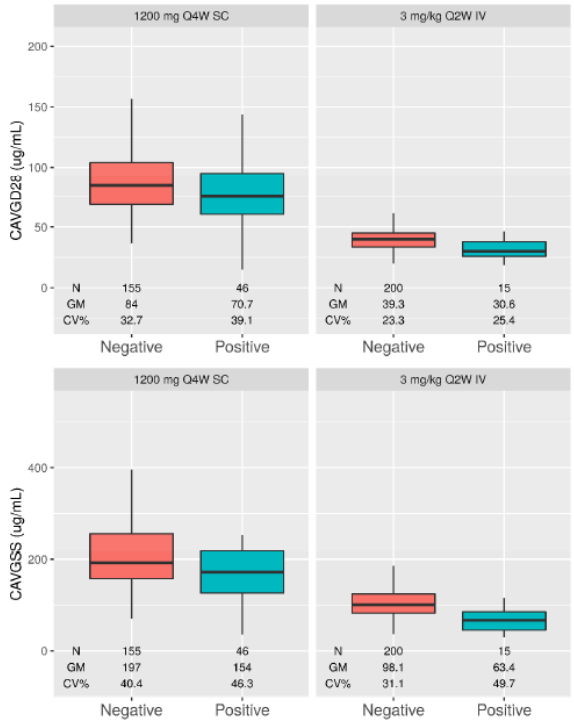
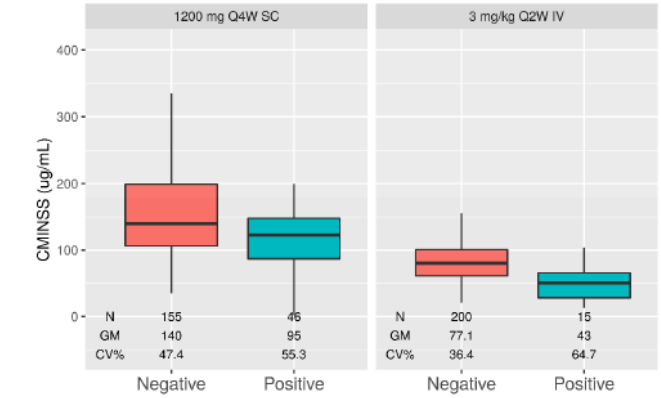


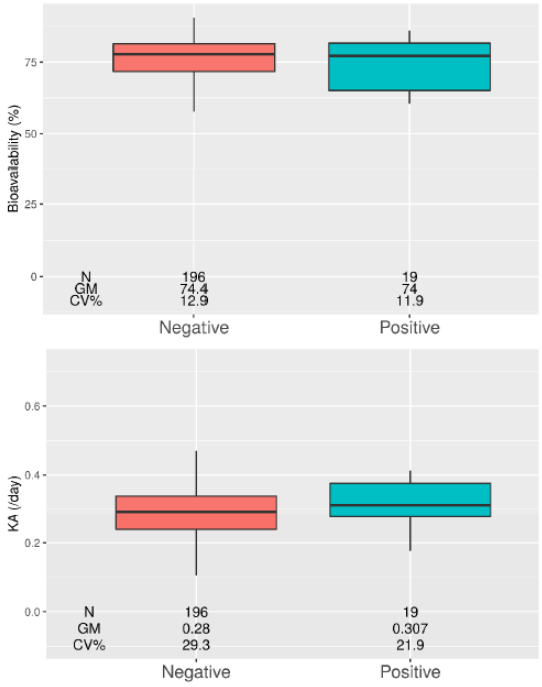
Figure 24: Comparison of Nivolumab Exposures (Cavgd28, Cavgss, and Cminss) by Nivolumab ADA Status (SC and IV)



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.

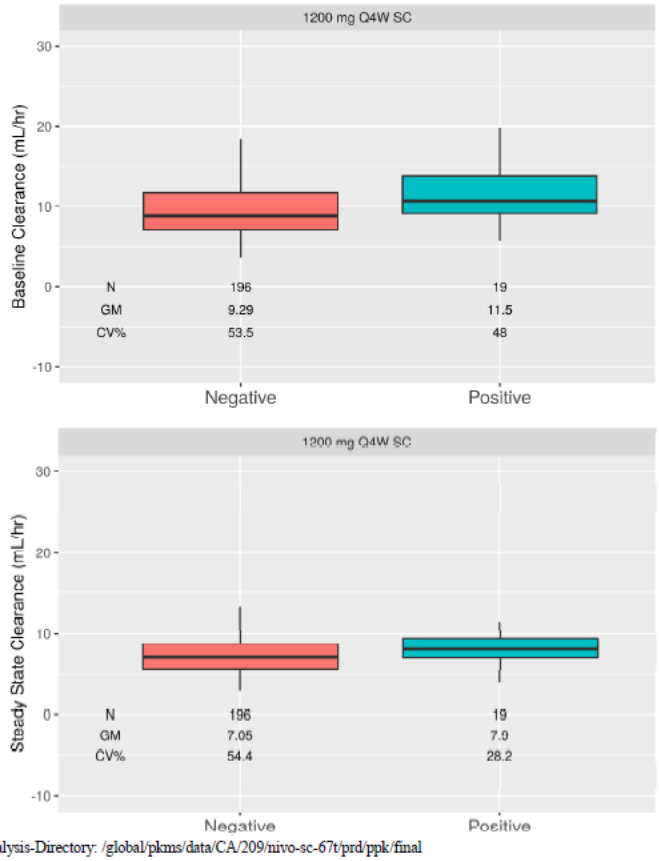
Comparison of Nivolumab SC PK Parameters and Exposure Measures by rHuPH20 ADA Status

Figure 25: Comparison of Nivolumab SC PK Parameters (Bioavailability and Absorption Rate) by rHuPH20 ADA Status



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.

Figure 26: Comparison of Nivolumab SC Baseline and Steady State CL by rHuPH20 ADA Status



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.

Figure 27: Comparison of Nivolumab SC Exposures (Cavgd28, Cavgss, and Cminss) by rHuPH20 ADA Status

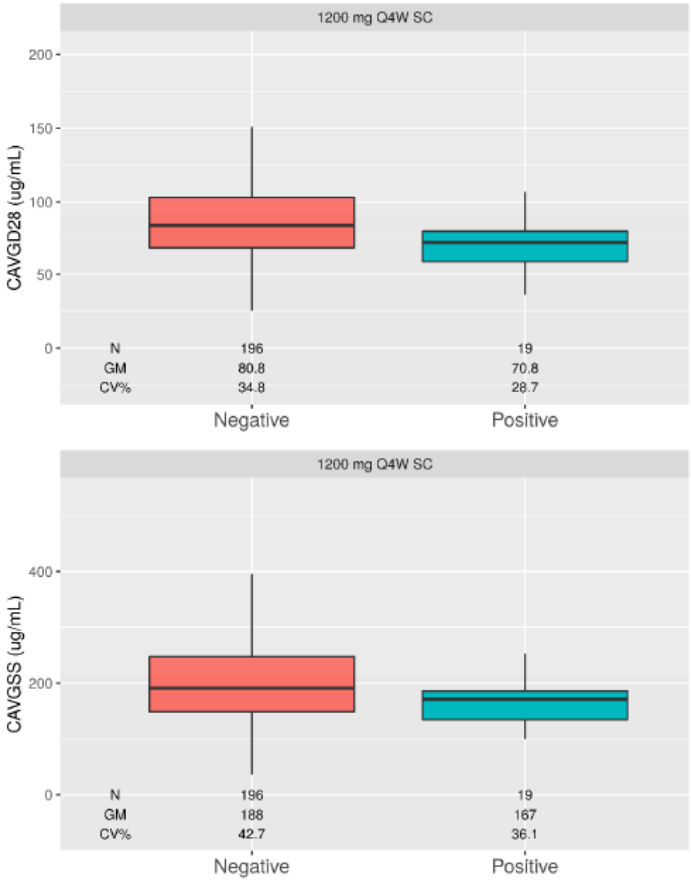
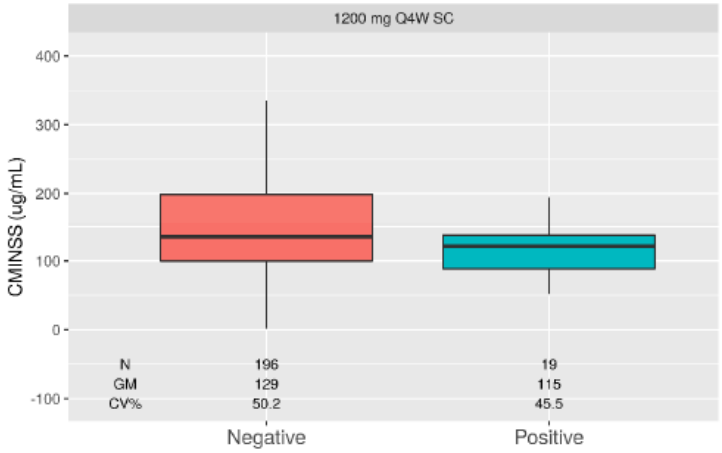


Figure 28: Comparison of Nivolumab SC Exposures (Cavgd28, Cavgss, and Cminss) by rHuPH20 ADA Status



Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html
Note: A subject was considered ADA+ if ADA was positive relative to baseline for any visit post treatment.

Comparison of Nivolumab Exposures by Administration Route

Figure 29: Summary of Nivolumab Exposures by Administration Route (SC and IV)

Exposures	SC 1200 mg Q4W Geo.Mean (%CV) (N=242)	IV 3 mg/kg Q2W Geo.Mean (%CV) (N=245)	IV 10 mg/kg Q2W Geo.Mean (%CV) (N=245)
CAVG1	78.8 (35.6)	29.8 (24.8)	99.3 (24.8)
CMAX1	108 (32.7)	91.7 (35.5)	247 (33.9)
CMIN1	50.8 (44.2)	19.6 (28.6)	65.5 (28.6)
CAVGD28	78.8 (35.6)	37.7 (25.3)	126 (25.3)
CMIND28	50.8 (44.2)	31.9 (29.6)	106 (29.6)
CAVGSS	182 (43.5)	92.5 (34.4)	308 (34.4)
CMAXSS	230 (39.2)	160 (27.6)	517 (35.4)
CMINSS	126 (51)	71.5 (40.1)	238 (40.1)

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd, 5-simulation-10mg.Rmd
Source: Analysis-Directory/R/export/ exp_nivo_stats.csv, exp_nivo_stats_10.csv
Note: 1 cycle =28 days for SC and 14 days for IV.

Special populations

Impaired renal function

The effect of renal impairment on the CL of nivolumab was previously evaluated in patients with mild (GFR <90 and ≥60 mL/min/1.73 m^2; n = 379), moderate (GFR <60 and ≥30 mL/min/1.73 m^2; n = 179), or severe (GFR <30 and ≥15 mL/min/1.73 m^2; n = 2) renal impairment compared to patients with normal renal function (GFR ≥90 mL/min/1.73 m^2; n = 342) in population PK analyses.

No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Impaired hepatic function

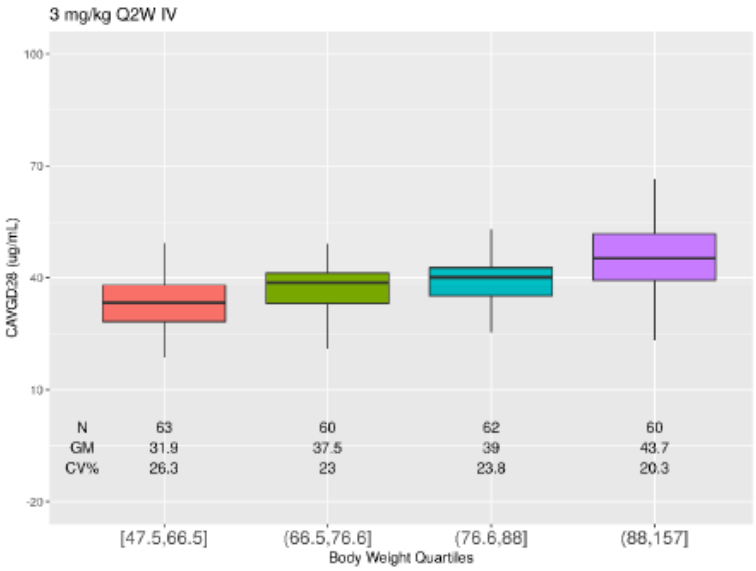
The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n=92) compared to patients with normal hepatic function (total bilirubin and AST ≤ULN; n=804) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin >1.5 × to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin >3 × ULN and any AST).

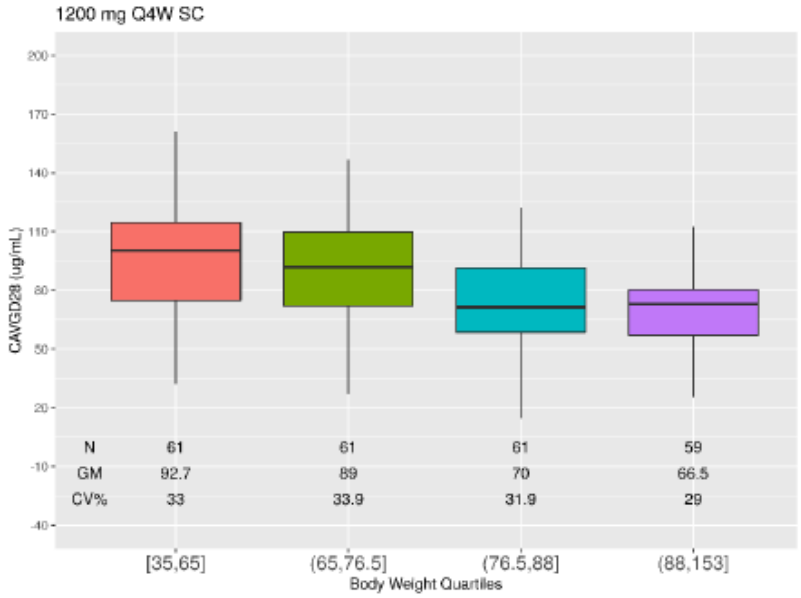
Weight

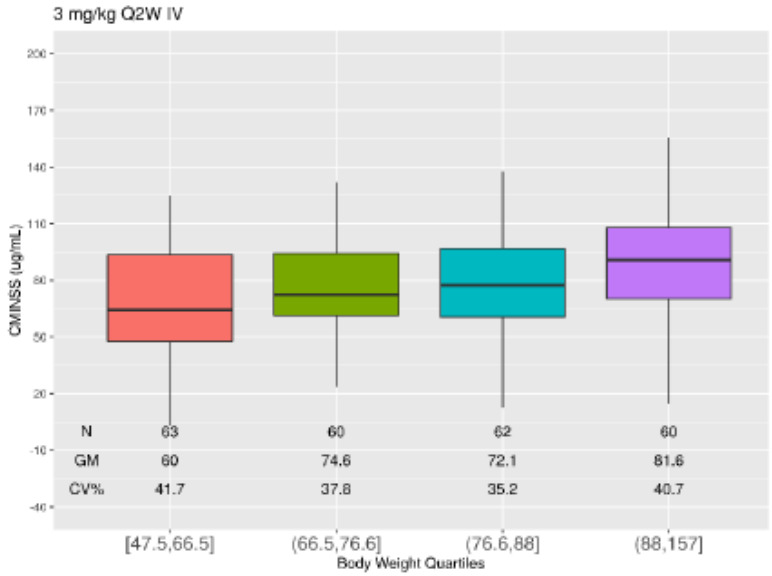
Final Population PK analysis (see section "Pharmacokinetics in the target population")

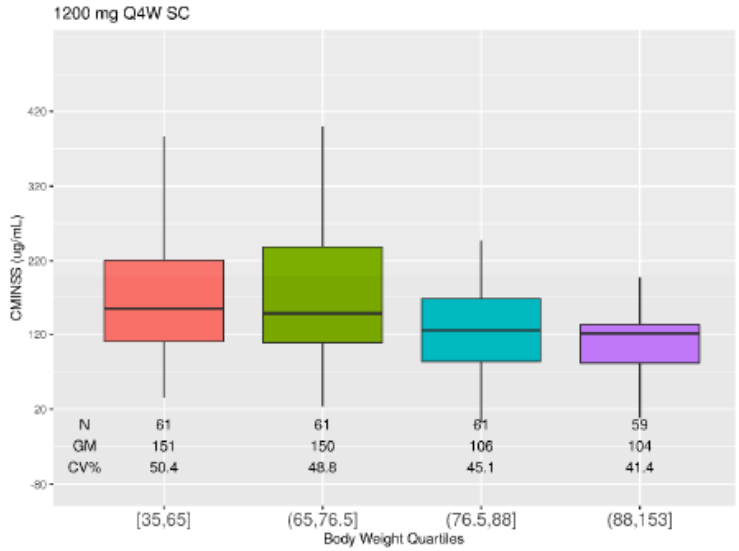
Comparison of Nivolumab Exposures by Body Weight Quartiles

Figure 30: Comparison of Nivolumab Exposures (Cavgd28 and Cminss) by Body Weight Quartiles (IV and SC)









Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/scripts/4-model-application.html

Table 15: Predicted Nivolumab SC 1200 mg Q4W Exposures at 5th and 95th Percentile of Body Weight Distributions

	5th Percentile[a]		95th Percentile[b]		Reference[c]
Exposure (µg/mL)	Geo. Mean (%CV) N = 12	% Diff GM[d]	Geo. Mean (%CV) N = 15	% Diff GM[d]	Geo. Mean (%CV) N = 23
CAVG1	112 (25.1)	30.1	56.1 (24.5)	-34.8	86.1 (29)
CMAX1	147 (23.3)	27.8	82.7 (24.9)	-28.1	115 (29.1)
CMIN1	78.1 (33.2)	33.3	30.5 (37.8)	-48	58.6 (33.3)
CAVGD28	112 (25.1)	30.1	56.1 (24.5)	-34.8	86.1 (29)
CAVGSS	263 (37)	32.8	120 (30.6)	-39.4	198 (33.2)
CMAXSS	326 (31.7)	32.5	159 (25.9)	-35.4	246 (29.4)
CMINSS	187 (45.8)	34.5	74.9 (40.9)	-46.1	139 (41.2)

Analysis-Directory: /global/pkms/data/CA/209/nivo-sc-67t/prd/ppk/final
Program Source: Analysis-Directory/R/scripts/4-model-application.Rmd
Source: Analysis-Directory/R/export/exp.stats.bw.sc.csv

[a] 5th percentile of body weight range (>=35 kg to < 52 kg)

[b] 95th percentile of body weight range (>= 110 kg to < 153 kg)

[c] Reference body weight range (>=74 to < 78 kg)

[d] Percent difference in geometric mean is relative to reference body weight

Distribution of older subjects across the different subgroups of age for the studies contributing to the PK evaluation of nivolumab SC, CA20967T and CA2098KX.

Table 16: Age Ranges Studied in the Elderly Population

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Study CA20967T			
Nivolumab SC	85/248	30/248	4/248
Nivolumab IV	97/247	30/247	4/247
Total	182/495	60/495	8/495
Study CA2098KX			
Part A - Group 1	10/22	4/22	2/22
Part B - Group 2	2/18	4/18	0/18
Part B - Group 3	5/10	0/10	0/10
Part B - Group 4	5/17	6/17	0/17
Part D - Group 5	17/36	4/36	1/36
Part E - Group 6	10/36	7/36	0/36
Total	49/139	25/139	3/139

Pharmacokinetic interaction studies

Not Applicable

Pharmacokinetics using human biomaterials

Not Applicable

2.6.2.2. Pharmacodynamics

Mechanism of action

Not Applicable

Primary and Secondary pharmacology

Study CA20967T

IFNγ, monokine induced by gamma interferon (CXCL9), and interferon gamma induced protein 10 (CXCL10) were measured for SC and IV treatment arms at baseline, and on Days 8, 15, and 29 post treatment. Relatively similar increases in key PD immune activation markers, IFNγ, CXCL9, and CXCL10, were observed when comparing nivo SC with nivo IV treatment arms, and the interquartile ranges (IQRs) were overlapping between treatment arms for each of these markers.

- Median percent increase from baseline to Day 8 for IFNγ for nivo SC and nivo IV treatment arms were 85.5% (IQR [12.2, 210.0]) and 70.5% (IQR [14.3, 200.0]), respectively, and from baseline to Day 15 were 66.7% (IQR [0.0, 214.3]) and 55.6% (IQR [0.0, 183.3]), respectively, and from baseline to Day 29 were 38.9% (IQR [-11.8, 169.7]) and 40.8% (IQR [-17.4, 150.0]), respectively.
- Median percent increase from baseline to Day 8 for CXCL9 for nivo SC and nivo IV treatment arms were 77.1% (IQR [30.8, 129.5]) and 71.9% (IQR [36.0, 133.4]), respectively, and from baseline to Day 15 were 90.1% (IQR [36.7, 175.4]) and 91.2% (IQR [35.4, 166.7]), respectively, and from baseline to Day 29 were 105.6% (IQR [36.3, 201.0]) and 76.8% (IQR [39.4, 200.0]), respectively.
- Median percent increase from baseline to Day 8 for CXCL10 for nivo SC and nivo IV treatment arms were 51.3% (IQR [19.7, 94.1]) and 44.3% (IQR [20.2, 89.0]), respectively, and from baseline to Day 15 were 61.0% (IQR [22.0, 114.3]) and 47.3% (IQR [14.4, 115.1]), respectively, and from baseline to Day 29 were 65.1% (IQR [16.2, 150.5]) and 50.3% (IQR [14.9, 126.8]), respectively.

Immunological events

The difference in ADA development by route of administration for nivolumab SC versus nivolumab IV was assessed with immunogenicity data from Pivotal Study CA20967T. The effect of dose and dosing frequency was assessed with data from Phase 1 / 2 Study CA2098KX. Immunogenicity data from CA2098KX should be interpreted with caution due to the small number of subjects in the subgroups and the impact of SC treatment being confounded with IV treatment for subjects in Parts A, B, and C. Based on the CA2098KX study design, subjects in Parts A and B received a single dose of nivolumab SC (720 mg or 960 mg) with or without rHuPH20 followed by nivolumab IV 480 mg Q4W; and then subjects who remained on study at the time of protocol amendment entered Part C and were switched to nivolumab SC 1200 mg with rHuPH20 Q4W. Subjects in Parts D (1200 mg Q4W) and E (600 mg Q2W) received nivolumab SC with rHuPH20 from the start of study treatment.

Study CA20967T

All nivolumab and rHuPH20 immunogenicity results for Study CA20967T are based in the primary CSR data cutoff of 24-Jul-2023. Assessment of the immunogenicity of nivolumab and rHuPH20 were secondary and exploratory endpoints of CA20967T, respectively.

In CA20967T, 492 subjects were treated (247 in the nivolumab SC arm [Arm A] and 245 in the nivolumab IV arm [Arm B]). Of these, the following subjects were evaluable for ADA:

- Nivolumab SC arm: of 247 treated subjects, 202 were nivolumab ADA evaluable and 215 were rHuPH20 ADA evaluable
- Nivolumab IV arm: of 245 treated subjects, 215 were nivolumab ADA evaluable

Table 17: Anti-Drug Antibody Assessments Summary - All Immunogenicity Evaluable Subjects with Baseline and at Least One Post-Baseline Assessment - CA20967T

	Arm A (Nivolumab SC)		Arm B (Nivolumab IV)
ADA Status (%)	Nivolumab N = 202	rHuPH20 N = 215	Nivolumab N = 215
BASELINE ADA POSITIVE	12 (5.9)	20 (9.3)	9 (4.2)
ADA POSITIVE	46 (22.8)	19 (8.8)	15 (7.0)
PERSISTENT POSITIVE (PP)	2 (1.0)	7 (3.3)	0
NOT PP - LAST SAMPLE POSITIVE	17 (8.4)	11 (5.1)	6 (2.8)
OTHER POSITIVE	27 (13.4)	1 (0.5)	9 (4.2)
NEUTRALIZING POSITIVE	2 (1.0)	5 (2.3)	0
ADA NEGATIVE	155 (76.7)	196 (91.2)	200 (93.0)
N.A.	1 (0.5)	0	0

Source: Table 11.1.1-1 of the CA20967T Primary CSR[4]

Baseline ADA Positive: A subject with baseline ADA-positive sample.

ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater [≥] than baseline positive titer) at any time after initiation of treatment. Subject 95-286 in nivolumab SC arm had post-baseline positive anti-nivolumab antibodies but was not included in this table since this subject was not immunogenicity evaluable as Day 1 ADA sample was not collected before the start of treatment and could not be considered as baseline.

Persistent Positive: ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart

Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling time point

Other Positive: Not persistent but some ADA-positive samples with the last sample being negative

Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline. Subject 65-190 was not included in the "Neutralizing Positive" category for rHuPH20 due to the subject's "ADA Negative" subject level status.

ADA Negative: A subject with only ADA-negative sample after initiation of treatment

N.A.: Subject 103-555, baseline nivolumab ADA sample was positive with titer as 8, but the titer for the post-baseline positive ADA sample could not be determined due to insufficient quantity, resulting in an undetermined ADA status.

The assessment of onset and duration of anti-nivolumab ADAs was based on the subset of subjects who became nivolumab ADA-positive after the start of treatment with either nivolumab SC or nivolumab IV. The median time to first detection of ADAs to nivolumab was similar between nivolumab SC and nivolumab IV (4.14 weeks versus 4.86 weeks, respectively). The median duration of ADAs to nivolumab was longer for nivolumab SC (11.86 weeks) versus nivolumab IV (5.57 weeks).

ADA Status (%)	Arm A (Nivolumab SC)		Arm B (Nivolumab IV)
	Nivolumab N = 202	rHuPH20 N = 215	Nivolumab N = 215
BASELINE ADA POSITIVE	12 (5.9)	20 (9.3)	9 (4.2)
ADA POSITIVE	46 (22.8)	19 (8.8)	15 (7.0)
PERSISTENT POSITIVE (PP)	2 (1.0)	7 (3.3)	0
NOT PP - LAST SAMPLE POSITIVE	17 (8.4)	11 (5.1)	6 (2.8)
OTHER POSITIVE	27 (13.4)	1 (0.5)	9 (4.2)
NEUTRALIZING POSITIVE	2 (1.0)	5 (2.3)	0
ADA NEGATIVE	155 (76.7)	196 (91.2)	200 (93.0)
N.A.	1 (0.5)	0	0

Source: Table 11.1.1-1 of the CA20967T Primary CSR[4]

Baseline ADA Positive: A subject with baseline ADA-positive sample.

ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater [≥] than baseline positive titer) at any time after initiation of treatment. Subject 95-286 in nivolumab SC arm had post-baseline positive anti-nivolumab antibodies but was not included in this table since this subject was not immunogenicity evaluable as Day 1 ADA sample was not collected before the start of treatment and could not be considered as baseline.

Persistent Positive: ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart

Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling time point

Other Positive: Not persistent but some ADA-positive samples with the last sample being negative

Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline. Subject 65-190 was not included in the "Neutralizing Positive" category for rHuPH20 due to the subject's "ADA Negative" subject level status.

ADA Negative: A subject with only ADA-negative sample after initiation of treatment

N.A.: Subject 103-555, baseline nivolumab ADA sample was positive with titer as 8, but the titer for the post-baseline positive ADA sample could not be determined due to insufficient quantity, resulting in an undetermined ADA status.

Table 18: Onset and Duration of ADA to Nivolumab - All Treated Subjects with Nivolumab ADA-Positive Status for Whom Nivolumab ADA is Not Detected at Baseline - CA20967T

	Nivolumab SC N = 43	Nivolumab IV N = 15
TIME TO FIRST DETECTION OF ADA TO NIVO (WEEKS)		
N	43	15
MEDIAN	4.14	4.86
Q1, Q3	4.14, 4.43	4.14, 9.43
MIN, MAX	3.9, 32.1	3.9, 28.4
DURATION OF ADA TO NIVO (WEEKS)		
N	43	15
MEDIAN	11.86	5.57
Q1, Q3	4.14, 24.00	4.29, 16.86
MIN, MAX	0.1*, 30.0	0.1*, 41.3
NUMBER OF DOSE BEFORE 1ST DETECTION OF ADA TO NIVO		
N	43	15
MEDIAN	1.0	2.0
MIN, MAX	1, 8	2, 8
NUMBER OF DOSE AFTER 1ST DETECTION OF ADA TO NIVO		
N	43	15
MEDIAN	6.0	7.0
MIN, MAX	0, 19	0, 30

Source: Table 11.1.3-1 of the CA20967T Primary CSR[4]

Note: Onset of ADA refers to the time period between the first dose of the treatment and the first instance of ADA detection. Duration of ADA is defined as the time from the first on-study ADA-positive date to the first ADA-negative date after the last on-study ADA-positive date. Duration of ADA is estimated by Kaplan-Meier method. Subjects who do not have an ADA-negative date after the last on-study ADA-positive date is censored on the date of their last ADA-evaluable assessment. Excluded those subjects with baseline ADA-positive sample and had an increased titer at post-baseline since this type of immune response differs mechanistically.

*Censored observation.

Dose justification

Nivolumab IV

Nivolumab IV 3 mg/kg Q2W was selected as the dose for the pivotal studies.

Nivolumab SC

Nivolumab SC 1200 mg co-formulated with rHuPH20 (2,000 units/mL) Q4W was selected as the dosing regimen for evaluation of PK non-inferiority relative to nivolumab IV 3 mg/kg Q2W in **Study CA20967T**.

Dose selection was based on data from participants in **Phase 1/2 Study CA2098KX** where nivolumab SC was evaluated at single doses of 720 mg and 960 mg with or without rHuPH20, and at 1200 mg with rHuPH20 Q4W. PK data from CA2098KX was combined with historical nivolumab IV monotherapy data from 19 studies across the clinical development program to develop a combined SC/IV population PK model that would characterize the absorption profile (absorption rate and bioavailability) of nivolumab SC and predict exposure measures for SC regimens of interest relative to 3 mg/kg IV Q2W and 10 mg/kg IV Q2W.

The first interim popPK analysis conducted in CA2098KX included available PK data from the 720 mg and 960 mg dose levels administered without rHuPH20. The base model estimated typical values (95% CI) for bioavailability and absorption rate constant were 67% (60% to 75%) and 0.0127 hr-1 (0.010 to 0.015 hr-1), respectively. A full model with covariates on the SC PK parameters (bioavailability and absorption rate constant) was not developed due to limited data.

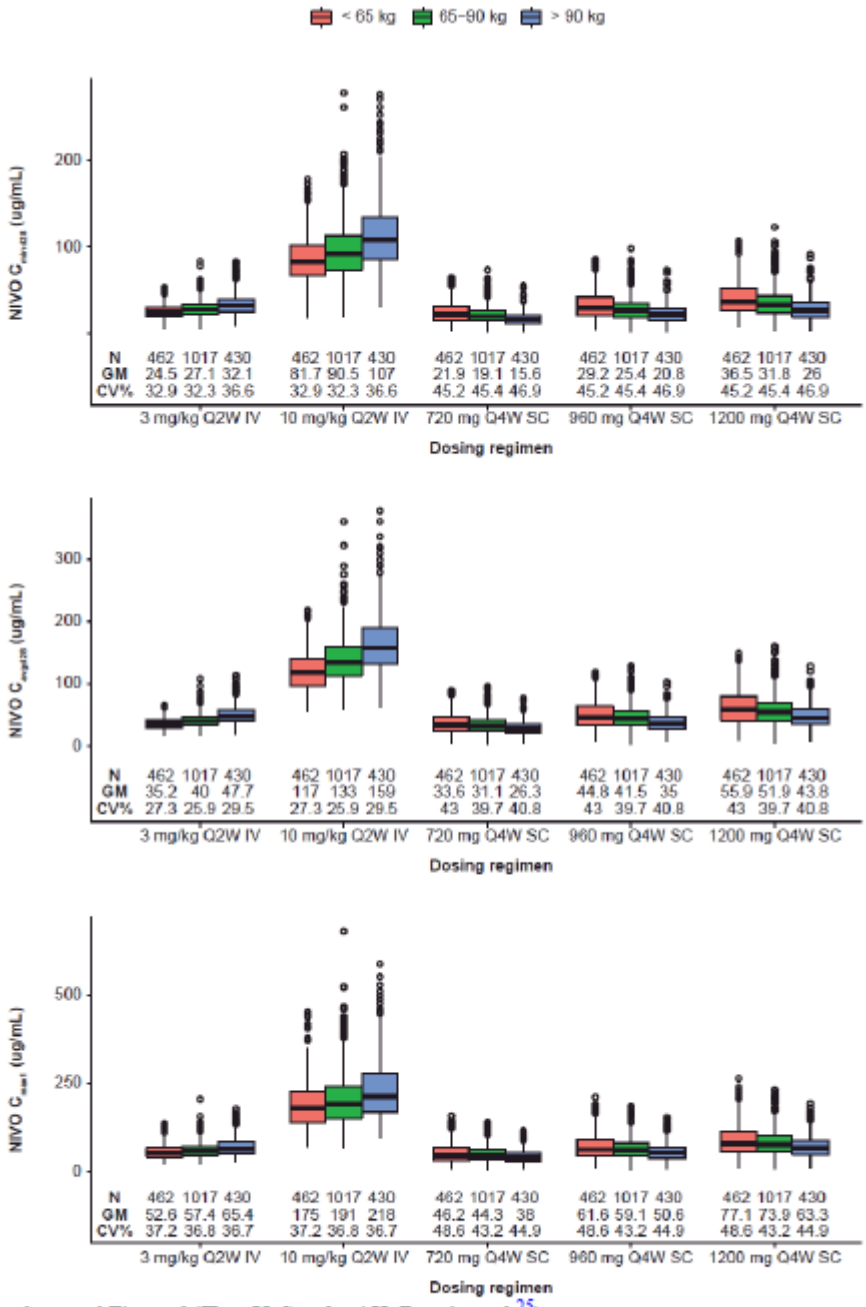
Based on the estimated bioavailability and uncertainty (95% CI, with a lower bound of 60%), a dosage of 1200 mg with rHuPH20 Q4W was evaluated in CA2098KX.

The next interim popPK analysis helped to confirm the 1200 mg dosing regimen as the selected dose and included available data from 720 mg and 960 mg administered with rHuPH20 and 1200 mg Q4W. The full model estimated typical values (95% CI) for bioavailability and the absorption rate constant were ~77% (69% to 85%) and 0.0165 hr-1 (0.0134 to 0.0195), respectively. Other systemic PK parameters (clearance and volume of distribution terms) were estimated and found to be consistent with those for nivolumab IV.

The full popPK model was then used to predict nivolumab exposure measures (Cavgd28, Cmind28, Cmax1, Cavgss, Cminss, and Cmaxss) for all SC dosing regimens of interest (720 mg Q4W, 960 mg Q4W and 1200 mg Q4W) relative to exposure measures for 3 mg/kg IV Q2W and 10 mg/kg IV Q2W. The aim was to identify the optimal nivolumab SC dosing regimen that could achieve exposures that were similar to or greater than those for nivolumab 3 mg/kg IV Q2W across the body weight range in **CA2098KX**, particularly in the highest weight category (>90 kg) where exposures following a flat dose would be the lowest, and for a scenario of low bioavailability (ie, 60%; the lower bound of the 95% CI from the first interim popPK analysis) given the uncertainty in this PK parameter. Other considerations were the unknown immunogenicity profile of nivolumab SC and any clinically meaningful impact on PK. Further, the results from the planned registrational study in RCC would be used to bridge to other patient populations/indications where nivolumab IV was already approved; therefore, ensuring adequate exposure was important.

Distributions of predicted Cmind28, Cavgd28, and Cmax1 values indicated that for base case bioavailability (~77%) and across the body weight range, geometric mean Cmind28 and Cavgd28 following 720 mg SC Q4W would fall below the reference geometric mean values for 3 mg/kg IV Q2W. In contrast, the 960 mg and 1200 mg Q4W SC regimens were expected to produce similar or higher Cmind28 and Cavgd28 relative to 3 mg/kg IV Q2W exposures in patients with moderate (65 to 90 kg) and low (< 65 kg) body weights. However, in the event of low bioavailability (60%) when administered to a broader patient population, 960 mg SC Q4W would likely produce lower Cmind28 and Cavgd28 exposures in patients with a higher body weight (> 90 kg) when compared with 3 mg/kg IV Q2W (below figure). Therefore, the 1200 mg SC Q4W regimen was selected over 960 mg SC Q4W because it overcame these limitations and would provide the best chance to achieve noninferior geometric mean exposures after the first dose where exposures would be the lowest and at steady state relative to nivolumab 3 mg/kg IV Q2W while not exceeding exposures (Cavgd28, Cminss, and Cmax1) predicted for nivolumab 10 mg/kg IV Q2W.

Figure 31: Predicted Nivolumab Exposures (Cavgd28, Cmind28, and Cmax1) by Body Weight Groups, Dose, and Route of Administration for Worst Case Bioavailability (60%)



Source: Supplemental Figure 6 (Zhao Y, Sanghavi K, Roy A, et al.[25])
Note: Boxes extend from the 25th to the 75th percentile. The middle line shows the median, and the whiskers extend to the 5th and 95th percentiles of predicted exposures. Circles indicate outlier predicted values.

In addition to 1200 mg SC Q4W, an alternative posology is proposed in this application. Nivolumab SC 600 mg Q2W was selected and evaluated in CA2098KX because it was expected to have a linear exposure profile (ie, approximately 50% lower Cmax and AUC over the first 2 doses) to that of nivolumab SC 1200 mg Q4W and would provide SC dosing optionality for patients and prescribers.

The recommended dosing regimen of 1200 mg SC Q4W for the treatment of advanced or metastatic ccRCC was studied in the Phase 3 Study CA20967T in which assessment of PK non-inferiority of nivolumab SC 1200 mg Q4W relative to nivolumab IV 3 mg/kg Q2W was concluded for the co-primary endpoints Cavgd28 and Cminss. The geometric mean ratios (90% CI) were 2.098 (2.001, 2.200) and

1.774 (1.633, 1.927) for Cavgd28 and Cminss, respectively, and the lower bounds of the 2-sided 90% CIs for both endpoints were above 0.8. In addition, all geometric mean exposure measures (Cavgd28, Cmax1, Cmind28, Cavgss, Cmaxss and Cminss) predicted for nivolumab SC 1200 mg Q4W were higher than those predicted for nivolumab IV 3 mg/kg Q2W and lower than those predicted for nivolumab IV 10 mg/kg Q2W, a regimen shown to be safe and well tolerated in early clinical studies and used to define nivolumab's exposure safety margin. Understanding early exposures achieved following nivolumab SC 1200 mg Q4W in CA20967T is particularly important because early metrics are the drivers used in exposure-response analyses that have supported the benefit-risk profile of nivolumab. Furthermore, extensive exposure-safety analyses have been conducted previously for nivolumab IV with pooled safety data from across multiple tumour types and dosages (1 to 10 mg/kg Q2W and 0.3 to 10 mg/kg Q3W) and for several safety endpoints (AEs-DC/D, TRAEs-DC/D, Grade ≥3 AEs, Grade ≥2 TRAEs, Grade ≥2 IMAEs). Exposure-safety relationships were mostly flat and supported nivolumab's benefit-risk profile when an extended dosing frequency IV regimen (480 mg Q4W) was being introduced. Achieving PK non-inferiority in CA20967T, especially after the first nivolumab SC dose where exposures are lowest, also increased confidence in the simulation-based analysis strategy to bridge from RCC to other solid tumour indications.

In addition to PK non-inferiority, nivolumab SC demonstrated efficacy non-inferiority (powered secondary endpoint of ORR by BICR) relative to nivolumab IV in CA20967T, and additional efficacy endpoints of TTR, DCR, and PFS by BICR were comparable between the two regimens.

Further, a consistent clinical safety profile was observed, and additional safety analyses were performed for adverse events by weight categories. In subjects who were < 80 kg or ≥80 kg (a study stratification factor), all-causality and drug related adverse event incidences were comparable between nivolumab SC and nivolumab IV for most SOCs and PTs.

In subjects who were <50 kg, ≥50 kg to <70 kg, ≥70 kg to <90 kg, ≥90 kg to <110 kg, and ≥110 kg, all-causality and drug-related adverse event incidences for nivolumab SC were comparable to or lower than the incidences for nivolumab IV for most SOCs across all weight categories, and no clusters or patterns for PTs were identified.

Supportive clinical safety data for nivolumab SC 1200 mg Q4W is also provided by the multicohort, multi-tumour Phase 1/2 Study CA2098KX where the observed safety data was consistent with the known safety profile of nivolumab IV, and no new safety signals were identified.

The recommended dosing regimens of 1200 mg Q4W and 600 mg Q2W for the treatment of other solid tumours (ie, OSCC, NSCLC, GC/GEJC/OAC, RCC, SCCHN, MEL, UC, mCRC, and adjuvant melanoma, UC, and EC) in adults where nivolumab IV is approved as monotherapy, monotherapy maintenance, or in combination with chemotherapy or cabozantinib, are supported by simulation-based bridging analyses.

The 600 mg SC Q2W regimen is further supported by clinical safety data from the multi-cohort, multi-tumour CA2098KX study where the observed safety profile was consistent with the known safety profile of nivolumab IV, and no new safety signals were identified. In addition, observed PK data for 600 mg SC Q2W (Part E) was found to be relatively similar to that of 1200 mg SC Q4W (Part D) when considering differences in dose and administration schedule as well as expected accumulation with Q2W dosing (PK parameters for CA2098KX).

2.6.3. Discussion on clinical pharmacology

The clinical pharmacology includes pharmacokinetic data from the pivotal phase 3 Study CA20967T to evaluate PK non-inferiority of the subcutaneous formulation compared with the IV formulation (dose of

1200 mg SC Q4W vs 3 mg/kg IV Q2W) in patients with RCC and from Study CA2098KX to characterize nivolumab subcutaneous pharmacokinetics in multiple tumour types administered with and without the permeation enhancer rHuPH20. A simulation-based analysis has been performed in order to bridge the 1200 mg SC Q4W in 2L RCC to an alternative SC posology of 600 mg SC Q2W and to other solid tumour indications where nivolumab IV formulation is already approved.

Analytical methods

For Studies CA20967T and CA2098KX, different determinations were carried out: nivolumab concentrations, anti-nivolumab antibodies, anti-nivolumab neutralizing antibodies, anti-rHuPH20 antibodies and anti-rHuPH20 neutralizing antibodies. Method validation ICD 416, ICDIM 140 and VSDCBA 68 (concerning nivolumab analysis) were assessed and found acceptable in previous procedures.

Quantification of nivolumab concentrations with method ICD 416 is interfered by the presence of anti-nivolumab antibodies. According to the results provided, 1.00 µg/mL of ADA interferes to 0.60 µg/mL of nivolumab and 10.0 µg/mL of ADA interferes to 4.80 µg/mL of nivolumab. It can be noted that, as more concentration of nivolumab is in the sample, more concentration of ADA is needed to cause interference to the analysis. Regarding the effect of immunogenicity on nivolumab pharmacokinetics, ADA positive patients had slightly less nivolumab levels than ADA negative patients. This difference could be due to the influence of ADA on nivolumab determination. Acknowledging that ADA assay is not quantitative, an analysis was performed to approximately calculate the concentration of ADA in study samples. After this analysis, it could be considered that the worst-case scenario would be the current differences in PK shown between ADA positive and ADA negative patients, and that, in case that ADA did not influence nivolumab quantification, the concentrations of nivolumab would be apparently similar to ADA negative patients.

Method ECL 0346 and ENZYMATIC-0005, concerning rHuPH20 analysis, have been assessed in the current procedure. Overall, validation of method ECL 0346 to determine anti-rHuPH20 antibodies and method ENZYMATIC-005 to determine anti-rHuPH20 neutralizing antibodies was, in general, in accordance with ICH M10 Guideline and the state of the art. For further procedures, for ADA and NAbs analytical methods, the MAH should consider that, according to the state of the art (Myler, Heather et al.), the acceptance criteria between duplicates of NC and PC controls should be CV≤20% for ADA analysis and CV≤25% for NAb analysis.

Sample analysis

During Study CA20967T different analysis were carried out: nivolumab concentrations, anti-nivolumab antibodies, anti-nivolumab neutralizing antibodies, anti-rHuPH20 antibodies and anti-rHuPH20 neutralizing antibodies. Overall, sample analysis was carried out according to method validation.

During Study CA2098KX different analysis were carried out: nivolumab concentrations, anti-nivolumab antibodies and anti-nivolumab neutralizing antibodies. Anti-rHuPH20 antibodies and anti-rHuPH20 neutralizing antibodies were not determined. Overall, sample analysis was carried out according to method validation as well.

Study CA2098KX

In Study CA2098KX, 3 doses of nivolumab SC (720 mg with and without rHuPH20, 960 mg with and without rHuPH20, and 1,200 mg + rHuPH20 Q4W) were evaluated. In addition, an alternative SC dosing regimen of 600 mg + rHuPH20 Q2W was assessed. A Tmax of 5.41 days was observed following the administration of 1200 mg or 600 mg of subcutaneous nivolumab co-formulated with rHuPH20 2000 units/ml, which is reflective of absorption processes following SC administration. Results

from the non-compartmental PK analysis of cycle 1 suggest an increase in AUCtau greater than dose proportional between the 600 mg Q2W and 1200 mg Q4W doses.

Data from study CA2098KX was combined with nivolumab IV data from 19 historical monotherapy studies in different tumour types to develop a SC/IV popPK model and characterize the absorption PK of nivolumab SC. This model will be used to pre-specify the structural, covariate, inter-individual variability (IIV) and the prior information on the distribution of the structural model to be used for the development of the of final phase 3 CA20967T popPK model.

The dataset includes 3407 adult subjects and 18887 PK observations (17828 IV vs 1059 SC observations). Nivolumab SC without the co-administration with rHuPH20 were excluded from the analysis. PK samples below the lower limit of quantification were low 1.29% and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable.

An extravascular absorption compartment was added to the previously established nivolumab IV popPK model to establish the base model. Nivolumab PK was described using a linear, 2-compartment model with zero-order IV infusion when nivolumab was administered by the IV route and first order absorption when nivolumab was administered by the SC route, first-order elimination and time-varying CL with proportional residual error model and random effects on CL, VC, VP, EMAX, KA, and F. The final model was developed by removing non-significant covariates from the base model. The effect of sex on Ka was a significant covariate as the 95% CI from the base model did not include the null value. Only limited samples were collected during the absorption phase at the first cycle. Consequently, it was not possible to perform a robust covariate evaluation on Ka. Adding sex as a covariate effect on Ka led to an over-parametrized model, therefore, Ka was removed from the final model.

Subsequently, a regimen effect was tested on F, however, no significant differences were observed. Moderate inter-individual variability has been characterized on several PK parameters CL (34.42%), VC (29.84%), VP (48.59%), Emax (23.48%), KA (37.56%) and very high inter-individual variability on F1 (111.40%).

The final population PK model incorporates 7 covariate effects, PS, Sex, eGFR and BW on CL, Sex and BW on VC and Sex on F. A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the main PK parameters (CL, VC and F). The impact of selected covariates on exposure metrics (Cavg, Cmax and Cmin at cycle 1 and at steady-state) was assessed by obtaining individual exposures for subjects for whom EBE of PK parameters were available. Similar exposure levels were observed across the different sub-groups with point estimates of the GMR close to 1 and CI very close to the 80 to 125% boundary for most of them. However, the effect of body weight was evaluated by grouping subjects into Quartile 1 and quartile 4 with quartiles 2-3 as the reference group. A more appropriate approach would have been to group subjects into the 5th percentile and the 95th percentile with the 5th-95th percentile as the reference group.

Nivolumab subcutaneous PK parameters F and Ka were compared across tumour types using popPK analysis. The values of F ranged from 66.6 in CRC to 89.8 in SCCHN and the values Ka from 0.292 in RCC to 0.457 in SCCHN. The exposures (Cavgd28 and Cavgss) were also estimated for the different tumour types and dosing regimens. The results showed differences < 20% in exposure compared to RCC, except for HCC patients and CRC patients who received 1200 mg SC Q4W with increases of Cavgss of 42.93% and 30.18% respectively. The differences in the geometric means of KA and F between both SC dosing regimens 600 mg SC Q2W and 1200 mg SC Q4W were 4.23% and 5.94% respectively.

A comparison of nivolumab SC PK parameters (F and KA) and exposures by ADA status was also provided. A small decrease in the geometric mean of F and KA was observed in ADA positive patients,

15.97% and 15.29% respectively. The geometric means of Cavgd28 and Cavgss were also comparable between nivolumab ADA positive and nivolumab ADA negative subjects with differences of 16.6% and 12.8% respectively. The effect of nivolumab ADA status on nivolumab SC PK is not expected to be clinically meaningful.

Study CA20967T

In Study CA20967T, the non-inferiority of PK and efficacy of the subcutaneous formulation vs the intravenous formulation was evaluated in order to demonstrate clinical comparability between both formulations. The co-primary PK endpoints (Cavgd28 and Cminss) and secondary PK endpoints (Cmind28, Cmax1, Cmaxss, and Cavgss) were derived from all PK-evaluable subjects using popPK analysis. Non-inferiority was defined as 0.8 or greater for the lower limit of 2-sided 90% CI of geometric mean ratio of nivo SC to IV Cavgd28 and Cminss.

The Study CA20967T popPK analysis was based on the previous Phase 1/2 study CA2098KX popPK analysis by using the $PRIOR subroutine in NONMEM. $PRIOR was implemented for the following parameters: CL, VC, VP, Q, EMAX, T50, HILL, KA, F, and IIV on CL, VC, VP and EMAX. The parameters were re-estimated using PK data from the Phase 3 study CA20967T. The dataset includes nivolumab SC and IV data from 487 adult subjects and 3734 PK observations. PK samples below the lower limit of quantification were low 0.42% and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable. Moderate inter-individual variability was observed on several PK parameters CL (38.01%), VC (29.36%), VP (48.46%), Emax (24.26%), KA (48.46%) and very high inter-individual variability on F1 (92.17%)

A sensitivity analysis was performed in order to compare parameter estimates using $PRIOR vs sensitivity approach. Slight differences were observed in the primary PK parameters (<10%), and greater differences were observed on the covariate effects, GFR on CL (52.2%) and SEX on VC (67.6%), probably due to the different subject disposition between both datasets.

pcVPC of cycle 1 stratified by administration route, dosing regimen and bodyweight quartiles have been provided. pcVPC by administration route of the final population PK model show good performance for both SC and IV administration. Moreover, pcVPC containing IV and SC data stratified body weight quartiles show relatively good performance across the whole body-weight range.

On the other hand, pcVPC stratified by SC dosing regimen (1200 mg Q4W and 600 mg Q2W), showed the adequacy of the overall framework to describe the data. However, when VPCs were stratified by body weight quartiles, it is observed that it slightly under-estimates the median tendency in patients in the first bodyweight quartile, which could be probably explained by the lack of PK data. Overall, the model is considered adequate to conduct simulations.

A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the main PK parameters (CL, VC and F). The impact of selected covariates on exposure metrics (Cavg, Cmax and Cmin at cycle 1 and at steady-state) was assessed by obtaining individual exposures for subjects for whom EBE of PK parameters were available. Similar exposure levels were observed across the different sub-groups with point estimates of the GMR close to 1 and CI very close to the 80 to 125% boundary for most of them. However, the effect of body weight was evaluated by grouping subjects into Quartile 1 and quartile 4 with quartiles 2-3 as the reference group. A more appropriate approach would be to group subjects into the 5th percentile and the 95th percentile with the 5th-95th percentile as the reference group.

The impact of ADA status for nivolumab and rHuPH20 on nivolumab PK parameters and exposure metrics was assessed. Very small differences were observed in the geometric mean of F and KA (<10%) between ADA positive and ADA negative subjects for both nivolumab and rHuPH20. A small increase on nivolumab CL and a small decrease on geometric mean Cavgss and Cminss was observed

in ADA positive subjects for both nivolumab and rHuPH20. The effect of nivolumab and rHUPH20 ADA status does not seem to be clinically meaningful.

Cavg28 and Cminss are appropriate endpoints for the purpose of comparison of SC and IV regimens. Noninferiority of nivo SC to nivo IV was concluded for a Cavgd28 GMR (90% CI) of 2.098 (2.001, 2.200) and a Cminss GMR (90% CI) of 1.774 (1.633, 1.927). The geometric mean Ctrough at Week 17 (observed) was 123 µg/mL for nivo SC and 66.3 µg/mL for nivo IV, and the geometric mean Cminss (popPK analysis) was 126 µg/mL for nivo SC and 71.5 µg/mL for nivo IV.

Model predicted nivolumab exposure measures for SC 1200 mg Q4W, IV 3 mg/kg Q2W, IV 10 mg/kg Q2W were compared. The geometric means of the exposure measures for the SC 1200 mg Q4W regimen were higher than achieved for IV 3 mg/kg Q2W but they were lower than achieved for IV 10 mg/kg Q2W. No upper boundary for comparable exposure between SC and IV was considered needed as long as nivolumab exposure following SC administration is lower than exposures achieved with 10 mg/kg Q2W IV. Then, a simulation-based analysis to bridge from nivolumab IV to nivolumab SC for different solid tumour indications in adults has been performed with 1200 mg Q4W SC and the proposed alternative SC 600 mg Q2W with the IV flat dose IV Q2W 240 mg and IV Q4W 480 mg. Nivolumab SC administration 1200 mg Q4W and 600 mg Q2W showed consistently higher exposures Cavgd28 and Cminss than both nivolumab IV flat regimens across different solid tumour indications. For Cmaxss, the 75th percentile of the simulated exposures for both SC dosing regimens (1200mg Q4W and 600 mg Q2W) are below the 25th percentile of the simulated exposures at 10 mg/kg IV Q2W across all tumours. However, for Cavg and Cminss, for some tumours, the 75th percentile of simulated exposures for the SC dosing regimens are even or above the median value of the simulated exposures at 10 mg/kg IV Q2W.

Previously, an exposure-response analysis of safety was performed with a pooled dataset across multiple tumour types who received nivolumab IV dosage ranging between 1-10 mg/kg Q2W and 0.3-10 mg/kg Q3W. The CPH models were characterized with respect to Cavgday (most likely scenario) and Cmax1 (worst-case scenario). The results showed that Cavgday was a significant predictor for Gr2+ AE. The exposure achieved for the 10 mg/kg IVQ2W was Cavg1 GM 86 ug/ml. CA20967T popPK analysis showed values of GM of Cavg1 at the 5th and 95th percentiles of body weight of 112 ug/mL and 56.1.1 ug/mL, respectively, as compared to the reference value 86.1 ug/mL.

Ka and F estimates were expected to be tumour agnostic factors based on the preliminary study CA2098KX population PK analysis, however, differences were observed between tumour indications that have previously affected other PK parameters. In this regard, the absorption PK parameters could be affected by disease status and disease progression, which could explain differences in the absorption process across the different tumour indications. In additional simulations using the RCC population with different Ka values (±20% and ±50%), the differences observed in the overall exposure were small (<12%). Despite the fact that the MAH did not evaluate simultaneously differences in bioavailability together with differences in Ka, no relevant changes in exposure could be expected.

On the other hand, simulation-based analyses in order to bridge nivolumab IV to nivolumab SC in patients with stage IIB/C resected melanoma have not been conducted. Nivolumab PK in patients with Stage IIB/C resected melanoma is expected to be similar to nivolumab PK in later stage III/IV resected melanoma. Therefore, the simulation-based bridging analysis performed for the treatment of adjuvant stage III/IV resected melanoma can be extrapolated to stage IIB/C resected melanoma.

Special populations

The covariate analysis revealed an effect of body weight on CL and VC, showing differences >20% are expected in patients with body weight <53 kg compared to the reference patient (74-78 kg). Despite

the fact that differences in exposure were predicted in patients with extreme body weight (<57 kg), no relevant differences in efficacy or safety are expected based on the model predicted HR. The analysis including experimental evidence stratified by body weight on adverse events after IV and SC administration did not show any relevant trend of higher exposure in low body weight patients.

Immunogenicity

The difference in ADA development between the SC and IV dose regimens was assessed in Study CA20967T. 46 out of 202 (22.8 %) patients treated with SC nivolumab tested positive for nivolumab ADA and 2 of them (1%) were persistent positive whereas only 15 out of 215 (7%) patients treated with IV nivolumab tested positive for ADA and none of them were persistent positive. The immunogenicity as expected was higher for the SC regimen. Development of anti-rHuPH20 antibodies was also assessed in Study CA20967T. The results showed that 19 out of 215 (8.8%) patients treated with SC nivolumab tested positive for ADA and 7 of them (3.3%) were persistent positive. These results are consistent with the reported ADA incidence for this hyaluronidase.

Pharmacodynamics

Increases in peripheral pharmacodynamic biomarkers (PD-1 RO, interferon gamma [IFNγ], and IFNγ-inducible chemokines) demonstrate immune activation post nivolumab treatment. On-treatment level of RO demonstrates extent of target engagement, as measured by PD-1 RO assay, to determine the degree of saturation on peripheral effector T-cells by nivolumab treatment. Similarly, levels of IFNγ and IFNγ-inducible chemokines reflect cytotoxic cytokine production primarily by activated T cells post nivolumab treatment. In Study CA20967T, biomarker measures from the periphery, with endpoint measurement of changes from baseline in these peripheral pharmacodynamic biomarkers, were characterized to demonstrate comparable biological activity of nivolumab SC against nivolumab IV.

Dose justification

Some concerns were raised on the fact that predicted exposures at 1200mg SC Q4W for patients below 50 kg exceeded those with the approved dosing regimens at 3 mg/kg IV Q2W. The MAH provided additional comparisons of steady-state exposure measures (Cavgss, Cminss, Cmaxss) including both flat SC regimens with the body-weight base dose regimen of 10 mg/kg IV Q2W (safety margin) by body weight cohort and base case bioavailability (76%) and high bioavailability (86%). When comparing dosing regimens by body weight cohort, patients in the lowest body weight (30-40 kg) category receiving the SC regimens showed higher exposures (CAVGSS, CMINSS) than patients in the same body weight cohort receiving the 10 mg/kg IV Q2W. However, when comparing against the exposure in the whole population, the exposure with the flat dosing regimen is below the exposure in subjects with 150kg body weight following 10 mg/kg IV Q2W. Overall, figures representing the predicted exposure in both bioavailability scenarios (76 and 86%) showed that the flat dosing regimen of 1200 mg Q4W SC provided exposures within the 5^{th} and 95^{th} percentiles of exposures achieved with the 10 mg/kg IV Q2W regimen, which indicates no safety concern. Even though the proposed flat dosing regimen does not exceed the safety margin, the higher exposures achieved with 1200 mg Q4W SC compared to the 3 mg/kg IV Q2W regimen do not guarantee a better efficacy profile considering that the exposure-response efficacy analysis showed a flat exposure relationship. Alternative flat SC dosing regimens with lower dose levels could demonstrate similar benefit-risk balance and could be subject to a future dose optimization strategy.

2.6.4. Conclusions on clinical pharmacology

Non-inferiority was met for both PK co-primary endpoints, Cavgd28 and Cminss, for nivolumab SC and nivolumab IV. The submitted PK data demonstrated the bridging of 1200 mg Q4W SC and 600 mg

Q2W SC with the IV flat dose across different solid tumour. A simulation-based analysis to bridge from nivolumab IV to nivolumab SC for different solid tumour indications in adults have been performed with 1200 mg Q4W SC and 600 mg Q2W SC with the IV flat dose IV Q2W 240 mg and IV Q4W 480 mg. Although the proposed flat dosing regimen does not exceed the safety margin, the higher exposures achieved with Nivolumab SC administration compared to the 3 mg/kg IV Q2W regimen do not guarantee a better efficacy profile, as the exposure-response efficacy analysis showed a flat exposure relationship.Alternative flat SC dosing regimens with lower dose levels could demonstrate similar benefit-risk balance and could be subject to a future treatment optimization strategy.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

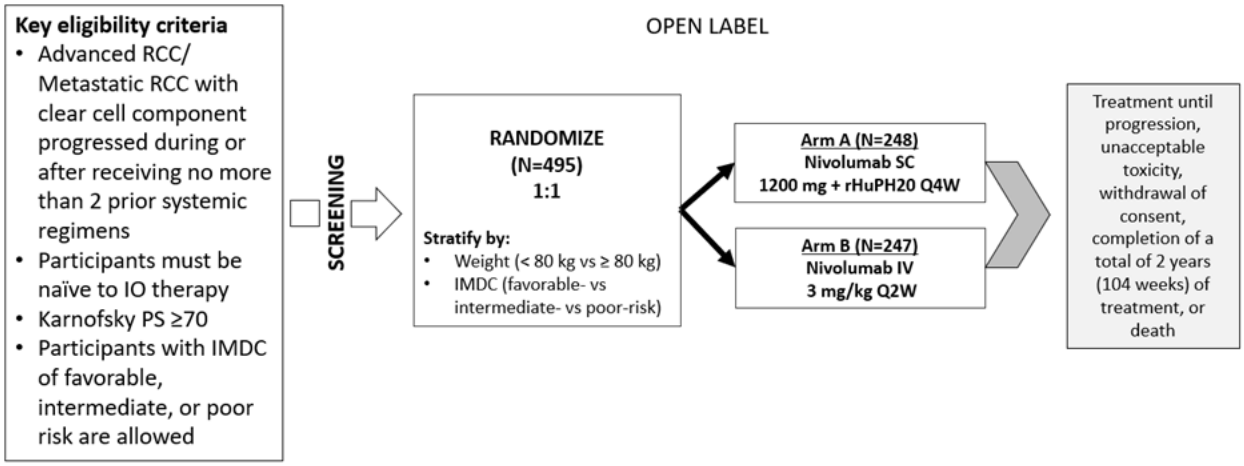
No specific dose response studies were submitted for this application. See section 2.6.2 for dose justification. Study CA2098KX is also described in section 2.6.5.6.

2.6.5.2. Main study(ies)

Study CA20967T: A phase 3, open-label, randomized, non-inferiority trial of subcutaneous formulation of nivolumab versus intravenous nivolumab in participants with advanced or metastatic clear cell renal cell carcinoma who have received prior systemic therapy

Methods

Figure 32. CA20967T Study Design Schematic



Study Participants

Main inclusion criteria

a) Females and males, ages 18 years, or age of majority, or older at time of consent

b) Histological confirmation of RCC with a clear cell component, including participants who may also have sarcomatoid features.

c) Advanced RCC (not amenable to curative surgery or radiation therapy) or mRCC (stage IV) (American Joint Committee on Cancer, 8th edition).

d) Measurable disease as defined by Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 criteria within 28 days prior to randomization.

e) Must have received no more than 2 prior systemic treatment regimens.

f) Must have evidence of intolerance or progression on or after the last treatment regimen received and within 6 months prior to randomization on the study.

g) Karnofsky PS ≥ 70 at Screening.

Main exclusion criteria

Medical conditions:

a) Untreated, symptomatic central nervous system (CNS) metastases. Patients are eligible if CNS metastases are asymptomatic and do not require immediate treatment, or have been treated and patients have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment).

b) Leptomeningeal metastases

c) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to randomization (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the patient has no evidence of disease).

d) Participants with an active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

e) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

f) Known human immunodeficiency virus (HIV) positive with an acquired immunodeficiency syndrome (AIDS) defining opportunistic infection within the last year, or a current CD4 count < 350 cells/µL.

g) Participants with serious or uncontrolled medical disorders including for example, active SAR-CoV-2 infection within approximately 4 weeks prior to screening

Prior/concomitant therapy:

a) Treatment with complementary medications (eg, herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to first study treatment.

b) Prior radiation therapy within 2 weeks prior to first study treatment. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study treatment.

c) Prior treatment with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways.

d) Anticancer therapy less than 14 days prior to the first dose of study drug (less than 28 days for bevacizumab).

e) Major surgery (eg, nephrectomy, hip, or spine surgery) less than 28 days prior to the first dose of study drug. Minor surgery (eg, biopsy or chest tube placement) less than 14 days prior to the first dose of study drug.

Laboratory findings:

a) White blood cells <2,000/μ L

b) Neutrophils <1,500/μ L

c) Platelets < 100 × 103/μ L

d) Hemoglobin <9.0g/dL

e) Blood creatinine >2.0 × ULN, unless creatinine clearance ≥ 30 mL/min (measured or calculated using the Cockcroft-Gault formula)

f) AST or alanine aminotransferase (ALT): >3.0 × ULN

g) T.bili >1.5 × ULN (except participants with Gilbert Syndrome who must have a T.bili level of <3.0 × ULN)

h) Any positive test result for hepatitis B virus indicating presence of virus.

i) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV ribonucleic acid [RNA]).

Treatments

Arm A: SC nivolumab was to be administered Q4W ± 3 days on Day 1 of each treatment cycle until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years (104 weeks) of treatment, death, or the end of study, whichever occurs first.

Arm B: Participants were to receive nivolumab at a dose of 3 mg/kg over an approximately 30-minute IV infusion Q2W ± 3 days on Day 1 of each treatment cycle, until progression, unacceptable toxicity, withdrawal of consent, completion of 2 years (104 weeks) of treatment, or the study ends, whichever occurs first.

In both arms, participants should begin study treatment within 3 calendar days of randomization. Doses of nivolumab could be interrupted, delayed, or discontinued depending on how well the participant tolerated the treatment. Dosing visits were not to be skipped, only delayed.

Table 19. Selection and Timing of Dose

Study Treatment	Unit Dose Strength(s)/ Dosage Level(s)	Dosage Formulation Frequency of Administration	Route of Administration
Arm A Nivo SC (BMS-986298)	Nivo 1200 mg coformulated with rHuPH20 20,000 units	Q4W	SC
Arm B Nivo IV (BMS-936558)	3 mg/kg	Q2W	IV

Source: Table 7.1-1 in the CA20967T Protocol (Appendix 1.1)

A list of the investigational products along with the strength and the batch numbers used in this study are provided in the table below.

Table 20. List of investigational products with the strength and batch numbers

Product Description and Dosage Form	Strength	Batch Numbers
Nivo coformulated with rHuPH20[a] (BMS-986298) Solution for SC Injection	600 mg and 10,000 units (120 mg/mL and 2000 units/mL)	ABK8901, ABQ5962, ABU6847, ABS3100, ACC2842
Nivo (BMS-936558) Solution for IV Infusion	100 mg (10 mg/mL)	ABC4706, ABJ3629, ABN0538, ABQ8805, ABR7999, ABQ8818, ABT5753, ABX7823, ABX7839

Source: Appendix 1.7 (batch numbers listing)

[a] rHuPH20 is classified as an IP per local guidelines (as an active ingredient in the United States and as an excipient in the European Union).

Objectives and endpoints

Table 21. Study objectives and endpoints

Objective	Endpoint	Endpoint Description
Primary		
To demonstrate PK noninferiority of nivo SC vs nivo IV administration	Cavgd28 and Cminss	The co-primary endpoints were derived from all PK evaluable subjects using popPK analysis. Cavgd28 is defined as the time--averaged serum nivo concentration over the first 28 days of treatment. Cminss is defined as the trough serum nivo concentration at steady state. A linear fixed effect model with treatment and stratification factors (at randomization as per CRF) as fixed effects was fitted to the log-transformed Cavgd28 and Cminss for use in estimation of effects and construction of CIs. To assess noninferiority of nivo SC to nivo IV, point estimate and the 2-sided 90% CIs for treatment differences on the log scale will be exponentiated to obtain estimates for ratio of geometric means and respective 90% CIs for Cavgd28 and Cminss on the original scale. Noninferiority of nivo SC to nivo IV will be concluded if the lower limit of the 2-sided 90% CIs for the ratio of geometric means for both nivo Cavgd28 and Cminss is not lower than 0.8.
Secondary		
To demonstrate the ORR noninferiority of nivo SC vs nivo IV administration (efficacy key secondary endpoint)	ORR by BICR, with a minimum of 6 months follow-up	ORR is defined as the number of subjects with a confirmed best response of CR or PR, both by BICR, divided by the number of randomized subjects. BOR is defined as the best response designation, as determined by BICR, recorded between the date of randomization and the date of radiographically documented progression per RECIST v1.1 or the date of subsequent anticancer therapy (including on-treatment palliative therapy), whichever occurred first. Efficacy noninferiority determined by assessment of ORR by BICR, with a minimum of 6 months of follow-up, of Nivo SC compared with Nivo IV was the key secondary endpoint tested in a hierarchical fashion[1] to preserve overall experiment-wise Type I error rate. Noninferiority needs to be met for both PK co-primary

		endpoints before key secondary endpoint of ORR by BICR can be assessed. ORR by BICR noninferiority will be tested using noninferiority margin as a 60% retention of ORR (nivo SC vs nivo IV), and CI will be based on 2-sided α of 0.05.
To evaluate PK of nivo SC and nivo IV administration	Cmind28, Cmax1, Cmaxss, and Cavgss, and Ctrough at Week 17 (observed)	The following secondary PK endpoints were derived from all PK -evaluable subjects using popPK analysis. • Cmind28: trough nivo serum concentration at Day 28 • Cmax1: peak nivo serum concentration after the first dose • Cmaxss: peak serum concentration at steady state • Cavgss: time-averaged nivo serum concentration at steady state • Ctrough at Week 17 (trough serum concentration observed at Week 17) was determined from all PK-evaluable participants using observed concentration-time data.
To evaluate the safety profile of nivo SC and nivo IV administration	Incidence of AEs, SAEs, AEs leading to discontinuation, deaths, and laboratory abnormalities	Adverse events were coded using the MedDRA, and the most recent version of the dictionary at the time of the database lock was used. Adverse event results were graded for severity using the NCI CTCAE (version 5). In addition, clinical laboratory tests were analyzed. On study lab parameters including hematology, chemistry, liver function, and renal function were summarized using worst grade NCI CTCAE per subject.
To evaluate efficacy of nivo SC and nivo IV administration	With a minimal of 6 and 12 months follow-up and at end of study[a]: • DCR by BICR • DOR by BICR • TTR by BICR • PFS by BICR • OS ORR by BICR, with a minimal of 12 months follow-up and at end of study[b]	Disease Control Rate (DCR) is defined as the number of subjects with a BOR of CR, PR, or stable disease (SD), per RECIST v1.1 as per BICR, divided by the number of randomized subjects. DOR by BICR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression as determined by investigator (per RECIST v1.1), or death due to any cause, whichever occurs first. TTR is defined as the time from randomization to the date of the first confirmed CR or PR as determined by BICR. DOR and TTR will be evaluated for responders (confirmed CR or PR) only. PFS is defined as the time from randomization to the date of the first documented tumor progression as determined by BICR (per RECIST v1.1) or death due to any cause. OS is defined as the time from randomization to the date of death. A participant who has not died will be censored at last known date alive. ORR is defined as the number of subjects with a confirmed best response of CR or PR, both by BICR, divided by the number of randomized subjects.
To evaluate AEs in the broad SMQ of Anaphylactic reaction in the nivo SC arm and the nivo IV arm	Incidence of anaphylactic, hypersensitivity, and systemic infusion reactions/systemic injection reactions Incidence of local injection- or infusion-site reactions	The following were summarized by treatment group for each category: • anaphylactic, hypersensitivity, and systemic infusion or injection reactions, as AEs within the Broad SMQ of Anaphylactic Reaction • administration-site reactions (ie, infusion- or injection-site erythema/swelling/pruritis/pain)

To evaluate the immunogenicity of nivo SC and nivo IV	Incidence of anti-nivo antibodies and neutralizing antibodies, if applicable	Number (%) of subjects were reported for the following parameters based on Evaluable Subjects. • Baseline ADA-positive • ADA-positive – Persistent Positive (PP) – Not PP-Last Sample Positive – Other positive – Neutralizing Positive (if applicable) • ADA-negative
Exploratory		
To explore translational biomarkers for SC and nivo IV pharmacodynamic activity	Summary measures of change (or % change) from baseline in peripheral markers of immune activation in both arms Summary measures in baseline levels of peripheral biomarkers in both treatment arms	Descriptive summary statistics of the following biomarker assessments are presented by treatment arm at baseline and at each on-study time point described in the protocol (including change from baseline and/or percent change from baseline), unless otherwise specified: • CXCL9, CXCL10, and IFNγ • PD-1 receptor occupancy
To explore the impact of SARS-CoV-2 serologic status on RCC subjects receiving nivo (IV or SC)[b]	Exploratory measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG), from serum samples collected at baseline, every 6 months, after 4 weeks of confirmed/suspected SARS-CoV-2 infection, after study treatment discontinuation, and the potential association between these measurements and selected endpoints related to safety, efficacy, and/or biomarkers, if deemed appropriate	A listing of subjects with diagnosis tests related to COVID-19 diagnosis (including antibodies if available) are provided, including the date, type, and outcome of the test. AEs within the narrow SMQ of COVID-19 were summarized by treatment group.
To explore the impact of immunogenicity of nivo SC and nivo IV on AEs	Explore the impact of anti-nivo antibodies on AEs, administration-related reactions, and events within MedDRA SMQ Anaphylactic reactions	Effect of anti-nivolumab ADA response on safety were explored by examining the frequency and type of AEs of interest such as administration-related reactions and events within MedDRA broad SMQ Anaphylactic reactions. Graphical presentation (eg, swimmer plot) of all occurrences of AEs of interest (depicting severity) relative to ADA sample status at each assessment time point were provided for ADA-positive subjects versus ADA-negative subjects, as appropriate.
To explore the immunogenicity of rHuPH20 in nivo SC arm and the impact of anti-rHuPH20 antibodies on AEs	Percentage of subjects who develop anti-rHuPH20 antibodies and neutralizing antibodies, if applicable, and the impact of anti-rHuPH20 antibodies on AEs, administration-related reactions, and events within MedDRA SMQ Anaphylactic Reactions	Effect of anti-rHuPH20 ADA response on safety was explored by examining the frequency and type of AEs of interest, such as administration-related reactions and events within MedDRA broad SMQ Anaphylactic reactions. Graphical presentation (eg, swimmer plot) of all occurrences of AEs of interest (depicting severity) relative to ADA sample status at each assessment time point were provided for ADA-positive subjects versus ADA-negative subjects, as appropriate.
To explore changes in disease-related symptoms and impacts on HRQoL using the FKSI-19 questionnaire in the nivo SC and nivo IV arms To explore the participant's perception of the bothersomeness of symptomatic AEs using the FACIT GP5 item of the FKSI-19 questionnaire	Mean FKSI-19 total and subscale scores at baseline and post-baseline score changes Mean FACIT GP5 scores at baseline and post-baseline score changes and assessment of changes in patterns of item responses over time (response category percentages)	The NCCN FKSI-19 is a 19-item scale that measures tumor-specific HRQoL in kidney cancer subjects.[2,3] The symptom index questionnaire includes The symptom index questionnaire includes a total score (19 items, score range 0 to 76) and 4 subscales: disease-related symptoms - physical (DRS-P; 12 items, score range 0 to 48), disease-related symptoms - emotional (DRS-E;1 item, score range 0 to 4), treatment side effects (TSE; 3 items, score range 0 to 12), and general function and well-being (F/WB; 3 items, score range 0 to 12). FACIT GP5, which is included as part of the FKSI-19, will be used to assess the extent of perceived bother due to symptomatic AEs.
To explore changes in health status and HRQoL in the nivo SC and nivo IV arms	Mean EQ-5D-5L utility index and EQ-VAS scores at baseline and post-baseline score changes Change from baseline in healthcare resource utilization	Subjects' reports of general health status will be assessed using the EuroQoL Group's EQ-5D-5L. EQ-5D-5L essentially has 2 components: the descriptive system and the VAS.[4]

To explore healthcare resource utilization between nivo SC and nivo IV	Healthcare resource use at each assessment time point and in total were summarized using descriptive statistics by treatment group as randomized.

[a] The endpoints with a minimal of 12 months follow-up and at end of study are not included in this primary CSR. End of study is defined as the time when the respective clinical cutoff for the final OS analysis has been achieved, which is at a minimum of 3 years after the last subject's first treatment.

[b] Not included in this primary CSR.

Sample size

PK Co-primary Endpoints**:** Non-inferiority was defined as 0.8 or greater for the lower limit of 2-sided 90% CI of geometric mean ratio of nivo SC to IV Cavgd28 and Cminss. In this 2-arm study, 46 PK-evaluable subjects per arm would be needed to provide > 99% and 90% power (1-sided alpha 0.05) for Cavgd28 and Cminss, respectively, assuming 0.351 CV and 0.549 CV (observed between-subject CVs in the Phase 1/2, dose finding and safety Study CA2098KX) and with expected geometric mean ratio for nivo SC to nivo IV of 1.1 for both PK endpoints. The GMR of 1.1 is an assumption based on the estimated GMRs for nivo SC exposures in Study CA2098KX relative to exposures for historical nivo IV 3 mg/kg Q2W. With these assumptions, the overall power of PK co-primary endpoints will be approximately 90%, assuming independence between co-primary endpoints. Non-inferiority needs to be met for both PK co-primary endpoints, before key secondary endpoint of ORR could be statistically tested.

Efficacy Key Secondary Endpoint: The assumed non-inferiority margin is defined using a 60% retention of ORR (nivo SC vs nivo IV). The non-inferiority hypothesis for ORR can be stated as:

H0: ORRSC / ORRIV < 60%

H1: ORRSC / ORRIV = 60% (non-inferiority)

To declare non-inferiority, the lower bound of the 95% CI of the relative risk (RR) of ORR (nivo SC vs nivo IV) has to be ≥ 0.60. At least 454 randomized subjects (randomized 1:1 to Arm A or B) are needed to demonstrate ORR by BICR non-inferiority of nivo SC compared with nivo IV.

This provides at least 80% power, assuming true proportion nivo SC = nivo IV = 21% ORR point estimate (similar to what is presented in the Phase 3, nivo vs everolimus, aRCC Study CA209025 [ORR by investigator was 21.5% with 95% CI: 17.6 to 25.8]) at 1-sided overall significance level (alpha) of 0.025.

The analysis for the PK primary endpoint takes into account all PK evaluable subjects. With a total sample of N = 454 randomized subjects, the overall power for the study is driven by the power of key secondary endpoint of ORR, which would be approximately 80% (the overall power for PK co-primary endpoints would be > 99% with N = 454). PK samples were collected in all randomized subjects. The power calculation of PK co-primary endpoints allows approximately 80% of the randomized subjects to be PK non-evaluable, but still to maintain a 90% overall power on PK co-primary endpoints.

Approximately 604 subjects were planned for enrolment in the study to ensure at least 227 subjects were randomly assigned to each arm.

Randomisation and blinding (masking)

Eligible subjects were randomized 1:1 in the study using an IRT system. Subjects were stratified by weight (< 80 kg vs ≥ 80 kg) and IMDC (favourable- vs intermediate- vs poor-risk disease).

Of note, there was a discrepancy in the IMDC risk classification between the IRT and the CRF (see Baseline data section)

This is an open-label study; therefore, blinding procedures were not applicable.

Statistical methods

The protocol pre-defined three database locks:

1. Primary analysis/database lock 1 will occur at a minimum of 6 months after the last participant is randomized. Scope of the primary lock will be participant status, demographics, exposure, previous and concomitant medications, safety, co-primary (Cavgd28 and Cminss) and secondary PK endpoints (Cmind28, Cmax1, Cmaxss, Cavgss, and Ctrough at Week 17 [observed]), nivolumab and rHuPH20 immunogenicity, key secondary ORR by BICR, and secondary endpoints DCR, DOR, TTR, PFS (all by BICR) and OS.
2. Secondary analysis/database lock 2 will occur at a minimum of 12 months after the last participant is randomized. Scope of the lock will be participant status, demographics, exposure, previous and concomitant medications, safety, nivolumab and rHuPH20 immunogenicity data, ORR, DCR, DOR, TTR, PFS (all by BICR), and OS
3. Final analysis/database lock for the study will be performed at the end of the study. Scope of the final lock will be participant status, demographics, exposure, previous and concomitant medications, safety, immunogenicity, and efficacy endpoints (end of study ORR, DCR, DOR, TTR, PFS [all by BICR], and OS)

Analyses of efficacy secondary endpoints

Principal analyses of the ORR (key secondary endpoint) were based on the BICR evaluation, unless noted otherwise. A similar approach was used for other efficacy endpoints including DCR, TTR, DOR, and PFS.

Analyses in this section were tabulated for all randomized subjects by treatment arm as randomized, unless otherwise specified.

Analysis of Objective response rate

The number and percentage of subjects in each category of best overall response (BOR) per BICR (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or unable to determine [UTD]) are presented by treatment arm. Estimates of response rate, along with its exact two-sided 95% CI by Clopper and Pearson are presented by treatment arm. A two-sided 95% CI for difference of response rate between the treatment arms were computed for all randomized subjects using the following Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for the stratification factors.

The stratified Mantel-Haenszel estimate of the relative risk (RR) of achieving response for nivo SC vs nivo IV and corresponding two-sided 95% CI were be computed. The CI were based on the Robins, Breslow, and Greenland variance estimate.

To declare non-inferiority, the lower bound of the two-sided 95% CI of the relative risk (RR) must be $\geq$ 0.60. If non-inferiority in ORR is established and the lower limit of the 95% CI of the RR is > 1.00, the superiority of nivo SC relative to nivo IV will be concluded.

Analysis of Progression-Free Survival

One of the objectives of the study is to compare the progression-free survival (as determined by BICR) between treatment arms in all randomized subjects.

The primary definition of PFS, adjusting for subsequent anticancer therapy, was used in this analysis. The estimate of the PFS hazard ratio between treatment arms was calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate. Ties were handled using the exact method. A two-sided 95% CI for the hazard ratio is also presented.

The PFS function for each treatment arm was estimated using the KM product limit method and is displayed graphically. A two-sided 95% CI for median PFS in each treatment arm was calculated via the log(-log) transformation method. PFS rates at 6 months, 12 months, and end of the study are presented along with their associated 95% CIs. These estimates were derived from the Kaplan-Meier estimate, and corresponding CIs were derived based on the Greenwood formula for variance derivation and on log(-log) transformation applied on the survival function. Analyses of PFS were also conducted based on the secondary definition of PFS. These analyses are the same as those specified above.

The source of PFS event (progression or death) are summarized by treatment arm. The status of subjects who are censored in the PFS KM analysis are tabulated for each treatment arm including the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdraw consent, never treated)
- No baseline tumour assessment
- No on-study tumour assessment and no death
- Received subsequent anticancer therapy

Analysis of Overall Survival

One of the objectives of the study is to compare the overall survival between treatment arms in all randomized subjects. The stratified OS hazard ratio between the treatment arms is presented along with 95% CI.OS was estimated using the KM product limit method and is displayed graphically. A two-sided 95% CI for median OS in each treatment arm was calculated via the log(-log) transformation method. OS rates at 6 months, 12 months, and end of the study are presented along with their associated 95% CIs. These estimates were derived from the Kaplan-Meier estimate, and corresponding CIs were derived based on Greenwood17 formula for variance derivation and on log(-log) transformation applied on the survivor function. The status of subjects who were censored in the OS KM analysis were tabulated for each treatment arm using the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdraw consent, never treated)

A supplementary analysis of OS will also be performed using stratification factors as obtained from the IRT (instead of CRF). This analysis will be performed only if at least one stratification variable/factor at randomization as per IRT and as per CRF are not concordant for at least 10% of the randomized subjects.

Results

Participant flow

In total, 572 subjects were enrolled, 495 subjects were randomized, and 492 subjects were treated (Table 22).

Table 22. Subject Disposition - All Enrolled, Randomized, and Treated Subjects

All Enrolled Status (%)	Total N = 572
ENROLLED	572 (100.0)
RANDOMIZED	495 (86.5)
NOT RANDOMIZED	77 (13.5)
REASON NOT RANDOMIZED	
SUBJECT WITHDREW CONSENT	2 (0.3)
DEATH	1 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	74 (12.9)
NOT RANDOMIZED DUE TO COVID-19	0

All Randomized Status (%)	Nivolumab SC N = 248	Nivolumab IV N = 247	Total N = 495
TREATED	247 (99.6)	245 (99.2)	492 (99.4)
NOT TREATED	1 (0.4)	2 (0.8)	3 (0.6)
REASON FOR NOT TREATED			
SUBJECT WITHDREW CONSENT	1 (0.4)	2 (0.8)	3 (0.6)
NOT TREATED DUE TO COVID-19	0	0	0

All Treated Status (%)	Nivolumab SC N = 247	Nivolumab IV N = 245	Total N = 492
ONGOING TREATMENT	87 (35.2)	86 (35.1)	173 (35.2)
COMPLETED TREATMENT	0	1 (0.4)	1 (0.2)
DISCONTINUED TREATMENT	160 (64.8)	158 (64.5)	318 (64.6)
REASON FOR DISCONTINUATION OF TREATMENT			
DEATH	1 (0.4)	0	1 (0.2)
POOR/NON-COMPLIANCE	0	1 (0.4)	1 (0.2)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.4)	1 (0.2)
DISEASE PROGRESSION	109 (44.1)	110 (44.9)	219 (44.5)
STUDY DRUG TOXICITY	14 (5.7)	15 (6.1)	29 (5.9)
ADVERSE EVENT UNRELATED TO STUDY DRUG	20 (8.1)	14 (5.7)	34 (6.9)
OTHER	1 (0.4)	1 (0.4)	2 (0.4)
SUBJECT WITHDREW CONSENT	9 (3.6)	7 (2.9)	16 (3.3)
LOST TO FOLLOW-UP	0	1 (0.4)	1 (0.2)
ADMINISTRATIVE REASONS BY SPONSOR (CLOSURE OF RUSSIAN SITES)	6 (2.4)	8 (3.3)	14 (2.8)
DISCONTINUED TREATMENT DUE TO COVID-19	1 (0.4)	0	1 (0.2)
REASON FOR DISCONTINUATION OF TREATMENT DUE TO COVID-19			
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (0.4)	0	1 (0.2)
ONGOING STUDY	152 (61.5)	161 (65.7)	313 (63.6)
DISCONTINUED STUDY	95 (38.5)	84 (34.3)	179 (36.4)
REASON FOR DISCONTINUATION OF STUDY			
DEATH	72 (29.1)	59 (24.1)	131 (26.6)
LOST TO FOLLOW-UP	5 (2.0)	1 (0.4)	6 (1.2)
SUBJECT WITHDREW CONSENT	11 (4.5)	11 (4.5)	22 (4.5)
OTHER	0	4 (1.6)	4 (0.8)
ADMINISTRATIVE REASONS BY SPONSOR (CLOSURE OF RUSSIAN SITES)	7 (2.8)	9 (3.7)	16 (3.3)
DISCONTINUED STUDY DUE TO COVID-19	1 (0.4)	0	1 (0.2)
REASON FOR DISCONTINUATION OF STUDY DUE TO COVID-19			
DEATH	1 (0.4)	0	1 (0.2)

Recruitment

This study was conducted at 73 sites in 17 countries (Argentina, Brazil, Chile, Czech Republic, Finland, France, Ireland, Italy, Mexico, New Zealand, Poland, Portugal, Romania, Russian Federation, Spain, Turkey, and United States of America [US]). The enrolment period was approximately 18 months from 24-May-2021 to 24-Nov-2022.

Table 23. Key dates and follow-up in Study CA20967T

FPFV	24-May-2021
Data Cutoff Date (LPLV)	24-Jul-2023
Database Lock	21-Aug-2023
Minimum Follow-up[a], months	8.0

[a] Time from last subject's randomization to clinical data cutoff date

Conduct of the study

The original protocol for this study was dated 21-Oct-2020. As of the 24-Jul-2023 data cut-off date, there were a total of two global revisions (with 2 global amendments), and 2 administrative letters. Key changes are summarized in the table below.

Table 24. Summary of Key Changes to Protocol CA20967T

Document (Amendment) /Date	Summary of Key Changes	Planned Sample Size	Subjects Randomized Under Protocol Version
Administrative Letter 01 24-Feb-2021	• Alignment of language in protocol Section 9.2.5 (Pregnancy) with Section 6.1. (Inclusion Criteria)	454	0
Protocol Amendment 01 17-Mar-2021	• Added co-primary pharmacokinetic (PK) endpoints of time-averaged serum concentration over the first 28 days (Cavgd28) and trough serum concentration at steady-state (Cminss) and add trough serum concentration at Day 28 (Cmind28) as a secondary endpoint. • Changed mandatory tumor tissue submission at screening to optional. • Added additional PK collection at Cycle 1 Day 4. • Clarified pregnancy testing timing and removed reporting and surveillance of female partners of male subjects. • Added details regarding the coronavirus disease 2019 (COVID-19) vaccine permissibility. • Specified blood creatinine assessment instead of serum creatinine.	454	0
Administrative Letter 02 28-Jan-2022	• Updated study personnel.	454	127
Protocol Amendment 02 18-May-2023	• Added new secondary PK endpoint of nivo trough concentration at Week 17. • Clarified the criteria to discontinue regular (every 24 weeks) tumor assessments in subjects at ≥ 2 years after randomization. • Appendix 9: Country-specific Requirements/Differences has been updated to consolidate country-specific differences in order to comply with European Union Clinical Trial Regulation (EU-CTR) requirements. • Updated end of study definition.	454	495

Protocol deviations

Important protocol deviations 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. Monthly monitoring of protocol deviations was conducted and where appropriate additional follow-up and training was conducted with sites and site-facing roles.

Relevant protocol deviations are important protocol deviations that could affect the interpretability of key study results, are programmable deviations from clinical database and are protocol specific.

Table 25. Summary of Relevant Protocol Deviations - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab SC N = 248	Nivolumab IV N = 247	Total N = 495
SUBJECTS WITH AT LEAST ONE DEVIATION	1 (0.4)	1 (0.4)	2 (0.4)
AT ENTRANCE			
SUBJECT WITH BASELINE KPS < 70	0	0	0
SUBJECT WITHOUT SITES OF MEASURABLE DISEASES AT BASELINE	1 (0.4)	1 (0.4)	2 (0.4)
ON-TREATMENT DEVIATIONS			
SUBJECT WHO RECEIVED ANTI-CANCER THERAPY	0	0	0
SUBJECT TREATED DIFFERENTLY THAN AS RANDOMIZED	0	0	0

Source: Table S.2.4

Note: Subject who received anti-cancer therapy is defined as subject receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) or non-palliative radiotherapy while on study therapy.

Baseline data

Table 26. Demographic Summary - All Randomized Subjects

	Nivolumab SC N = 248	Nivolumab IV N = 247	Total N = 495
AGE (YEARS)			
N	248	247	495
MEAN	63.6	64.1	63.8
MEDIAN	64.0	66.0	65.0
MIN , MAX	35 , 93	20 , 87	20 , 93
SD	10.5	10.2	10.3
AGE CATEGORIZATION 1 (%)			
< 65	129 (52.0)	116 (47.0)	245 (49.5)
>= 65	119 (48.0)	131 (53.0)	250 (50.5)
AGE CATEGORIZATION 2 (%)			
< 75	214 (86.3)	213 (86.2)	427 (86.3)
>= 75	34 (13.7)	34 (13.8)	68 (13.7)
AGE CATEGORIZATION 3 (%)			
< 65	129 (52.0)	116 (47.0)	245 (49.5)
>= 65 AND < 75	85 (34.3)	97 (39.3)	182 (36.8)
>= 75 AND < 85	30 (12.1)	30 (12.1)	60 (12.1)
>= 85	4 (1.6)	4 (1.6)	8 (1.6)
SEX (%)			
MALE	164 (66.1)	171 (69.2)	335 (67.7)
FEMALE	84 (33.9)	76 (30.8)	160 (32.3)
RACE (%)			
WHITE	205 (82.7)	217 (87.9)	422 (85.3)
BLACK OR AFRICAN AMERICAN	0	2 (0.8)	2 (0.4)
ASIAN	3 (1.2)	1 (0.4)	4 (0.8)
AMERICAN INDIAN OR ALASKA NATIVE	2 (0.8)	3 (1.2)	5 (1.0)
OTHER	38 (15.3)	24 (9.7)	62 (12.5)
ETHNICITY (%)			
HISPANIC OR LATINO	93 (37.5)	84 (34.0)	177 (35.8)
NOT HISPANIC OR LATINO	80 (32.3)	83 (33.6)	163 (32.9)
NOT REPORTED	75 (30.2)	80 (32.4)	155 (31.3)
COUNTRY BY GEOGRAPHIC REGION (%)			
US AND EU	67 (27.0)	76 (30.8)	143 (28.9)
CZECH REPUBLIC	7 (2.8)	6 (2.4)	13 (2.6)
FINLAND	0	2 (0.8)	2 (0.4)
FRANCE	2 (0.8)	2 (0.8)	4 (0.8)
IRELAND	2 (0.8)	3 (1.2)	5 (1.0)
ITALY	7 (2.8)	15 (6.1)	22 (4.4)
POLAND	21 (8.5)	27 (10.9)	48 (9.7)
PORTUGAL	2 (0.8)	0	2 (0.4)
ROMANIA	6 (2.4)	5 (2.0)	11 (2.2)
SPAIN	18 (7.3)	10 (4.0)	28 (5.7)
UNITED STATES OF AMERICA	2 (0.8)	6 (2.4)	8 (1.6)
MEXICO AND SOUTH AMERICA	159 (64.1)	148 (59.9)	307 (62.0)
ARGENTINA	41 (16.5)	45 (18.2)	86 (17.4)
BRAZIL	41 (16.5)	36 (14.6)	77 (15.6)
CHILE	27 (10.9)	30 (12.1)	57 (11.5)
MEXICO	50 (20.2)	37 (15.0)	87 (17.6)
REST OF THE WORLD	22 (8.9)	23 (9.3)	45 (9.1)
NEW ZEALAND	15 (6.0)	13 (5.3)	28 (5.7)
RUSSIAN FEDERATION	7 (2.8)	9 (3.6)	16 (3.2)
TURKEY	0	1 (0.4)	1 (0.2)
WEIGHT (KG)			
N	248	247	495
MEAN	77.84	77.77	77.80
MEDIAN	76.80	76.70	76.80
MIN, MAX	35.0, 152.6	47.5, 157.4	35.0, 157.4
SD	18.21	16.40	17.32
WEIGHT CATEGORIZATION 1 (CRF) (%)			
< 80 KG	140 (56.5)	141 (57.1)	281 (56.8)
>= 80 KG	108 (43.5)	106 (42.9)	214 (43.2)
WEIGHT CATEGORIZATION 2 (%)			
< 65 KG	59 (23.8)	58 (23.5)	117 (23.6)
>= 65 AND < 90 KG	134 (54.0)	139 (56.3)	273 (55.2)
>= 90 KG	55 (22.2)	50 (20.2)	105 (21.2)

Even though IMDC was a stratification factor, at baseline, less subjects in the nivolumab SC arm (19.4%) were in the IMDC favourable risk category (Score 0) compared with the nivolumab IV arm (23.1%) per CRF; whereas the numbers were balanced per IRT (24.2% for nivolumab SC and 23.5% for nivolumab IV). The total number of subjects with a discrepancy in IMDC risk classification between the IRT and CRF was 38 (15.3%) for the nivolumab SC arm and 44 (17.8%) for the nivolumab IV arm.

Table 27. Baseline Disease Characteristics Summary - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab SC N = 248	Nivolumab IV N = 247	Total N = 495
INITIAL CELL TYPE (%)			
CLEAR CELL	231 (93.1)	240 (97.2)	471 (95.2)
CLEAR CELL COMPONENT WITH SARCOMATOID FEATURES	15 (6.0)	6 (2.4)	21 (4.2)
OTHER	2 (0.8)	1 (0.4)	3 (0.6)
CELL TYPE AT STUDY ENTRY (%)			
CLEAR CELL	232 (93.5)	241 (97.6)	473 (95.6)
CLEAR CELL COMPONENT WITH SARCOMATOID FEATURES	16 (6.5)	6 (2.4)	22 (4.4)
INITIAL DISEASE STAGE (%)			
STAGE I	26 (10.5)	30 (12.1)	56 (11.3)
STAGE II	38 (15.3)	47 (19.0)	85 (17.2)
STAGE III	49 (19.8)	57 (23.1)	106 (21.4)
STAGE IV	128 (51.6)	112 (45.3)	240 (48.5)
NOT REPORTED	7 (2.8)	1 (0.4)	8 (1.6)
INITIAL DISEASE STAGE (%)			
STAGE IV	128 (51.6)	112 (45.3)	240 (48.5)
NON-STAGE IV	113 (45.6)	134 (54.3)	247 (49.9)
NOT REPORTED	7 (2.8)	1 (0.4)	8 (1.6)
DISEASE STAGE AT STUDY ENTRY (%)			
STAGE III	1 (0.4)	3 (1.2)	4 (0.8)
STAGE IV	247 (99.6)	244 (98.8)	491 (99.2)
CNS METASTASIS (%)			
YES	34 (13.7)	23 (9.3)	57 (11.5)
NO	214 (86.3)	224 (90.7)	438 (88.5)
TIME FROM INITIAL DISEASE DIAGNOSIS TO FIRST SYSTEMIC TREATMENT FOR METASTATIC DISEASE (%)			
<1 YEAR	124 (50.0)	106 (42.9)	230 (46.5)
>=1 YEAR	124 (50.0)	141 (57.1)	265 (53.5)
TIME FROM INITIAL DISEASE DIAGNOSIS TO RANDOMIZATION (%)			
<1 YEAR	40 (16.1)	32 (13.0)	72 (14.5)
>=1 YEAR	208 (83.9)	215 (87.0)	423 (85.5)
KARNOFSKY PERFORMANCE STATUS (%)			
70	17 (6.9)	19 (7.7)	36 (7.3)
80	52 (21.0)	49 (19.8)	101 (20.4)
90	78 (31.5)	88 (35.6)	166 (33.5)
100	101 (40.7)	91 (36.8)	192 (38.8)
IMDC RISK GROUP (CRF) (%)			
FAVORABLE [SCORE 0]	48 (19.4)	57 (23.1)	105 (21.2)
INTERMEDIATE [SCORE 1-2]	158 (63.7)	147 (59.5)	305 (61.6)
POOR [SCORE 3-6]	42 (16.9)	43 (17.4)	85 (17.2)
PRIOR SURGERY (%)			
YES	212 (85.5)	226 (91.5)	438 (88.5)
NO	36 (14.5)	21 (8.5)	57 (11.5)
PRIOR NEPHRECTOMY (%)			
YES	203 (81.9)	205 (83.0)	408 (82.4)
NO	45 (18.1)	42 (17.0)	87 (17.6)
PRIOR RADIOTHERAPY (%)			
YES	65 (26.2)	60 (24.3)	125 (25.3)
NO	183 (73.8)	187 (75.7)	370 (74.7)
PRIOR LINES OF THERAPIES (%)			
1	221 (89.1)	234 (94.7)	455 (91.9)
2	27 (10.9)	13 (5.3)	40 (8.1)
COVID-19 VACCINE STATUS (%)			
YES	150 (60.5)	149 (60.3)	299 (60.4)
NO	98 (39.5)	98 (39.7)	196 (39.6)

Source: Table S.3.2.7

Table 28. Prior Cancer Therapy Summary - All Randomized Subjects

	Number of Subjects (%)		
	Nivolumab SC N = 248	Nivolumab IV N = 247	Total N = 495
SUBJECTS WITH PRIOR SYSTEMIC THERAPY			
YES	248 (100.0)	247 (100.0)	495 (100.0)
NO	0	0	0
TYPE OF PRIOR SYSTEMIC THERAPY RECEIVED (A)			
INVESTIGATIONAL ANTINEOPLASTIC AGENTS	0	1 (0.4)	1 (0.2)
MTOR INHIBITORS	7 (2.8)	10 (4.0)	17 (3.4)
UNASSIGNED	4 (1.6)	10 (4.0)	14 (2.8)
VEGFR TARGETED THERAPY	245 (98.8)	244 (98.8)	489 (98.8)
PRIOR SYSTEMIC THERAPY REGIMEN SETTING (A)			
LOCALLY ADVANCED	19 (7.7)	21 (8.5)	40 (8.1)
METASTATIC	219 (88.3)	217 (87.9)	436 (88.1)
NEO-ADJUVANT	2 (0.8)	2 (0.8)	4 (0.8)
ADJUVANT	9 (3.6)	9 (3.6)	18 (3.6)
MULTIMODAL	0	0	0
TIME FROM COMPLETION OF MOST RECENT PRIOR SYSTEMIC THERAPY REGIMEN TO RANDOMIZATION			
< 3 MONTHS	190 (76.6)	202 (81.8)	392 (79.2)
3 - <= 6 MONTHS	42 (16.9)	27 (10.9)	69 (13.9)
> 6 MONTHS	16 (6.5)	18 (7.3)	34 (6.9)
TIME FROM COMPLETION OF MOST RECENT PRIOR ADJUVANT/NEOADJUVANT THERAPY TO RANDOMIZATION			
< 6 MONTHS	7 (2.8)	8 (3.2)	15 (3.0)
>= 6 MONTHS	4 (1.6)	3 (1.2)	7 (1.4)
BEST RESPONSE TO MOST RECENT PRIOR SYSTEMIC THERAPY REGIMEN			
COMPLETE RESPONSE	6 (2.4)	3 (1.2)	9 (1.8)
PARTIAL RESPONSE	49 (19.8)	61 (24.7)	110 (22.2)
STABLE DISEASE	57 (23.0)	52 (21.1)	109 (22.0)
PROGRESSIVE DISEASE	94 (37.9)	91 (36.8)	185 (37.4)
UNABLE TO DETERMINE	23 (9.3)	28 (11.3)	51 (10.3)
NOT APPLICABLE	18 (7.3)	10 (4.0)	28 (5.7)
NOT REPORTED	1 (0.4)	2 (0.8)	3 (0.6)
PRIOR SURGERY RELATED TO CANCER			
YES	212 (85.5)	226 (91.5)	438 (88.5)
NO	36 (14.5)	21 (8.5)	57 (11.5)
TIME FROM COMPLETION OF MOST RECENT PRIOR SURGERY RELATED TO CANCER TO RANDOMIZATION			
< 3 MONTHS	6 (2.4)	8 (3.2)	14 (2.8)
3 - <= 6 MONTHS	13 (5.2)	13 (5.3)	26 (5.3)
> 6 MONTHS	193 (77.8)	205 (83.0)	398 (80.4)
PRIOR RADIOTHERAPY			
YES	65 (26.2)	60 (24.3)	125 (25.3)
NO	183 (73.8)	187 (75.7)	370 (74.7)
TYPE OF PRIOR RADIOTHERAPY (A)			
ADJUVANT THORACIC RADIATION THERAPY	1 (0.4)	0	1 (0.2)
CONSOLIDATIVE THORACIC RADIATION THERAPY	1 (0.4)	0	1 (0.2)
EXTERNAL BEAM	4 (1.6)	6 (2.4)	10 (2.0)
INTENSITY-MODULATED RT (IMRT)	2 (0.8)	2 (0.8)	4 (0.8)
OTHER	11 (4.4)	8 (3.2)	19 (3.8)
PALLIATIVE RT	35 (14.1)	33 (13.4)	68 (13.7)
PALLIATIVE THORACIC RADIATION	1 (0.4)	1 (0.4)	2 (0.4)
STEREOTACTIC RADIATION THERAPY	11 (4.4)	9 (3.6)	20 (4.0)
THREE-DIMENSIONAL CONFORMAL RT (3DCRT)	6 (2.4)	2 (0.8)	8 (1.6)
WHOLE BRAIN RADIATION THERAPY	0	1 (0.4)	1 (0.2)
TIME FROM COMPLETION OF MOST RECENT PRIOR RADIOTHERAPY TO RANDOMIZATION			
< 3 MONTHS	16 (6.5)	11 (4.5)	27 (5.5)
3 - <= 6 MONTHS	6 (2.4)	10 (4.0)	16 (3.2)
> 6 MONTHS	43 (17.3)	38 (15.4)	81 (16.4)
NOT REPORTED	0	1 (0.4)	1 (0.2)

Numbers analysed

Table 29. Analysis Populations

Population	Description	Nivo SC N	Nivo IV N	Total N
All Enrolled	All subjects who signed an ICF and are registered into the IRT. This is the primary dataset for disposition.			572
All Randomized	All subjects who are randomized to any treatment arm in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, outcome research and biomarkers.	248	247	495
All Treated	All subjects who receive at least 1 dose of nivo. This is the primary dataset for dosing and safety analyses.	247	245	492
PK Evaluable	The PK evaluable population is a subset of PK population who have adequate dosing and nivo serum concentration time data for estimation of PK endpoints. Detailed criteria will be defined in the Pharmacometrics Analysis Plan. All available PK endpoints in the PK evaluable population will be reported and included in the summary statistics and statistical analysis of PK endpoints.	242	245	487
Immunogenicity Evaluable	All treated subjects with baseline and at least 1 post-baseline assessment for immunogenicity data.			
Nivolumab		202	215	417
rHuPH20		215	-	-

Outcomes and estimation

Efficacy endpoints results presented in this section are based on the clinical data cut-off of 24-Jul-2023 and the database lock of 21-Aug-2023, unless otherwise specified. The minimum follow up (time from the last subject's randomization date to the clinical cut-off date) was 8.0 months, and median follow-up (between randomization date and last known alive date or death date) was 10.35 months for the nivo SC arm and 11.17 months for the nivo IV arm.

Co-primary endpoints: Cavgd28 and Cminss

- Non-inferiority of nivo SC to nivo IV was concluded with GMR (90% CI) of 2.098 (2.001, 2.200) for Cavgd28 and GMR (90% CI) of 1.774 (1.633, 1.927) for Cminss, as the lower bounds of the 2-sided 90% CIs for both endpoints were above 0.8.
- The geometric mean ratios of nivo SC to nivo IV for the secondary PK endpoints Cmax1, Cmind28, Cmaxss, Cavgss, and Ctrough at Week 17 (observed) were above 1.0.For more details on the PK results, refer to Clinical pharmacology section of this report.

Secondary endpoints

Table 30. Summary of Efficacy - All Randomized Subjects in Study CA20967T

	Nivolumab SC (N = 248)	Nivolumab IV (N = 247)
Confirmed BOR per BICR, n (%)		
CR	5 (2.0)	4 (1.6)
PR	55 (22.2)	41 (16.6)
SD	96 (38.7)	110 (44.5)
PD	62 (25.0)	66 (26.7)
UTD	30 (12.1)	26 (10.5)
ORR per BICR (CR + PR)[a]		
n (%)	60 (24.2)	45 (18.2)
95% CI	(19.0, 30.0)	(13.6, 23.6)
Estimate of Objective Response Risk Ratio (95% CI)[b,c]	1.33 (0.94, 1.87)	
Difference of ORR, % (95% CI)[b,d]	6 (-1.2, 13.1)	
DCR per BICR		
n (%)	156 (62.9)	155 (62.8)
95% CI	(56.6, 68.9)	(56.4, 68.8)
Estimate of Disease Control Risk Ratio (95% CI)[b,c]	1.01 (0.88, 1.15)	
Difference of DCR, % (95% CI)[b,d]	0.6 (-7.7, 8.9)	
TTR per BICR, months		
Median	3.70	3.68
Min, Max	1.7, 11.1	1.6, 11.3
Q1, Q3	1.92, 5.62	1.94, 5.52
Standard Deviation	2.51	2.35
DOR per BICR		
N events/N responders (%)	19/60 (31.7)	5/45 (11.1)
Median, months (95% CI)[e]	14.49 (7.52, N.A.)	N.A. (13.90, N.A.)
Min, Max, months[f]	1.6+, 20.4+	1.6+, 20.2+
PFS per BICR (Primary Definition)		
Events, n (%)	152 (61.3)	147 (59.5)
Median PFS, months (95% CI)[e]	7.23 (5.13, 7.49)	5.65 (5.29, 7.39)
HR (95% CI)[g]	1.06 (0.84, 1.34)	
6-month PFS Rates (95% CI)	50.8 (44.1, 57.2)	47.7 (40.9, 54.2)
OS		
Events, n (%)	73 (29.4)	61 (24.7)
Median OS, months (95% CI)[e]	N.A. (19.22, N.A.)	N.A. (22.57, N.A.)
HR (95% CI)[g]	1.25 (0.89, 1.77)	
6-month OS Rates (95% CI)	84.1 (78.8, 88.2)	87.9 (82.9, 91.5)

[a] CR+PR, confidence interval based on the Clopper and Pearson method.

[b] Stratified by weight categorization (< 80 kg vs ≥ 80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF.

[c] Strata adjusted risk ratio (nivolumab SC over nivolumab IV) using Mantel-Haenszel method.

[d] Strata adjusted difference in objective response rate or disease control rate (Arm A - Arm B) based on CMH method of weighting.

[e] Median computed using Kaplan-Meier method.

[f] Symbol + indicates a censored value.

[g] Cox proportional hazard model, stratified by weight categorization (< 80 kg vs ≥ 80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF. Hazard Ratio is nivolumab SC over nivolumab IV.

ORR by BICR (key secondary endpoint)

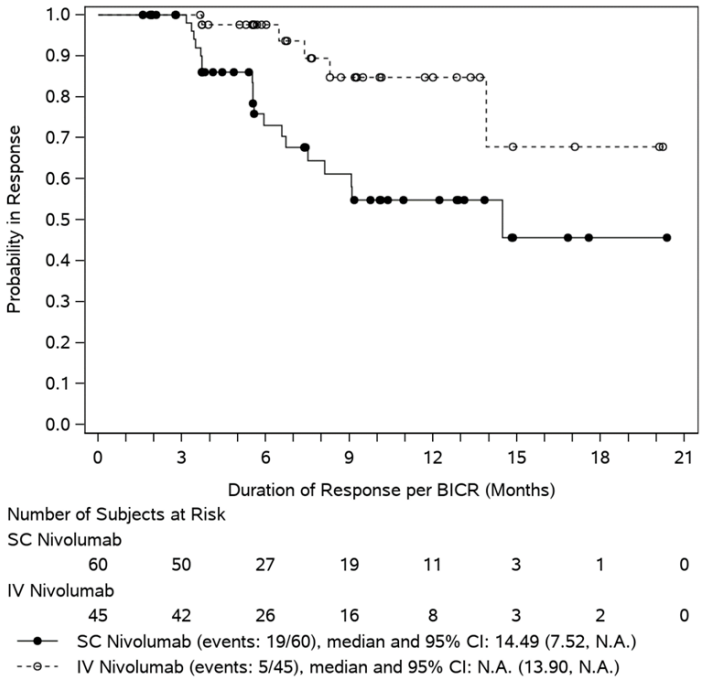
Table 31. Additional Supportive Analyses of ORR - All Randomized Subjects

Analysis	ORR (95% CI) Nivo SC	ORR (95% CI) Nivo IV	RR (95% CI)
Main analysis of ORR per BICR based on stratification factors from the CRF	24.2% (19.0, 30.0)	18.2% (13.6, 23.6)	1.33 (0.94, 1.87)
ORR per BICR based on stratification factors from IRT	24.2% (19.0, 30.0)	18.2% (13.6, 23.6)	1.33 (0.94, 1.88)
ORR per investigator based on stratification factors from CRF	21.0% (16.1, 26.6)	21.5% (16.5, 27.1)	0.98 (0.70, 1.38)
ORR per BICR based on stratification factors from the CRF excluding subjects from Russia	24.5% (19.2, 30.4)	18.9% (14.1, 24.5)	1.30 (0.92, 1.83)

Concordance rate between BICR and investigator assessment for responders (CR, PR) and non-responders/UTD was 87.9% for the nivo SC arm and 89.5% for the nivo IV arm.

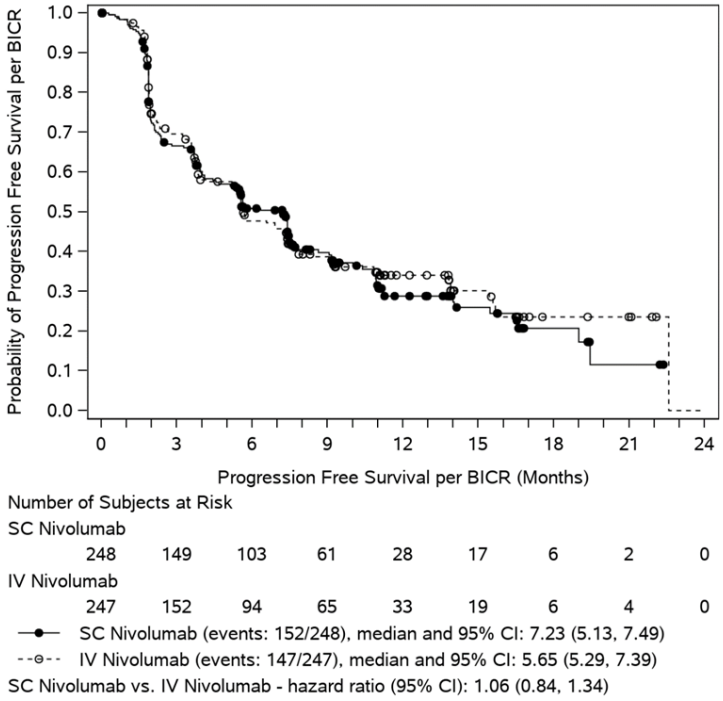
Duration of response per BICR

Figure 33: Kaplan-Meier Plot of Duration of Response per BICR - All Responders in Study CA20967T



Progression-free survival (primary definition)

Figure 34: Kaplan-Meier Plot of Progression-Free Survival per BICR, Primary Definition - Stratification Factors from CRF - All Randomized Subjects in Study CA20967T



Note: Statistical model for hazard ratio: Stratified Cox proportional hazard model. Symbols represent censored observations.

Primary definition of PFS in this study accounts for subsequent therapy.

Table 32. Reason for Censoring, PFS Primary Definition per BICR - All Randomized Subjects in Study CA20967T

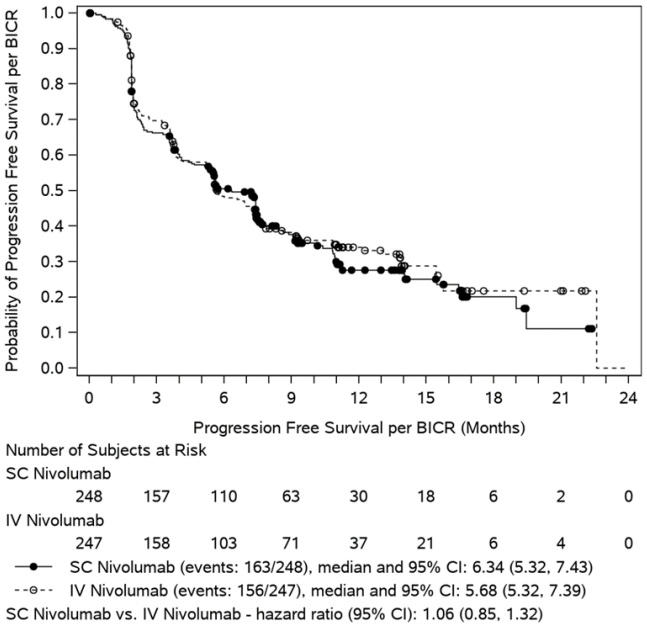
	Nivolumab SC N = 248	Nivolumab IV N = 247
NUMBER OF EVENTS (%)	152 (61.3)	147 (59.5)
TYPE OF EVENTS (%)		
PROGRESSION (1)	125 (50.4)	125 (50.6)
DEATH	27 (10.9)	22 (8.9)
NUMBER OF SUBJECTS CENSORED (%)	96 (38.7)	100 (40.5)
CENSORED ON DATE OF RANDOMIZATION	7 (2.8)	12 (4.9)
INCOMPLETE OR NO BASELINE TUMOR ASSESSMENT (2)	1 (0.4)	4 (1.6)
NEVER TREATED	0	0
OTHER	1 (0.4)	4 (1.6)
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	6 (2.4)	8 (3.2)
NEVER TREATED	1 (0.4)	1 (0.4)
OTHER	5 (2.0)	7 (2.8)

Per **investigator**, median PFS was 7.16 months (95% CI: 5.49, 8.80) for nivolumab SC vs 7.43 months (95% CI: 5.55, 9.23) for nivolumab IV; HR = 1.14 (95% CI: 0.90, 1.43).

Progression-free survival (secondary definition)

The secondary definition is irrespective of subsequent therapy and does not account for subsequent therapy.

Figure 35. Kaplan-Meier Plot of Progression Free Survival per BICR, Secondary Definition - All Randomized Subjects in Study CA20967T



Note: Statistical model for hazard ratio: Stratified Cox proportional hazard model with stratification factors from CRF. Symbols represent censored observations. Secondary definition of PFS in this study does not account for subsequent therapy.

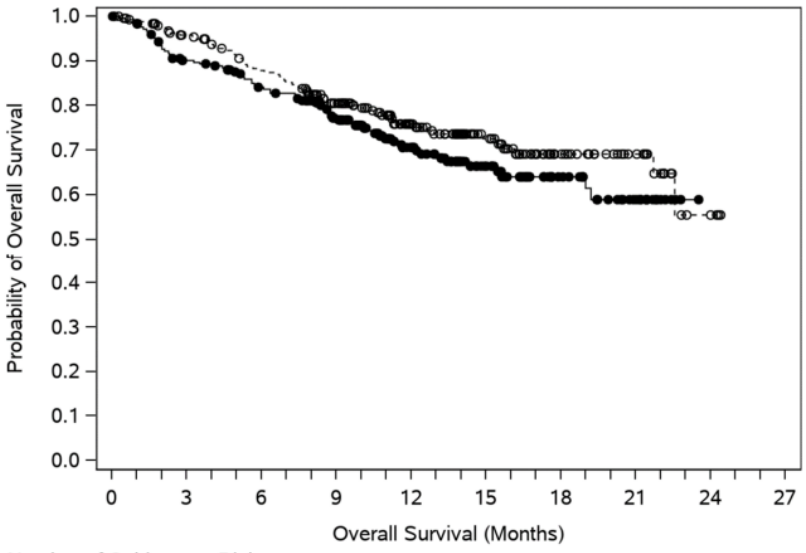
Table 33. Reason for Censoring, PFS Secondary Definition per BICR - All Randomized Subjects in Study CA20967T

	Nivolumab SC N = 248	Nivolumab IV N = 247
NUMBER OF EVENTS (%)	163 (65.7)	156 (63.2)
TYPE OF EVENTS (%)		
PROGRESSION (1)	131 (52.8)	130 (52.6)
DEATH	32 (12.9)	26 (10.5)
NUMBER OF SUBJECTS CENSORED (%)	85 (34.3)	91 (36.8)
CENSORED ON DATE OF RANDOMIZATION	7 (2.8)	12 (4.9)
INCOMPLETE OR NO BASELINE TUMOR ASSESSMENT	1 (0.4)	4 (1.6)
NEVER TREATED	0	0
OTHER	1 (0.4)	4 (1.6)
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH	6 (2.4)	8 (3.2)
NEVER TREATED	1 (0.4)	1 (0.4)
OTHER	5 (2.0)	7 (2.8)
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY	78 (31.5)	79 (32.0)
STILL ON-TREATMENT	52 (21.0)	52 (21.1)
IN FOLLOW-UP	20 (8.1)	20 (8.1)
OFF STUDY	6 (2.4)	7 (2.8)
LOST TO FOLLOW-UP	0	0
SUBJECT WITHDREW CONSENT	3 (1.2)	1 (0.4)
ADMINISTRATIVE REASONS BY SPONSOR (CLOSURE OF RUSSIAN SITES)	3 (1.2)	6 (2.4)
OTHER	0	0

Per **investigator**, median PFS was 5.72 months (95% CI: 5.36, 7.56) for nivolumab SC vs 7.36 months (95% CI: 5.55, 9.00) for nivolumab IV; HR = 1.12 (95% CI: 0.90, 1.40).

Overall survival

Figure 36. Kaplan-Meier Plot of Overall Survival - Stratification Factors from CRF - All Randomized Subjects



Number of Subjects at Risk

SC Nivolumab	248	215	193	155	97	60	31	15	0	0
IV Nivolumab	247	223	197	163	106	69	36	21	4	0

SC Nivolumab (events: 73/248), median and 95% CI: N.A. (19.22, N.A.)

IV Nivolumab (events: 61/247), median and 95% CI: N.A. (22.57, N.A.)

SC Nivolumab vs. IV Nivolumab - hazard ratio (95% CI): 1.25 (0.89, 1.77)

Source: Figure S.5.30.3.1

Note: Statistical model for hazard ratio: Stratified Cox proportional hazard model. Symbols represent censored observations.

Table 34. Piecewise Hazard Ratio of Overall Survival All Randomized Subjects (DCO 24-Jul-2023)

Overall Survival Interval in Months	SC Nivolumab N = 248 # EVENTS / # SUBJECTS (%)	IV Nivolumab N = 247 # EVENTS / # SUBJECTS (%)	HR (95% CI)
0 to <= 3	24/248 (9.7)	10/247 (4.0)	2.39 (1.14, 5.00)
> 3 to <= 6	14/215 (6.5)	18/223 (8.1)	0.77 (0.38, 1.56)
> 6 to <= 9	15/193 (7.8)	16/197 (8.1)	0.97 (0.48, 1.96)
> 9 to <= 12	11/155 (7.1)	8/163 (4.9)	1.47 (0.59, 3.67)
> 12 to <= 15	5/ 97 (5.2)	4/106 (3.8)	1.30 (0.35, 4.86)
> 15 to <= 18	2/ 60 (3.3)	3/ 69 (4.3)	0.88 (0.15, 5.25)
> 18	2/ 31 (6.5)	2/ 36 (5.6)	2.17 (0.19, 24.21)

Cox proportional hazard model, stratified by weight categorization (=80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF. Hazard Ratio is SC Nivolumab over IV Nivolumab. N = numbers of subjects at risk

Updated OS Analyses (Data Cutoff: 21-Feb-2024)

A CA20967T protocol prespecified second DBL occurred on 18-Mar-2024 with data cutoff on 21-Feb-2024. The minimum follow-up was 15 months.

Figure 37. Kaplan-Meier Plot of OS - Stratification Factors from CRF - All Randomized Subjects in CA20967T (Data cutoff: 21-Feb-2024)

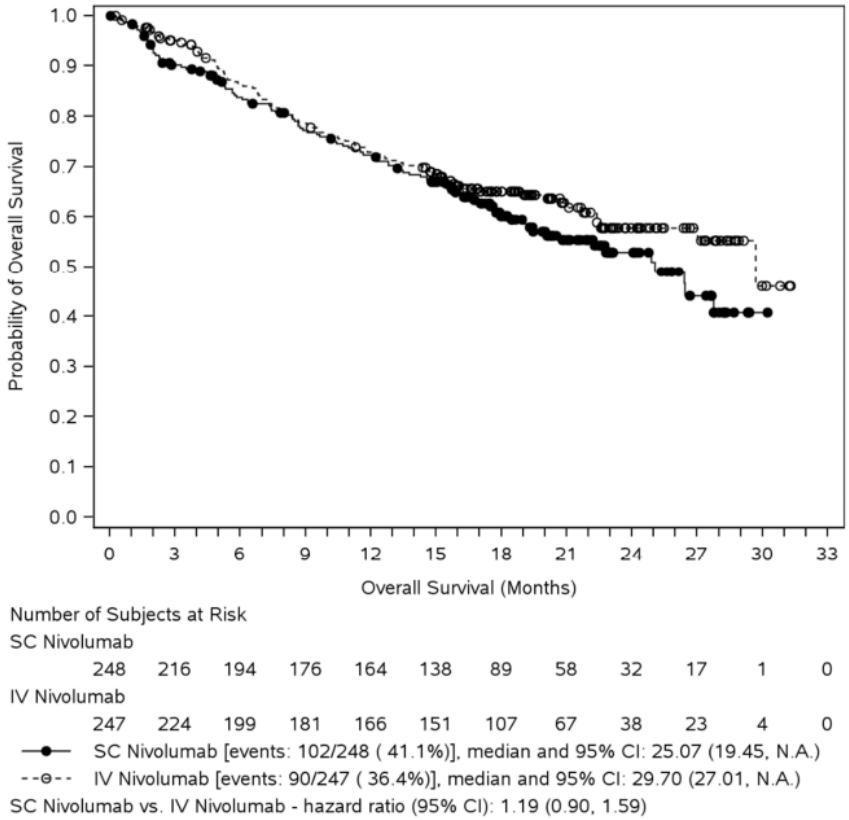


Table 35. Overall Survival Rates - All Randomized Subjects in CA20967T (Data cutoff: 21-Feb-2024)

Overall Survival Rate (95% CI)	SC Nivolumab N = 248	IV Nivolumab N = 247
6-MONTH	83.8 (78.5, 87.9)	86.4 (81.3, 90.2)
12-MONTH	72.4 (66.2, 77.6)	72.9 (66.7, 78.2)
18-MONTH	N.A.	N.A.

Based on Kaplan-Meier Estimates. N.A: Not Available: minimum follow up not reached.

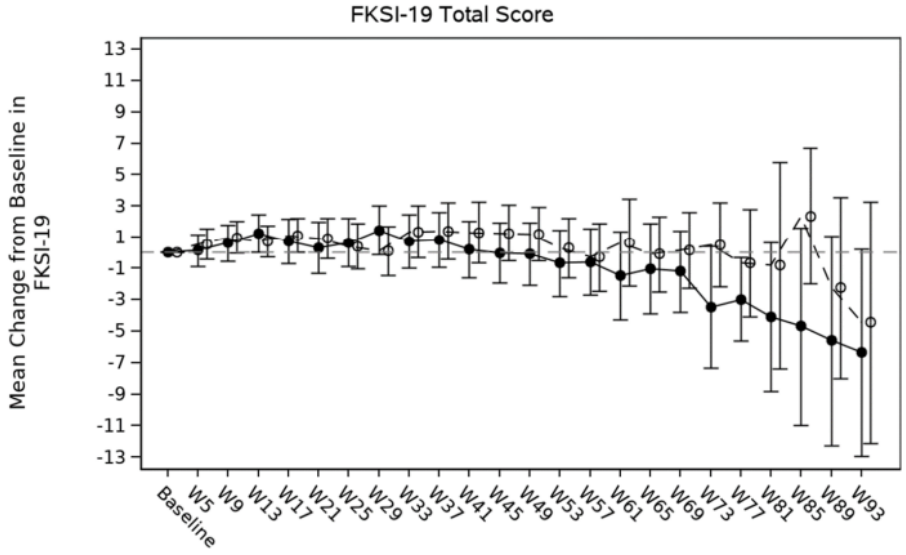
Clinical Outcomes Assessment (Patient-Reported Outcomes) Results

FKSI-19

The FKSI-19 and its subscales measure tumour-specific HRQoL in kidney cancer. FKSI-19 completion rates were > 99% at baseline and ≥ 80% in both treatment arms at all on-treatment assessments through Week 81.

Mean FKSI-19 total scores were 57.63 (SD: 10.19) in the nivo SC arm and 57.95 (SD: 9.49) in the nivo IV arm at baseline. Mean changes from baseline were generally stable and similar between the nivo SC and nivo IV treatment arms throughout most on-treatment time points. Post-Week 65, fewer than 15% of subjects remained in treatment and greater differences are seen between subjects in the nivo SC arm (with lower scores) than the nivo IV arm. The confidence intervals between arms at those time points overlapped. (Figure 38).

Figure 38. Mean Changes in FKSI-19 from Baseline - All Randomized Subjects



Number of Subjects with Measurement at time point

SC Nivolumab	247	221	198	193	166	138	137	123	114	96	81	72	56	53	43	38	30	28	19	15	10	8	8	5
IV Nivolumab	244	224	200	187	167	154	143	131	114	107	91	83	73	56	46	34	33	31	27	20	13	13	10	8

Source: Figure S.10.10.1

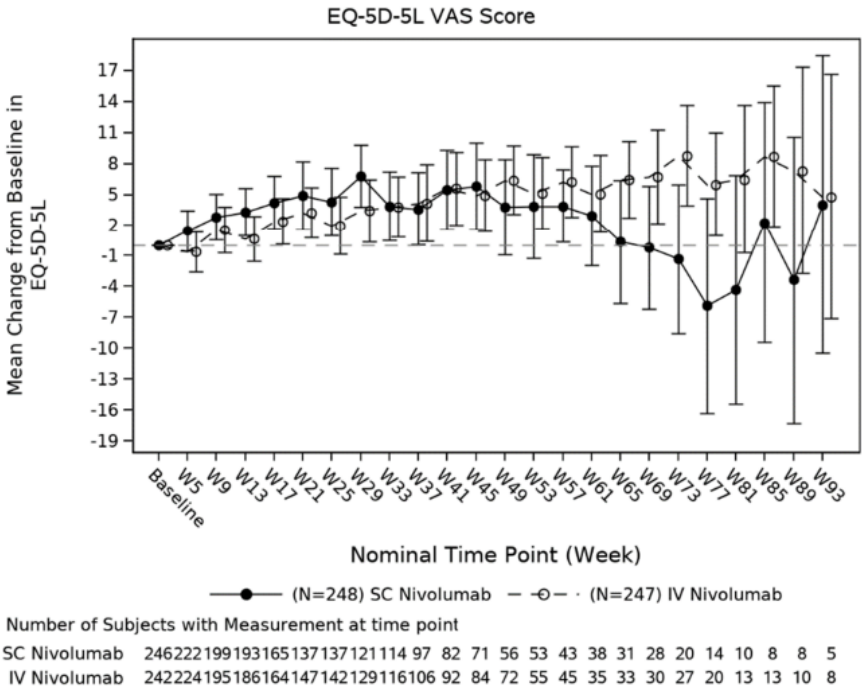
Note: Error bars represent 95% CI for the mean. Only time points where data available for ≥ 5 subjects in each treatment arm are plotted.

EQ-5D-5L

The EQ-5D-5L assesses health status and utility. EQ-5D-5L completion rates were > 99% at baseline and ≥ 80% in both treatment arms at all subsequent on-treatment assessments through Week 81.

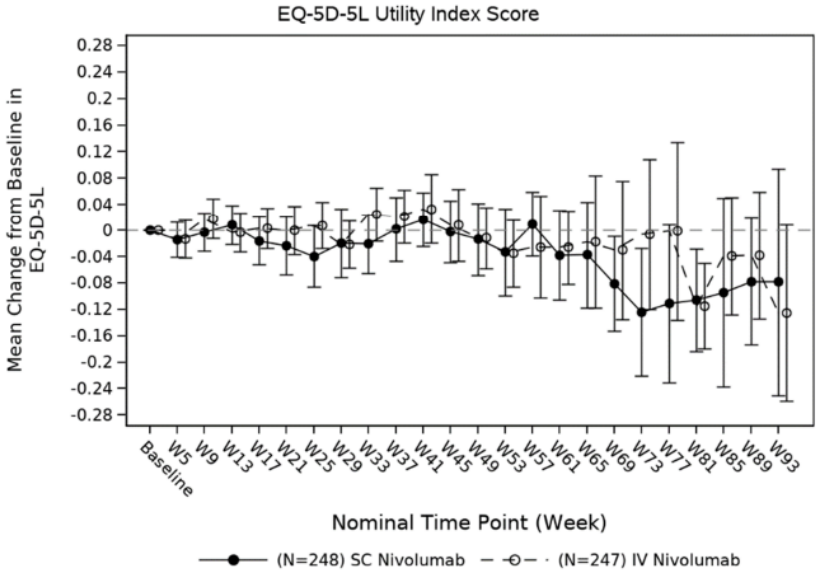
Mean EQ-5D-5L VAS scores were 74.1 (SD: 18.9) in the nivo SC arm and 76.5 (SD: 18.2) in the nivo IV arm at baseline.

Figure 39. Mean changes in EQ-5D-5L VAS from Baseline – All Randomized Subjects



Mean EQ-5D-5L utility index scores were 0.7559 (SD: 0.2139) in the nivo SC arm and 0.7355 (SD: 0.2549) in the nivo IV arm at baseline. Mean changes from baseline were generally stable and similar between the nivo SC and nivo IV treatment arms although subjects remaining in the arms showed some decreases in Year 2, particularly in the nivo SC arm.

Figure 40. Mean Changes in EQ-5D-5L Utility Index Score from Baseline - All Randomized Subjects

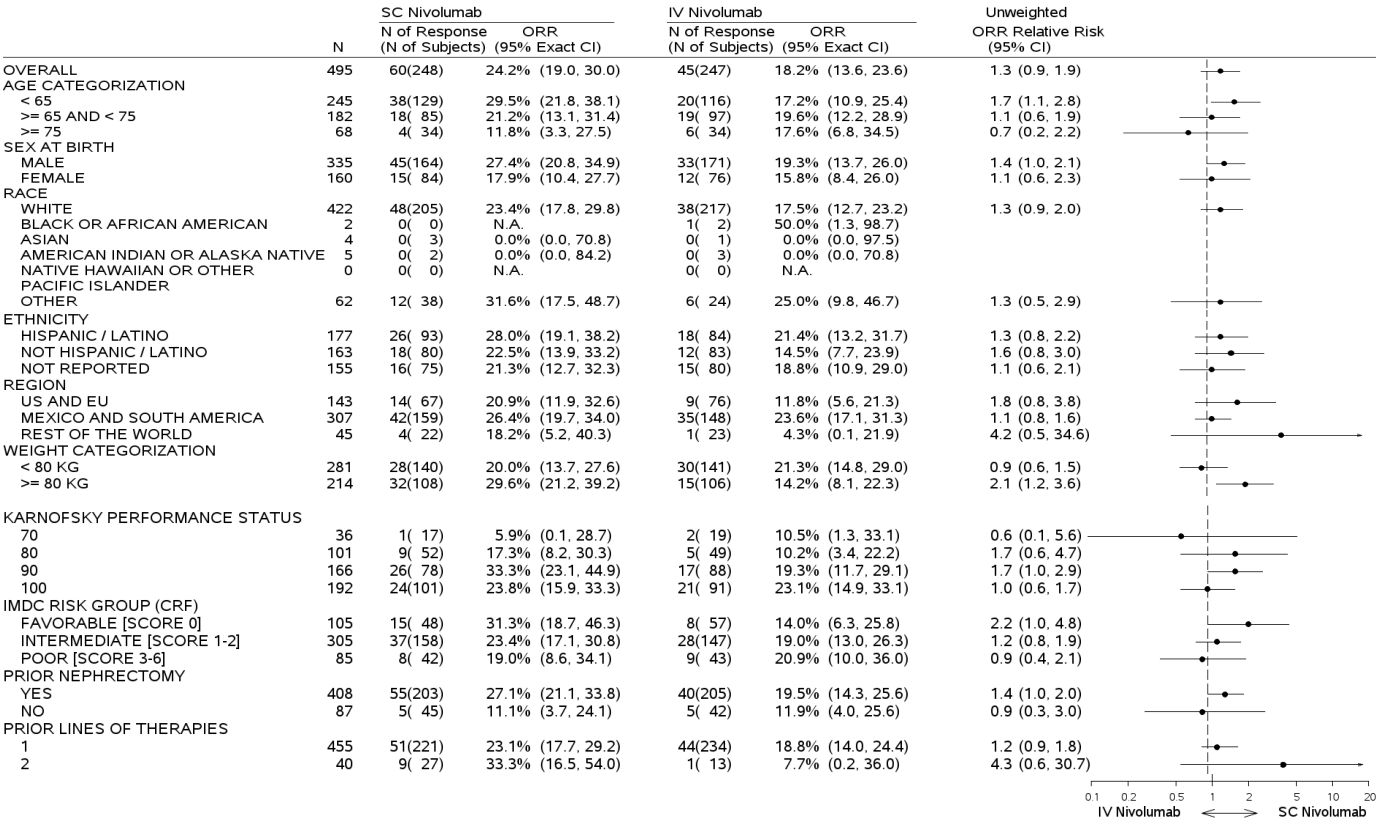


Source: Figure S.10.10.2

Note: Error bars represent 95% CI for the mean. Only time points where data available for ≥ 5 subjects in each treatment arm are plotted.

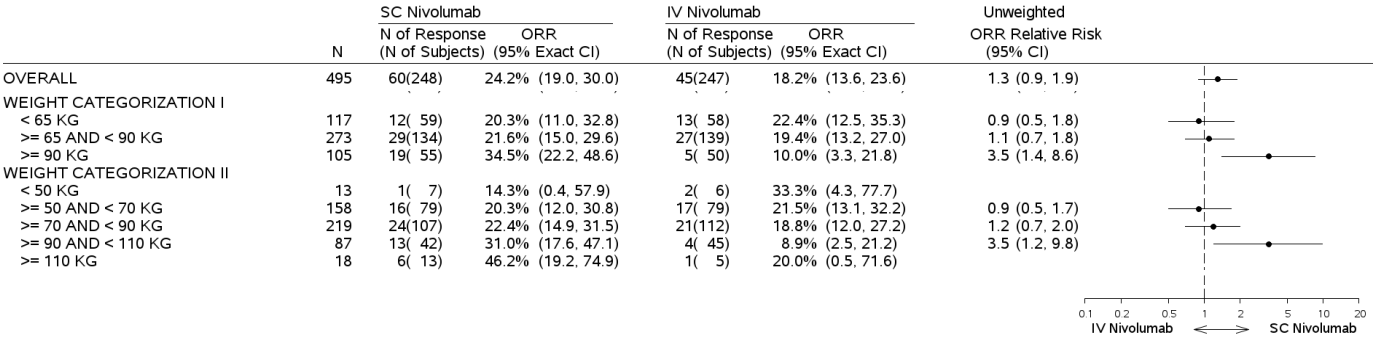
Ancillary analyses

Figure 41. Forest Plot of Treatment Effect on ORR per BICR in Pre-Defined Subsets - All Randomized Subjects in Study CA20967T (DCO: 24-Jul-2023)



Two-sided 95% confidence interval for un-weighted relative risk was calculated using Wald method. Two-sided 95% exact confidence interval for proportion of responders are computed using Clopper-Pearson method. ORR relative risk is not computed for subset with less than 10 subjects per treatment group.

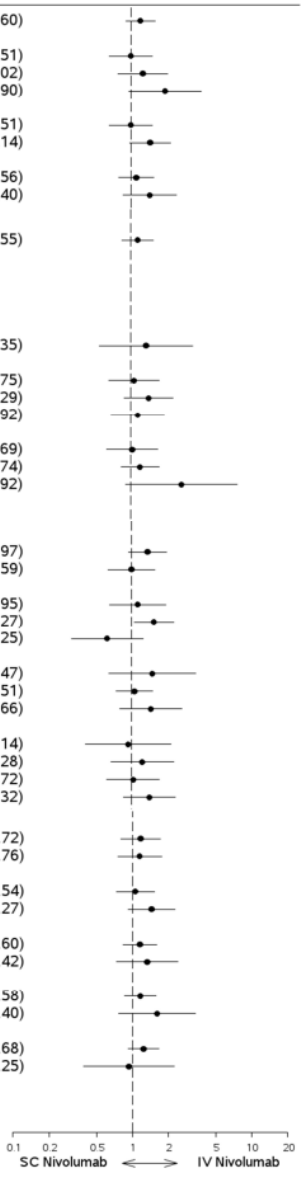
Figure 42. Forest Plot of Treatment Effect on ORR per BICR in Additional Subsets (Weight Categories) - All Randomized Subjects in Study CA20967T (DCO: 24-Jul-2023)



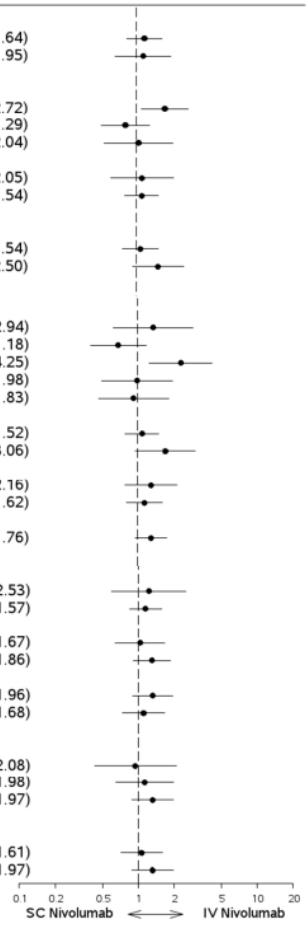
Two-sided 95% confidence interval for un-weighted relative risk was calculated using Wald method. Two-sided 95% exact confidence interval for proportion of responders are computed using Clopper-Pearson method. ORR relative risk is not computed for subset with less than 10 subjects per treatment group.

Figure 43. Forest Plot of Treatment Effect on Overall Survival in Subsets - All Randomized Subjects in CA20967T (Data cutoff: 21-Feb-2024)

		SC Nivolumab		IV Nivolumab		Unstratified
	N	N of events (N of Subjects)	mOS (95% CI)	N of events (N of Subjects)	mOS (95% CI)	Hazard Ratio (95% CI) SC vs IV Nivolumab
OVERALL	495	102 (248)	25.07 (19.45, N.A.)	90 (247)	29.70 (27.01, N.A.)	1.20 (0.90, 1.60)
AGE CATEGORIZATION I						
< 65	245	47 (129)	26.45 (22.24, N.A.)	43 (116)	N.A. (22.37, N.A.)	1.00 (0.66, 1.51)
>= 65 AND < 75	182	35 (85)	26.41 (17.51, N.A.)	34 (97)	29.70 (21.72, N.A.)	1.26 (0.78, 2.02)
>= 75	68	20 (34)	12.29 (8.38, N.A.)	13 (34)	N.A. (12.62, N.A.)	1.93 (0.96, 3.90)
AGE CATEGORIZATION II						
< 65	245	47 (129)	26.45 (22.24, N.A.)	43 (116)	N.A. (22.37, N.A.)	1.00 (0.66, 1.51)
>= 65	250	55 (119)	20.76 (15.77, N.A.)	47 (131)	29.70 (21.72, N.A.)	1.45 (0.98, 2.14)
SEX AT BIRTH						
MALE	335	67 (164)	26.41 (19.22, N.A.)	65 (171)	N.A. (21.72, N.A.)	1.11 (0.79, 1.56)
FEMALE	160	35 (84)	24.90 (17.94, N.A.)	25 (76)	29.70 (22.37, N.A.)	1.43 (0.86, 2.40)
RACE						
WHITE	422	85 (205)	25.07 (19.45, N.A.)	83 (217)	29.70 (22.37, N.A.)	1.15 (0.85, 1.55)
BLACK OR AFRICAN AMERICAN	2	0 (0)		0 (2)	N.A.	
ASIAN	4	2 (3)	6.34 (0.30, N.A.)	0 (1)	N.A.	
AMERICAN INDIAN OR ALASKA NATIVE	5	1 (2)	N.A. (5.29, N.A.)	0 (3)	N.A.	
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0 (0)		0 (0)		
OTHER	62	14 (38)	N.A. (16.89, N.A.)	7 (24)	N.A. (14.69, N.A.)	1.35 (0.54, 3.35)
ETHNICITY						
HISPANIC/LATINO	177	34 (93)	N.A. (19.45, N.A.)	30 (84)	N.A. (22.37, N.A.)	1.07 (0.65, 1.75)
NOT HISPANIC/LATINO	163	38 (80)	24.90 (13.08, 27.76)	31 (83)	29.70 (18.86, N.A.)	1.42 (0.88, 2.29)
NOT REPORTED	155	30 (75)	N.A. (17.51, N.A.)	29 (80)	N.A. (20.73, N.A.)	1.15 (0.69, 1.92)
REGION						
US AND EU	143	30 (67)	26.45 (14.62, N.A.)	33 (76)	N.A. (15.70, N.A.)	1.03 (0.63, 1.69)
MEXICO AND SOUTH AMERICA	307	62 (159)	22.80 (18.99, N.A.)	51 (148)	N.A. (27.01, N.A.)	1.20 (0.83, 1.74)
REST OF THE WORLD	45	10 (22)	11.53 (6.08, N.A.)	6 (23)	29.70 (8.41, N.A.)	2.68 (0.91, 7.92)
WEIGHT CATEGORIZATION I						
< 80 KG	281	65 (140)	20.76 (16.89, 27.76)	52 (141)	N.A. (22.37, N.A.)	1.37 (0.95, 1.97)
>= 80 KG	214	37 (108)	N.A. (22.80, N.A.)	38 (106)	29.70 (27.01, N.A.)	1.01 (0.64, 1.59)
WEIGHT CATEGORIZATION II						
< 65 KG	117	27 (59)	17.74 (13.47, N.A.)	25 (58)	22.37 (11.83, N.A.)	1.13 (0.65, 1.95)
>= 65 AND < 90 KG	273	61 (134)	22.24 (16.16, N.A.)	46 (139)	29.70 (27.01, N.A.)	1.55 (1.06, 2.27)
>= 90 KG	105	14 (55)	N.A. (26.41, N.A.)	19 (50)	N.A. (16.95, N.A.)	0.63 (0.31, 1.25)
IMDC RISK GROUP (CRF)						
FAVORABLE [SCORE 0]	105	12 (48)	N.A. (22.24, N.A.)	10 (57)	N.A.	1.50 (0.65, 3.47)
INTERMEDIATE [SCORE 1-2]	305	66 (158)	24.90 (18.30, N.A.)	60 (147)	N.A. (20.73, N.A.)	1.06 (0.75, 1.51)
POOR [SCORE 3-6]	85	24 (42)	13.47 (4.76, N.A.)	20 (43)	20.96 (9.07, N.A.)	1.46 (0.80, 2.66)
KARNOFSKY PERFORMANCE STATUS						
70	36	11 (17)	8.64 (2.43, N.A.)	12 (19)	8.67 (4.17, 20.96)	0.94 (0.41, 2.14)
80	101	24 (52)	17.74 (13.77, N.A.)	19 (49)	29.70 (14.39, N.A.)	1.24 (0.67, 2.28)
90	166	27 (78)	N.A. (17.94, N.A.)	33 (88)	N.A. (20.73, N.A.)	1.04 (0.62, 1.72)
100	192	40 (101)	26.45 (22.80, N.A.)	26 (91)	N.A. (27.01, N.A.)	1.42 (0.86, 2.32)
TIME FROM INITIAL DISEASE DIAGNOSIS TO FIRST SYSTEMIC TREATMENT FOR METASTATIC DISEASE						
<1 YEAR	230	60 (124)	20.11 (16.13, 26.41)	47 (106)	29.70 (15.34, N.A.)	1.17 (0.80, 1.72)
>=1 YEAR	265	42 (124)	27.76 (25.07, N.A.)	43 (141)	N.A. (27.01, N.A.)	1.15 (0.75, 1.76)
BASELINE HEMOGLOBIN						
< LLN	273	55 (136)	25.07 (17.71, N.A.)	58 (137)	29.70 (15.70, N.A.)	1.06 (0.73, 1.54)
>= LLN	222	47 (112)	26.41 (19.45, N.A.)	32 (110)	N.A. (27.01, N.A.)	1.45 (0.93, 2.27)
CORRECTED CALCIUM						
<= 10 MG/DL	403	77 (200)	25.07 (20.76, N.A.)	71 (203)	N.A. (27.01, N.A.)	1.16 (0.84, 1.60)
> 10 MG/DL	92	25 (48)	16.69 (8.11, N.A.)	19 (44)	20.73 (15.70, N.A.)	1.33 (0.73, 2.42)
ABSOLUTE NEUTROPHIL COUNT						
<= ULN	440	87 (224)	26.41 (22.24, N.A.)	77 (216)	29.70 (29.70, N.A.)	1.16 (0.86, 1.58)
> ULN	55	15 (24)	16.13 (2.37, N.A.)	13 (31)	16.95 (9.07, N.A.)	1.61 (0.77, 3.40)
PLATELET COUNT						
<= ULN	442	92 (221)	24.90 (19.22, N.A.)	80 (221)	29.70 (27.01, N.A.)	1.24 (0.92, 1.68)
> ULN	53	10 (27)	N.A. (8.41, N.A.)	10 (26)	N.A. (8.67, N.A.)	0.94 (0.39, 2.25)



	N	SC Nivolumab N of events (N of Subjects)	SC Nivolumab mOS (95% CI)	IV Nivolumab N of events (N of Subjects)	IV Nivolumab mOS (95% CI)	Unstratified Hazard Ratio (95% CI) SC vs IV Nivolumab
BASELINE LDH LEVEL						
<=ULN	388	69 (189)	26.45 (22.24, N.A.)	67 (199)	29.70 (27.01, N.A.)	1.17 (0.84, 1.64)
>ULN	107	33 (59)	16.16 (10.41, N.A.)	23 (48)	15.44 (8.64, N.A.)	1.14 (0.67, 1.95)
EGFR						
15-29	9	1 (4)		2 (5)		
30-59	226	48 (109)	22.80 (15.64, N.A.)	33 (117)	29.70 (29.70, N.A.)	1.74 (1.12, 2.72)
60-89	191	34 (99)	27.76 (22.24, N.A.)	39 (92)	22.57 (20.73, N.A.)	0.81 (0.51, 1.29)
>=90	69	19 (36)	19.45 (8.11, N.A.)	16 (33)	27.01 (7.33, N.A.)	1.05 (0.54, 2.04)
ALBUMIN						
<LLN	77	28 (45)	13.08 (5.62, 18.30)	17 (32)	11.83 (4.17, N.A.)	1.12 (0.61, 2.05)
>=LLN	410	73 (199)	26.45 (24.90, N.A.)	72 (211)	29.70 (27.01, N.A.)	1.11 (0.80, 1.54)
NOT REPORTED	8	1 (4)		1 (4)		
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS PER BICR						
<Q3	362	65 (181)	26.45 (22.80, N.A.)	61 (181)	29.70 (29.70, N.A.)	1.08 (0.76, 1.54)
>=Q3	123	37 (63)	16.13 (7.39, 19.45)	28 (60)	22.57 (11.83, N.A.)	1.53 (0.93, 2.50)
NOT REPORTED	10	0 (4)		1 (6)		
NUMBER OF DISEASE SITES PER BICR						
1	108	13 (49)	26.45 (25.07, N.A.)	13 (59)	N.A.	1.36 (0.63, 2.94)
2	162	26 (84)	N.A. (22.80, N.A.)	28 (78)	N.A. (15.34, N.A.)	0.69 (0.41, 1.18)
3	101	25 (45)	17.51 (7.39, 27.76)	19 (56)	29.70 (27.01, N.A.)	2.32 (1.26, 4.25)
4	63	20 (36)	16.89 (11.53, N.A.)	14 (27)	18.86 (7.43, N.A.)	1.00 (0.50, 1.98)
>4	55	18 (32)	13.08 (2.30, N.A.)	16 (23)	10.32 (5.06, 22.57)	0.93 (0.47, 1.83)
PRIOR NEPHRECTOMY						
YES	408	74 (203)	27.76 (22.80, N.A.)	70 (205)	29.70 (27.01, N.A.)	1.10 (0.79, 1.52)
NO	87	28 (45)	13.77 (6.34, 17.94)	20 (42)	21.72 (9.53, N.A.)	1.72 (0.97, 3.06)
PRIOR RADIOTHERAPY						
YES	125	35 (65)	17.71 (13.08, 25.07)	27 (60)	27.01 (14.65, N.A.)	1.31 (0.79, 2.16)
NO	370	67 (183)	26.45 (22.80, N.A.)	63 (187)	29.70 (29.70, N.A.)	1.15 (0.81, 1.62)
PRIOR LINES OF THERAPIES						
1	454	91 (220)	24.90 (18.99, N.A.)	82 (234)	29.70 (27.01, N.A.)	1.30 (0.97, 1.76)
2	41	11 (28)	26.45 (16.89, N.A.)	8 (13)		
CNS METASTASIS						
YES	57	20 (34)	17.71 (4.76, 24.90)	12 (23)	14.88 (7.43, N.A.)	1.23 (0.60, 2.53)
NO	438	82 (214)	26.45 (22.80, N.A.)	78 (224)	29.70 (27.01, N.A.)	1.15 (0.84, 1.57)
LIVER METASTASIS						
YES	143	34 (72)	18.30 (13.77, N.A.)	33 (71)	20.73 (12.65, N.A.)	1.04 (0.64, 1.67)
NO	352	68 (176)	26.41 (22.24, N.A.)	57 (176)	29.70 (27.01, N.A.)	1.30 (0.92, 1.86)
BONE METASTASIS						
YES	211	55 (104)	17.74 (13.08, 26.41)	47 (107)	22.57 (16.95, N.A.)	1.32 (0.90, 1.96)
NO	284	47 (144)	N.A. (24.90, N.A.)	43 (140)	N.A.	1.11 (0.73, 1.68)
INITIAL DISEASE STAGE I						
STAGE I	56	8 (26)		7 (30)		
STAGE II	85	11 (38)	N.A. (22.24, N.A.)	14 (47)	N.A.	0.94 (0.43, 2.08)
STAGE III	106	24 (49)	26.41 (12.29, N.A.)	27 (57)	20.96 (13.21, N.A.)	1.14 (0.65, 1.98)
STAGE IV	240	56 (128)	20.11 (16.89, N.A.)	42 (112)	N.A. (21.72, N.A.)	1.32 (0.88, 1.97)
NOT REPORTED	8	3 (7)		0 (1)		
INITIAL DISEASE STAGE II						
NON-STAGE IV AND NOT REPORTED	255	46 (120)	27.76 (25.07, N.A.)	48 (135)	29.70 (22.57, N.A.)	1.07 (0.72, 1.61)
STAGE IV	240	56 (128)	20.11 (16.89, N.A.)	42 (112)	N.A. (21.72, N.A.)	1.32 (0.88, 1.97)



Effect of immunogenicity on efficacy

Table 36. Implications of Nivolumab ADA on Anti-tumor Activity - Confirmed Objective Response Rate per BICR by ADA Status - Immunogenicity Evaluable Subjects with Baseline and at Least One Post- Baseline Evaluable Nivolumab ADA Assessment

	Group: Subjects with ADA Positive		Group: Subjects with ADA Negative	
	Nivolumab SC N = 46	Nivolumab IV N = 15	Nivolumab SC N = 155	Nivolumab IV N = 200
CONFIRMED BEST OVERALL RESPONSE				
COMPLETE RESPONSE (CR)	0	0	4 (2.6)	4 (2.0)
PARTIAL RESPONSE (PR)	7 (15.2)	0	39 (25.2)	37 (18.5)
STABLE DISEASE (SD)	25 (54.3)	8 (53.3)	55 (35.5)	96 (48.0)
PROGRESSIVE DISEASE (PD)	10 (21.7)	7 (46.7)	47 (30.3)	52 (26.0)
UNABLE TO DETERMINE (UTD)	4 (8.7)	0	10 (6.5)	11 (5.5)
OBJECTIVE RESPONSE RATE (1) (95% CI)	7/46 (15.2%) (6.3, 28.9)	0/15 (0.0%) (0.0, 21.8)	43/155 (27.7%) (20.9, 35.5)	41/200 (20.5%) (15.1, 26.8)
DISEASE CONTROL RATE (95% CI)	32/46 (69.6%) (54.2, 82.3)	8/15 (53.3%) (26.6, 78.7)	98/155 (63.2%) (55.1, 70.8)	37/200 (68.5%) (61.6, 74.9)

Source: Table S.7.13.1

Note: Per RECIST 1.1, confirmation of response required.

(1) CR+PR, confidence interval based on the Clopper and Pearson method.

Additional Overall Survival Analyses (Data Cut-off: 21-Feb-2024)

To identify possible risk factors associated with death, a broad range of factors including clinically relevant, plausible, and baseline covariates such as patient characteristics, disease-related factors, laboratory values, and previous treatment-related factors were considered.

A multivariable Cox proportional hazard model was developed. The model identified the following prognostic factors for OS: CNS metastasis, Karnofsky performance status, time from initial disease diagnosis to first systemic treatment for metastatic disease, prior radiotherapy, initial disease stage, sum of reference diameters of target lesions per BICR, albumin, and LDH standardized.

The adjusted HR of nivolumab SC vs nivolumab IV is 1.109 (95% CI: 0.825, 1.490).

Table 37. Multivariable Cox Regression: OS Events Selected from Prognostic Covariates and Interaction Effects - Stepwise Selection - All Randomized Subjects in CA20967T (Data cutoff: 21-Feb-2024)

	Hazard Ratio (95% Wald CI)	P-value
TREATMENT (SC NIVOLUMAB, REFERENCE = IV NIVOLUMAB)	1.109 (0.825, 1.490)	0.493
CNS METASTASIS (YES, REFERENCE = NO)	1.585 (1.057, 2.378)	0.026
KARNOFSKY PERFORMANCE STATUS (70, 80, 90, REFERENCE = 100)		<0.001
KARNOFSKY PERFORMANCE STATUS (70, REFERENCE = 100)	2.734 (1.614, 4.631)	
KARNOFSKY PERFORMANCE STATUS (80, REFERENCE = 100)	0.968 (0.631, 1.487)	
KARNOFSKY PERFORMANCE STATUS (90, REFERENCE = 100)	1.092 (0.758, 1.574)	
TIME FROM INITIAL DISEASE DIAGNOSIS TO FIRST SYSTEMIC TREATMENT FOR METASTATIC DISEASE (< 1 YEAR, REFERENCE = >= 1 YEAR)	1.608 (1.120, 2.308)	0.010
PRIOR RADIOTHERAPY (YES, REFERENCE = NO)	1.533 (1.107, 2.123)	0.010
INITIAL DISEASE STAGE (STAGE II, STAGE III, STAGE IV, NOT REPORTED, REFERENCE = STAGE I)		0.013
INITIAL DISEASE STAGE (STAGE II, REFERENCE = STAGE I)	1.269 (0.665, 2.422)	
INITIAL DISEASE STAGE (STAGE III, REFERENCE = STAGE I)	2.301 (1.265, 4.186)	
INITIAL DISEASE STAGE (STAGE IV, REFERENCE = STAGE I)	1.344 (0.724, 2.493)	
INITIAL DISEASE STAGE (NOT REPORTED, REFERENCE = STAGE I)	1.439 (0.404, 5.126)	
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS PER BICR (MM) (CONTINUOUS)	1.004 (1.002, 1.006)	<0.001
ALBUMIN (G/DL) (CONTINUOUS)	0.643 (0.475, 0.869)	0.004
LDH STANDARDIZED (LOG[VALUE/ULN]) (CONTINUOUS)	1.475 (1.042, 2.087)	0.028

Covariates considered include Sex (ref=Female); CNS Metastasis (ref=No); Liver Metastasis (ref=No); Bone Metastasis (ref=No); Prior Nephrectomy (ref=No); Prior Radiotherapy (ref=No); eGFR (ref= >=90); Initial Disease Stage (ref=Stage I); Karnofsky Performance Status (ref=100); Time from Initial Disease Diagnosis to First Systemic Treatment for Metastatic Disease (ref= >=1 Year); Baseline Hemoglobin (ref= >=LLN); Corrected Calcium (ref= <= 10 mg/dl); Absolute Neutrophil Count (ref= <=ULN); Platelet Count (ref= <=ULN); Age (year, continuous); Weight (kg, continuous); Sum of reference diameters of target lesions per BICR (mm, continuous); Albumin (g/dL, continuous); LDH standardized (log[value/ULN], continuous).
Covariates and treatment arm by covariate interaction effects are selected using Stepwise selection method (SLSTAY=0.15 and SLENTRY=0.15). Only those selected covariates and treatment arm by covariate interaction effects if any are presented.
18 subjects with missing Albumin or missing Sum of reference diameters of target lesions per BICR are excluded from the model. Among these 18 subjects, there are 3 OS events (1 from SC Nivolumab arm and 2 from IV Nivolumab arm).

Multivariable logistic regression model was also developed. This model identified similar prognostic factors as the multivariable Cox regression model. The common prognostic factors identified from both the models include: CNS metastasis, time from initial disease diagnosis to first systemic treatment for metastatic disease, prior radiotherapy, initial disease stage, sum of reference diameters of target lesions per BICR, albumin, and LDH standardized.

Multivariable logistic regression model did not identify Karnofsky performance status as a prognostic factor. Instead, this model identified two additional prognostic factors: bone metastasis, and prior nephrectomy.

The adjusted odds ratio of nivolumab SC vs nivolumab IV is 1.151 (95% CI: 0.768, 1.726).

Table 38. Multivariable Logistic Regression: OS Events Selected from Prognostic Covariates and Interaction Effects - Stepwise Selection - All Randomized Subjects in CA20967T (Data cutoff: 21-Feb-2024)

	Odds Ratio (95% Wald CI)	P-value
TREATMENT (SC NIVOLUMAB, REFERENCE = IV NIVOLUMAB)	1.151 (0.768, 1.726)	0.495
CNS METASTASIS (YES, REFERENCE = NO)	1.776 (0.952, 3.315)	0.071
BONE METASTASIS (YES, REFERENCE = NO)	1.497 (0.959, 2.337)	0.076
TIME FROM INITIAL DISEASE DIAGNOSIS TO FIRST SYSTEMIC TREATMENT FOR METASTATIC DISEASE (< 1 YEAR, REFERENCE = >= 1 YEAR)	1.730 (1.045, 2.864)	0.033
PRIOR NEPHRECTOMY (YES, REFERENCE = NO)	0.623 (0.347, 1.119)	0.113
PRIOR RADIOTHERAPY (YES, REFERENCE = NO)	1.482 (0.891, 2.465)	0.130
INITIAL DISEASE STAGE (STAGE II, STAGE III, STAGE IV, NOT REPORTED, REFERENCE = STAGE I)		0.013
INITIAL DISEASE STAGE (STAGE II, REFERENCE = STAGE I)	1.354 (0.605, 3.029)	
INITIAL DISEASE STAGE (STAGE III, REFERENCE = STAGE I)	2.548 (1.187, 5.469)	
INITIAL DISEASE STAGE (STAGE IV, REFERENCE = STAGE I)	0.945 (0.435, 2.052)	
INITIAL DISEASE STAGE (NOT REPORTED, REFERENCE = STAGE I)	1.790 (0.347, 9.235)	
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS PER BICR (MM) (CONTINUOUS)	1.005 (1.002, 1.008)	0.004
ALBUMIN (G/DL) (CONTINUOUS)	0.566 (0.373, 0.859)	0.008
LDH STANDARDIZED (LOG[VALUE/ULN]) (CONTINUOUS)	1.616 (0.970, 2.690)	0.065

Covariates considered include Sex (ref=Female); CNS Metastasis (ref=No); Liver Metastasis (ref=No); Bone Metastasis (ref=No); Prior Nephrectomy (ref=No); Prior Radiotherapy (ref=No); eGFR (ref= >=90); Initial Disease Stage (ref=Stage I); Karnofsky Performance Status (ref=100); Time from Initial Disease Diagnosis to First Systemic Treatment for Metastatic Disease (ref= >=1 Year); Baseline Hemoglobin (ref= >=LLN); Corrected Calcium (ref= <= 10 mg/dl); Absolute Neutrophil Count (ref= <=ULN); Platelet Count (ref= <=ULN); Age (year, continuous); Weight (kg, continuous); Sum of reference diameters of target lesions per BICR (mm, continuous); Albumin (g/dL, continuous); LDH standardized (log[value/ULN], continuous).
Covariates and treatment arm by covariate interaction effects are selected using Stepwise selection method (SLSTAY=0.15 and SLENTRY=0.15).
Only those selected covariates and treatment arm by covariate interaction effects if any are presented.
18 subjects with missing Albumin or missing Sum of reference diameters of target lesions per BICR are excluded from the model. Among these 18 subjects, there are 3 OS events (1 from SC Nivolumab arm and 2 from IV Nivolumab arm).

Updated efficacy results (DCO: 21-Feb-2024)

Table 39. Summary of Efficacy - All Randomized Subjects in CA20967T (21-Feb-2024 data cutoff)

	Nivo SC (N = 248)	Nivo IV (N = 247)
Confirmed BOR per BICR, n (%)		
CR	5 (2.0)	7 (2.8)
PR	61 (24.6)	44 (17.8)
SD	89 (35.9)	104 (42.1)
PD	63 (25.4)	66 (26.7)
UTD	30 (12.1)	26 (10.5)
ORR per BICR (CR + PR)[a]		
n (%) (95% CI)	66/248 (26.6) (21.2, 32.6)	51/247 (20.6) (15.8, 26.2)
Estimate of Objective Response Risk Ratio (95% CI)[b,c]	1.28 (0.93, 1.77)	
Difference of ORR, % (95% CI)[b,d]	5.9 (-1.5, 13.3)	
DCR per BICR (CR + PR + SD)		
n (%)(95% CI)	155/248 (62.5) (56.2, 68.5)	155/247 (62.8) (56.4, 68.8)
Estimate of Disease Control Risk Ratio (95% CI)[b,c]	1.00 (0.88, 1.15)	
Difference of DCR, % (95% CI)[b,d]	0.2 (-8.2, 8.5)	
TTR per BICR, months		

Table 39. Summary of Efficacy - All Randomized Subjects in CA20967T (21-Feb-2024 data cutoff)

	Nivo SC (N = 248)	Nivo IV (N = 247)
Median (Min, Max)	3.71 (1.7, 11.3)	3.68 (1.6, 13.8)
Standard Deviation	2.85	3.15
DOR per BICR		
N events/N responders (%)	31/66 (47.0)	13/51 (25.5)
Median, months (95% CI)[e]	13.57 (8.57, NA)	NA (15.70, NA)
Min, Max (months)[f]	1.6+, 25.9+	2.8+, 25.8+
PFS per BICR (Primary Definition)		
Events, n (%)	169/248 (68.1)	166/247 (67.2)
Median, months (95% CI)[e]	6.34 (5.13, 7.49)	5.65 (5.19, 7.39)
HR (95% CI)[g]	1.06 (0.85, 1.32)	
PFS per BICR (Secondary Definition)		
Events, n (%)	186/248 (75.0)	176/247 (71.3)
Median, months (95% CI)[e]	6.28 (5.39, 7.49)	5.68 (5.29, 7.39)
HR (95% CI)[g]	1.07 (0.87, 1.32)	

[a] CR+PR, confidence interval based on the Clopper and Pearson method.

[b] Stratified by weight categorization (< 80 kg vs ≥ 80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF.

[c] Strata adjusted risk ratio (nivolumab SC over nivolumab IV) using Mantel-Haenszel method.

[d] Strata adjusted difference in objective response rate or disease control rate (Arm A - Arm B) based on Cochran Mantel-Haenszel (CMH) method of weighting.

[e] Median computed using Kaplan-Meier method.

[f] Symbol + indicates a censored value.

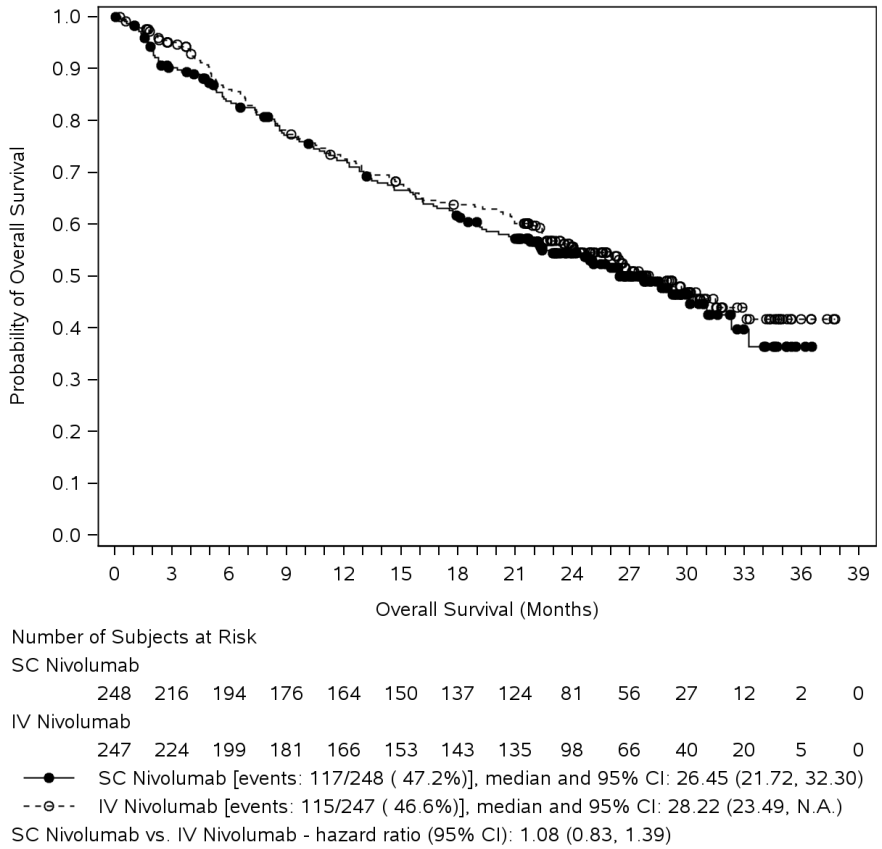
[g] Cox proportional hazard model, stratified by weight categorization (< 80 kg vs ≥ 80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF. Hazard Ratio is nivo SC over nivo IV.

Efficacy results by age categories (DCO 21-Feb-2024)

- Among subjects <65 years, median PFS was 7.33 months (95% CI: 4.11, 10.38) for the nivo SC arm, and 5.55 months (95% CI: 3.71, 6.93) for the nivo IV arm (HR = 0.92 [95% CI: 0.68, 1.24]).
- Among subjects ≥65 years, median PFS was 6.34 months (95% CI: 4.01, 7.69) for the nivo SC arm, and 7.36 months (95% CI: 5.45, 11.04) for the nivo IV arm (HR = 1.21 [95% CI: 0.89 1.65]).
- Among responders <65 years (n=40 [nivo SC]; n=23 [nivo IV]), the median DOR was 11.33 months (95% CI: 7.52, N.A.) for the nivo SC arm, and the median was not reached for the nivo IV arm.
- Among responders ≥65 years (n=26 [nivo SC]; n=28 [nivo IV]), the median DOR was 13.57 months (95% CI: 5.59, N.A.) for the nivo SC arm, and the median was not reached (95% CI: 10.15, N.A.) for the nivo IV arm.

Updated OS results (DCO: 05-Sep-2024)

Figure 44. Kaplan-Meier Plot of Overall Survival - Stratification Factors from CRF - All Randomized Subjects (DCO: 05-Sep-2024)



Statistical model for hazard ratio:
Stratified Cox proportional hazard model.
Symbols represent censored observations.

The following table summarises the efficacy results from the main study 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 40. Summary of efficacy for trial CA20967T

Title: A Phase 3, Open-label, Randomized, Non-inferiority Trial of Subcutaneous Formulation of Nivolumab versus Intravenous Nivolumab in Participants with Advanced or Metastatic Clear Cell Renal Cell Carcinoma who have Received Prior Systemic Therapy (CheckMate-67T: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 67T).	
Study identifier	CA20967T
Design	Multicenter, randomized, open-label, Phase 3 study evaluating the PK and efficacy non-inferiority of nivolumab SC vs nivolumab IV, and safety and tolerability of nivolumab SC in subjects with advanced or metastatic clear cell RCC who have evidence of progression after having received no more than 2 prior systemic treatment regimens. Subjects were randomized 1:1 to the following treatment groups: Arm A (N = 248): nivolumab SC (BMS-986298) 1200 mg co-formulated with rHuPH20 20,000 units Q4W ± 3 days Arm B (N = 247): nivolumab IV (BMS-936558) 3 mg/kg Q2W ± 3 days

	Randomization into treatment groups was stratified by weight (< 80 kg vs ≥ 80 kg) and IMDC risk classification (favourable vs intermediate vs poor risk).	
	Duration: FPFV: 24-May-2021; LPLV:24-Jul-2023	
Hypothesis	PK of nivolumab SC is noninferior to nivolumab IV in subjects with advanced or metastatic clear cell RCC who have received prior systemic therapy	
Treatments groups	Nivolumab SC (BMS-986298)	1200 mg co-formulated with rHuPH20 20,000 units Q4W ± 3 days Dosing continued until disease progression as assessed by investigator, unacceptable toxicity, withdrawal of consent, completion of 2 years (104 weeks) of treatment, death, or the end of study, whichever occurs first.
	Nivolumab IV (BMS-936558)	3 mg/kg Q2W ± 3 days Dosing continued until disease progression as assessed by investigator, unacceptable toxicity, withdrawal of consent, completion of 2 years (104 weeks) of treatment, death, or the end of study, whichever occurs first

ENDPOINTS AND ANALYSES

Objectives	**Endpoint**	**Endpoint Description**
Co-Primary Endpoints		
To demonstrate PK non-inferiority of nivolumab SC vs nivolumab IV administration.	Cavgd28 Cminss	Time-averaged nivolumab serum concentration over 28 days Trough nivolumab serum concentration at steady state.
Key Secondary Efficacy Endpoint		
To demonstrate the ORR non-inferiority of nivolumab SC vs nivolumab IV administration.	ORR by BICR with a minimum of 6 months follow-up	The number of subjects with a confirmed best response of CR or PR both by BICR divided by the number of all randomized subjects. BOR is defined as the best response designation, as determined by the BICR, recorded between the date of randomization and the date of radiographically documented progression per RECIST v1.1 criteria or the date of subsequent anticancer therapy (including on-treatment palliative therapy), whichever occurs first.
Other Secondary Efficacy Endpoints		
To evaluate the efficacy of nivolumab SC and nivolumab IV administration.	With a minimum of 6 and 12 months follow-up and at end of study[a]: DCR by BICR DOR by BICR TTR by BICR	**DCR by BICR**: The number of subjects with a BOR of CR, PR, or stable disease (SD), per RECIST v1.1 as per BICR, divided by the number of randomized subjects. **DOR by BICR**: the time between the date of first confirmed documented response (CR or PR) to the date of the first documented tumor progression as determined by the BICR (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first. **TTR by BICR**: the time from randomization to the date of the first confirmed documented

	PFS by BICR OS • ORR by BICR with a minimum of 12 months follow-up and at end of study[a]	response (CR or PR), as assessed by the BICR. TTR will be evaluated for responders (confirmed CR or PR) only. **PFS by BICR**: the time between the date of randomization and the date of first documented tumor progression, based on BICR assessments (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first. **OS**: the time from randomization to the date of death from any cause. For subjects that are alive, their survival time will be censored at the date of last contact. **ORR by BICR**: The number of subjects with a confirmed best response of CR or PR both by BICR divided by the number of all randomized subjects. .
Exploratory Endpoints		
To explore changes in disease-related symptoms and impacts on HRQoL using the FKSI-19 questionnaire in the nivolumab SC and nivolumab IV arms.	Mean FKSI-19 total and subscale scores at baseline and post-baseline score changes	**FKSI-19:** a 19-item scale. The symptom index questionnaire includes a total score and 4 subscales: disease-related symptoms - physical, disease-related symptoms - emotional, treatment side effects, and general function and well-being. Response categories range from 0 = "not at all" to 4 = "very much."
To explore changes in health status and HRQoL in the nivolumab SC and nivolumab IV arms.	Mean EQ-5D-5L utility and EQ-VAS scores at baseline and post-baseline score changes	**EQ-5D-5L**: a generic multi-attribute health - state classification system has 2 components: the descriptive system and the VAS.
[a] End of study is defined as the time when the clinical cutoff for the final OS analysis has been achieved, which is 3 years after the last subject's first dose date.		
Database Lock	Primary CSR based on 21-Aug-2023 DBL	
Analysis Population	572 subjects were enrolled, 495 subjects were randomized (248 subjects received nivolumab SC and 247 received nivolumab IV) and 492 subjects were treated. Efficacy Analysis: All Randomized Subjects (N = 495)	
RESULTS AND ANALYSES		
Summary of Efficacy - All Randomized Subjects (CA20967T)		

	Nivo SC N = 248	**Nivo IV N = 247**
Confirmed BOR per BICR, n (%)		
CR	5 (2.0)	4 (1.6)
PR	55 (22.2)	41 (16.6)
SD	96 (38.7)	110 (44.5)
PD	62 (25.0)	66 (26.7)
UTD	30 (12.1)	26 (10.5)
ORR per BICR (CR + PR)[a]		
n (%)	60 (24.2)	45 (18.2)
95% CI	(19.0, 30.0)	(13.6, 23.6)
Estimate of Objective Response Risk Ratio (95% CI)[b,c]	1.33 (0.94, 1.87)	
Difference of ORR, % (95% CI)[b,d]	6 (-1.2, 13.1)	
DCR per BICR		

n (%)	156 (62.9)	155 (62.8)
95% CI	(56.6, 68.9)	(56.4, 68.8)
Estimate of Disease Control Risk Ratio (95% CI)[b,c]	1.01 (0.88, 1.15)	
Difference of DCR, % (95% CI)[b,d]	0.6 (-7.7, 8.9)	
TTR per BICR, months		
Median	3.70	3.68
Min, Max	1.7, 11.1	1.6, 11.3
Q1, Q3	1.92, 5.62	1.94, 5.52
Standard Deviation	2.51	2.35
DOR per BICR		
N events/N responders (%)	19/60 (31.7)	5/45 (11.1)
Median, months (95% CI) [e]	14.49 (7.52, N.A.)	N.A. (13.90, N.A.)
Min, Max, months[f]	1.6+, 20.4+	1.6+, 20.2+
PFS per BICR (Primary Definition)		
Events, n (%)	152 (61.3)	147 (59.5)
Median PFS, months (95% CI)[e]	7.23 (5.13, 7.49)	5.65 (5.29, 7.39)
HR (95% CI)[g]	1.06 (0.84, 1.34)	
6-month PFS Rates (95% CI)	50.8 (44.1, 57.2)	47.7 (40.9, 54.2)
OS		
Events, n (%)	73 (29.4)	61 (24.7)
Median OS, months (95% CI)[e]	N.A. (19.22, N.A.)	N.A. (22.57, N.A.)
HR (95% CI)[g]	1.25 (0.89, 1.77)	
6-month OS Rates (95% CI)	84.1 (78.8, 88.2)	87.9 (82.9, 91.5)

[a] CR+PR, confidence interval based on the Clopper and Pearson method.

[b] Stratified by weight categorization (< 80 kg vs ≥ 80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF.

[c] Strata adjusted risk ratio (nivolumab SC over nivolumab IV) using Mantel-Haenszel method.

[d] Strata adjusted difference in objective response rate or disease control rate (Arm A - Arm B) based on CMH method of weighting.

[e] Median computed using Kaplan-Meier method.

[f] Symbol + indicates a censored value.

[g] Cox proportional hazard model, stratified by weight categorization (< 80 kg vs ≥ 80 kg) and IMDC risk group (favorable vs intermediate vs poor) as entered into the CRF. Hazard Ratio is nivolumab SC over nivolumab IV

2.6.5.3. Clinical studies in special populations

Table 41. Clinical studies in special populations

	Controlled Trials		**Non-controlled trials**
	CA20967T		**CA2098KX**
	All randomized subjects		All subjects assigned to Parts D or E and treated
	Nivo SC N=248 n (%)	Nivo IV N=247 n (%)	Nivo SC N=72 n (%)
Renal impairment* patients (Subjects number /total number)	Not Available	Not Available	Not Available

	Controlled Trials		Non-controlled trials
	CA20967T		CA2098KX
	All randomized subjects		All subjects assigned to Parts D or E and treated
	Nivo SC N=248 n (%)	Nivo IV N=247 n (%)	Nivo SC N=72 n (%)
Hepatic impairment** patients (Subjects number /total number)	Not Available	Not Available	Not Available
Paediatric patients <18 years (Subjects number /total number)	0 (0.0)	0 (0.0)	0 (0.0)
Age 65-74 (Subjects number /total number)	85 (34.3)	97 (39.3)	27 (37.5)
Age 75-84 (Subjects number /total number)	30 (12.1)	30 (12.1)	11 (15.3)
Age 85+ (Subjects number /total number)	4 (1.6)	4 (1.6)	1 (1.4)

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

Note: Does not include Parts A, B, or C for CA2098KX.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study(ies)

Study CA2098KX: Phase 1/2 Pharmacokinetic Multi-Tumor Study of Subcutaneous Formulation of Nivolumab Monotherapy

Study CA2098KX is a multicentre, randomized, open-label, Phase 1/2 study that evaluated the PK, safety, and tolerability of nivolumab SC (BMS-986298) administered subcutaneously in subjects with 1 of the following tumour types in Parts A-D: metastatic non-small cell cancer (NSCLC); advanced or metastatic renal cell carcinoma (RCC); unresectable or metastatic melanoma; hepatocellular carcinoma (HCC); or metastatic colorectal cancer (CRC) (microsatellite instability - high [MSI-H] or deficient mismatch repair [dMMR]). In addition to the above tumours, Part E included subjects with metastatic urothelial carcinoma (mUC).

Table 42. Study objectives

Objectives
Primary
Parts A - D: To describe the pharmacokinetics (PK) of nivolumab administered subcutaneously (SC), with or without rHuPH20
Part E: To evaluate the PK of nivolumab SC 600 mg every 2 weeks (Q2W) co-formulated with rHuPH20
Secondary
To assess the safety profile of nivolumab SC
To evaluate incidence of adverse events (AEs) in the broad standardization MedDRA query (SMQ) of Anaphylactic Reaction and the select AE hypersensitivity/infusion reaction category
To assess the immunogenicity of nivolumab

The study was divided into the following periods: Screening period; Treatment period consisting of Part A, Part B, Part C, Part D, and Part E; and a Safety Follow-up period (Figure 45).

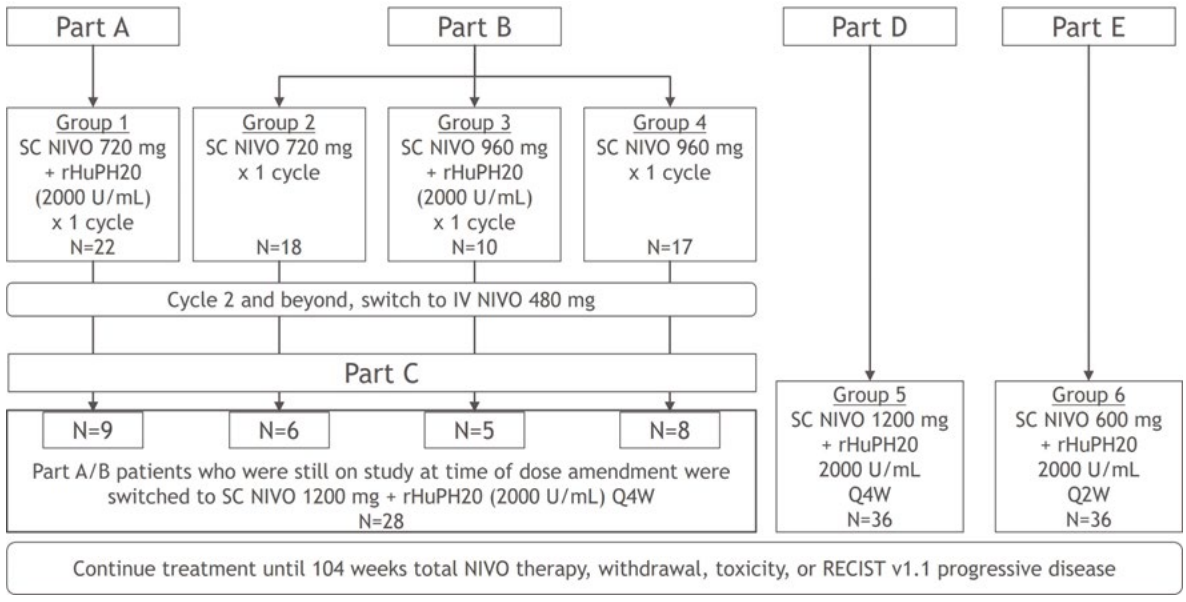
In Parts A and B, subjects were allocated into one of four groups (Groups 1-4) to be treated with either 720 mg or 960 mg nivolumab SC with or without rHuPH20 administered manually by syringe or syringe pump. Four weeks after a single nivolumab SC dose, all subjects in Parts A and B received nivolumab IV 480 mg Q4W until progression (per RECIST v1.1), unacceptable toxicity, withdrawal of consent, completion of 104 weeks of treatment, crossover to 1200 mg nivolumab SC with rHuPH20 Q4W dosing in Part C, or study termination by the sponsor, whichever occurred first.

Subjects in Parts A and B who were still on study at the time of the dose amendment were switched to nivolumab SC 1200 mg with rHuPH20 (2000 units/mL) Q4W manually by syringe in Part C.

In Part D, subjects were treated with 1200 mg nivolumab SC with rHuPH20 (2000 units/mL) Q4W manually by syringe (Group 5).

In Part E, subjects were treated with 600 mg nivolumab SC co-formulated with rHuPH20 (2000 units/mL) Q2W manually by syringe (Group 6). The 600 mg Q2W regimen was expected to have a linear exposure profile (ie, ~50% lower Cmax and AUCtau) to that of the 1200 mg Q4W regimen assessed in previous cohorts.

Figure 45. CA2098KX Study Design Schematic



Actual enrollment: 22 subjects were allocated to Part A. In Part B, the first 10 subjects were assigned to Group 3; the next 35 subjects were randomized 1:1 into Group 2 (n = 18) and Group 4 (n = 17).

Patient disposition

Table 43. End of Treatment and End of Study Period Subject Status Summary for Parts A, B, D, and Part E - All Treated Subjects in Parts A, B, D and Part E

	PART A GRP 1 N = 22	PART B GRP 2 N = 18	PART B GRP 3 N = 10	PART B GRP 4 N = 17	PART D GRP 5 N = 36	PART E GRP 6 N = 36	Total N = 139
CONTINUING TREATMENT IN THE CURRENT PART OF THE STUDY	0	0	0	0	0	14 (38.9)	14 (10.1)
[a]COMPLETED THE CURRENT PART OF THE STUDY	10 (45.5)	6 (33.3)	5 (50.0)	9 (52.9)	7 (19.4)	1 (2.8)	38 (27.3)
NOT COMPLETED THE CURRENT PART OF THE STUDY	12 (54.5)	12 (66.7)	5 (50.0)	8 (47.1)	29 (80.6)	21 (58.3)	87 (62.6)
REASON FOR NOT COMPLETED THE CURRENT PART OF THE STUDY							
DISEASE PROGRESSION	8 (36.4)	11 (61.1)	4 (40.0)	6 (35.3)	20 (55.6)	14 (38.9)	63 (45.3)
COMPLETED TREATMENT AS PER PROTOCOL	0	0	0	0	0	0	0
STUDY DRUG TOXICITY	2 (9.1)	1 (5.6)	1 (10.0)	2 (11.8)	4 (11.1)	1 (2.8)	11 (7.9)
DEATH	1 (4.5)	0	0	0	0	2 (5.6)	3 (2.2)
ADVERSE EVENT UNRELATED TO STUDY DRUG	0	0	0	0	4 (11.1)	0	4 (2.9)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	1 (4.5)	0	0	0	0	1 (2.8)	2 (1.4)
SUBJECT WITHDREW CONSENT	0	0	0	0	0	0	0
LOST TO FOLLOW-UP	0	0	0	0	0	0	0
MAXIMUM CLINICAL BENEFIT	0	0	0	0	0	0	0
POOR/NON-COMPLIANCE	0	0	0	0	0	0	0
PREGNANCY	0	0	0	0	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	0	0	0	0	0
ADMINISTRATIVE REASON BY SPONSOR	0	0	0	0	0	0	0
OTHER	0	0	0	0	1 (2.8)	3 (8.3)	4 (2.9)
NOT COMPLETED THE CURRENT PART OF THE STUDY DUE TO COVID-19	0	1 (5.6)	0	0	1 (2.8)	0	2 (1.4)
REASON FOR NOT COMPLETED THE CURRENT PART OF THE STUDY DUE TO COVID-19							
DEATH	0	1 (5.6)	0	0	1 (2.8)	0	2 (1.4)
CONTINUING IN THE STUDY	20 (90.9)	17 (94.4)	10 (100.0)	16 (94.1)	33 (91.7)	34 (94.4)	130 (93.5)
NOT CONTINUING IN THE STUDY	2 (9.1)	1 (5.6)	0	1 (5.9)	3 (8.3)	2 (5.6)	9 (6.5)
REASON FOR NOT CONTINUING IN THE STUDY							
SUBJECT WITHDREW CONSENT	0	0	0	0	1 (2.8)	0	1 (0.7)
DEATH	2 (9.1)	0	0	0	2 (5.6)	2 (5.6)	6 (4.3)
LOST TO FOLLOW-UP	0	0	0	0	0	0	0
OTHER	0	1 (5.6)	0	1 (5.9)	0	0	2 (1.4)
NOT CONTINUING IN THE STUDY DUE TO COVID-19	0	0	0	0	1 (2.8)	0	1 (0.7)
REASON FOR NOT CONTINUING IN THE STUDY DUE TO COVID-19							
DEATH	0	0	0	0	1 (2.8)	0	1 (0.7)
PART OF THE STUDY THE SUBJECT WILL ENTER							
PART C	9 (40.9)	6 (33.3)	5 (50.0)	8 (47.1)	0	0	28 (20.1)
FOLLOW-UP	8 (36.4)	9 (50.0)	5 (50.0)	8 (47.1)	30 (83.3)	15 (41.7)	75 (54.0)
SURVIVAL FOLLOW-UP	3 (13.6)	2 (11.1)	0	0	3 (8.3)	5 (13.9)	13 (9.4)
NOT REPORTED	0	0	0	0	0	0	0

[a]Subjects who completed Part A and Part B were transferred into Part C with the exception of 2 subjects.

Table 44. Key Baseline/Demographic Characteristics Summary - All Treated Subjects in Parts A, B, D and E

	PART A GRP 1 N = 22	PART B GRP 2 N = 18	PART B GRP 3 N = 10	PART B GRP 4 N = 17	PART D GRP 5 N = 36	PART E GRP 6 N = 36	Total N = 139
AGE (YEARS)							
MEAN	68.0	63.5	63.5	68.6	64.6	63.6	65.1
MEDIAN	68.5	62.5	64.0	71.0	69.0	64.0	66.0
MIN , MAX	48 , 90	49 , 80	52 , 74	56 , 80	24 , 93	37 , 80	24 , 93
Q1 , Q3	60 , 75	56 , 69	56 , 70	63 , 75	59 , 73	58 , 73	58 , 74
SD	10.8	9.3	7.4	8.0	13.0	11.0	10.8
AGE CATEGORIZATION 1 (%)							
< 65	6 (27.3)	12 (66.7)	5 (50.0)	6 (35.3)	14 (38.9)	19 (52.8)	62 (44.6)
>= 65	16 (72.7)	6 (33.3)	5 (50.0)	11 (64.7)	22 (61.1)	17 (47.2)	77 (55.4)
SEX (%)							
MALE	10 (45.5)	13 (72.2)	4 (40.0)	12 (70.6)	26 (72.2)	27 (75.0)	92 (66.2)
FEMALE	12 (54.5)	5 (27.8)	6 (60.0)	5 (29.4)	10 (27.8)	9 (25.0)	47 (33.8
RACE (%)							
WHITE	18 (81.8)	18 (100.0)	8 (80.0)	17 (100.0)	31 (86.1)	34 (94.4)	126 (90.6)
BLACK OR AFRICAN AMERICAN	2 (9.1)	0	0	0	1 (2.8)	0	3 (2.2)
ASIAN	0	0	0	0	1 (2.8)	1 (2.8)	2 (1.4)
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0	0	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0	0	0	0	0
OTHER	2 (9.1)	0	2 (20.0)	0	3 (8.3)	1 (2.8)	8 (5.8)
WEIGHT (KG)							
MEAN	80.8	68.7	65.1	75.2	80.4	75.9	76.0
MEDIAN	78.5	68.5	65.0	76.5	80.7	73.5	75.0
MIN , MAX	58 ,121	53 , 84	42 , 96	43 , 96	48 ,133	44 ,121	42 ,133
Q1 , Q3	67 , 93	64 , 76	52 , 76	72 , 81	65 , 91	67 , 89	65 , 85
SD	16.0	8.7	16.2	13.3	19.6	17.4	16.9
TUMOR TYPE							
COLORECTAL CANCER (MSI-h)	6 (27.3)	5 (27.8)	3 (30.0)	3 (17.6)	7 (19.4)	4 (11.1)	28 (20.1)
GASTRIC CANCER	0	3 (16.7)	0	0	0	0	3 (2.2)
HEAD AND NECK CANCER	0	0	1 (10.0)	0	0	0	1 (0.7)
HEPATOCELLULAR CARCINOMA	2 (9.1)	7 (38.9)	0	7 (41.2)	6 (16.7)	7 (19.4)	29 (20.9)
MELANOMA	2 (9.1)	0	0	0	3 (8.3)	0	5 (3.6)
NON-SMALL CELL LUNG CARCINOMA	7 (31.8)	3 (16.7)	3 (30.0)	4 (23.5)	11 (30.6)	10 (27.8)	38 (27.3)
RENAL CELL CARCINOMA	5 (22.7)	0	3 (30.0)	2 (11.8)	9 (25.0)	6 (16.7)	25 (18.0)
UROTHELIAL CANCER	0	0	0	1 (5.9)	0	9 (25.0)	10 (7.2)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	19 (86.4)	15 (83.3)	4 (40.0)	12 (70.6)	17 (47.2)	10 (27.8)	77 (55.4)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	9 (47.4)	2 (13.3)	4 (100.0)	3 (25.0)	3 (17.6)	1 (10.0)	22 (28.6)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	10 (52.6)	13 (86.7)	0	9 (75.0)	14 (82.4)	9 (90.0)	55 (71.4)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	7 (36.8)	2 (13.3)	3 (75.0)	1 (8.3)	2 (11.8)	1 (10.0)	16 (20.8)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	12 (63.2)	13 (86.7)	1 (25.0)	11 (91.7)	15 (88.2)	9 (90.0)	61 (79.2)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 50%	3 (15.8)	1 (6.7)	0	1 (8.3)	2 (11.8)	0	7 (9.1)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 50%	16 (84.2)	14 (93.3)	4 (100.0)	11 (91.7)	15 (88.2)	10 (100.0)	70 (90.9)
PRIOR LINES OF THERAPIES							
ADJUVANT THERAPY	1 (4.5)	2 (11.1)	2 (20.0)	0	2 (5.6)	3 (8.3)	10 (7.2)
0	2 (9.1)	1 (5.6)	0	1 (5.9)	5 (13.9)	0	9 (6.5)
1	11 (50.0)	7 (38.9)	4 (40.0)	10 (58.8)	24 (66.7)	22 (61.1)	78 (56.1)
2	8 (36.4)	5 (27.8)	1 (10.0)	5 (29.4)	4 (11.1)	8 (22.2)	31 (22.3)
>=3	0	3 (16.7)	3 (30.0)	1 (5.9)	1 (2.8)	3 (8.3)	11 (7.9)
PERFORMANCE STATUS (ECOG) [%]							
0	9 (40.9)	11 (61.1)	3 (30.0)	4 (23.5)	13 (36.1)	13 (36.1)	53 (38.1)
1	13 (59.1)	7 (38.9)	7 (70.0)	13 (76.5)	23 (63.9)	23 (63.9)	86 (61.9)

Efficacy results

Due to the interceding IV nivolumab administered in Parts A, B, and C of CA2098KX, efficacy results are presented only for Parts D and E in this report.

Efficacy endpoints were exploratory for this study. Minimum follow-up for OS (defined as the time from last subject's first dose date to clinical cut-off date [07-Sep-2022]) was 24.4 and 6.0 months for Parts D and E, respectively.

Table 45. Efficacy Summary (Exploratory Endpoints) - All Treated Subjects in Parts D and E of Study CA2098KX

	PART D N = 36 Nivolumab SC 1200 mg + rHuPH20 2000 U/mL Q4W	PART E N = 36 Nivolumab SC 600 mg + rHuPH20 2000 U/mL Q2W
BOR per Investigator[a], n (%)		
Complete Response	0	0
Partial Response	9 (25.0)	9[c] (25.0)
Stable Disease	11 (30.6)	10 (27.8)
Progressive Disease	14 (38.9)	13 (36.1)
Unable to Determine	2 (5.6)	4 (11.1)
Death prior to disease assessment	1 (2.8)	4 (11.1)
Other	1 (2.8)	0
ORR per Investigator[a]	9/36 (25.0)	9/36 (25.0)
ORR[b] (95% CI), %	(12.1, 42.2)	(12.1, 42.2)
PFS per Investigator		
Median (95% CI), months	4.14 (2.66, 8.05)	6.16 (2.79, 8.15)
6-month	40.0 (24.0, 55.5)	52.9 (35.1, 67.9)
12-month	31.2 (16.8, 46.7)	N.A
OS		
Events, n (%)	19/36	14/36
Median OS (95% CI), months	23.10 (13.96, N.A)	9.59 (6.08, N.A)
6-month	77.8 (60.4, 88.2)	68.7 (50.6, 81.3)
12-month	69.0 (51.0, 81.5)	N.A

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal trial for this application is study CA20967T, a phase 3, open-label, randomized, non-inferiority trial of nivolumab SC vs nivolumab IV in patients with advanced or metastatic clear cell RCC. Patients were randomized 1:1 to receive either nivolumab SC 1200 mg (co-formulated with rHuPH20 20,000 units) Q4W or nivolumab IV 3 mg/kg Q2W. The design of the study, including the comparator arm (nivolumab IV) and its dose (3 mg/kg) had been previously agreed during Scientific Advice. Randomisation was stratified by weight (< 80 kg vs ≥ 80 kg) and IMDC risk classification (favourable vs intermediate vs poor risk).

The trial enrolled patients 18 years of age or older with histologically confirmed advanced or metastatic RCC with a clear cell component (including those with sarcomatoid features), and who received no more than 2 prior systemic treatment regimens. Patients with untreated, symptomatic CNS metastases; leptomeningeal metastases; or who received prior treatment with a checkpoint inhibitor, among others, were excluded from the study. The inclusion and exclusion criteria of the trial are deemed acceptable.

The primary objective of the study was to demonstrate PK non-inferiority of nivo SC vs nivo IV, and the co-primary endpoints of Cavgd28 and Cminss were agreed during the latest SA. Additionally, the demonstration of ORR non-inferiority (with a minimum of 6 months of follow-up) was the key

secondary endpoint, tested in a hierarchical fashion to preserve overall experiment-wise Type I error rate (i.e. non-inferiority needs to be met for both PK co-primary endpoints, before ORR can be statistically tested). The other efficacy secondary endpoints (DCR, DOR, TTR, PFS and OS) were not powered.

No formal interim analyses were planned. Instead, the protocol predefined three data-base locks, with its corresponding analyses. The primary analysis was planned to occur at a minimum of 6 months after the last patient was randomized, while the secondary analysis was to occur 12 months after the last patient was randomized. The final analysis was planned to be performed at the end of the study.

During the conduct of the study, the MAH implemented 2 amendments to the protocol. The first amendment, which included the addition of Cavgd28 and Cminss as co-primary endpoints, occurred before any patient had been randomised, therefore no impact to the study results is expected. With the second amendment, among other minor changes, the MAH added nivo through concentration at week 17 as a PK secondary endpoint, following a request from FDA. These modifications are acceptable from a regulatory point of view. In general, important protocol deviations occurred in a similar frequency in both treatment arms.

In total, 495 subjects were randomized, and 492 were treated (247 subjects in the nivo SC vs 245 in the nivo IV arm). At the time of the first DCO, only one patient in the nivo IV arm had completed treatment, while 64.8% in the nivo SC arm and 64.5% in the nivo IV arm had discontinued treatment. Among the reasons for treatment discontinuation, the most common was disease progression in both arms (approximately 44%), followed by adverse event unrelated to study drug (8.1% in the nivo SC arm vs 5.7% in the nivo IV arm) and study drug toxicity (5.7% in the nivo SC arm vs 6.1% in the nivo IV arm).

Overall, baseline characteristics were balanced between both treatment arms. A higher proportion of patients in the nivo SC arm had metastatic disease compared with the nivo IV arm, both at initial diagnosis (51.6% vs 45.3%) and at study entry (99.6% vs 98.8%). Additionally, a higher proportion of patients in the nivo SC arm had a disease with sarcomatoid features at study entry (6.5% vs 2.4%), and the proportion of patients with CNS metastasis was also higher in the nivo SC arm (13.7% vs 9.3%). Moreover, 10.9% of patients in the nivo SC arm had received two prior lines of therapy compared with 5.3% of patients in the nivo IV arm.

Of note, IMDC risk category at baseline was a stratification factor, but some imbalances were detected since IMDC category per IRT and per CRF did not concur. Less subjects in the nivolumab SC arm (19.4%) were in the IMDC favourable risk category (Score 0) compared with the nivolumab IV arm (23.1%) per CRF; whereas the numbers were balanced per IRT (24.2% for nivolumab SC and 23.5% for nivolumab IV) which is understood, as these were the data considered for the randomization scheme. Considering that the total number of subjects with a discrepancy in IMDC risk classification between the IRT and CRF was 38 (15.3%) for the nivolumab SC arm and 44 (17.8%) for the nivolumab IV arm, the MAH has performed sensitivity analyses per both IRT and CRF and the results seem consistent, which is reassuring. Of note, these discrepancies were recorded as important protocol deviations, and stratification factors at randomization as per IRT were planned as supplementary analyses in SAP V2.

Efficacy data and additional analyses

At the DBL 21-Aug-2023, ORR per BICR was 24.2% (95% CI: 19.0, 30.0) for the nivo SC arm and 18.2% (95% CI: 13.6, 23.6) for the nivo IV arm. Nivo SC demonstrated non-inferiority to nivo IV based on the ORR RR =1.33 (95% CI: 0.94, 1.87), as the lower bound of the 95% CI for RR was ≥ 0.60. Nevertheless, superiority of nivo SC vs nivo IV in terms of ORR cannot be claimed as the lower bound of the 95% CI for RR was not >1.00. Results of ORR by investigator were in line with the results

obtained by BICR.

Among all responders, median DOR per BICR was 14.49 months (95% CI: 7.52, N.A.) in the nivo SC arm, while the median was not reached in the nivo IV arm (95% CI: 13.90, N.A.). Indeed, more subjects had an event of progression or death in the nivo SC arm (31.7%) compared to the nivo IV arm (11.7%). Updated DOR results with the second DCO (21-Feb-2024) were provided during the procedure, and these were in line with the ones from the previous DCO: mDOR was 13.57 months (95% CI: 8.57, NA) in the nivo SC arm but was not reached in the nivo IV arm (95% CI: 15.70, NA). Even though it is acknowledged that the number of censored patients is still high in both SC and IV arm (42% and 72%, respectively), it is also unlikely that these results will completely revert. The fact that the duration of response is lower in the nivo SC gives rise to concerns. However, considering that the trial was not designed to show non-inferiority in DOR, no further regulatory action is proposed.

Additional supportive analyses of ORR (based on stratification factors from IRT, CRF and CRF excluding subjects from Russia) also support the main ORR analysis. In addition, with the aim of giving robustness to the primary analysis results, the MAH was asked to present as supplementary analysis, alternative strategies for managing intercurrent events, such as a treatment policy approach. The study also demonstrated ORR non-inferiority between the nivo SC and nivo IV arms with a treatment policy.

Slightly higher or similar ORRs were observed with nivolumab SC vs nivolumab IV across different subgroups. Unweighted ORR RRs were < 1 in a few subgroups (such as age ≥ 75 years, weight < 80 kg, KPS of 70), however the 95% CI were wide and the sample size is small, therefore hampering the interpretation of the results. Of note, it seems that patients with a higher body weight, especially ≥90 kg, have a higher ORR in the nivo SC arm compared to the nivo IV arm (ORR RR=3.5; 95% CI: 1.2, 9.8); whereas patients with a lower body weight (<65 kg) seem to achieve higher responses in the nivo IV arm (ORR RR=0.9; 95% CI: 0.5, 1.8).

Similar results between the nivo SC arm and the nivo IV arm were observed for disease control rate (62.9% vs 62.8% respectively, RR = 1.01) and median time to objective response (3.70 vs 3.68 months, respectively).

The primary definition of PFS accounts for subsequent therapy by censoring at the last evaluable tumour assessment on or prior to the date of subsequent therapy and was based on stratification factors from CRF. At the DBL 21-Aug-2023, 61.3% of subjects in the nivo SC arm had a PFS event (progression or death) compared to 59.5% of patients in the nivo IV arm. The proportions of patients censored and the reasons for censoring were balanced between both arms. Median PFS per BICR was 7.23 months (95% CI: 5.13, 7.49) for the nivo SC arm and 5.65 months (95% CI: 5.29, 7.39) for the nivo IV arm (HR = 1.06 [95% CI: 0.84, 1.34]). The KM curves of PFS overlap and no major differences between both arms are observed. PFS per investigator results were overall consistent (HR = 1.14 [95% CI: 0.90, 1.43]) with the results by BICR. PFS results based on stratification factors from CRF and IRT (HR = 1.07, 95% CI: 0.85, 1.35) were also consistent.

The secondary definition of PFS is irrespective of subsequent therapy. Following this definition, 65.7% of subjects in the nivo SC arm had a PFS event (progression or death) compared to 63.2% of patients in the nivo IV arm. Median PFS per BICR 6.34 months (95% CI: 5.32, 7.43) for the nivo SC arm, and 5.68 months (95% CI: 5.32, 7.39) for the nivo IV arm (HR = 1.06 [95% CI: 0.85, 1.32]). Also in this case, PFS per BICR results were consistent with PFS per investigator results (HR = 1.12 (95% CI: 0.90, 1.40) and with results based on stratification factor from IRT (HR = 1.07, 95% CI: 0.86, 1.34).

During the procedure assessment, the MAH presented updated efficacy results with the second DCO of 21-Feb-2024 for ORR, DOR, PFS (primary and secondary definition), TTR and DCR. Overall, updated results were aligned with the ones previously submitted. However, median PFS (primary definition) in

the nivo SC arm, which is 6.34 months, was slightly lower than the one reported in the previous DCO, which was 7.23 months. During the procedure, the MAH clarified that this difference was due to 5 patients (out of 248) who had a shorter PFS in the second DCO compared to the primary analysis, and the justification provided was deemed acceptable.

At the first DCO (24 Jul 2023), with a minimum follow-up of 8 months, a higher number of death events were observed in the nivo SC arm (29.4%) compared with the nivo IV arm (24.7%); HR = 1.25 (95% CI: 0.89, 1.77). OS analysis results based on stratification factors from IRT (HR = 1.28 [95% CI: 0.91, 1.80]) were consistent with the primary analysis results (based on CRF).

The MAH presented additional OS results (DCO of 21-Feb-2024) with a minimum follow-up of 15 months. In the nivo SC arm, OS events were observed for 102/248 patients (41.1%) compared with 90/247 subjects (36.4%) in the nivo IV arm. Even though the HR for OS had improved compared with the previous DCO (HR = 1.19 [95% CI: 0.90, 1.59]) it still favoured the nivo IV arm. Of note, at the latest round of the procedure, the MAH provided an updated ad-hoc OS analysis (DCO: 05-Sep-2024), with an additional 6.5 months of follow-up, which showed a HR of 1.08 (95% CI: 0.83, 1.39). Considering that PFS and OS were descriptive endpoints, not protected by multiplicity, and that the study was not powered to find differences in these endpoints, the observed results should be interpreted with caution, and also these were not included in SmPC section 5.1.

Differences in the number of deaths could be due to imbalances in the number of early deaths (especially between the first three months) caused by the worse prognostic categories of the patients in the nivo SC arm. A summary table of demographic and baseline disease characteristics by treatment arm in patients who died during the first three and six months showed a higher prevalence of CNS metastasis compared with the overall population. Also, the proportion of patients with poor IMDC risk group was higher in patients who died during the first three months compared with the overall population. Even though CNS metastasis and poor IMDC risk group are considered risk factors for poor outcomes in RCC, numbers are too small to draw definitive conclusions. The MAH was recommended to provide final OS results once available, which is expected to occur around end of Q2 2026 (PAM REC).

Subgroup analyses for OS were presented with the with the DCO of 21/02/2024. For almost all subgroups, HR was greater than one, therefore confirming the trend in favour of the IV arm observed in the overall population. Elderly patients (≥75 years old) seem to derive more survival benefit in the IV arm (HR=1.93, 95% CI: 0.96, 3.90) compared with younger patients (<65 years old), in which no apparent difference in terms of OS is observed between both arms (HR=1.0; 95% CI: 0.66, 1.51). Additionally, ORR RR for patients ≥75 years old is 0.7 (95% CI: 0.2, 2.2), therefore also favouring the IV arm. PFS results by age categories were requested during the procedure, and these were in line with the observations for OS and ORR: patients older than 75 years have worse PFS results in the nivo SC arm compared with the nivo IV arm (HR=1.41); while patients <65 years seem to obtain similar results regardless of the treatment arm (HR=0.92). However, the sample size of elderly patients is limited, and the study was not powered to detect differences in efficacy by age subgroups; therefore, no definitive conclusions can be drawn.

Clinical outcome assessment results were generally similar in both arms, and it seems that patients generally maintain their baseline quality of life. However, considering that this was an open-label trial, these results should be interpreted with caution.

When assessing the effect of immunogenicity on efficacy, for subjects who were nivolumab ADA positive on nivo SC (N=46) or nivo IV (N=15), ORR per BICR was numerically lower than for subjects who were nivolumab ADA negative. Nevertheless, in the nivo SC arm, the proportion of patients with stable disease was higher in the nivo ADA positive (54.5% vs 35.5% in ADA negative patients), while a higher number of patients had progressive disease in the nivo ADA negative (30.3%) compared with the nivo ADA positive (21.7%).

Finally, supportive study CA2098KX evaluated nivo SC across different tumour types, with and without rHuPH20, and at different doses (600, 720, 960 and 1200 mg). Considering that efficacy endpoints were exploratory and the limited sample size of the study, the results of this study should be interpreted with caution.

Claimed indications

For this new Opdivo SC formulation, the MAH is applying for all approved indications in solid tumours where nivolumab is administered as monotherapy (including maintenance after combination therapy) or in combination with chemotherapy or cabozantinib as long as the recommended dose for nivolumab is 240 mg administered Q2W and/or 480 mg administered Q4W. Treatment of adolescents (melanoma indications) is excluded from this extension application.

This extrapolation approach is acceptable based on the several analyses and simulations that the MAH has performed (see Clinical Pharmacology section).

2.6.7. Conclusions on the clinical efficacy

Study CA20967T demonstrated non-inferiority in terms of ORR between the nivo SC and nivo IV arms, as the lower bound of the 95% CI of the ORR RR was above the pre-defined non-inferiority margin of 0.60. Median duration of response in the nivo SC arm was lower compared with the nivo IV arm but progression-free survival, time to response and disease control rate seem similar in both arms. In addition, the number of deaths in the nivo SC arm was higher compared with the nivo IV arm, and the OS HR was around 1.08, based on the latest data cut-off. Considering that OS, as well as other efficacy analyses such as DOR or PFS, were descriptive, not protected by multiplicity, results should be interpreted with caution. The MAH was recommended to provide final OS results once available (PAM-REC). In conclusion, the results from study CA20967T support the use of nivolumab SC when administered in 600 mg every 2 weeks or 1200 mg every 4 weeks regimen in the applied indications.

2.6.8. Clinical safety

The pivotal safety data supporting this extension is based on all 492 treated subjects receiving at least one dose of nivolumab SC (n = 247) or nivolumab IV (n = 245) in the pivotal Phase 3 Study CA20967T, with a data cut-off of 24-Jul-2023.

2.6.8.1. Patient exposure

Subjects in the nivolumab SC arm received 8.6 doses on average, while subjects in the nivolumab IV arm received 17.7 doses on average (Table 46). Of note, the nivolumab SC regimen was 1200 mg Q4W and the nivolumab IV regimen was 3 mg/kg Q2W.

Table 46. Cumulative Dose and Relative Dose Intensity Summary Study CA20967T- All Treated Subjects

	Nivo SC N = 247	Nivo IV N = 245
NUMBER OF DOSES RECEIVED		
MEAN (SD)	8.6 (5.8)	17.7 (12.1)
MEDIAN (MIN - MAX)	8.0 (1 - 25)	17.0 (1 - 52)
CUMULATIVE DOSE (MG)		
MEAN (SD)	10338.462 (6990.640)	
MEDIAN (MIN - MAX)	9600.000 (1200.00 - 30000.00)	

	Nivo SC N = 247	Nivo IV N = 245
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)		53.191 (36.174)
MEDIAN (MIN - MAX)		50.681 (3.00 - 156.41)
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	0
90% TO < 110%	223 (90.3)	194 (79.2)
70% TO < 90%	19 (7.7)	44 (18.0)
50% TO < 70%	4 (1.6)	7 (2.9)
< 50%	1 (0.4)	0

Table 47. Duration of Study Therapy Summary - All Treated Subjects

	Nivo SC N = 247	Nivo IV N = 245
DURATION OF THERAPY (MONTHS)		
MEAN (MIN, MAX)	7.31 (0.0, 22.4)	8.23 (0.0, 24.0)
MEDIAN	6.60	7.69
> 3 MONTHS (%)	176 (71.3)	190 (77.6)
> 6 MONTHS (%)	129 (52.2)	144 (58.8)
> 9 MONTHS (%)	85 (34.4)	105 (42.9)
> 12 MONTHS (%)	49 (19.8)	57 (23.3)

Source: Table S.4.61

Note: Nivo SC regimen is 1200 mg Q4W. Nivo IV regimen is 3 mg/kg Q2W.

Dose modifications and dose delays

In the nivolumab SC arm, most subjects received all doses of the study medications without an injection interruption or dose delay (Table 48).

Table 48. Dose Delays and Infusion/Injection Interruptions of Study Therapy - All Treated Subjects

Table 6.3-1: Dose Delays and Infusion Interruptions of Study Therapy - All Treated Subjects

	Nivo SC N = 247	Nivo IV N = 245
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	89 (36.0)	134 (54.7)
NUMBER OF DOSES DELAYED PER SUBJECT (%)		
0	158 (64.0)	111 (45.3)
1	58 (23.5)	67 (27.3)
2	22 (8.9)	37 (15.1)
3	7 (2.8)	16 (6.5)
>= 4	2 (0.8)	14 (5.7)
TOTAL NUMBER OF DOSES DELAYED/ TOTAL NUMBER OF DOSES RECEIVED (%) (A)	131/1881 (7.0)	251/4097 (6.1)
REASON FOR DOSE DELAY (%) (B)		
HEMATOLOGIC TOXICITY	0	1 (0.4)
NON-HEMATOLOGIC TOXICITY	0	0
ADVERSE EVENT	74 (56.5)	158 (62.9)
DOSING ERROR	0	0
PROTOCOL DEFINED	0	0
OTHER	34 (26.0)	67 (26.7)
NOT REPORTED	23 (17.6)	25 (10.0)
LENGTH OF DOSE DELAY (%) (B)		
4 - 7 DAYS	61 (46.6)	117 (46.6)
8 - 14 DAYS	30 (22.9)	68 (27.1)
15 - 42 DAYS	31 (23.7)	57 (22.7)
SUBJECTS WITH AT LEAST ONE DOSE DELAYED DUE TO COVID-19 (%)	10 (4.0)	23 (9.4)
TOTAL NUMBER OF DOSES DELAYED DUE TO COVID-19/ TOTAL NUMBER OF DOSES RECEIVED (%) (A)	10/1881 (0.5)	23/4097 (0.6)
REASON FOR DOSE DELAY DUE TO COVID-19 (%) (C)		
HEMATOLOGIC TOXICITY	0	0
NON-HEMATOLOGIC TOXICITY	0	0
ADVERSE EVENT	10 (100.0)	23 (100.0)
DOSING ERROR	0	0
PROTOCOL DEFINED	0	0
OTHER	0	0
SUBJECTS WITH AT LEAST ONE INFUSION/INJECTION INTERRUPTED (%)	1 (0.4)	10 (4.1)
NUMBER OF INFUSIONS/INJECTIONS INTERRUPTED PER SUBJECT (%)		
0	246 (99.6)	235 (95.9)
1	1 (0.4)	6 (2.4)
2	0	3 (1.2)
3	0	1 (0.4)
>= 4	0	0
TOTAL NUMBER OF INFUSIONS/INJECTIONS INTERRUPTED/ TOTAL NUMBER OF DOSES RECEIVED (%)	1/2128 (<0.1)	15/4342 (0.3)
REASON FOR INFUSION/INJECTION INTERRUPTION (%) (D)		
HYPERSENSITIVITY REACTION	0	11 (73.3)
ADMINISTRATION ISSUES	0	0
OTHER	1 (100.0)	4 (26.7)

Source: Table S.4.2.1 (dose delay summary), Table S.4.2.2 (dose infusion/injection interruption summary)

Note: A dose was considered as actually delayed if the delay is exceeding 3 days for nivo.

(A) Total number of doses received is excluding first dose.

(B) Percentages are computed out of the total number of doses delayed.

(C) Percentages are computed out of the total number of doses delayed due to COVID-19.

(D) Percentages are computed out of the total number of doses interrupted by treatment arm.

2.6.8.2. Adverse events

Key safety results of Study CA20967T are presented below.

Table 49. Summary of Safety Study CA20967T - All Treated Subjects

	Number of Subjects (%)	
Safety Parameters	**Nivo SC (N = 247)**	**Nivo IV (N = 245)**
Deaths (Any Time)	73 (29.6)	60 (24.5)
Primary Reason for Death		
Disease	53 (21.5)	48 (19.6)
Study Drug Toxicity	3 (1.2)	1 (0.4)

Safety Parameters	Number of Subjects (%)			
	Nivo SC (N = 247)		Nivo IV (N = 245)	
Cardiovascular disease	4 (1.6)		3 (1.2)	
Unknown	1 (0.4)		3 (1.2)	
Other[a]	12 (4.9)		5 (2.0)	
Deaths within 30 days of last dose	15 (6.1)		9 (3.7)	
Primary Reason for Death				
Disease	7 (2.8)		7 (2.9)	
Cardiovascular Disease	3 (1.2)		1 (0.4)	
Other	5 (2.0)		1 (0.4)	
Deaths within 100 days of last dose	47 (19.0)		35 (14.3)	
Primary Reason for Death				
Disease	31 (12.6)		27 (11.0)	
Study Drug Toxicity	2 (0.8)		1 (0.4)	
Cardiovascular Disease	3 (1.2)		2 (0.8)	
Unknown	1 (0.4)		0	
Other	10 (4.0)		5 (2.0)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	69 (27.9)	52 (21.1)	71 (29.0)	56 (22.9)
Drug-related SAEs	17 (6.9)	16 (6.5)	17 (6.9)	16 (6.5)
All-causality AEs leading to DC	25 (10.1)	18 (7.3)	29 (11.8)	21 (8.6)
Drug-related AEs leading to DC	10 (4.0)	6 (2.4)	12 (4.9)	9 (3.7)
All-causality AEs	230 (93.1)	87 (35.2)	229 (93.5)	100 (40.8)
Drug-related AEs	146 (59.1)	24 (9.7)	158 (64.5)	36 (14.7)
≥ 5% Drug-related AEs in Any Treatment				
Pruritus	37 (15.0)	1 (0.4)	48 (19.6)	0
Hypothyroidism	22 (8.9)	0	24 (9.8)	0
Rash	16 (6.5)	1 (0.4)	18 (7.3)	2 (0.8)
Asthenia	14 (5.7)	1 (0.4)	9 (3.7)	2 (0.8)
Diarrhea	13 (5.3)	0	12 (4.9)	1 (0.4)
Fatigue	10 (4.0)	0	27 (11.0)	2 (0.8)
Arthralgia	10 (4.0)	0	22 (9.0)	1 (0.4)
Anaemia	6 (2.4)	1 (0.4)	13 (5.3)	3 (1.2)
Blood thyroid stimulating hormone increased	6 (2.4)	0	13 (5.3)	0
All-causality Select AEs by Category				
Skin	64 (25.9)	4 (1.6)	74 (30.2)	3 (1.2)
Endocrine	40 (16.2)	6 (2.4)	52 (21.2)	3 (1.2)
Gastrointestinal	26 (10.5)	1 (0.4)	34 (13.9)	1 (0.4)
Hepatic	40 (16.2)	11 (4.5)	50 (20.4)	12 (4.9)
Renal	29 (11.7)	4 (1.6)	44 (18.0)	1 (0.4)
Pulmonary	13 (5.3)	4 (1.6)	9 (3.7)	3 (1.2)
Hypersensitivity/Infusion Reactions	3 (1.2)	1 (0.4)	9 (3.7)	0
Drug-related Select AEs by Category				
Skin	57 (23.1)	4 (1.6)	65 (26.5)	3 (1.2)
Endocrine	31 (12.6)	2 (0.8)	44 (18.0)	3 (1.2)
Gastrointestinal	15 (6.1)	0	13 (5.3)	1 (0.4)
Hepatic	20 (8.1)	5 (2.0)	27 (11.0)	9 (3.7)

Safety Parameters	Number of Subjects (%)			
	Nivo SC (N = 247)		Nivo IV (N = 245)	
Pulmonary	13 (5.3)	4 (1.6)	8 (3.3)	2 (0.8)
Renal	7 (2.8)	0	12 (4.9)	0
Hypersensitivity/Infusion Reactions	1 (0.4)	1 (0.4)	6 (2.4)	0
Drug-related Local Site Reactions within 100 Days of Last Dose[b]	17 (6.9)	0	5 (2.0)	0
≥ 2 subjects AEs in Any Treatment				
Injection site erythema	5 (2.0)	0	0	0
Application site pain	2 (0.8)	0	0	0
Injection site edema	2 (0.8)	0	0	0
Infusion related reaction	0	0	5 (2.0)	0
AEs in the Broad SMQ of Anaphylactic Reactions within 100 days of last dose	90 (36.4)	7 (2.8)	106 (43.3)	6 (2.4)
≥ 5% AEs in Any Treatment				
Pruritus	41 (16.6)	1 (0.4)	52 (21.2)	0
Cough	27 (10.9)	0	29 (11.8)	0
Rash	20 (8.1)	1 (0.4)	20 (8.2)	2 (0.8)
Dyspnea	11 (4.5)	5 (2.0)	18 (7.3)	1 (0.4)
All-causality Non-endocrine IMAEs within 100 days of last dose where Immune Modulating Medication was Initiated by Category				
Rash	17 (6.9)	2 (0.8)	12 (4.9)	3 (1.2)
Diarrhea/Colitis	7 (2.8)	1 (0.4)	5 (2.0)	0
Hepatitis	6 (2.4)	4 (1.6)	14 (5.7)	9 (3.7)
Pneumonitis	7 (2.8)	2 (0.8)	7 (2.9)	2 (0.8)
Nephritis and Renal Dysfunction	3 (1.2)	0	2 (0.8)	0
Hypersensitivity	1 (0.4)	0	2 (0.8)	0
All-causality Endocrine IMAEs within 100 days of last dose by Category				
Hypothyroidism/Thyroiditis	24 (9.7)	0	25 (10.2)	0
Hyperthyroidism	2 (0.8)	0	11 (4.5)	0
Adrenal Insufficiency	5 (2.0)	2 (0.8)	2 (0.8)	0
Diabetes Mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Hypophysitis	0	0	3 (1.2)	2 (0.8)
All-causality OESIs within 100 days of last dose by Category				
Myositis/Rhabdomyolysis	0	0	2 (0.8)	2 (0.8)
Uveitis	1 (0.4)	1 (0.4)	0	0
Myocarditis	1 (0.4)	1 (0.4)	0	0
Pancreatitis	1 (0.4)	1 (0.4)	1 (0.4)	0

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Note: Includes events reported between first dose and 30 days after last dose of study therapy except otherwise indicated.

a Other reasons for death (any time):

- Nivo SC: hip fracture related complications, suicide, diabetic ketoacidosis, shortness of breath, acute respiratory failure, left lung base pneumonia, multi-organ failure, COVID-related pneumonia, intraparenchymal hemorrhage, delirium, acute respiratory insufficiency, hyperkalemia
- Nivo IV: perforation of thin intestinal, acute diverticulitis, upper GI bleeding, kidney failure, multi-organ failure

b Local injection- or infusion-site reactions adverse events include PTs under SOC of "General disorders and administration site conditions" which contain the words of "Administration site", "Injection site", "Puncture site", "Infusion site", and PTs under SOC of "Injury, poisoning and procedural

complications" which contains the words "Injection related reaction" or "Infusion related reaction." For Study CA20967T, PTs containing the word "Application site" have also been included since the events were reported in reference to local injection reactions.

Table 50. Adverse Events by Worst CTC Grade in ≥ 5% of All Treated Subjects in Any Treatment

System Organ Class (%) Preferred Term (%)	Nivolumab SC N = 247			Nivolumab IV N = 245		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**230 (93.1)**	**87 (35.2)**	**10 (4.0)**	**229 (93.5)**	**100 (40.8)**	**6 (2.4)**
Gastrointestinal disorders	94 (38.1)	7 (2.8)	0	86 (35.1)	7 (2.9)	0
Diarrhoea	24 (9.7)	1 (0.4)	0	33 (13.5)	1 (0.4)	0
Nausea	20 (8.1)	0	0	22 (9.0)	0	0
Constipation	19 (7.7)	0	0	15 (6.1)	0	0
Abdominal pain	16 (6.5)	0	0	16 (6.5)	1 (0.4)	0
Vomiting	15 (6.1)	1 (0.4)	0	12 (4.9)	0	0
General disorders and administration site conditions	87 (35.2)	8 (3.2)	1 (0.4)	98 (40.0)	13 (5.3)	0
Asthenia	32 (13.0)	4 (1.6)	0	23 (9.4)	3 (1.2)	0
Fatigue	19 (7.7)	2 (0.8)	0	39 (15.9)	5 (2.0)	0
Oedema peripheral	11 (4.5)	1 (0.4)	0	24 (9.8)	2 (0.8)	0
Pyrexia	6 (2.4)	0	0	13 (5.3)	0	0
Metabolism and nutrition disorders	85 (34.4)	19 (7.7)	0	100 (40.8)	19 (7.8)	0
Hyperglycaemia	23 (9.3)	6 (2.4)	0	32 (13.1)	5 (2.0)	0
Decreased appetite	22 (8.9)	0	0	28 (11.4)	2 (0.8)	0
Hyperkalaemia	17 (6.9)	6 (2.4)	0	21 (8.6)	1 (0.4)	0
Hypercalcaemia	11 (4.5)	4 (1.6)	0	16 (6.5)	7 (2.9)	0
Hyponatraemia	4 (1.6)	0	0	16 (6.5)	5 (2.0)	0
Musculoskeletal and connective tissue disorders	80 (32.4)	8 (3.2)	0	105 (42.9)	11 (4.5)	0
Arthralgia	29 (11.7)	1 (0.4)	0	39 (15.9)	1 (0.4)	0
Back pain	19 (7.7)	2 (0.8)	0	27 (11.0)	4 (1.6)	0
Pain in extremity	10 (4.0)	0	0	17 (6.9)	0	0
Infections and infestations	74 (30.0)	7 (2.8)	0	75 (30.6)	12 (4.9)	0
COVID-19	20 (8.1)	0	0	29 (11.8)	2 (0.8)	0
Skin and subcutaneous tissue disorders	69 (27.9)	4 (1.6)	0	82 (33.5)	4 (1.6)	0
Pruritus	40 (16.2)	1 (0.4)	0	52 (21.2)	0	0
Rash	19 (7.7)	1 (0.4)	0	20 (8.2)	2 (0.8)	0
Investigations	66 (26.7)	10 (4.0)	0	108 (44.1)	14 (5.7)	0
Blood creatinine increased	27 (10.9)	1 (0.4)	0	40 (16.3)	0	0
Blood alkaline phosphatase increased	14 (5.7)	3 (1.2)	0	12 (4.9)	4 (1.6)	0
Alanine aminotransferase increased	13 (5.3)	1 (0.4)	0	18 (7.3)	3 (1.2)	0
Aspartate aminotransferase increased	13 (5.3)	1 (0.4)	0	23 (9.4)	3 (1.2)	0
Weight decreased	11 (4.5)	0	0	19 (7.8)	3 (1.2)	0
Blood thyroid stimulating hormone increased	7 (2.8)	0	0	15 (6.1)	0	0
Blood and lymphatic system disorders	65 (26.3)	17 (6.9)	0	76 (31.0)	25 (10.2)	0
Anaemia	54 (21.9)	14 (5.7)	0	63 (25.7)	21 (8.6)	0
Respiratory, thoracic and mediastinal disorders	61 (24.7)	14 (5.7)	2 (0.8)	68 (27.8)	12 (4.9)	0
Cough	27 (10.9)	0	0	28 (11.4)	0	0
Dyspnoea	11 (4.5)	5 (2.0)	0	18 (7.3)	1 (0.4)	0
Nervous system disorders	32 (13.0)	5 (2.0)	0	58 (23.7)	12 (4.9)	0
Headache	10 (4.0)	1 (0.4)	0	22 (9.0)	2 (0.8)	0
Endocrine disorders	29 (11.7)	3 (1.2)	0	41 (16.7)	2 (0.8)	0
Hypothyroidism	24 (9.7)	0	0	30 (12.2)	0	0
Vascular disorders	21 (8.5)	5 (2.0)	0	31 (12.7)	7 (2.9)	0
Hypertension	11 (4.5)	3 (1.2)	0	19 (7.8)	4 (1.6)	0

Source: Table S.6.1.31.1

MedDRA Version 26.0. CTC Version 5.0.

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

Table 51. Drug-related Adverse Events by Worst CTC Grade in ≥ 5% of All Treated Subjects in Any Treatment

System Organ Class (%) Preferred Term (%)	Nivolumab SC N = 247			Nivolumab IV N = 245		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**146 (59.1)**	**24 (9.7)**	**0**	**158 (64.5)**	**36 (14.7)**	**0**
Skin and subcutaneous tissue disorders	58 (23.5)	4 (1.6)	0	70 (28.6)	4 (1.6)	0
Pruritus	37 (15.0)	1 (0.4)	0	48 (19.6)	0	0
Rash	16 (6.5)	1 (0.4)	0	18 (7.3)	2 (0.8)	0
General disorders and administration site conditions	43 (17.4)	2 (0.8)	0	43 (17.6)	5 (2.0)	0
Asthenia	14 (5.7)	1 (0.4)	0	9 (3.7)	2 (0.8)	0
Fatigue	10 (4.0)	0	0	27 (11.0)	2 (0.8)	0
Gastrointestinal disorders	34 (13.8)	1 (0.4)	0	26 (10.6)	1 (0.4)	0
Diarrhoea	13 (5.3)	0	0	12 (4.9)	1 (0.4)	0
Investigations	29 (11.7)	3 (1.2)	0	55 (22.4)	8 (3.3)	0
Blood thyroid stimulating hormone increased	6 (2.4)	0	0	13 (5.3)	0	0
Endocrine disorders	25 (10.1)	2 (0.8)	0	35 (14.3)	2 (0.8)	0
Hypothyroidism	22 (8.9)	0	0	24 (9.8)	0	0
Musculoskeletal and connective tissue disorders	22 (8.9)	1 (0.4)	0	41 (16.7)	4 (1.6)	0
Arthralgia	10 (4.0)	0	0	22 (9.0)	1 (0.4)	0
Blood and lymphatic system disorders	10 (4.0)	1 (0.4)	0	21 (8.6)	4 (1.6)	0
Anaemia	6 (2.4)	1 (0.4)	0	13 (5.3)	3 (1.2)	0

Source: Table S.6.1.32.1

MedDRA Version 26.0. CTC Version 5.0.

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

Table 52. Summary of Drug-Related Adverse Events (Re-mapped Terms) by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) with 30 Days Follow-up in ≥ 5% of All Treated Subjects with Nivolumab Monotherapy

System Organ Class (%)	CA20967T (SC Arm) Nivolumab Monotherapy N = 247			CA20967T (IV Arm) Nivolumab Monotherapy N = 245		
Preferred Term (%)	**Any Grade**	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
Total Subjects with an Event	146 (59.1)	24 (9.7)	0	158 (64.5)	36 (14.7)	0
General disorders and administration site conditions	43 (17.4)	2 (0.8)	0	43 (17.6)	5 (2.0)	0
Fatigue	24 (9.7)	1 (0.4)	0	36 (14.7)	4 (1.6)	0
Skin and subcutaneous tissue disorders	58 (23.5)	4 (1.6)	0	70 (28.6)	4 (1.6)	0
Rash	28 (11.3)	3 (1.2)	0	23 (9.4)	3 (1.2)	0
Pruritus	37 (15.0)	1 (0.4)	0	48 (19.6)	0	0
Gastrointestinal disorders	34 (13.8)	1 (0.4)	0	26 (10.6)	1 (0.4)	0
Diarrhoea	13 (5.3)	0	0	12 (4.9)	1 (0.4)	0
Nausea	0	0	0	0	0	0
Investigations	30 (12.1)	3 (1.2)	0	52 (21.2)	6 (2.4)	0
Transaminases increased	12 (4.9)	1 (0.4)	0	18 (7.3)	5 (2.0)	0
Musculoskeletal and connective tissue disorders	22 (8.9)	1 (0.4)	0	41 (16.7)	4 (1.6)	0
Arthralgia	10 (4.0)	0	0	22 (9.0)	1 (0.4)	0
Musculoskeletal pain	9 (3.6)	0	0	18 (7.3)	1 (0.4)	0
Endocrine disorders	25 (10.1)	2 (0.8)	0	35 (14.3)	2 (0.8)	0
Hypothyroidism	22 (8.9)	0	0	24 (9.8)	0	0
Respiratory, thoracic, and mediastinal disorders	17 (6.9)	4 (1.6)	0	16 (6.5)	2 (0.8)	0
Metabolism and nutrition disorders	21 (8.5)	3 (1.2)	0	23 (9.4)	7 (2.9)	0
Decreased appetite	8 (3.2)	0	0	7 (2.9)	1 (0.4)	0
Nervous system disorders	0	0	0	0	0	0
Blood and lymphatic system disorders	0	0	0	0	0	0

MedDRA Version: 26.0; CTC Version 5.0 for CA20967T
Includes events reported between first dose and last dose of therapy + 30 days
Some preferred terms are re-mapped based on BMS medical review

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Table 53. Death Summary Study CA20967T - All Treated Subjects

	Number of Subjects (%)	
	Nivolumab SC N = 247	Nivolumab IV N = 245
NUMBER OF SUBJECTS WHO DIED (%)	73 (29.6)	60 (24.5)
PRIMARY REASON FOR DEATH (%)		
DISEASE	53 (21.5)	48 (19.6)
STUDY DRUG TOXICITY	3 (1.2)	1 (0.4)
CARDIOVASCULAR DISEASE	4 (1.6)	3 (1.2)
UNKNOWN	1 (0.4)	3 (1.2)
OTHER	12 (4.9)	5 (2.0)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	15 (6.1)	9 (3.7)
PRIMARY REASON FOR DEATH (%)		
DISEASE	7 (2.8)	7 (2.9)
CARDIOVASCULAR DISEASE	3 (1.2)	1 (0.4)
OTHER	5 (2.0)	1 (0.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	47 (19.0)	35 (14.3)
PRIMARY REASON FOR DEATH (%)		
DISEASE	31 (12.6)	27 (11.0)
STUDY DRUG TOXICITY	2 (0.8)	1 (0.4)
CARDIOVASCULAR DISEASE	3 (1.2)	2 (0.8)
UNKNOWN	1 (0.4)	0
OTHER	10 (4.0)	5 (2.0)

In the nivo SC arm, "other reasons" for death were the following: fracture related complications, suicide, diabetic ketoacidosis, shortness of breath, acute respiratory failure, left lung base pneumonia, multi-organ failure, COVID-related pneumonia, intraparenchymal hemorrhage, delirium, acute respiratory insufficiency and hyperkalemia.

In the nivo IV arm, "other" reasons included: perforation of thin intestinal, acute diverticulitis, upper GI bleeding, kidney failure, multi-organ failure. None of these deaths were considered to be study-drug related according to the investigator.

Deaths related to the medicinal product

In the SC arm, 3 deaths due to study drug toxicity according to the investigator:

- A 73-year-old male subject who died 33 days after his last dose (total 2 doses received) due to myopathy (muscular weakness - myasthenia) and respiratory failure. Fourteen days after the 2nd nivo SC dose, it was reported that the subject presented with Grade 3 muscular weakness. The subject received treatment with corticosteroids, furosemide, and enoxaparin while study therapy was discontinued; however, the condition did not improve.
- An 82-year-old male subject who died 57 days after a single dose of study therapy with death reported as due to colitis complications. Study drug was withheld one month after the first dose due to health deterioration. Forty-five days after the initiation of study therapy, it was reported that the subject presented with Grade 4 colitis along with intestinal perforation and abscess, bloody diarrhea and sepsis.
- A 74-year-old male subject who died 133 days after his last dose of study therapy with death reported as due to myocarditis. The study drug was withdrawn 18 days after the third cycle of study due to myocarditis, however the subject´s condition continued to deteriorate and the patient died.

In the nivo IV arm, there was one death due to study drug toxicity. This was a 61-year old male who died 38 days after his last dose of study therapy with death reported as due to immune-mediated pneumonitis and pneumocystis jirovecii bronchopneumonia, and disease progression. The study treatment was first delayed when the patient was diagnosed with Grade 2 immune-mediated lung

disease associated with dyspnea, and then study drug was discontinued when the pneumonia was reported.

Serious adverse events

Table 54. Serious Adverse Events Reported in ≥ 1% of All Treated Subjects in Any Treatment

System Organ Class (%) Preferred Term (%)	Nivolumab SC N = 247			Nivolumab IV N = 245		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**69 (27.9)**	**52 (21.1)**	**10 (4.0)**	**71 (29.0)**	**56 (22.9)**	**6 (2.4)**
Respiratory, thoracic and mediastinal disorders	14 (5.7)	12 (4.9)	2 (0.8)	15 (6.1)	11 (4.5)	0
Pleural effusion	4 (1.6)	4 (1.6)	0	1 (0.4)	1 (0.4)	0
Pneumonitis	4 (1.6)	4 (1.6)	0	1 (0.4)	1 (0.4)	0
Pulmonary embolism	0	0	0	4 (1.6)	3 (1.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (4.9)	6 (2.4)	4 (1.6)	10 (4.1)	3 (1.2)	6 (2.4)
Malignant neoplasm progression	7 (2.8)	3 (1.2)	4 (1.6)	7 (2.9)	1 (0.4)	6 (2.4)
Metabolism and nutrition disorders	9 (3.6)	9 (3.6)	0	8 (3.3)	7 (2.9)	0
Hyperglycaemia	3 (1.2)	3 (1.2)	0	1 (0.4)	1 (0.4)	0
Hyperkalaemia	3 (1.2)	3 (1.2)	0	0	0	0
Hyponatraemia	0	0	0	3 (1.2)	3 (1.2)	0
Gastrointestinal disorders	6 (2.4)	3 (1.2)	0	5 (2.0)	5 (2.0)	0
Diarrhoea	3 (1.2)	1 (0.4)	0	1 (0.4)	1 (0.4)	0
Infections and infestations	6 (2.4)	5 (2.0)	0	11 (4.5)	10 (4.1)	0
Urinary tract infection	1 (0.4)	1 (0.4)	0	3 (1.2)	3 (1.2)	0
Nervous system disorders	6 (2.4)	4 (1.6)	0	10 (4.1)	9 (3.7)	0
Spinal cord compression	1 (0.4)	1 (0.4)	0	3 (1.2)	3 (1.2)	0
Blood and lymphatic system disorders	2 (0.8)	2 (0.8)	0	5 (2.0)	4 (1.6)	0
Anaemia	2 (0.8)	2 (0.8)	0	4 (1.6)	3 (1.2)	0
Injury, poisoning and procedural complications	2 (0.8)	1 (0.4)	0	8 (3.3)	5 (2.0)	0
Femur fracture	0	0	0	4 (1.6)	3 (1.2)	0

Source: Table S.6.3.1.2.1

MedDRA Version 26.0. CTC Version 5.0.

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

Table 55. Drug-related Serious Adverse Events Reported in ≥ 2 Subjects of All Treated Subjects in Any Treatment

System Organ Class (%) Preferred Term (%)	Nivolumab SC N = 247			Nivolumab IV N = 245		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**17 (6.9)**	**16 (6.5)**	**0**	**17 (6.9)**	**16 (6.5)**	**0**
Respiratory, thoracic and mediastinal disorders	4 (1.6)	4 (1.6)	0	2 (0.8)	2 (0.8)	0
Pneumonitis	4 (1.6)	4 (1.6)	0	1 (0.4)	1 (0.4)	0
Hepatobiliary disorders	2 (0.8)	2 (0.8)	0	1 (0.4)	1 (0.4)	0
Immune-mediated hepatitis	2 (0.8)	2 (0.8)	0	0	0	0
Metabolism and nutrition disorders	2 (0.8)	2 (0.8)	0	4 (1.6)	4 (1.6)	0
Hyponatraemia	0	0	0	2 (0.8)	2 (0.8)	0
Endocrine disorders	1 (0.4)	1 (0.4)	0	2 (0.8)	2 (0.8)	0
Hypophysitis	0	0	0	2 (0.8)	2 (0.8)	0
Investigations	0	0	0	2 (0.8)	2 (0.8)	0
Alanine aminotransferase increased	0	0	0	2 (0.8)	1 (0.4)	0
Aspartate aminotransferase increased	0	0	0	2 (0.8)	2 (0.8)	0

Source: Table S.6.3.1.2.3

MedDRA Version 26.0. CTC Version 5.0.

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

Select AEs

Table 56. Select Adverse Events by Worst CTC Grade in ≥ 1% of All Treated Subjects in Any Treatment

	Nivolumab SC N = 247			Nivolumab IV N = 245		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
GASTROINTESTINAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**26 (10.5)**	**1 (0.4)**	**0**	**34 (13.9)**	**1 (0.4)**	**0**
Diarrhoea	24 (9.7)	1 (0.4)	0	33 (13.5)	1 (0.4)	0
HEPATIC ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**40 (16.2)**	**11 (4.5)**	**0**	**50 (20.4)**	**12 (4.9)**	**0**
Blood alkaline phosphatase increased	14 (5.7)	3 (1.2)	0	12 (4.9)	4 (1.6)	0
Alanine aminotransferase increased	13 (5.3)	1 (0.4)	0	18 (7.3)	3 (1.2)	0
Aspartate aminotransferase increased	13 (5.3)	1 (0.4)	0	23 (9.4)	3 (1.2)	0
Gamma-glutamyltransferase increased	8 (3.2)	3 (1.2)	0	2 (0.8)	1 (0.4)	0
Hypertransaminasaemia	5 (2.0)	2 (0.8)	0	3 (1.2)	0	0
Hyperbilirubinaemia	2 (0.8)	2 (0.8)	0	4 (1.6)	1 (0.4)	0
Blood bilirubin increased	1 (0.4)	0	0	9 (3.7)	1 (0.4)	0
PULMONARY ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**13 (5.3)**	**4 (1.6)**	**0**	**9 (3.7)**	**3 (1.2)**	**0**
Pneumonitis	12 (4.9)	4 (1.6)	0	6 (2.4)	1 (0.4)	0
RENAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**29 (11.7)**	**4 (1.6)**	**0**	**44 (18.0)**	**1 (0.4)**	**0**
Blood creatinine increased	27 (10.9)	1 (0.4)	0	40 (16.3)	0	0
Blood urea increased	1 (0.4)	0	0	5 (2.0)	0	0
SKIN ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**64 (25.9)**	**4 (1.6)**	**0**	**74 (30.2)**	**3 (1.2)**	**0**
Pruritus	40 (16.2)	1 (0.4)	0	52 (21.2)	0	0
Rash	19 (7.7)	1 (0.4)	0	20 (8.2)	2 (0.8)	0
Rash maculo-papular	8 (3.2)	1 (0.4)	0	6 (2.4)	0	0
Erythema	3 (1.2)	0	0	3 (1.2)	0	0
Psoriasis	3 (1.2)	0	0	0	0	0
HYPERSENSITIVITY/INFUSION REACTION						
TOTAL SUBJECTS WITH AN EVENT	**3 (1.2)**	**1 (0.4)**	**0**	**9 (3.7)**	**0**	**0**
Hypersensitivity	2 (0.8)	1 (0.4)	0	3 (1.2)	0	0
Infusion related reaction	0	0	0	5 (2.0)	0	0
ENDOCRINE ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**40 (16.2)**	**6 (2.4)**	**0**	**52 (21.2)**	**3 (1.2)**	**0**
THYROID DISORDER	32 (13.0)	0	0	49 (20.0)	0	0
Hypothyroidism	24 (9.7)	0	0	30 (12.2)	0	0
Blood thyroid stimulating hormone increased	7 (2.8)	0	0	15 (6.1)	0	0
Blood thyroid stimulating hormone decreased	3 (1.2)	0	0	3 (1.2)	0	0
Hyperthyroidism	1 (0.4)	0	0	11 (4.5)	0	0
ADRENAL DISORDER	5 (2.0)	3 (1.2)	0	2 (0.8)	0	0
Adrenal insufficiency	5 (2.0)	3 (1.2)	0	2 (0.8)	0	0
DIABETES	4 (1.6)	3 (1.2)	0	1 (0.4)	1 (0.4)	0
Diabetes mellitus	3 (1.2)	2 (0.8)	0	0	0	0
PITUITARY DISORDER	0	0	0	3 (1.2)	2 (0.8)	0
Hypophysitis	0	0	0	3 (1.2)	2 (0.8)	0

Source: Table S.6.5.1.3.1 (all-causality select AEs), Table S.6.5.1.3.3 (all-causality select endocrine AEs)

MedDRA Version 26.0. CTC Version 5.0.

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

Table 57. Drug-Related Select Adverse Events by Worst CTC Grade in All Treated Subjects in Any Treatment

	Nivolumab SC N = 247			Nivolumab IV N = 245		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
GASTROINTESTINAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**15 (6.1)**	**0**	**0**	**13 (5.3)**	**1 (0.4)**	**0**
Diarrhoea	13 (5.3)	0	0	12 (4.9)	1 (0.4)	0
Colitis	2 (0.8)	0	0	0	0	0
Enterocolitis	0	0	0	1 (0.4)	0	0
HEPATIC ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**20 (8.1)**	**5 (2.0)**	**0**	**27 (11.0)**	**9 (3.7)**	**0**
Alanine aminotransferase increased	8 (3.2)	0	0	12 (4.9)	3 (1.2)	0
Aspartate aminotransferase increased	8 (3.2)	1 (0.4)	0	12 (4.9)	3 (1.2)	0
Blood alkaline phosphatase increased	6 (2.4)	1 (0.4)	0	4 (1.6)	1 (0.4)	0
Hypertransaminasaemia	2 (0.8)	0	0	2 (0.8)	0	0
Immune-mediated hepatitis	2 (0.8)	2 (0.8)	0	1 (0.4)	1 (0.4)	0
Hepatotoxicity	1 (0.4)	0	0	1 (0.4)	1 (0.4)	0
Hyperbilirubinaemia	1 (0.4)	1 (0.4)	0	1 (0.4)	0	0
Blood bilirubin increased	0	0	0	6 (2.4)	1 (0.4)	0
Gamma-glutamyltransferase increased	0	0	0	1 (0.4)	1 (0.4)	0
Hepatic enzyme increased	0	0	0	1 (0.4)	0	0
Hepatic failure	0	0	0	1 (0.4)	1 (0.4)	0
Transaminases increased	0	0	0	2 (0.8)	1 (0.4)	0
PULMONARY ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**13 (5.3)**	**4 (1.6)**	**0**	**8 (3.3)**	**2 (0.8)**	**0**
Pneumonitis	12 (4.9)	4 (1.6)	0	6 (2.4)	1 (0.4)	0
Lung infiltration	1 (0.4)	0	0	1 (0.4)	0	0
Immune-mediated lung disease	0	0	0	1 (0.4)	1 (0.4)	0
RENAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**7 (2.8)**	**0**	**0**	**12 (4.9)**	**0**	**0**
Blood creatinine increased	7 (2.8)	0	0	11 (4.5)	0	0
Blood urea increased	0	0	0	1 (0.4)	0	0
Renal failure	0	0	0	1 (0.4)	0	0
SKIN ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**57 (23.1)**	**4 (1.6)**	**0**	**65 (26.5)**	**3 (1.2)**	**0**
Pruritus	37 (15.0)	1 (0.4)	0	48 (19.6)	0	0
Rash	16 (6.5)	1 (0.4)	0	18 (7.3)	2 (0.8)	0
Rash maculo-papular	8 (3.2)	1 (0.4)	0	4 (1.6)	0	0
Dermatitis acneiform	2 (0.8)	1 (0.4)	0	2 (0.8)	0	0
Erythema	2 (0.8)	0	0	1 (0.4)	0	0
Psoriasis	2 (0.8)	0	0	0	0	0
Skin exfoliation	2 (0.8)	0	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	1 (0.4)	0	0	0	0	0
Rash erythematous	1 (0.4)	0	0	1 (0.4)	0	0
Rash papular	1 (0.4)	0	0	1 (0.4)	0	0
Erythema multiforme	0	0	0	1 (0.4)	1 (0.4)	0
Rash pruritic	0	0	0	1 (0.4)	0	0
Skin hypopigmentation	0	0	0	2 (0.8)	0	0
HYPERSENSITIVITY/INFUSION REACTION						
TOTAL SUBJECTS WITH AN EVENT	**1 (0.4)**	**1 (0.4)**	**0**	**6 (2.4)**	**0**	**0**
Hypersensitivity	1 (0.4)	1 (0.4)	0	0	0	0
Infusion related hypersensitivity reaction	0	0	0	1 (0.4)	0	0
Infusion related reaction	0	0	0	5 (2.0)	0	0
ENDOCRINE ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**31 (12.6)**	**2 (0.8)**	**0**	**44 (18.0)**	**3 (1.2)**	**0**
THYROID DISORDER	29 (11.7)	0	0	41 (16.7)	0	0
Hypothyroidism	22 (8.9)	0	0	24 (9.8)	0	0
Blood thyroid stimulating hormone increased	6 (2.4)	0	0	13 (5.3)	0	0
Blood thyroid stimulating hormone decreased	3 (1.2)	0	0	2 (0.8)	0	0
Hyperthyroidism	1 (0.4)	0	0	11 (4.5)	0	0
Thyroiditis	1 (0.4)	0	0	0	0	0
Thyroxine decreased	1 (0.4)	0	0	0	0	0
Thyroxine free decreased	1 (0.4)	0	0	0	0	0
Thyroxine free increased	0	0	0	1 (0.4)	0	0
ADRENAL DISORDER	3 (1.2)	2 (0.8)	0	2 (0.8)	0	0
Adrenal insufficiency	3 (1.2)	2 (0.8)	0	2 (0.8)	0	0
DIABETES	0	0	0	1 (0.4)	1 (0.4)	0
Diabetic ketoacidosis	0	0	0	1 (0.4)	1 (0.4)	0
Type 1 diabetes mellitus	0	0	0	1 (0.4)	0	0
PITUITARY DISORDER	0	0	0	3 (1.2)	2 (0.8)	0
Hypophysitis	0	0	0	3 (1.2)	2 (0.8)	0

Source: Table S.6.5.1.3.2 (drug-related select AEs), Table S.6.5.1.3.4 (drug-related select endocrine AEs)

MedDRA Version 26.0. CTC Version 5.0.

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

Table 58. Onset, Management, and Resolution of Drug-Related Select AEs - All Nivolumab SC (N=247) and Nivolumab IV (N=245) Treated Subjects

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE		Median Time to Onset of Drug-related Select AE (range), wks		% Treated Subj. with Drug-related Select AE Leading to DC		% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]		Median Time[b] to Resolution of Drug-related Select AE (range), wks[c,d,e]		% Subj. with Drug-related Select AE that Resolved[d,e]	
	Nivo SC	Nivo IV	Nivo SC	Nivo IV	Nivo SC	Nivo IV	Nivo SC	Nivo IV	Nivo SC	Nivo IV	Nivo SC	Nivo IV
Endocrine	12.6/0.8	18.0/1.2	13.14 (3.9-63.0)	10.36 (2.0-63.1)	0	0.8	9.7/0	9.1/2.3	N.A. (1.0-73.3+)	N.A. (1.0-100.1+)	22.6	22.7
GI	6.1/0	5.3/0.4	19.43 (4.3-50.1)	19.14 (0.3-55.3)	0	0	40.0/26.7	46.2/30.8	1.86 (0.4-21.3)	1.71 (0.7-7.7)	100.0	100.0
Hepatic	8.1/2.0	11.0/3.7	16.57 (3.7-76.4)	8.00 (2.0-69.9)	0.4	1.6	30.0/25.0	51.9/51.9	8.14 (0.1+ -57.0)	5.14 (1.1-91.6+)	70.0	74.1
Pulmonary	5.3/1.6	3.3/0.8	23.00 (2.0-96.4)	12.71 (7.3-54.3)	2.0	0.8	46.2/38.5	87.5/87.5	N.A. (0.1+ -65.9+)	6.00 (0.3-35.9+)	46.2	87.5
Renal	2.8/0	4.9/0	32.14 (4.1-40.0)	20.07 (4.3-54.3)	0	0	28.6/28.6	16.7/16.7	8.00 (2.1-60.9+)	4.14 (1.1-86.1+)	57.1	66.7
Skin	23.1/1.6	26.5/1.2	11.14 (0.1-51.1)	7.00 (0.4-77.7)	0	0	42.1/3.5	33.8/7.7	N.A. (0.6-94.3+)	9.57 (0.1-98.7+)	43.9	67.7
Hypersensitivity / Infusion Reaction	0.4/0.4	2.4/0	0.29 (0.3-0.3)	2.14 (0.1-4.1)	0.4	0	0/0	33.3/16.7	0.43 (0.4-0.4)	0.14 (0.1-0.1)	100.0	100.0

Source: Table S.6.5.1.3.2 (drug-related select AEs), Table S.6.5.1.3.4 (drug-related select endocrine AEs), Table S.6.117.1 (time to onset of drug-related select AEs), Table S.6.5.1.3.6 (drug-related select AEs leading to DC), Table S.6.5.1.3.8 (drug-related select endocrine AEs leading to DC), Table S.4.12.9.1 (duration of IMM for drug-related select AEs), Table S.6.121.1 (time to resolution of select AEs). These outputs also include Grade 3-5 and chemotherapy results.

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

[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 adverse event 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.

Immune-mediated AEs

Table 59. Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose - All Nivo SC (N=247) and Nivo IV (N=245) Treated Subjects

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[d] Time to Resolution (range), wks[b,c]	
	SC	IV	SC	IV	SC	IV	SC	IV	SC	IV	SC	IV	SC	IV
Pneumonitis	7(2.8)/ 2(0.8)	7(2.9)/ 2(0.8)	23.00 (2.0,48.7)	11.29 (7.3,54.3)	1.6/1.6	0.8/2.4	100/71.4	100/100	6.57 (3.4,52.3)	6.86 (0.6,38.9)	42.9	100	36.29 (1.6,65.9+)	4.86 (0.3,14.0)
Diarrhea/Colitis	7(2.8)/ 1(0.4)	5(2.0)/ 0	22.14 (4.3,41.4)	34.14 (19.1,53.6)	0/2.0	0/0.8	100/71.4	100/80	3.71 (0.1,10.1)	2.00 (0.7,8.1)	71.4	100	11.14 (1.0,21.3)	1.29 (0.7,7.7)
Hepatitis	6(2.4)/ 4(1.6)	14(5.7)/ 9(3.7)	18.64 (3.9,67.1)	11.50 (3.9,54.3)	0.8/1.6	2.0/4.1	100/100	100/100	5.43 (0.9,26.7)	9.29 (0.4,24.7)	66.7	57.1	10.14 (1.7,23.7+)	12.14 (1.1,23.0+)
Nephritis/Renal Dysfunction	3(1.2)/ 0	2(0.8)/ 0	32.14 (15.9,39.1)	34.07 (26.0,42.1)	0/1.2	0/0.4	100/66.7	100/100	5.29 (1.1,12.9)	3.14 (1.1,5.1)	100	50	6.86 (5.0,8.1)	N.A. (1.1,12.7+)
Rash	17(6.9)/ 2(0.8)	12(4.9)/ 3(1.2)	14.86 (1.6,48.0)	24.14 (1.7,54.4)	0/1.2	0/1.2	100/11.8	100/25	4.14 (0.6,51.1)	4.21 (1.1,44.1)	76.5	58.3	2.86 (0.7,65.7+)	14.14 (0.7,95.9+)
Hypersensitivity	1(0.4)/ 0	2(0.8)/ 0	19.57 (19.6,19.6)	3.07 (0.1,6.0)	0/0.4	0/0	100/0	100/50	0.71 (0.7,0.7)	0.14 (0.1,0.1)	100	100	2.43 (2.4,2.4)	0.14 (0.1,0.1)
Adrenal Insufficiency	5(2.0)/ 2(0.8)	2(0.8)/ 0	18.00 (16.0,63.0)	27.86 (20.7,35.0)	0.4/0.4	0/0	100/20	100/0	28.57 (3.4,69.1)	58.86 (44.4,73.3)	20.0	0	NA (1.0,69.1+)	NA (44.4+,73.7+)
Hypothyroidism/ Thyroiditis	24(9.7)/ 0	25(10.2)/ 0	16.00 (3.9,53.0)	15.43 (2.1,63.1)	0/0.8	0/1.2	0/0	0/0	NA	NA	8.3	8.0	NA (2.7+,73.3+)	NA (4.0+,100.1+)
Diabetes Mellitus	1(0.4)/ 1(0.4)	1(0.4)/ 1(0.4)	17.43 (17.4,17.4)	10.43 (10.4,10.4)	0/0	0.4/0	0/0	0/0	NA	NA	0	0	NA (40.0+,40.0+)	NA (56.0+,56.0+)
Hyperthyroidism	2(0.8)/ 0	11(4.5)/ 0	14.71 (12.0,17.4)	10.00 (2.3,28.0)	0/0	0/0.4	0/0	0/0	NA	NA	50.0	72.7	4.29 (2.4+,4.3)	7.71 (2.1-58.1+)
Hypophysitis	0/0	3(1.2)/ 2(0.8)	--	31.57 (6.1,52.3)	0/0	0.4/0.8	0/0	66.7/33.3	NA	27.21 (16.0,38.4)	0	33.3	--	NA (1.3-38.6+)

Source: Table S.6.2.02.1 (endocrine IMAEs), Table S.6.2.02.2 (endocrine IMAEs, DC), Table S.6.2.02.3 (endocrine IMAEs, dose delay), Table S.6.2.02.4 (non-endocrine IMAEs), Table S.6.2.02.5 (non-endocrine IMAEs, DC), Table S.6.2.02.6 (non-endocrine IMAEs, dose delay), Table S.4.12.91.1 (duration of IMM for IMAE), Table S.6.217.1 (time to onset, endocrine IMAEs), Table S.6.217.2 (time to onset, non-endocrine IMAEs), Table S.6.219.1 (time to resolution, endocrine IMAEs), Table S.6.219.2 (time to resolution, non-endocrine IMAEs). These outputs also include Grade 3-5.

Other events of special interest

Table 60. Treatment, Onset, and Resolution Information for Other Events of Special Interest - All Treated Subjects

OESI Category Grade, Relationship to Study Therapy, PT	Immune-modulating Medication	Onset Date (Study Day)	Duration of Event (Days)	Resolution (Yes/No)
Nivolumab SC				
Pancreatitis				
Grade 3 drug-related SAE pancreatitis	dexamethasone	31	11	Yes
Uveitis				
Grade 1 drug-related AE uveitis		49	4	Yes
Grade 2 drug-related AE uveitis	prednisolone acetate	57	7	Yes
Grade 3 drug-related AE uveitis	prednisolone acetate, prednisone, betamethasone, azathioprine, mycophenolate mofetil	64	-	No
Myocarditis				
Grade 4 drug-related SAE myocarditis	methylprednisone, prednisone	77	-	No

Nivolumab IV				
Pancreatitis				
Grade 2 drug-related AE pancreatitis	prednisone	172	28	Yes
Myositis (2 subjects)				
Grade 3 drug-related AE myositis	prednisone	92	1	Yes
Grade 1 drug-related AE myositis	prednisone	94	19	Yes
Grade 2 drug-related AE myositis	prednisone	167	8	Yes
Grade 4 drug-related SAE myositis	prednisone	29	20	Yes
Grade 1 drug-related AE myositis	prednisone	50	163	Yes

Source: Appendix 6.84.1 (OESI and IMM), Appendix 6.1.1 (for seriousness and duration of event)
MedDRA Version 26.0. CTC Version 5.0.
Note: Other Events of Special Interest included preferred terms describing specific events reported within 100 days of last dose.

A higher proportion of subjects in the nivo SC arm were reported with local injection site reactions compared with subjects in the nivo IV arm, regardless of causality (Table 61). The median duration of infusion/injection AEs was 2.00 vs 0.01 days in the nivo SC and nivo IV arms, respectively. No Grade 3-5 events were reported.

Table 61. Local Injection or Infusion-site Reactions Summary with 100 Days Follow Up by Worst CTC Grade - (Any Grade, Grade 3-4, Grade 5) - All Treated Subjects

	Nivolumab SC N = 247			Nivolumab IV N = 245		
Preferred Term (%)	**Any Grade**	**Grade 3-4**	**Grade 5**	**Any Grade**	**Grade 3-4**	**Grade 5**
TOTAL SUBJECTS WITH AN EVENT	**20 (8.1)**	**0**	**0**	**5 (2.0)**	**0**	**0**
Injection site erythema	6 (2.4)	0	0	0	0	0
Application site pain	2 (0.8)	0	0	0	0	0
Injection site oedema	2 (0.8)	0	0	0	0	0
Injection site pain	2 (0.8)	0	0	0	0	0
Injection site reaction	2 (0.8)	0	0	0	0	0
Administration site pain	1 (0.4)	0	0	0	0	0
Application site erythema	1 (0.4)	0	0	0	0	0
Application site rash	1 (0.4)	0	0	0	0	0
Infusion site reaction	1 (0.4)	0	0	0	0	0
Injection site discolouration	1 (0.4)	0	0	0	0	0
Injection site inflammation	1 (0.4)	0	0	0	0	0
Injection site pruritus	1 (0.4)	0	0	0	0	0
Puncture site erythema	1 (0.4)	0	0	0	0	0
Infusion related reaction	0	0	0	5 (2.0)	0	0

Source: Table S.6.5.1.5.2
MedDRA Version 26.0. CTC Version 5.0.
Note: Includes events reported between first dose and 100 days after last dose of study therapy.

There were no reported cases of anaphylactic reactions in either the nivolumab SC or the nivolumab IV arm. Most of the AEs in the broad SMQ of anaphylactic reaction were non-serious and mild to moderate (Grade 1-2) in severity.

Table 62. Adverse Events in the Broad SMQ of Anaphylactic Reaction Summary with 100 Days Follow Up by Worst CTC Grade - (Any Grade, Grade 3-4, Grade 5) in Study CA20967T - All Treated Subjects

	Nivolumab SC N = 247			Nivolumab IV N = 245		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**90 (36.4)**	**7 (2.8)**	**6 (2.4)**	**106 (43.3)**	**6 (2.4)**	**3 (1.2)**
Pruritus	41 (16.6)	1 (0.4)	0	52 (21.2)	0	0
Cough	27 (10.9)	0	0	29 (11.8)	0	0
Rash	20 (8.1)	1 (0.4)	0	20 (8.2)	2 (0.8)	0
Dyspnoea	11 (4.5)	5 (2.0)	0	18 (7.3)	1 (0.4)	0
Erythema	3 (1.2)	0	0	3 (1.2)	0	0
Hypotension	3 (1.2)	0	0	5 (2.0)	1 (0.4)	0
Respiratory failure	3 (1.2)	1 (0.4)	2 (0.8)	3 (1.2)	1 (0.4)	2 (0.8)
Cardio-respiratory arrest	2 (0.8)	0	2 (0.8)	1 (0.4)	0	1 (0.4)
Chest discomfort	2 (0.8)	0	0	1 (0.4)	0	0
Acute respiratory failure	1 (0.4)	0	1 (0.4)	1 (0.4)	1 (0.4)	0
Bronchospasm	1 (0.4)	0	0	0	0	0
Cardiovascular insufficiency	1 (0.4)	0	1 (0.4)	0	0	0
Ocular hyperaemia	1 (0.4)	0	0	1 (0.4)	0	0
Rash erythematous	1 (0.4)	0	0	1 (0.4)	0	0
Cardiac arrest	0	0	0	1 (0.4)	1 (0.4)	0
Choking sensation	0	0	0	1 (0.4)	0	0
Face oedema	0	0	0	1 (0.4)	0	0
Flushing	0	0	0	1 (0.4)	0	0
Rash pruritic	0	0	0	1 (0.4)	0	0
Urticaria	0	0	0	1 (0.4)	0	0

Note: Includes events reported between first dose and 100 days after last dose of study therapy.
MedDRA Version 26.0. CTC Version 5.0.

2.6.8.4. Laboratory findings

A summary of on-treatment laboratory parameters that worsened relative to baseline is provided in table below.

Table 63. Summary of On-treatment Worst CTC Grade (Grade 1-4 and Grade 3-4) Laboratory Parameters that Worsened Relative to Baseline within 30 Days Follow-up (SI Units) in Study CA20967T and in the Pooled Nivolumab IV Monotherapy Group Excluding Study CA20967T- All Treated Subjects

	CA20967T (SC Arm) Nivolumab Monotherapy			CA20967T (IV Arm) Nivolumab Monotherapy			Pooled Nivolumab IV Monotherapy Excluding Study CA20967T		
Lab Test Description (%)	N	Grade 1-4	Grade 3-4	N	Grade 1-4	Grade 3-4	N	Grade 1-4	Grade 3-4
HEMOGLOBIN	234	108 (46.2)	16 (6.8)	244	116 (47.5)	21 (8.6)	4553	1474 (32.4)	157 (3.4)
PLATELET COUNT	234	27 (11.5)	2 (0.9)	244	29 (11.9)	3 (1.2)	4550	533 (11.7)	30 (0.7)
LEUKOCYTES	234	17 (7.3)	1 (0.4)	244	25 (10.2)	1 (0.4)	4561	680 (14.9)	33 (0.7)
LYMPHOCYTES (ABSOLUTE)	232	84 (36.2)	14 (6.0)	242	109 (45.0)	21 (8.7)	4494	1706 (38.0)	393 (8.7)
ABSOLUTE NEUTROPHIL COUNT	232	13 (5.6)	1 (0.4)	242	13 (5.4)	1 (0.4)	4538	593 (13.1)	39 (0.9)
ALKALINE PHOSPHATASE	234	75 (32.1)	5 (2.1)	244	81 (33.2)	5 (2.0)	4515	1010 (22.4)	78 (1.7)
ASPARTATE AMINOTRANSFERASE	235	45 (19.1)	4 (1.7)	243	71 (29.2)	9 (3.7)	4529	1235 (27.3)	120 (2.6)
ALANINE AMINOTRANSFERASE	234	48 (20.5)	3 (1.3)	243	64 (26.3)	10 (4.1)	4540	1019 (22.4)	106 (2.3)
BILIRUBIN, TOTAL	235	18 (7.7)	3 (1.3)	244	38 (15.6)	6 (2.5)	4535	397 (8.8)	37 (0.8)
CREATININE	235	88 (37.4)	3 (1.3)	244	107 (43.9)	1 (0.4)	4545	1045 (23.0)	31 (0.7)
ALBUMIN	232	54 (23.3)	4 (1.7)	240	81 (33.8)	1 (0.4)	1133	225 (19.9)	7 (0.6)
HYPERNATREMIA	235	19 (8.1)	1 (0.4)	243	21 (8.6)	1 (0.4)	4493	264 (5.9)	3 (<0.1)
HYPONATREMIA	235	80 (34.0)	6 (2.6)	243	97 (39.9)	6 (2.5)	4493	1133 (25.2)	210 (4.7)
HYPERKALEMIA	235	79 (33.6)	7 (3.0)	243	109 (44.9)	7 (2.9)	4485	855 (19.1)	73 (1.6)
HYPOKALEMIA	235	10 (4.3)	2 (0.9)	243	8 (3.3)	1 (0.4)	4485	470 (10.5)	59 (1.3)
HYPERCALCEMIA	235	70 (29.8)	5 (2.1)	244	77 (31.6)	11 (4.5)	3899	400 (10.3)	44 (1.1)

HYPOCALCEMIA	235	40 (17.0)	0	244	60 (24.6)	2 (0.8)	3899	633 (16.2)	25 (0.6)
HYPOGLYCEMIA	231	13 (5.6)	0	241	24 (10.0)	0	1183	107 (9.0)	8 (0.7)

Notes:

Toxicity Scale: CTC Version 5.0 for CA20967T and CA20976K, 4.0 for rest of the pooled studies. Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy, except for ONO-4538-24. For ONO-4538-24 include events reported between first dose and the earlier date between 28 days after the end of the treatment period or the start date of the post-treatment observation period. For CA20976K, study therapy is narrowed to blinded study phase.

N: Subjects with a CTC Graded Laboratory Result for the given parameter from both Baseline and On-treatment Percentages are based on N as denominator. Per Anemia criteria in CTC Version 4.0 and 5.0 there is no Grade 4 for hemoglobin.

Nivolumab IV Monotherapy group consists of nivolumab monotherapy treatment arm from studies CA209017, CA209025, CA209032 (BC cohort), CA209037, CA209039 (cHL subjects), CA209057, CA209063, CA209066, CA209067, CA209141, CA209205, CA209238, CA209274, CA209275, CA209577, CA20976K, ONO-4538-24.

Source: Appendix SC.142.1-EUSMPC.

Liver tests

During the treatment period, abnormalities (increases) in hepatic parameters (ALP, AST, ALT, and total bilirubin) were primarily Grade 1-2 in each treatment arm. A greater proportion of subjects in the nivo IV arm had concurrent ALT or AST >3 × ULN with total bilirubin >1.5 × ULN within 30 days (2.5%) compared to the nivo SC arm (1.3%).

Kidney function tests

Most abnormalities in creatinine (increases from baseline) were reported as Grade 1 or 2. In the nivo SC arm, 2 subjects had a Grade 3 increased creatinine level, and 1 subject had a Grade 4 increased creatinine level. In the nivo IV arm, 1 subject had a Grade 3 increased creatinine level.

Thyroid function tests

TSH (SI units) increases (>ULN) from baseline (≤ ULN) were reported in similar proportions of subjects in the nivo SC and nivo IV treatment arms (26.9% and 26.8%, respectively). Decreases (<LLN) from baseline with TSH LLN at baseline were reported in a numerically higher number of subjects in the nivo IV arm (56 [23.4%]) than in the nivo SC arm (44 [19.4%]).

Electrolytes

Most subjects had normal electrolyte levels during the treatment reporting period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. The following Grade 3 electrolyte abnormalities were reported in all treated subjects with on-treatment laboratory results:

- Nivo SC: hyponatremia (3.0%), hyperkalemia (3.0%), hypercalcemia (2.1%), hypokalemia (0.9%), hypernatremia (0.4%).
- Nivo IV: hyperkalemia (2.9%), hypercalcemia (2.0%), hyponatremia (1.6%), hypocalcemia (0.8%), hypernatremia (0.4%), hypokalemia (0.4%).

Grade 4 electrolyte abnormalities were reported in 1-2 subjects in each treatment arm, with the exception of hypercalcemia, which was reported in 5 (2.0%) subjects in the nivo IV arm.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Table 64. All-Causality AEs Classified by Worst CTC Grade and by Age, Sex, Race, and Region - All Treated Subjects

All-Causality AEs (n [%])								
	Nivolumab SC				Nivolumab IV			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	247	230 (93.1)	87 (35.2)	10 (4.0)	245	229 (93.5)	100 (40.8)	6 (2.4)
By Age (years)								
< 65	129	120 (93.0)	44 (34.1)	4 (3.1)	115	107 (93.0)	46 (40.0)	3 (2.6)
≥ 65 and < 75	84	78 (92.9)	29 (34.5)	1 (1.2)	97	90 (92.8)	42 (43.3)	2 (2.1)
≥ 75 and < 85	30	28 (93.3)	13 (43.3)	4 (13.3)	30	29 (96.7)	12 (40.0)	1 (3.3)
≥ 65	118	110 (93.2)	43 (36.4)	6 (5.1)	130	122 (93.8)	54 (41.5)	3 (2.3)
≥ 75	34	32 (94.1)	14 (41.2)	5 (14.7)	33	32 (97.0)	12 (36.4)	1 (3.0)
≥ 85	4	4 (100.0)	1 (25.0)	1 (25.0)	3	3 (100.0)	0	0
By Sex								
Male	163	152 (93.3)	54 (33.1)	8 (4.9)	171	159 (93.0)	74 (43.3)	4 (2.3)
Female	84	78 (92.9)	33 (39.3)	2 (2.4)	74	70 (94.6)	26 (35.1)	2 (2.7)
By Race								
White	204	189 (92.6)	72 (35.3)	9 (4.4)	215	200 (93.0)	86 (40.0)	6 (2.8)
Black or African American	0	0	0	0	2	2 (100.0)	1 (50.0)	0
Asian	3	3 (100.0)	0	1 (33.3)	1	1 (100.0)	1 (100.0)	0
American Indian or Alaska Native	2	2 (100.0)	1 (50.0)	0	3	3 (100.0)	2 (66.7)	0
Other	38	36 (94.7)	14 (36.8)	0	24	23 (95.8)	10 (41.7)	0
By Region								
US and EU	67	61 (91.0)	20 (29.9)	2 (3.0)	75	65 (86.7)	29 (38.7)	3 (4.0)
Mexico and South America	158	149 (94.3)	61 (38.6)	7 (4.4)	147	144 (98.0)	62 (42.2)	3 (2.0)
Rest of World	22	20 (90.9)	6 (27.3)	1 (4.5)	23	20 (87.0)	9 (39.1)	0

Table 65. Summary of On-treatment Adverse Events by Age Group - All Treated Subjects with Nivolumab Monotherapy

Treatment Group: CA20967T (SC Arm) Nivolumab Monotherapy N = 247

MedDRA Terms (%)	Age Group (Years) >=18 and <65 N = 129	>=65 and <75 N = 84	>=75 and <85 N = 30	>= 85 N = 4	Total N = 247
TOTAL SUBJECTS WITH AN EVENT	120 (93.0)	78 (92.9)	28 (93.3)	4 (100.0)	230 (93.1)
SERIOUS AE - TOTAL	35 (27.1)	20 (23.8)	12 (40.0)	2 (50.0)	69 (27.9)
FATAL (DEATH)	7 (5.4)	5 (6.0)	5 (16.7)	1 (25.0)	18 (7.3)
HOSPITALIZATION/PROLONGATION	33 (25.6)	18 (21.4)	10 (33.3)	1 (25.0)	62 (25.1)
LIFE THREATENING	11 (8.5)	6 (7.1)	1 (3.3)	1 (25.0)	19 (7.7)
CANCER	11 (8.5)	4 (4.8)	1 (3.3)	1 (25.0)	17 (6.9)
DISABILITY/INCAPACITY	4 (3.1)	3 (3.6)	0	0	7 (2.8)
IMPORTANT MEDICAL EVENT	6 (4.7)	5 (6.0)	1 (3.3)	2 (50.0)	14 (5.7)
AE LEADING TO DISCONTINUATION	9 (7.0)	11 (13.1)	4 (13.3)	1 (25.0)	25 (10.1)
PSYCHIATRIC DISORDERS	9 (7.0)	6 (7.1)	4 (13.3)	0	19 (7.7)
NERVOUS SYSTEM DISORDERS	19 (14.7)	11 (13.1)	2 (6.7)	0	32 (13.0)
ACCIDENT AND INJURIES	1 (0.8)	4 (4.8)	2 (6.7)	1 (25.0)	8 (3.2)
CARDIAC DISORDERS	2 (1.6)	6 (7.1)	3 (10.0)	0	11 (4.5)
VASCULAR DISORDERS	9 (7.0)	9 (10.7)	3 (10.0)	0	21 (8.5)
CEREBROVASCULAR DISORDERS	4 (3.1)	0	0	0	4 (1.6)
INFECTIONS AND INFESTATIONS	38 (29.5)	24 (28.6)	11 (36.7)	1 (25.0)	74 (30.0)
ANTICHOLINERGIC SYNDROME	20 (15.5)	6 (7.1)	3 (10.0)	0	29 (11.7)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	7 (5.4)	6 (7.1)	2 (6.7)	0	15 (6.1)

Treatment Group: CA20967T (IV Arm) Nivolumab Monotherapy N = 245

MedDRA Terms (%)	Age Group (Years) >=18 and <65 N = 115	>=65 and <75 N = 97	>=75 and <85 N = 30	>= 85 N = 3	Total N = 245
TOTAL SUBJECTS WITH AN EVENT	107 (93.0)	90 (92.8)	29 (96.7)	3 (100.0)	229 (93.5)
SERIOUS AE - TOTAL	31 (27.0)	34 (35.1)	6 (20.0)	0	71 (29.0)
FATAL (DEATH)	5 (4.3)	5 (5.2)	2 (6.7)	0	12 (4.9)
HOSPITALIZATION/PROLONGATION	27 (23.5)	33 (34.0)	5 (16.7)	0	65 (26.5)
LIFE THREATENING	3 (2.6)	5 (5.2)	0	0	8 (3.3)
CANCER	12 (10.4)	8 (8.2)	1 (3.3)	0	21 (8.6)
DISABILITY/INCAPACITY	4 (3.5)	3 (3.1)	1 (3.3)	0	8 (3.3)
IMPORTANT MEDICAL EVENT	7 (6.1)	5 (5.2)	2 (6.7)	0	14 (5.7)
AE LEADING TO DISCONTINUATION	12 (10.4)	13 (13.4)	4 (13.3)	0	29 (11.8)
PSYCHIATRIC DISORDERS	8 (7.0)	7 (7.2)	3 (10.0)	0	18 (7.3)
NERVOUS SYSTEM DISORDERS	30 (26.1)	20 (20.6)	8 (26.7)	0	58 (23.7)
ACCIDENT AND INJURIES	5 (4.3)	8 (8.2)	6 (20.0)	0	19 (7.8)
CARDIAC DISORDERS	4 (3.5)	6 (6.2)	2 (6.7)	0	12 (4.9)
VASCULAR DISORDERS	10 (8.7)	16 (16.5)	4 (13.3)	1 (33.3)	31 (12.7)
CEREBROVASCULAR DISORDERS	3 (2.6)	0	1 (3.3)	0	4 (1.6)
INFECTIONS AND INFESTATIONS	32 (27.8)	30 (30.9)	11 (36.7)	2 (66.7)	75 (30.6)
ANTICHOLINERGIC SYNDROME	20 (17.4)	16 (16.5)	6 (20.0)	0	42 (17.1)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	11 (9.6)	11 (11.3)	5 (16.7)	0	27 (11.0)

2.6.8.7. Immunological events

Table 66. Anti-drug Antibody Assessments Summary in Study CA20967T - All Immunogenicity Evaluable Subjects with Baseline and at Least One Post-baseline Assessment

	Arm A		Arm B
ADA Status (%)	Nivolumab N = 202	rHuPH20 N = 215	Nivolumab N = 215
BASELINE ADA POSITIVE	12 (5.9)	20 (9.3)	9 (4.2)
ADA POSITIVE	46 (22.8)	19 (8.8)	15 (7.0)
PERSISTENT POSITIVE (PP)	2 (1.0)	7 (3.3)	0
NOT PP - LAST SAMPLE POSITIVE	17 (8.4)	11 (5.1)	6 (2.8)
OTHER POSITIVE	27 (13.4)	1 (0.5)	9 (4.2)
NEUTRALIZING POSITIVE	2 (1.0)	5 (2.3)	0
ADA NEGATIVE	155 (76.7)	196 (91.2)	200 (93.0)
N.A.	1 (0.5)	0	0

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

Baseline ADA Positive: A subject with baseline ADA-positive sample.

ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater [≥] than baseline positive titer) at any time after initiation of treatment. Subject 95-286 in nivolumab SC arm had post-baseline positive anti-nivolumab antibodies but was not included in this table since this subject was not immunogenicity evaluable as Day 1 ADA sample was not collected before the start of treatment and could not be considered as baseline.

Persistent Positive: ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 16 weeks apart.

Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling time point

Other Positive: Not persistent but some ADA-positive samples with the last sample being negative

Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline. Subject 65-190 was not included in the "Neutralizing Positive" category for rHuPH20 due to the subject's "ADA Negative" subject level status.

ADA Negative: A subject with only ADA-negative sample after initiation of treatment

N.A.: Subject 103-555, baseline nivolumab ADA sample was positive with titer as 8, but the titer for the post-baseline positive ADA sample could not be determined due to insufficient quantity, resulting in an undetermined ADA status.

Source: Table 11.1.1-1 of the CA20967T Primary CSR.[2]

Of all treated subjects evaluable for ADA in the nivolumab SC arm, local site reaction AEs were reported in a greater proportion of ADA positive subjects compared to ADA negative subjects.

Table 67. Local Injection- or Infusion-Site Reactions Summary by Nivolumab ADA Status (Positive, Negative) - All Treated Subjects with Nivolumab ADA Positive or ADA Negative

	Nivolumab SC		Nivolumab IV	
Preferred Term (%)	Nivo ADA Positive N = 46	Nivo ADA Negative N = 155	Nivo ADA Positive N = 15	Nivo ADA Negative N = 200
TOTAL SUBJECTS WITH AN EVENT	7 (15.2)	10 (6.5)	0	4 (2.0)
Application site pain	1 (2.2)	0	0	0
Infusion related reaction	0	0	0	4 (2.0)
Infusion site reaction	0	1 (0.6)	0	0
Injection site discolouration	1 (2.2)	0	0	0
Injection site erythema	2 (4.3)	4 (2.6)	0	0
Injection site inflammation	0	1 (0.6)	0	0
Injection site oedema	2 (4.3)	0	0	0
Injection site pain	0	2 (1.3)	0	0
Injection site pruritus	1 (2.2)	0	0	0
Injection site reaction	1 (2.2)	1 (0.6)	0	0
Puncture site erythema	0	1 (0.6)	0	0

Note: Includes events reported between first dose and 100 days after last dose of study therapy.
MedDRA Version 26.0.

Source: Table 11.1.6.2-1 of the CA20967T Primary CSR.[2]

Table 68. Local Injection- or Infusion-Site Reactions Summary by rHuPH20 ADA Status (Positive, Negative) - All Treated Subjects with rHuPH20 ADA Positive or ADA Negative

	Nivolumab SC	
Preferred Term (%)	rHuPH20 ADA Positive N = 19	rHuPH20 ADA Negative N = 196
TOTAL SUBJECTS WITH AN EVENT	5 (26.3)	13 (6.6)
Application site erythema	0	1 (0.5)
Application site pain	0	2 (1.0)
Application site rash	0	1 (0.5)
Infusion site reaction	1 (5.3)	0
Injection site discolouration	0	1 (0.5)
Injection site erythema	2 (10.5)	3 (1.5)
Injection site inflammation	1 (5.3)	0
Injection site oedema	0	2 (1.0)
Injection site pain	0	2 (1.0)
Injection site pruritus	0	1 (0.5)
Injection site reaction	1 (5.3)	1 (0.5)
Puncture site erythema	0	1 (0.5)

Note: Includes events reported between first dose and 100 days after last dose of study therapy.
MedDRA Version 26.0.

Source: Table 11.1.6.2-2 of the CA20967T Primary CSR.[2]

Table 69. AEs in the Broad SMQ of Anaphylactic Reaction Summary by Nivolumab ADA Status (Positive, Negative) - All Treated Subjects with Nivolumab ADA Positive or ADA Negative

	Nivolumab SC		Nivolumab IV	
Preferred Term (%)	Nivo ADA Positive N = 46	Nivo ADA Negative N = 155	Nivo ADA Positive N = 15	Nivo ADA Negative N = 200
TOTAL SUBJECTS WITH AN EVENT	17 (37.0)	61 (39.4)	7 (46.7)	90 (45.0)
Acute respiratory failure	0	1 (0.6)	0	1 (0.5)
Bronchospasm	0	1 (0.6)	0	0
Cardio-respiratory arrest	0	1 (0.6)	0	1 (0.5)
Cardiovascular insufficiency	0	1 (0.6)	0	0
Chest discomfort	1 (2.2)	1 (0.6)	0	1 (0.5)
Choking sensation	0	0	0	1 (0.5)
Cough	9 (19.6)	15 (9.7)	3 (20.0)	24 (12.0)
Dyspnoea	3 (6.5)	7 (4.5)	1 (6.7)	14 (7.0)
Erythema	1 (2.2)	2 (1.3)	1 (6.7)	2 (1.0)
Flushing	0	0	0	1 (0.5)

	Nivolumab SC		Nivolumab IV	
Preferred Term (%)	Nivo ADA Positive N = 46	Nivo ADA Negative N = 155	Nivo ADA Positive N = 15	Nivo ADA Negative N = 200
Hypotension	0	3 (1.9)	0	4 (2.0)
Ocular hyperaemia	0	1 (0.6)	0	1 (0.5)
Pruritus	4 (8.7)	32 (20.6)	2 (13.3)	49 (24.5)
Rash	2 (4.3)	14 (9.0)	1 (6.7)	18 (9.0)
Rash erythematous	1 (2.2)	0	0	1 (0.5)
Rash pruritic	0	0	0	1 (0.5)
Respiratory failure	1 (2.2)	1 (0.6)	0	3 (1.5)

Source: Table S.7.11.2.1
MedDRA Version 26.0.
Note: Includes events reported between first dose and 100 days after last dose of study therapy.

Table 70. AEs in the Broad SMQ of Anaphylactic Reaction Summary by rHuPH20 ADA Status (Positive, Negative) - All Treated Subjects with rHuPH20 ADA Positive or ADA Negative

	Nivolumab SC	
Preferred Term (%)	rHuPH20 ADA Positive N = 19	rHuPH20 ADA Negative N = 196
TOTAL SUBJECTS WITH AN EVENT	**9 (47.4)**	**74 (37.8)**
Acute respiratory failure	0	1 (0.5)
Bronchospasm	0	1 (0.5)
Cardio-respiratory arrest	0	1 (0.5)
Cardiovascular insufficiency	0	1 (0.5)
Chest discomfort	0	2 (1.0)
Cough	4 (21.1)	22 (11.2)
Dyspnoea	0	10 (5.1)
Erythema	1 (5.3)	2 (1.0)
Hypotension	0	3 (1.5)
Ocular hyperaemia	0	1 (0.5)
Pruritus	7 (36.8)	31 (15.8)
Rash	0	18 (9.2)
Rash erythematous	0	1 (0.5)
Respiratory failure	0	2 (1.0)

Source: Table S.7.11.2.2

MedDRA Version 26.0.

Note: Includes events reported between first dose and 100 days after last dose of study therapy.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not applicable

2.6.8.9. Discontinuation due to adverse events

AEs leading to discontinuation

Table 71. Adverse Events Leading to Discontinuation in 2 or More Subjects of All Treated Subjects in Any Treatment

	Nivolumab SC N = 247			Nivolumab IV N = 245		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**25 (10.1)**	**18 (7.3)**	**1 (0.4)**	**29 (11.8)**	**21 (8.6)**	**0**
Respiratory, thoracic and mediastinal disorders	8 (3.2)	3 (1.2)	0	4 (1.6)	1 (0.4)	0
Pneumonitis	5 (2.0)	1 (0.4)	0	1 (0.4)	0	0
Dyspnoea	2 (0.8)	1 (0.4)	0	0	0	0
Musculoskeletal and connective tissue disorders	4 (1.6)	3 (1.2)	0	2 (0.8)	2 (0.8)	0
Muscular weakness	2 (0.8)	2 (0.8)	0	0	0	0
Myositis	0	0	0	2 (0.8)	2 (0.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.6)	2 (0.8)	1 (0.4)	2 (0.8)	2 (0.8)	0
Malignant neoplasm progression	2 (0.8)	1 (0.4)	1 (0.4)	0	0	0
General disorders and administration site conditions	2 (0.8)	2 (0.8)	0	3 (1.2)	2 (0.8)	0
Fatigue	1 (0.4)	1 (0.4)	0	2 (0.8)	2 (0.8)	0
Nervous system disorders	1 (0.4)	1 (0.4)	0	7 (2.9)	4 (1.6)	0
Spinal cord compression	0	0	0	2 (0.8)	2 (0.8)	0
Investigations	0	0	0	4 (1.6)	3 (1.2)	0
Aspartate aminotransferase increased	0	0	0	2 (0.8)	1 (0.4)	0

Source: Table S.6.4.2.1

MedDRA Version 26.0. CTC Version 5.0.

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

Table 72. Drug-related Adverse Events Leading to Discontinuation in All Treated Subjects in Any Treatment

System Organ Class (%) Preferred Term (%)	Nivolumab SC N = 247			Nivolumab IV N = 245		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**10 (4.0)**	**6 (2.4)**	**0**	**12 (4.9)**	**9 (3.7)**	**0**
Respiratory, thoracic and mediastinal disorders	5 (2.0)	1 (0.4)	0	2 (0.8)	1 (0.4)	0
Pneumonitis	5 (2.0)	1 (0.4)	0	1 (0.4)	0	0
Immune-mediated lung disease	0	0	0	1 (0.4)	1 (0.4)	0
Cardiac disorders	1 (0.4)	1 (0.4)	0	0	0	0
Myocarditis	1 (0.4)	1 (0.4)	0	0	0	0
Gastrointestinal disorders	1 (0.4)	1 (0.4)	0	0	0	0
Pancreatitis	1 (0.4)	1 (0.4)	0	0	0	0
Hepatobiliary disorders	1 (0.4)	1 (0.4)	0	1 (0.4)	1 (0.4)	0
Immune-mediated hepatitis	1 (0.4)	1 (0.4)	0	0	0	0
Hepatotoxicity	0	0	0	1 (0.4)	1 (0.4)	0
Immune system disorders	1 (0.4)	1 (0.4)	0	0	0	0
Hypersensitivity	1 (0.4)	1 (0.4)	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.4)	1 (0.4)	0	2 (0.8)	2 (0.8)	0
Muscular weakness	1 (0.4)	1 (0.4)	0	0	0	0
Myositis	0	0	0	2 (0.8)	2 (0.8)	0
Endocrine disorders	0	0	0	1 (0.4)	0	0
Hypophysitis	0	0	0	1 (0.4)	0	0
Investigations	0	0	0	3 (1.2)	3 (1.2)	0
Alanine aminotransferase increased	0	0	0	1 (0.4)	1 (0.4)	0
Aspartate aminotransferase increased	0	0	0	2 (0.8)	1 (0.4)	0
Transaminases increased	0	0	0	1 (0.4)	1 (0.4)	0
Metabolism and nutrition disorders	0	0	0	1 (0.4)	1 (0.4)	0
Diabetic ketoacidosis	0	0	0	1 (0.4)	1 (0.4)	0
Nervous system disorders	0	0	0	2 (0.8)	1 (0.4)	0
Ischaemic stroke	0	0	0	1 (0.4)	1 (0.4)	0
Neuropathy peripheral	0	0	0	1 (0.4)	0	0

AEs leading to dose delay

Table 73. Adverse Events Leading to Dose Delay in ê 1% of All Treated Subjects in Any Treatment

System Organ Class (%) Preferred Term (%)	Nivolumab SC N = 247			Nivolumab IV N = 245		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**85 (34.4)**	**42 (17.0)**	**0**	**116 (47.3)**	**53 (21.6)**	**0**
Infections and infestations	21 (8.5)	4 (1.6)	0	42 (17.1)	6 (2.4)	0
COVID-19	11 (4.5)	0	0	23 (9.4)	1 (0.4)	0
Respiratory tract infection	2 (0.8)	0	0	3 (1.2)	0	0
Urinary tract infection	1 (0.4)	1 (0.4)	0	4 (1.6)	2 (0.8)	0
Metabolism and nutrition disorders	15 (6.1)	7 (2.8)	0	16 (6.5)	8 (3.3)	0
Hyperglycaemia	5 (2.0)	3 (1.2)	0	6 (2.4)	3 (1.2)	0
Decreased appetite	3 (1.2)	0	0	1 (0.4)	1 (0.4)	0
Hypoalbuminaemia	3 (1.2)	1 (0.4)	0	1 (0.4)	0	0
Gastrointestinal disorders	13 (5.3)	3 (1.2)	0	13 (5.3)	4 (1.6)	0
Diarrhoea	5 (2.0)	1 (0.4)	0	6 (2.4)	1 (0.4)	0
Investigations	13 (5.3)	4 (1.6)	0	21 (8.6)	6 (2.4)	0
Blood creatinine increased	7 (2.8)	1 (0.4)	0	4 (1.6)	0	0
Aspartate aminotransferase increased	2 (0.8)	1 (0.4)	0	7 (2.9)	2 (0.8)	0
Alanine aminotransferase increased	1 (0.4)	0	0	7 (2.9)	2 (0.8)	0
Blood bilirubin increased	1 (0.4)	0	0	3 (1.2)	0	0
Platelet count decreased	0	0	0	3 (1.2)	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	13 (5.3)	5 (2.0)	0	13 (5.3)	3 (1.2)	0
Pneumonitis	5 (2.0)	2 (0.8)	0	5 (2.0)	0	0
Cough	2 (0.8)	0	0	4 (1.6)	0	0
General disorders and administration site conditions	9 (3.6)	2 (0.8)	0	18 (7.3)	6 (2.4)	0
Asthenia	3 (1.2)	1 (0.4)	0	6 (2.4)	3 (1.2)	0
Fatigue	3 (1.2)	0	0	6 (2.4)	1 (0.4)	0
Blood and lymphatic system disorders	8 (3.2)	5 (2.0)	0	12 (4.9)	8 (3.3)	0
Anaemia	6 (2.4)	3 (1.2)	0	11 (4.5)	7 (2.9)	0
Skin and subcutaneous tissue disorders	6 (2.4)	3 (1.2)	0	7 (2.9)	4 (1.6)	0
Rash	2 (0.8)	1 (0.4)	0	5 (2.0)	2 (0.8)	0
Endocrine disorders	3 (1.2)	1 (0.4)	0	6 (2.4)	2 (0.8)	0
Hypothyroidism	2 (0.8)	0	0	3 (1.2)	0	0
Injury, poisoning and procedural complications	2 (0.8)	0	0	7 (2.9)	3 (1.2)	0
Femur fracture	0	0	0	3 (1.2)	2 (0.8)	0
Investigations	9 (3.6)	3 (1.2)	0	16 (6.5)	3 (1.2)	0
Blood creatinine increased	4 (1.6)	0	0	4 (1.6)	0	0
Aspartate aminotransferase increased	2 (0.8)	1 (0.4)	0	5 (2.0)	1 (0.4)	0
Alanine aminotransferase increased	1 (0.4)	0	0	6 (2.4)	2 (0.8)	0
Gastrointestinal disorders	7 (2.8)	0	0	4 (1.6)	1 (0.4)	0
Diarrhoea	4 (1.6)	0	0	3 (1.2)	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	7 (2.8)	2 (0.8)	0	6 (2.4)	0	0
Pneumonitis	5 (2.0)	2 (0.8)	0	5 (2.0)	0	0
Skin and subcutaneous tissue disorders	6 (2.4)	3 (1.2)	0	7 (2.9)	4 (1.6)	0
Rash	2 (0.8)	1 (0.4)	0	5 (2.0)	2 (0.8)	0
Blood and lymphatic system disorders	3 (1.2)	1 (0.4)	0	4 (1.6)	3 (1.2)	0
Anaemia	3 (1.2)	1 (0.4)	0	3 (1.2)	2 (0.8)	0
Endocrine disorders	3 (1.2)	1 (0.4)	0	6 (2.4)	2 (0.8)	0
Hypothyroidism	2 (0.8)	0	0	3 (1.2)	0	0
General disorders and administration site conditions	2 (0.8)	0	0	9 (3.7)	4 (1.6)	0
Fatigue	2 (0.8)	0	0	5 (2.0)	1 (0.4)	0
Metabolism and nutrition disorders	2 (0.8)	2 (0.8)	0	7 (2.9)	5 (2.0)	0
Hyperglycaemia	0	0	0	4 (1.6)	2 (0.8)	0

Source: Table S.6.4.2.4

MedDRA Version 26.0. CTC Version 5.0.

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

Updated safety data (DCO: 21-Feb-2024)

A summary of safety data with the latest DCO that was provided during the procedure is shown below.

Table 74. Summary of Safety - All Treated Subjects in CA20967T (21-Feb-2024 data cutoff)

	Number of Subjects (%)	
Safety Parameters	**Nivo SC (N = 247)**	**Nivo IV (N = 245)**
Deaths (Any Time)	102 (41.3)	88 (35.9)

Safety Parameters	Number of Subjects (%)			
	Nivo SC (N = 247)		Nivo IV (N = 245)	
Primary Reason for Death				
Disease	75 (30.4)		71 (29.0)	
Study Drug Toxicity	3 (1.2)		2 (0.8)	
Cardiovascular disease	4 (1.6)		3 (1.2)	
Unknown	1 (0.4)		4 (1.6)	
Other[a]	19 (7.7)		8 (3.3)	
Deaths within 30 days of last dose	16 (6.5)		12 (4.9)	
Primary Reason for Death				
Disease	8 (3.2)		9 (3.7)	
Cardiovascular Disease	3 (1.2)		1 (0.4)	
Other	5 (2.0)		2 (0.8)	
Deaths within 100 days of last dose	53 (21.5)		42 (17.1)	
Primary Reason for Death				
Disease	35 (14.2)		32 (13.1)	
Study Drug Toxicity	2 (0.8)		1 (0.4)	
Cardiovascular Disease	3 (1.2)		2 (0.8)	
Unknown	1 (0.4)		0	
Other	12 (4.9)		7 (2.9)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	76 (30.8)	58 (23.5)	82 (33.5)	62 (25.3)
Drug-related SAEs	20 (8.1)	19 (7.7)	20 (8.2)	19 (7.8)
All-causality AEs leading to DC	31 (12.6)	23 (9.3)	34 (13.9)	24 (9.8)
Drug-related AEs leading to DC	11 (4.5)	7 (2.8)	13 (5.3)	9 (3.7)
All-causality AEs	230 (93.1)	99 (40.1)	231 (94.3)	114 (46.5)
Drug-related AEs	152 (61.5)	29 (11.7)	161 (65.7)	42 (17.1)
≥ 5% Drug-related AEs in Any Treatment				
Pruritus	39 (15.8)	1 (0.4)	49 (20.0)	0
Hypothyroidism	22 (8.9)	0	25 (10.2)	0
Rash	17 (6.9)	1 (0.4)	20 (8.2)	2 (0.8)
Asthenia	14 (5.7)	1 (0.4)	10 (4.1)	2 (0.8)
Diarrhea	13 (5.3)	0	15 (6.1)	1 (0.4)
Fatigue	12 (4.9)	0	28 (11.4)	5 (2.0)
Aspartate aminotransferase increased	10 (4.0)	1 (0.4)	16 (6.5)	4 (1.6)
Alanine aminotransferase increased	9 (3.6)	0	18 (7.3)	6 (2.4)
Blood creatinine increased	8 (3.2)	0	13 (5.3)	0
Arthralgia	14 (5.7)	0	27 (11.0)	1 (0.4)
Anaemia	11 (4.5)	2 (0.8)	15 (6.1)	3 (1.2)
Blood TSH increased	7 (2.8)	0	13 (5.3)	0
All-causality Select AEs by Category				
Skin	68 (27.5)	4 (1.6)	77 (31.4)	4 (1.6)
Endocrine	40 (16.2)	6 (2.4)	52 (21.2)	3 (1.2)
Gastrointestinal	30 (12.1)	1 (0.4)	44 (18.0)	1 (0.4)
Hepatic	43 (17.4)	14 (5.7)	55 (22.4)	14 (5.7)
Renal	34 (13.8)	4 (1.6)	51 (20.8)	3 (1.2)
Pulmonary	12 (4.9)	4 (1.6)	10 (4.1)	3 (1.2)
Hypersensitivity/Infusion Reactions	3 (1.2)	1 (0.4)	10 (4.1)	0
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Drug-related Select AEs by Category				
Skin	60 (24.3)	4 (1.6)	67 (27.3)	3 (1.2)

Safety Parameters	Number of Subjects (%)			
	Nivo SC (N = 247)		Nivo IV (N = 245)	
Endocrine	31 (12.6)	2 (0.8)	44 (18.0)	3 (1.2)
Gastrointestinal	15 (6.1)	0	17 (6.9)	1 (0.4)
Hepatic	23 (9.3)	8 (3.2)	31 (12.7)	10 (4.1)
Pulmonary	12 (4.9)	4 (1.6)	8 (3.3)	2 (0.8)
Renal	8 (3.2)	1 (0.4)	14 (5.7)	0
Hypersensitivity/Infusion Reactions	1 (0.4)	1 (0.4)	7 (2.9)	0
Drug-related Local Site Reactions within 100 Days of Last Dose[b]				
≥ 2 subjects AEs in Any Treatment	18 (7.3)	0	5 (2.0)	0
Injection site erythema	6 (2.4)	0	0	0
Application site pain	2 (0.8)	0	0	0
Injection site reaction	2 (0.8)	0	0	0
Injection site edema	2 (0.8)	0	0	0
Infusion related reaction	0	0	5 (2.0)	0
Drug-Related AEs in the Broad SMQ of Anaphylactic Reactions within 100 days of follow up				
≥ 5% AEs in Any Treatment				
Pruritus	40 (16.2)	1 (0.4)	49 (20.0)	0
Rash	17 (6.9)	1 (0.4)	20 (8.2)	2 (0.8)
All-causality Non-endocrine IMAEs within 100 days of last dose where Immune Modulating Medication was Initiated by Category				
Rash	18 (7.3)	2 (0.8)	15 (6.1)	3 (1.2)
Diarrhea/Colitis	8 (3.2)	1 (0.4)	7 (2.9)	0
Hepatitis	9 (3.6)	7 (2.8)	18 (7.3)	12 (4.9)
Pneumonitis	7 (2.8)	3 (1.2)	7 (2.9)	2 (0.8)
Nephritis and Renal Dysfunction	4 (1.6)	0	2 (0.8)	0
Hypersensitivity	1 (0.4)	0	2 (0.8)	0
All-causality Endocrine IMAEs within 100 days of last dose by Category				
Hypothyroidism/Thyroiditis	24 (9.7)	0	27 (11)	1 (0.4)
Hyperthyroidism	3 (1.2)	0	11 (4.5)	0
Adrenal Insufficiency	6 (2.4)	2 (0.8)	3 (1.2)	0
Diabetes Mellitus	1 (0.4)	1 (0.4)	3 (1.2)	2 (0.8)
Hypophysitis	0	0	3 (1.2)	2 (0.8)
All-causality OESIs within 100 days of last dose by Category				
Myositis/Rhabdomyolysis	0	0	3 (1.2)	3 (1.2)
Uveitis	1 (0.4)	1 (0.4)	0	0
Myocarditis	1 (0.4)	1 (0.4)	0	0
Pancreatitis	1 (0.4)	1 (0.4)	1 (0.4)	0

MedDRA Version 26.1. CTC Version 5.0.

Note: Includes events reported between first dose and 30 days after last dose of study therapy except otherwise indicated.

[a] Other reasons for death (any time), by subject; new events of death reported post DBL for the primary CSR are underlined. These events were not considered to be related to the study drug per Investigator's assessment, but rather to underlying disease or its complications and/or comorbidities.

- Nivo SC:
  - suicide (n=1), acute respiratory failure (n=1), shortness of breath (n=1), delirium (n=1), diabetic ketoacidosis (n=1), multi-organ failure (n=1), hyperkalemia (n=1), covid-related pneumonia (n=1), acute respiratory insufficiency (n=1), left lung base pneumonia (n=1), intraparenchymal hemorrhage (n=1), hip fracture related complications (n=1)
  - sars-cov2 positive bilateral pneumonia (n=1), pneumonia and progressive disease (n=1), pneumonia (n=1), acute kidney failure (n=1), covid-19 infection (n=1), septicemia, pleural effusion, and disease (n=1), klebsiella pneumoniae biliary sepsis (n=1)
- Nivo IV:

- upper GI bleeding (n=1), acute diverticulitis (n=1), perforation of thin intestinal wall (no colitis reported) (n=1), multi-organ failure (n=1), kidney failure (n=1)
- acute respiratory failure (n=1), AE unrelated to study drug (acute renal insufficiency) (n=1), respiratory failure (n=1)

[b] Local injection- or infusion-site reactions adverse events include PTs under SOC of "General disorders and administration site conditions" which contain the words of "Administration site", "Injection site", "Puncture site", "Infusion site", and PTs under SOC of "Injury, poisoning and procedural complications" which contains the words "Injection related reaction" or "Infusion related reaction." For Study CA20967T, PTs containing the word "Application site" have also been included since the events were reported in reference to local injection reactions.

2.6.8.10. Post marketing experience

Not applicable

2.6.9. Discussion on clinical safety

The pivotal safety data supporting this extension is based on all 492 treated subjects receiving at least one dose of nivolumab SC (n = 247) or nivolumab IV (n = 245) in the pivotal Phase 3 Study CA20967T, with a data cut-off of 24-Jul-2023. The minimum follow-up was 8 months, and the median follow-up was around 10 months. Although no major differences are expected in this trial, these data might be of interest for other claimed indications where exposure to nivolumab can be significantly longer.

The mean duration of therapy for the nivo SC arm and the nivo IV arm was 7.31 months and 8.23 months, respectively. A difference of 0.5 months between both arms was expected due to the differences in posology (Q4W vs Q2W, respectively). Still, the duration of therapy seems to be slightly higher in the nivo IV arm, and this could be explained due to the higher percentage of dose delays compared with the nivo SC arm (54.7% of patients in the nivo IV arm had at least one dose delayed compared to 36.0% in the nivo SC arm). Of note, both the length of dose delay and the reasons for dose delay were similar between both arms.

The proportion of patients who reported an AE during the trial was similar between both treatment arms (93.1% in the nivo SC arm vs 93.5% in the nivo IV arm). By SOC, only gastrointestinal disorders were slightly more common in the SC arm, whereas all the other AEs by SOC were more common in the IV arm, with the highest differences observed for: investigations (17.4% difference), nervous system disorders (10.7% difference) and musculoskeletal and connective tissue disorders (10.5% difference). By PT, constipation (7.7% vs 6.1%) and asthenia (13.0 vs 9.4%) were more common in the SC arm compared with the nivo IV arm, however no differences >10% were observed between both arms.

In the nivo SC arm, G3-4 AEs reported in ≥2% of patients were anemia (5.7%), hyperglycemia and hyperkalemia (2.4% each) and dyspnea (2.0%); while in the nivo IV arm, the most common G3-4 AEs were anemia (8.6%), hypercalcemia (2.9%), fatigue, hyperglycemia and hyponatremia (2.0% each). Pneumonitis, immune-mediated hepatitis and adrenal insufficiency were the three most frequently reported drug-related G3-4 AEs in the SC arm, compared to anemia and increased AST and ALT in the IV arm.

A higher proportion of patients had died by the time of the DCO in the nivo SC arm (29.6%), compared with 24.5% in the nivo IV arm. In both arms, the primary reason for death was disease progression (21.5% in the nivo SC arm vs 19.6% in the nivo IV arm). The percentage of patients who died within 30 and 100 days after the last dose was also higher in the nivo SC compared to nivo IV (6.1% vs 3.7% and 19.0% vs 14.3%, respectively). In total, three deaths due to study drug toxicity were reported in

the nivo SC arm (myopathy, colitis and myocarditis), compared with 1 death in the nivo IV arm (immune-mediated pneumonitis/pneumonia).

There were 12 deaths in the nivo SC arm classified as "other", which included respiratory events (shortness of breath, respiratory failure/insufficiency) but also others such as multi-organ failure and pneumonias. This number is quite high compared to the nivo IV arm, in which 5 deaths due to "other" reasons were reported, and were due to diverse reasons such as GI complications, multi-organ failure or kidney failure.

A similar proportion of patients reported a **SAE** in both arms (27.9% in the nivo SC arm and 29.0% in the nivo IV arm). Pleural effusion and pneumonitis were more commonly reported in the nivo SC arm (1.6% vs 0.4% in the nivo IV arm), and all cases were G3-4 in both arms. On the contrary, pulmonary embolism was more frequently reported in the nivo IV arm (1.6% vs 0% in the nivo SC arm). With regards to drug-related SAEs, pneumonitis was more frequently reported in the nivo SC arm (1.6% vs 0.4% in the nivo IV arm), followed by immune-mediated hepatitis (0.8% vs 0% in the nivo SC arm). In the nivo IV arm, drug-related SAEs were more diverse in nature, including hyponatremia, hypophysitis, ALT and AST increased (0.8% each), among others.

Overall, the incidence of **select AEs** was slightly lower in the nivo SC arm compared to the nivo IV arm. By PT, the select AEs that were slightly more frequent in the nivo SC arm compared with the nivo IV arm were: pneumonitis (4.9% vs 2.4%), rash maco-papular (3.2% vs 2.4%), psoriasis (1.2% vs 0%), adrenal insufficiency (2.0% vs 0.8%) and diabetes mellitus (1.2% vs 0%). Additionally, some hepatic laboratory alterations were also slightly more common in the nivo SC arm, for instance blood alkaline phosphatase increased (5.7% vs 4.9%), gamma-glutamyltransferase increased (3.2% vs 0.8%) and hypertransaminasaemia (2.0% vs 1.2%). No major differences could be detected in the nature or frequency of drug-related select AEs between both arms.

Immune-mediated AEs occurred in a similar incidence in both treatment arms. Among non-endocrine IMAEs in the nivo SC arm, rash was the most frequently reported (6.9%), followed by diarrhoea/colitis and pneumonitis (2.8% each); whereas in the nivo IV arm, hepatitis was the most common IMAE (5.7%) followed by rash (4.9%). Regarding endocrine IMAEs, hypothyroidism was the most common in the nivo SC arm (9.7%), however the incidence of this IMAE in the nivo IV arm was similar (10.2%). Additionally, the incidence of adrenal insufficiency was higher in the nivo SC arm (2.0% vs 0.8%), and 2 out of the 5 cases in the nivo SC arm were G3-4 (compared with none in the nivo IV arm).

In general, the percentage of patients requiring high-dose corticosteroids was higher in the nivo IV arm. At the time of the DCO, only nephritis and hypersensitivity IMAEs had completely resolved. For IMAEs such as rash or diarrhoea, the percentage of resolution was quite high (more than 70%). Nevertheless, for other IMAES, such as hypothyroidism, adrenal insufficiency or pneumonitis, less than 50% of the events were considered as resolved.

Other events of special interest were reported in three patients in each arm. In the nivo SC arm, there was one uveitis (not resolved), one myocarditis (not resolved) and one pancreatitis (resolved), and all of them were Grade 3 or Grade 4 at some point in time. In the nivo IV arm, there were two myositis (resolved) that were G3 or 4 at some point, and one pancreatitis (resolved).

A higher proportion of subjects in the nivo SC arm were reported with local injection site reactions compared with subjects in the nivo IV arm, regardless of causality. Nevertheless, no Grade 3-5 events were reported.

The proportion of patients who suffered an **AE that led to discontinuation** was similar in both treatment arms (10.1% vs 11.8%). A higher proportion of patients in the nivo IV arm had an AE that led to a dose delay (47.3%) compared to the nivo SC arm (34.4%), however it must be taken into

account that nivo IV was administered Q2W whereas nivo SC was administered Q4W, therefore the chances of having a dose delayed were higher in the IV arm. In both arms, infections were the most common cause of dose delay, especially in the nivo IV arm (17.1% vs 8.5% in the nivo SC arm).

Overall, the safety profile of both nivolumab formulations seems to be consistent across different subgroups (age, sex, race and region). Even though it seems that in the nivo SC arm, elderly patients (≥ 75 years) have a higher incidence of fatal SAEs and life-threatening SAEs, the sample size is too small to draw definitive conclusions.

On treatment worst alterations of laboratory parameters were in general higher in the nivo IV arm compared to the nivo SC arm, nevertheless the proportion of G3-4 alterations was overall low. Data regarding laboratory alterations from Study CA2096T is overall consistent with the pooled nivo dataset of nivolumab IV monotherapy. No major differences could be identified between both arms with regards to serum chemistry alterations (liver, kidney and thyroid function tests).

The incidence of ADA was higher in the nivo SC arm (22.8%) compared with the nivo IV arm (8.8%). Of all treated subjects evaluable for ADA in the nivolumab SC arm, local site reaction AEs were reported in a greater proportion of ADA positive subjects compared to ADA negative subjects. Nevertheless, the incidence of AEs in the broad SMQ of anaphylactic reaction were overall similar, independently of whether the patient was nivo ADA positive or nivo ADA negative. Of note, it seems that patients with anti-rHuPH20 antibodies have a higher incidence of AEs in the broad SMQ of anaphylactic reaction compared with rHuPH20 ADA negative patients, however the sample size is too small to draw conclusions.

Considering that at the time of the first DCO, approximately 35% of patients were still on treatment, the MAH was asked to provide an updated table of key safety results with the second DCO. Overall, frequencies of AEs, including IMAES and OESIS, was very similar to the previous DCO. Even though no new deaths due to study drug toxicity were reported during this period, seven new deaths due to "other" causes were reported in the nivo SC arm, and most of them were infection related (pneumonia, covid-19, sepsis). On the other hand, in the nivo IV arm, three new deaths were due to "other" causes, two of which were due to respiratory failures, and the last one due to kidney failure.

Overall, the safety profile of nivolumab was consistent with the one previously observed in other nivolumab studies, and no new safety concerns were identified in this study. However, the safety data obtained with the nivolumab subcutaneous formulation is still limited and, although no relevant differences, in terms of toxicity, are expected with the subcutaneous administration to the amount of accumulative data we have with the intravenous formulation, this will need to be confirmed with post-marketing data and any further studies that might be performed.

Product information

Considering that the safety profiles of nivo SC and nivo IV are similar, it was agreed not to pool SC and IV data in section 4.8 of the SmPC. Nevertheless, the ADR of "injection site reaction" has been added with frequency "common", as it was reported in 7% of patients in the nivo SC arm vs 0% in the nivo IV arm. This is adequately reflected in the product information.

2.6.10. Conclusions on the clinical safety

The overall safety profile of nivolumab was consistent with the safety profile previously observed in other nivolumab studies, and no new safety concerns were identified in this study. No changes in the safety concerns, PhV plan and RMM were included in this procedure.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 75. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin adverse reactions [ARs], and other immune-related adverse reactions [irARs]) Severe infusion reactions (IV only)
Important potential risks	Embryofetal toxicity Immunogenicity Risk of GVHD with nivolumab after allogeneic haematopoietic stem cell transplant (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 (IV only)[a]

[a] This safety concern is relevant to paediatric indications approved for nivolumab IV only.

2.7.2. Pharmacovigilance plan

Table 76. On-going and planned additional pharmacovigilance activities

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				
Study/status	***Summary of objectives***	***Safety concerns addressed***	***Milestones***	***Due dates***
Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557)[a] Voluntary PASS Ongoing	To assess safety and long-term outcomes in children and adolescents	Long-term safety in adolescent patients > 12 years of age (IV only)	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, was amended (29-Sep-2023) 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.

2.7.3. Risk minimisation measures

Summary of risk minimisation measures and pharmacovigilance activities

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: None
Severe infusion reactions (IV only)	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: None
Embryofetal 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: Nivo IV SmPC sections 4.4 and 4.8 Nivo SC 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 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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety in adolescent patients ≥ 12 years of age (IV only)[a]	Routine risk minimisation measures: SmPC Section 4.8, Paediatric Population Additional risk minimisation 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).

[a] This safety concern is relevant to paediatric indications approved for nivolumab IV only.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 40.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Opdivo. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

With this application, the MAH seeks approval of a subcutaneous (SC) formulation of nivolumab (BMS-986298) as an alternative formulation/route of administration to that of nivolumab IV. In this formulation, nivolumab is co-formulated with a non-novel excipient rHuPH20, a recombinant human hyaluronidase PH20 enzyme that facilitates the SC delivery by increasing the dispersion and absorption of the co-administered drug.

The MAH is seeking approval of nivolumab SC for adult solid tumour indications where nivolumab IV is administered as a flat dose of 480 mg Q4W and/or 240 mg Q2W as monotherapy treatment, as

monotherapy maintenance treatment following combination therapy as well as when nivolumab IV is administered in combination with chemotherapy or with cabozantinib.

3.1.1. Available therapies and unmet medical need

SC administration represents an important treatment option for patients with advanced or metastatic cancers and is expected to offer advantages over current nivolumab IV formulation to both healthcare providers (HCPs) and patients. Benefits to HCPs include efficient use of health care resources, with alleviation of IV infusion centre occupancy and decreased time needed for dose preparation. Benefits to patients include reducing administration times (to < 5 minutes from 30 to 60 minutes with IV), alleviate need for IV ports, when no other IV concomitant treatment is needed, and potentially improve patient quality of life with immuno-oncology therapy.

3.1.2. Main clinical studies

The pivotal study for this extension application is CA20967T, an open-label, randomized, Phase 3 study in which 495 patients with advanced or metastatic ccRCC who had progressed after having received prior therapy were randomized into either nivolumab SC 1200 mg Q4W (N=248) or nivolumab IV 3 mg/kg Q2W (N=247).

The primary objective was to demonstrate PK non-inferiority of the subcutaneous administration of nivo vs intravenous administration, while the key secondary objective was ORR non-inferiority (as determined by BICR) between the two formulations. Other secondary efficacy endpoints included DOR, TTR, DCR, PFS and OS, however these were not type-I error controlled.

Efficacy data were presented with a minimum 8-month follow up (DCO: 24-Jul-2023). Additional OS analyses were also submitted with DCO of 21-Feb-2024 (minimum follow-up of 15 months) and 05-Sep-2024 (minimum follow-up of 21 months.

3.2. Favourable effects

- Non-inferiority of nivo SC to nivo IV was concluded with GMR (90% CI) of 2.098 (2.001, 2.200) for Cavgd28 and GMR (90% CI) of 1.774 (1.633, 1.927) for Cminss, as the lower bounds of the 2-sided 90% CIs for both endpoints were above 0.8 (NI margin).
- Nivo SC demonstrated non-inferiority to nivo IV based on the ORR RR =1.33 (95% CI: 0.94, 1.87), as the lower bound of the 95% CI for RR was ≥ 0.60. Of note, ORR per BICR was 24.2% (95% CI: 19.0, 30.0) for the nivo SC arm and 18.2% (95% CI: 13.6, 23.6) for the nivo IV arm.
- Median PFS per BICR was 7.23 months (95% CI: 5.13, 7.49) for the nivo SC arm and 5.65 months (95% CI: 5.29, 7.39) for the nivo IV arm (HR = 1.06 [95% CI: 0.84, 1.34]), therefore no apparent differences in terms of PFS were observed between both arms.

3.3. Uncertainties and limitations about favourable effects

- Median DOR per BICR was 14.49 months (95% CI: 7.52, N.A.) in the nivo SC arm, and the median was not reached in the nivo IV arm (95% CI: 13.90, N.A.), therefore suggesting a longer duration of response in patients treated with nivo IV.
- A higher number of death events were observed in the nivo SC arm (29.4%) compared with the nivo IV arm (24.7%); HR for OS was 1.25 (95% CI: 0.89, 1.77), based on the initial analysis. Updated OS data seem to be more favourable (HR 1.08 [0.83, 1.39]). Considering OS was a

descriptive endpoint, not protected by multiplicity, results should be interpreted with caution. The MAH was recommended to provide final OS results once available (PAM REC).

3.4. Unfavourable effects

The proportion of patients who reported an AE during the trial was similar between both treatment arms (93.1% in the nivo SC arm vs 93.5% in the nivo IV arm). In the nivo SC arm, G3-4 AEs reported in ≥2% of patients were anemia (5.7%), hyperglycemia and hyperkalemia (2.4% each) and dyspnea (2.0%); while in the nivo IV arm, the most common G3-4 AEs were anemia (8.6%), hypercalcemia (2.9%), fatigue, hyperglycemia and hyponatremia (2.0% each).

A higher proportion of patients had died by the time of the DCO in the nivo SC arm (29.6%), compared with 24.5% in the nivo IV arm. Three deaths due to study drug toxicity were reported in the nivo SC arm (myopathy, colitis and myocarditis), compared with 1 death in the nivo IV arm (immune-mediated pneumonitis/pneumonia).

A similar proportion of patients reported a SAE in both arms (27.9% in the nivo SC arm and 29.0% in the nivo IV arm). Also, the incidence of immune-mediated AEs was similar in both treatment arms.

A higher proportion of subjects in the nivo SC arm were reported with local injection site reactions compared with subjects in the nivo IV arm, regardless of causality (7% in the SC arm vs 0% in the IV arm). Nevertheless, no Grade 3-5 events were reported.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Based on the results from Study CA20967T, nivolumab SC has shown to be non-inferior to nivolumab IV for the treatment of 2L+ RCC patients. Together with supportive data from a dose-finding, PK study in multiple tumour types (CA2098KX) and a simulation-based bridging strategy, the MAH is applying for approval of a new formulation of Opdivo SC (nivolumab + rHuPH20) 600 mg.

Non-inferiority of nivo SC to nivo IV was concluded with GMR (90% CI) of 2.098 (2.001, 2.200) for Cavgd28 and GMR (90% CI) of 1.774 (1.633, 1.927) for Cminss. In addition, per the study design, non-inferiority was also shown in terms of ORR. The reported ORR per BICR was 24.2% (95% CI: 19.0, 30.0) for the nivo SC arm and 18.2% (95% CI: 13.6, 23.6) for the nivo IV arm, RR =1.33 (95% CI: 0.94, 1.87).

Other efficacy endpoints were tested to support the non-inferiority claim. However, some uncertainties have been raised in relation to the results of DOR and OS. Median DOR per BICR was 14.49 months (95% CI: 7.52, N.A.) in the nivo SC arm, and the median was not reached in the nivo IV arm (95% CI: 13.90, N.A.), therefore suggesting a longer duration of response in patients treated with nivo IV. A possible explanation for such difference has not been found. In addition, a higher number of death events were observed in the nivo SC arm (29.4%) compared with the nivo IV arm (24.7%); HR for OS was 1.25 (95% CI: 0.89, 1.77). Updated OS results, with longer follow-up have been provided and seem to be more favourable but differences in survival favouring nivo IV vs nivo SC cannot be

completely ruled out at this stage (HR 1.08 [0.83, 1.39]). The MAH is recommended to provide final OS results once available (PAM REC).

Focusing on safety, no relevant differences have been identified for nivo SC in comparison with nivo IV, apart from the expected local reactions on the administration site.

A simulation-based analysis to bridge from nivolumab IV to nivolumab SC for different solid tumour indications in adults have been performed with 1200 mg Q4W SC and 600 mg Q2W SC with the IV flat dose IV Q2W 240 mg and IV Q4W 480 mg. Nivolumab SC administration 1200 mg Q4W and 600 mg Q2W showed consistently higher exposures Cavgd28 and Cminss than both nivolumab IV flat regimens across different solid tumour indications.

Even though the proposed flat dosing regimen does not exceed the safety margin, the higher exposures achieved with Nivolumab SC administration compared to the 3 mg/kg IV Q2W regimen do not guarantee a better efficacy profile considering that the exposure-response efficacy analysis showed a flat exposure relationship. Alternative flat SC dosing regimens with lower dose levels could demonstrate similar benefit-risk balance and could be subject to a future dose optimization strategy.

For this new Opdivo SC formulation, the MAH is applying for all approved indications in solid tumours where nivolumab is administered as monotherapy (including maintenance after combination therapy) or in combination with chemotherapy or cabozantinib as long as the recommended dose for nivolumab is 240 mg administered Q2W and/or 480 mg administered Q4W. Treatment of adolescents (melanoma indications) is also excluded from this extension application. This extrapolation approach is considered acceptable.

3.6.2. Balance of benefits and risks

Non-inferiority of the two formulations was concluded, with a consistent safety profile. The benefit/risk balance of nivo SC can be considered comparable to nivo IV.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable

3.7. Conclusions

The overall benefit/risk balance of OPDIVO is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, OPDIVO 600mg, solution for injection and a new route of administration (subcutaneous use) is favourable in the following indications:

Melanoma

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression.

Adjuvant treatment of melanoma

OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with Stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Non-small cell lung cancer (NSCLC)

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

Renal cell carcinoma (RCC)

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma .

OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma .

Squamous cell cancer of the head and neck (SCCHN)

OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.

Urothelial carcinoma

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

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.

Adjuvant treatment of urothelial carcinoma

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 .

Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer in the following settings:

- first-line treatment of unresectable or metastatic colorectal cancer;
- treatment of metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Oesophageal squamous cell carcinoma (OSCC)

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

Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC)

OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

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.

The CHMP therefore recommends the extensions of the marketing authorisation for OPDIVO subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.