25 January 2024
EMA/93617/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: Nivolumab

Procedure No. EMEA/H/C/003985/X/0132

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

ADA	Anti-drug antibody
AE	Adverse event
AJCC	American Joint Committee on Cancer
AUC(0-336h)	Area under the concentration-time curve from 0 to 336 hours
AUC(TAU)	Area under the concentration-time curve over the dosing interval
BMS	Bristol Myers Squibb
cHL	Classical Hodgkin's lymphoma
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum (or peak) concentration
CMC	Chemistry, Manufacturing, and Controls
CPAs	Critical performance attributes
CPP	Critical process parameter
CRC	Colorectal cancer
CO	Clinical Overview
CSR	Clinical Study Report
Ctau	Observed concentration at the end of a dosing interval
Ctrough	Observed nivolumab serum trough concentration
CTC	Common Terminology Criteria
DBL	Database lock
DC	Discontinuation
dMMR	Mismatch repair deficient
eCTD	Electronic Common Technical Document
OC	Oesophageal cancer
EMA	European Medicines Agency
EPCBs	End of Production Cell Banks
OSCC	Oesophageal squamous cell carcinoma
EU	European Union
FPFV	First patient first visit
GCP	Good Clinical Practice
GEO	Geometric
GEJC	Gastro-oesophageal junction cancer
HCP	Host Cell Protein
HR	Hazard ratio
hrs	Hours
HuMAb	human monoclonal immunoglobulin G4 (IgG4) antibody
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IMAE	Immune-mediated adverse event
IPC	In-process control
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRT	Interactive response technology

IV	Intravenous
LIVCA	Limit of In Vitro Cell Age
MAA	Marketing Authorization Application
MAX	Maximum
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MIN	Minimum
MSI-H	Microsatellite instability-high
N.A.	Not applicable
NAb	Neutralizing antibody
NSCLC	Non-small cell lung cancer
PAs	Performance attributes
PAM	Post-authorization measures
PD-1	Programmed cell death protein 1
PD-L1	Programmed death–ligand 1
PK	Pharmacokinetic
PP	Persistent Positive
PP	Process parameters
PPQ	Process Performance Qualification
PRS	Primary Reference Standard
PT	Preferred term
Q1, Q3	Quartile 1, quartile 3
Q2W	Once every two week dosing
Q4W	Once every four week dosing
RCB	Research cell bank
RCC	Renal cell carcinoma
RFS	Recurrence-free survival
SAE	Serious adverse event
SCCHN	Squamous cell carcinoma of head and neck
SOC	System organ class
SOP	Standard Operating Procedure
T_{max}	Time at which maximum concentration (C_{max}) occurs
TSE	Transmissible spongiform encephalopathy
UC	Urothelial carcinoma
UF/DF	Ultrafiltration/Diafiltration
US	United States
Vd	Volume of distribution
VF	Viral Filtration
WCB	Working Cell Bank
WRS	Working Reference Standard

1. Background information on the procedure

1.1. Submission of the dossier

Bristol-Myers Squibb Pharma EEIG submitted on 26 April 2023 an extension of the marketing authorisation.

Extension application to introduce a new recombinant Chinese hamster ovary (CHO) host cell line and a new manufacturing process of the active substance (Process D).

The RMP (version 34) is updated in accordance. In addition, the MAH took the opportunity to update the Annex II in the PI.

Consequentially, a few manufacturers of the biological active substance have been removed from Annex II of the PI.

- Lonza Biologics, Inc. (USA)

- Samsung Biologics Co. Ltd. (Korea)

- Lotte Biologics USA, LLC (USA)

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, (1) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Not applicable

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 submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The MAH received scientific advice from the CHMP on 22 February 2018 (EMEA/H/SA/2253/6/2018/III) on quality and clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Carolina Prieto Fernandez

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Martin Huber

The application was received by the EMA on	26 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 August 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	14 September 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 October 2023
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	22 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	14 December 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	20 December 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 January 2024
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	25 January 2024
The CHMP adopted a report on similarity of OPDIVO with name of the authorised orphan medicinal product on	25 January 2024

2. Scientific discussion

2.1. Problem statement

Nivolumab drug substance for commercial manufacturing is currently produced using an approved Process C, which utilizes the Master Cell Bank (MCB) that serves as the global clinical and commercial supply of nivolumab.

At the time of the initial marketing authorisation application (MAA) for nivolumab, the MAH committed to establish a new MCB for long-term commercial active substance manufacturing.

In order to meet the quality commitment the MAH has developed a new recombinant Chinese hamster ovary (CHO) host cell line for commercial manufacture of nivolumab, together with an optimized drug substance manufacturing process (Process D). Process D has been developed for the manufacture of nivolumab at the registered manufacturing site, located in Dublin, Ireland, to increase process robustness and enhance overall process yield while maintaining product quality. There is no change to the drug substance (DS) formulation, final concentration, container closure or storage conditions.

With the submission of this Extension Application, there is no change to the drug product (DP) manufacturers, DP formulation and DP manufacturing process and overall flow of the process remains the same between Process C and Process D. The new drug substance manufacturing Process D is intended to replace the current manufacturing Process C for nivolumab.

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.

Opdivo is currently approved in the EU for the treatment of patients with melanoma, non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell cancer of the head and neck (SCCHN), urothelial carcinoma, colorectal cancer (CRC), oesophageal squamous cell carcinoma (OSCC), oesophageal or gastro-oesophageal junction cancer and gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

2.3. Type of Application and aspects on development

This procedure for the nivolumab manufacturing process change is based on data from the Phase 1 biocomparability Study CA2098FC.

Scientific advice

The MAH received scientific advice on 22 February 2018 (EMEA/H/SA/2253/6/2018/III) on quality and clinical aspects and a follow-up scientific advice on 24 February 2021 (EMA/SA/0000074196).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as concentrate for solution for infusion, containing 10 mg/ml of nivolumab as active substance.

Other ingredients are: sodium citrate dihydrate, sodium chloride, mannitol (E421), pentetic acid (diethylenetriaminepentaacetic acid), polysorbate 80 (E433), sodium hydroxide, hydrochloric acid and water for injections.

The product is available in the following presentations: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), 120 mg/12 mL (10 mg/mL) and 240 mg/24 mL (10 mg/mL).

Nivolumab active substance is currently produced in Chinese hamster ovary (CHO) cells using an approved manufacturing Process C, that uses the current approved Master Cell Bank (MCB). At the time of the initial marketing authorisation (MA) for OPDIVO (nivolumab), the applicant Bristol-Myers Squibb Company (BMS) committed to establish a new MCB for long-term commercial active substance manufacturing.

With the intention to fulfil the quality recommendation, BMS has developed a new recombinant CHO host cell line for manufacture of nivolumab, together with an optimised active substance manufacturing Process D, to increase process robustness and enhance overall process yield while maintaining comparable product quality.

2.4.2. Active Substance

2.4.2.1. General Information

The INN name of the active substance 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.

Nothing changes in section 3.2.S.1 in relation with product manufactured with current Process C and new Process D.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturer

This extension application is being submitted to fulfil the quality commitment, and to transition to a new cell line with related active substance manufacturing Process D, for nivolumab manufactured at the currently approved manufacturing site, Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics, located in Ireland.

With this procedure, the following manufacturers of the biological active substance have been removed from Annex II of the Product Information:
- Lonza Biologics, Inc. (USA)
- Samsung Biologics Co. Ltd. (Korea)

- Lotte Biologics USA, LLC (USA).

Description of manufacturing process and process controls

Process D utilises a new cell line, chemically defined media (containing no hydrolysates or animal-sourced components) and has higher yield compared to the current process, Process C.

The overall flow of the unit operations, i.e., vial thaw, inoculum expansion, cell culture, harvest followed by downstream purification remains the same as the current approved process. Nivolumab is manufactured in production bioreactors. One production bioreactor produces one unique active substance batch. Active substance batches are not combined at the active substance stage. There is no change to the active substance formulation, final concentration, or storage condition.

Control of materials

No materials of animal or human origin are used in the nivolumab active substance manufacturing Process D. Compendial and non-compendial materials used in the manufacturing process are purchased from qualified vendors. Non-compendial materials are controlled by specifications for each raw material.

To replace the current cell line, a new cell line for nivolumab active substance manufacturing was established that is clonally derived. Details of the development of this clonal cell line are provided. The same host cell line was used for the new clonal cell line. In the generation of the new Master Cell Bank (MCB), a new expression plasmid was created to produce the light and heavy chains of nivolumab different from the previously used in the original nivolumab marketing authorisation application. The Applicant was requested to explain and justify why a new expression plasmid is required. The Applicant clarified that the introduction of a new expression plasmid is to align this product with others in their platform technology. The MCBs and WCBs are re-evaluated every 5 years and tested according to acceptance criteria.

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 in regard to site-specific equipment or procedures. The IPC strategy utilises a tiered set of in-process action and acceptable ranges to ensure the consistent monitoring and control of the nivolumab active substance process. Critical process parameters (CPPs) and critical performance attribute are well described. The limits for in-process holds were established via a combination of biochemical stability and product vessel microbial ingress (vessel hold time) studies. The clearance of process-related impurities in the manufacturing process is also described.

Process validation

The nivolumab process performance qualification (PPQ) campaign qualified the nivolumab Process D performance for the media preparation, upstream, downstream, buffer preparation, and active substance handling at the approved manufacturing site (BMS-Cruiserath). The PPQ active substance batches produced at manufacturing-scale met release acceptance criteria in effect at the time of PPQ and also conform to the commercial specification described in this application.

Additional data from scale-down and manufacturing-scale studies were obtained to support PPQ.

Manufacturing process development

The in-process control strategy for the nivolumab manufacturing process was established based on toxicological assessments, process development, manufacturing-scale impurity mapping, stability testing, and manufacturing-scale experience. Identification and justification of CPPs, process parameters (PPs), critical performance attributes (CPAs), and performance attributes (PAs) are

described. The biochemical stability of process intermediates was evaluated at scale-down using in-process material from nivolumab Process D produced at intermediate manufacturing-scale.

Development of the manufacturing process was conducted to ensure that critical quality attributes (CQAs) of the molecule were maintained within acceptable ranges. Identification and assessment of potential CQAs is described.

Process D is the process designation given to the next generation active substance manufacturing process which was developed utilising new cell line. Additional changes have been made to increase upstream productivity and downstream throughput. Comparability of active substance quality has been established through release testing, extended characterisation testing, and a stress degradation study of the active substance batches manufactured at BMS-Cruiserath using the next generation Process D with active substance manufactured using the current commercial Process C.

To support the transition of nivolumab active substance commercial manufacturing from Process C to Process D, BMS has conducted both clinical biocomparability and analytical comparability studies. In addition, two further analytical comparability studies are provided: (i) Process D commercial-scale comparability versus Process C, and (ii) Process D commercial-scale comparability versus Process D intermediate-scale. All such data supports the transition from the former Process C to the new Process D which will be used in the future.

Together, the clinical biocomparability data from CA2098FC and the analytical comparability data support the conclusion that the implementation of Process D active substance manufacturing will not have an adverse impact on the quality, safety and efficacy of nivolumab injection active product.

Characterisation

There is no change in section Elucidation of Structure and other Characteristics in relation to product manufactured with previous Process C.

For process-related impurities, all potential impurities are common between Process C with the exception of one, which is a new media additive for Process D. In the case of product-related impurities, there are no modifications, due to the analytical comparability between nivolumab Process D and Process C, and since there are no changes to formulation or protein concentration, such conclusion remains valid for nivolumab Process D.

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 (Process D) are considered acceptable. 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.

Justification of specification

The Applicant justifies the specifications and compares those for Process C with the new Process D. A summary of the chronology of events that established the nivolumab active substance specification prior to Process D is also provided, including the initial Process C Specification and its lifecycle updates.

Analytical procedures

The analytical methods used for control of nivolumab Process D active substance are presented and summaries of each non-compendial method procedure are provided. There are also method histories of

analytical methods used for release and stability testing of nivolumab active substance batches throughout product development.

Batch analysis

The Applicant provided detailed results of analytical testing for the active substance batches manufactured from Processes D batches at intermediate and commercial scales. Min-max ranges for the tested parameters were summarised and they met the specifications for both scales.

Nitrosamines

A "Nitrosamine Risk Assessment Summary - Drug 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 below a level of concern and the risk level is negligible to low and no specific testing is required.

Reference standards of materials

Reference Standard was established as the reference standard prior to PPQ, and served as the initial Working Reference Standard (WRS) for release and stability testing of commercial lots. As the Primary Reference Standard (PRS) it is now used to qualify subsequent WRSs that are used for routine testing. The methods and acceptance criteria for qualification of WRS are presented. Further justification for acceptance criteria for qualification of WRS in regards to quantity/identity and potency was provided upon request. The stability of the WRS will be assessed annually by trend analysis.

The Reference Standard was prepared using Process B active substance; finished product manufactured from this lot was used in pivotal clinical trials for lung cancer and melanoma and thus provides a direct link to clinical experience.

Container closure

There is no change to the container closure system. Process D active substance is stored in the same bioprocess bag as the Process C active substance.

2.4.2.4. Stability

Previous stability studies with Process C supported the current approved active substance shelf-life of 36 months at the recommended storage condition of 2°C to 8°C and protected from light.

Additionally, stability studies have been performed using active substance manufactured using Process D, at the intermediate-scale (one of these batches was used the Process D finished product batch used to establish biocomparability with the CA2098FC clinical study). These studies are also complete, with real-time stability data at the long-term, 2°C to 8°C, condition available through 36 months.

Minor change was observed for photostability studies at room temperature or room light or for temperature cycling studies for Process C active substance, and given that analytical comparability was demonstrated between Process D and Process C, the studies were not repeated for Process D active substance.

To support the transition to Process D, stability studies have been initiated using active substance manufactured using Process D. Samples were stored in 50-mL bioprocess containers representative of the larger bioprocess containers used for active substance storage. Real-time stability data at the long-term (2ºC to 8ºC) are available through 12 months for a number of batches. Accelerated (25ºC/40%RH) stability studies are now complete through 6 months for the same batches. All results met the proposed acceptance criteria through the study period, and all stability profiles align with

those of the historical Process C batches and the Process D batches (intermediate scale) batches. As expected, slight changes were observed at the accelerated conditions. Stress (40ºC/75%RH) stability studies were conducted on the PPQ batches through 3 months, showing greater changes than observed for the accelerated studies, which are not unexpected at the stress condition. However, the stability profiles for all attributes are aligned with those of historical Process C batches, as well as the Process D (intermediate scale) batches.

A protocol for long-term (up to 36 months), accelerated (up to 6 months), and stress (up to 3 months) stability studies is presented. The Applicant commits to the completion of all ongoing long-term stability studies on nivolumab active substance batches according to that protocol. The Applicant also commits to place one batch annually thereafter into the post-approval stability program.

The Applicant requests that the stability data presented here, along with the active substance comparability, support the proposal to retain the currently approved Process C shelf-life of 36 months for Process D active substance manufactured at the approved facility, stored at 2ºC to 8ºC and protected from light. This is accepted.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

Description of the product

There are no changes in this section and the finished product is prepared in these four presentations: 40 mg/4 mL (10 mg/mL), 100 mg/10 mL (10 mg/mL), 120 mg/12 mL (10 mg/mL) and 240 mg/24 mL (10 mg/mL). The four presentations have the same formulation and protein concentration, and are only different in terms of fill volumes and vial sizes. Nivolumab injection is formulated in sodium citrate, sodium chloride, mannitol, pentetic acid, with polysorbate 80.

Pharmaceutical development

For finished product manufacturing, there are no changes to the currently approved nivolumab injection manufacturing process. Therefore, the active substance comparability data also supports that finished product manufactured with Process D active substance is comparable to finished product manufactured with Process C active substance. To further support that finished product quality is not impacted by this change in the active substance manufacturing process, a supplemental analytical comparability evaluation of finished product release data was performed.

The pre-change comparator group consisted of multiple commercial batches manufactured with Process C active substance batches including all four presentations. The post-change data set consists of the PPQ batches (one batch of each presentation) manufactured with Process D active substance (representative of the quality of Process D sourced finished product manufactured at any of the approved finished product manufacturing sites). The comparative release data confirm that Process D sourced finished product is comparable to Process C sourced finished product across all approved finished product manufacturing sites.

Combined with the active substance analytical comparability data and with the finished product comparative stability data, it can be concluded that there is no adverse impact on nivolumab finished product due to the change from Process C active substance to the new Process D active substance.

2.4.3.2. Manufacture of the product and process controls

Manufacturers and manufacturing process

There are no changes, to the finished product manufacturing sites, or finished product manufacturing process with this Process D introduction. There is no change in the formulation and composition.

Process validation/verification

Since the finished product process and formulation are identical for both Process C and Process D sourced finished product, the PPQ was completed at one manufacturing site based on a bracketing approach, with one finished product validation batch per presentation (40 mg/4 mL, 100 mg/10 mL, 120 mg/12 mL, and 240 mg/24 mL). The results were satisfactory without major deviations and they serve to qualify Process D active substance for use to manufacturing all Process D sourced finished product presentations at the approved manufacturing sites.

2.4.3.3. Product specification, analytical procedures, batch analysis

Specifications

The specifications for release and stability testing of Process D sourced finished product are considered acceptable. The specifications for release and stability testing of Process D sourced finished product include tests for appearance, semi-quantitative visible particles, quantity, pH, polysorbate 80, osmolality, particulate matter, extractable volume, purity, identity, potency, host cell protein, bacterial endotoxins, sterility and container closure system.

With the introduction of Process D sourced finished product, the only significant change proposed is to remove endotoxin and sterility from the stability specification (container closure integrity test (CCIT) is performed in lieu of sterility for stability testing, and endotoxin does not increase on stability).

For three attributes, minor changes are made to the specification for Process D sourced finished product compared to the specification for Process C sourced finished product: appearance, quantity and endotoxin (there is no change to the acceptance criteria).

Analytical procedures and reference standards

The analytical procedures used for control of Process D sourced finished product and the method histories are presented.

A new quantity method was validated and is introduced for Process D sourced finished product testing. For all other methods, the existing method validations performed to support testing of Process C sourced finished product also support use of the same methods for Process D sourced finished product.

Batch analyses

The Applicant provided detailed results of analytical testing for the PPQ Process D sourced finished product batches and also the clinical/stability batch used for the biocomparability study.

Nitrosamines

A "Nitrosamine Risk Assessment Summary - Drug Product" is included in the dossier. The conclusion was that the risk level is negligible to low and that there are no actionable risks identified for the presence of nitrosamines in the finished product.

Container closure

No changes are introduced in this section.

2.4.3.4. Stability of the product

The finished product (10 mg/mL) is manufactured using Process C active substance and the results from the completed and on-going studies support a shelf-life of 36 months at the recommended storage condition of 2°C to 8°C, protected from light.

Stability studies of finished product formulated with Process D active substance made at intermediate bioreactor-scale are complete at real-time, long-term, 2°C to 8°C, condition through 36 months.

Since minor changes were observed for Process C, and given that analytical comparability was demonstrated between Process D and Process C active substance, photostability and freeze/thaw temperature cycling studies were not repeated for Process D.

To support the transition to Process D, stability studies have been initiated using PPQ batches of finished product (10 mg/mL) using Process D active substance. Stability studies are being conducted on a few batches of finished product at the long-term (2°C to 8°C), accelerated (25°C/60% RH) and stress (40°C/75% RH) storage conditions. The finished product was packaged in the same packaging components that are used for the current approved commercial product.

At the long-term (2°C to 8°C) and accelerated (25°C/60% RH) storage conditions, stability test results from the finished product PPQ batches meet the acceptance criteria for all attributes through the 3-month and 2-month timepoints, respectively, and are aligned with historical data from finished product manufactured using approved commercial Process C active substance and Process D sourced finished product (using intermediate scale active substance). At the stress condition (40°C/75% RH), the results through the 2-month timepoints are consistent with the historical data from Process C sourced finished product and Process D sourced finished product (using intermediate scale active substance).

A protocol for long-term (up to 36 months), accelerated (up to 6 months), and stress (up to 3 months) stability studies is presented. The Applicant commits to the completion of all ongoing long-term stability studies on nivolumab finished product batches according to that protocol. The Applicant also commits to place one batch annually thereafter into the post-approval stability program for each calendar year that commercial manufacturing occurs. The post-approval stability protocol is presented in the dossier.

The Applicant requests that the stability data presented, along with the finished product comparability studies, support the proposal to retain the currently approved Process C sourced finished product shelf-life of 36 months for Process D sourced finished product, stored at 2ºC to 8ºC and protected from light. This is accepted.

2.4.3.5. Adventitious agents

In order to minimise the risk of transmissible spongiform encephalopathy (TSE), no raw material of animal origin (primary source) was used in the manufacture and cryopreservation of the research cell bank (RCB), MCB and WCB for nivolumab. The nivolumab active substance manufacturing process from WCB does not use any material of animal or human origin.

The TSE risk is considered negligible.

Viral testing and characterization was performed for the cell banks. In the bulks pre-harvest material critical performance attributes were bioburden, mycoplasma, adventitious virus and Minute virus of mice (MVM).

Viral clearance studies were conducted using a panel of model viruses with a wide range of physio-chemical characteristics. Scale-down studies were performed to evaluate the capacity of orthogonal

steps with the capacity to inactivate or remove potential adventitious viral agents. The calculated viral safety assessment is considered acceptable.

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

Nivolumab active substance is currently produced using an approved manufacturing Process C, that uses the approved MCB cell line. At the time of the initial marketing authorisation for OPDIVO (nivolumab), Bristol-Myers Squibb Company (BMS) committed to establish a new MCB for long-term commercial active substance manufacturing. With the intention to fulfil the quality recommendation, BMS has developed a new recombinant CHO host cell line for manufacture of nivolumab, together with an optimised active substance manufacturing Process D, to increase process robustness and enhance overall process yield while maintaining comparable product quality.

The quality dossier submitted is well organised and provides comprehensive information regarding the new development of manufacturing Process D. There were no major objections. Only a few other concerns were raised during the evaluation procedure and were adequately addressed.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

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 have been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

Not applicable

2.5. Non-clinical aspects

No new non-clinical data have been submitted with this application.

2.5.1. Ecotoxicity/environmental risk assessment

Nivolumab is a protein composed of natural amino acids expected to biodegrade in the environment and not be a significant risk. Nivolumab is therefore exempt from preparation of an Environmental Risk Assessment under the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00).

2.6. Clinical aspects

2.6.1. Introduction

The transition of nivolumab drug substance manufacturing Process C to new optimized Process D (using new cell line), is supported by a clinical Phase 1 Study CA2098FC in adjuvant melanoma patients to assess biocomparability between the material from both drug substance manufacturing Process C and Process D.

GCP aspects

The clinical trial was performed in accordance with GCP as claimed by the MAH.

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

- **Tabular overview of clinical studies**

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Study Population	Study Status, Type of Report
Pivotal Clinical Study							
Bioequivalence	Study identifier: CA2098FC (NCT03980314) Report location: Primary CSR: Module 5.3.5.1; Addendum 01 to Primary CSR: Module 5.3.5.1; Erratum to Primary CSR: Module 5.3.5.1	To compare the PK (AUC [0-336h] at Week 1, Day 1 and Week 17, Day 1] of Process D relative to Process C.	Phase 1, randomized, double-blind study. Subjects were randomized 1:1 to nivolumab Process C (Arm A) or Process D (Arm B) and stratified by: - AJCC Staging (8th edition) [Stage IIIa/b/c/d or IV] - Weight categories (< 70 kg, 70 to 90 kg, and > 90 kg	**Arm A**: Nivo Process C 3 mg/kg IV Q2W for Week 1 to Week 17 followed by 480 mg IV Q4W for Week 19 to Week 51 **Arm B**: Nivo Process D 3 mg/kg IV Q2W for Week 1 to Week 17 followed by 480 mg IV Q4W for Week 19 to Week 51 All subjects were treated until recurrence, unacceptable toxicity, withdrawal of consent, completion of 1 year of treatment, or study end, whichever occurred first.	**Total: 261** **- Arm A (Process C):** 129 **- Arm B (Process D):** 132	Subjects ≥ 18 years old with histologically confirmed completely resected Stage IIIa/b/c/d or Stage IV (AJCC Staging, 8th edition) NED melanoma.	**Study status:** Ongoing **Type of reports:** Primary CSR (includes primary endpoint [PK], secondary endpoints [safety, immunogenicity and PK], and exploratory endpoints [efficacy and PK]); Addendum 01 to Primary CSR[a] (includes updated analyses of secondary and exploratory endpoints, excluding PK); Erratum to Primary CSR (includes revised Appendix 2.3 [important protocol deviations])

[a] Note that there were no updates to the immunogenicity results for Process C and Process D in Addendum 01 to the CA2098FC Primary CSR, as no new ADA positive subjects were reported in either arm at the Addendum 01 to the Primary CSR database lock.

Abbreviations: AJCC: American Joint Committee on Cancer; AUC (0-336h): Area under the concentration- time curve from 0 to 336 hours; CSR: clinical study report; IV: intravenous; NED: no evidence of disease; nivo: nivolumab; PK: pharmacokinetics; QxW: every x weeks

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Quantitation of Nivolumab in Human Serum

Method validation

Method ICD 416 is an electrochemiluminescent (ELC) assay and was used to analyse the human serum samples that were obtained for PK evaluations from Study CA2098FC. .

Sample analysis

The quantification of nivolumab in human serum samples from Study CA2098FC was performed by ECL method over a quantitative range of 0.2 µg/mL and 6.5 µg/mL. Each run consisted of one set of standards [0.100 (anchor), 0.200, 0.300, 1.000, 2.500, 4.000, 5.500 and 6.500 µg/mL], two sets of three QCs (0.600, 1.50 and 4.80 µg/mL) and three sets of DQCs (for study samples that required dilution).

Sample analysis started on 01 July 2020 and was completed on 29 April 2021. Overall, 176 out of 178 runs were accepted (98.7%). Two runs were rejected, one due to unacceptable QC samples and the other one due to unacceptable matrix blanks.

Multiple samples were received and analysed according to protocol. From the samples analysed, the majority was reported, but a few samples were not reported or were pending analysis. One sample shipment was received in a thawed condition, and for this reason, those samples were classified as "not reported".

The between-run precision (%CV) and accuracy (%Bias) of the calibration curve standards and of the QCs met the acceptance criteria.

Samples were reassayed per protocol/SOP.

Incurred sample reanalysis was performed on 11.2% of samples, and for 99.8% of samples the relative percent difference (RPD) of the original and repeat results was ≤ ±30%.

No temperature excursions were reported. The maximum storage time was 848 days at -80ºC, and the validated stability of nivolumab for method ICD 416 is 2373 days at -80 °C.

Detection of Anti-Nivolumab Antibodies in Human Serum

Method validation

For ADA analysis, method ICDIM 140 was used. This is a qualitative bridging ECL immunoassay performed using bead extraction with acid dissociation on the MSD platform.

The detection of ADA is based on a three-tiered testing approach (screen, confirm, and titer), as described in the table below.

Table 1: Three-tiered testing for the detection of ADA

Analysis conducted according to	Bioanalytical Plan[11]
PPD Method Number	ICDIM 140 V 2.04 (Appendix B)
PPD Method Title[a]	An Electrochemiluminescence Method for the Detection of Anti-BMS-936558 in Disease State Human Serum
Method Validation Project Code	JRY2[1,2,3,4,5,6,7,8,9,10]
Tier 1: Screening Cut Point (ACP)	Samples with raw responses at or above the assay cut point (1.52*Mean NC Response) are considered potentially positive for anti-BMS-936558 antibodies.
Tier 2: Confirmatory Cut Point (CCP)	Samples are confirmed positive if suppression ≥ 77.2%.
Tier 3: Titer Cut Point (TCP)[b]	Samples are titered until a raw response below the sample TCP (2.11*Mean NC Response) is obtained.
Validated Stability Parameters[c]	
Freeze/Thaw Stability[3]	Ten cycles, thawed at room temperature and frozen at -80°C
Room Temperature Stability[1]	24 hours at room temperature

a Manual modifications to the method:
- Footer, Page 1 of 21: ICDIM 140 Version 2.04
- Critical Reagents Table, Page 6 of 21: Use of Tag-BMS-936558 six months or more after aliquoting is acceptable as long as plate specific method acceptance criteria continue to be met. Assay performance should be monitored closely for trends in NC raw signal to alert reviewer to possible performance issues that warrant aliquoting a new vial.

b Reportable titer = reciprocal of highest dilution detected at or above the sample TCP. If lowest diluted sample tested is below the TCP, the titer result is reported as 1.

c Samples analyzed within validated stability parameters.

Sample analysis

Human serum samples from Study CA2098FC were analysed for anti-BMS-936558 antibodies. Sample analysis started on 02 July 2020 and was completed in 05 April 2021. A total of 62 runs were performed, and 60 of them were accepted (96.8%).

Multiple samples were received. Of those, majority was analysed and reported. Some samples were not analysed per protocol/SOP, and one sample was pending analysis when the report was issued.

Prior to the analysis of study samples, positive and negative control samples were prepared and qualified according to protocol. All negative controls, positive controls, confirmatory controls, titer controls, and study samples were analysed in duplicate wells.

In the screening assay, some samples were identified as "potential positive". Of those several were negative in the confirmatory assay, whilst some were classified as positive. Of those, a few samples had insufficient volume for the titer assay.

Reasons for sample reassay were according to protocol/SOP.

An evaluation of the false positive screening rate was conducted during this study.

Detection of Anti-Nivolumab Neutralising Antibodies in Human Serum

Method validation

Method VSDCBA was used for the detection of BMS-936558 (nivolumab) neutralizing antibodies (NAbs).

It is expected that all anti-drug antibody (ADA) positive clinical serum samples will contain a high concentration of BMS-936558, resulting in potential interference in the NAb assay. In this assay, anti-

BMS-936558 NAb positive controls (low, high positive, and an extraction control containing drug) are analyzed on each plate.

Samples are stored at a nominal temperature of -80 °C (-90 °C to -60 °C) prior to analysis. This assay requires a minimum 100 µL human serum aliquot for analysis. Samples at or below the assay cut point will be characterized as having neutralizing antibodies present.

The plate map is designed in such a way that each single well on preparatory plate will be duplicated on bioassay plate.

All drug controls, positive controls, and study samples are analyzed in duplicate wells. Based on the results of the validation, the acceptance criteria for sample analysis was specified in the protocol.

Sample analysis

Multiple samples from study CA2098FC were received and of those, some samples that were confirmed positive for ADA and had sufficient volume for the titer assay were analysed for NAb.

A total of 6 runs were performed and were acceptable according to pre-defined criteria.

No sample reassay was required and no deviations were reported.

Regarding neutralising activity results, some samples were reported as "not neutralising", whereas for a few samples the result was not recorded (NRR) due to insufficient sample volume for analysis.

Bioequivalence

Study CA2098FC: A Randomized, Double-Blind, Parallel, Phase 1 Study to Compare the Pharmacokinetics of Nivolumab Process D to Nivolumab Process C after Complete Resection of Stage IIIa/b/c/d or Stage IV Melanoma

Methodology

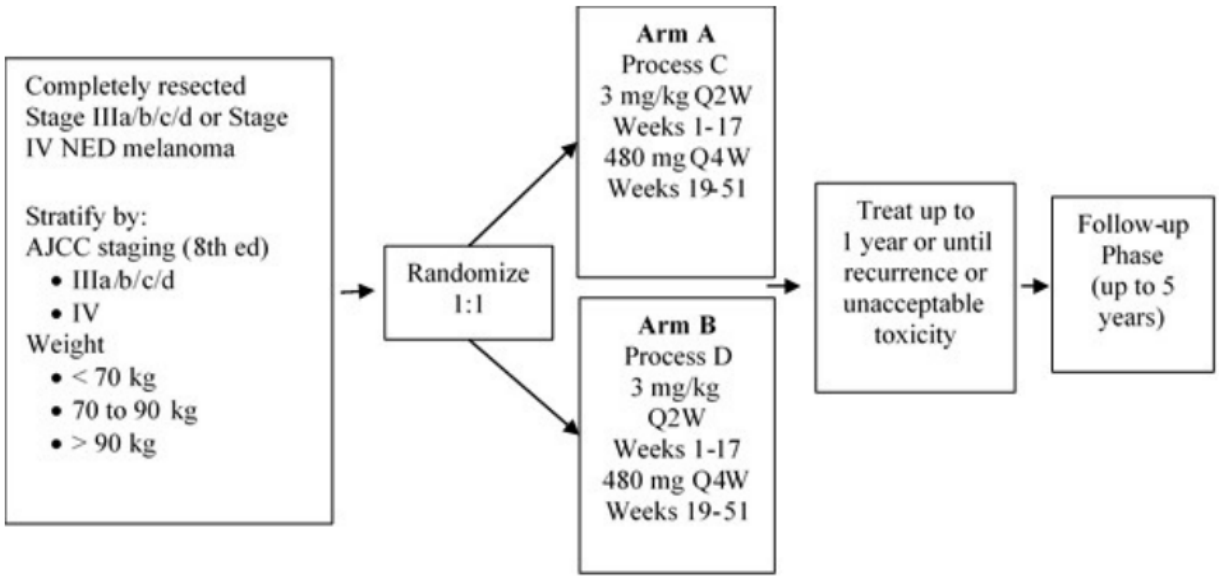
The study was divided into a Screening Period; a Treatment Period consisting of Arm A and Arm B (described below); and a Follow-up Period. The nivolumab drug product used in this study was manufactured from Process C and Process D drug substance, respectively.

- Arm A: Process C 3 mg/kg IV Q2W for Week 1 to Week 17 followed by 480 mg IV Q4W for Week 19 to Week 51
- Arm B: Process D 3 mg/kg IV Q2W for Week 1 to Week 17 followed by 480 mg IV Q4W for Week 19 to Week 51

Subjects were randomly assigned within stratified AJCC Staging (8th edition) [Stage IIIa/b/c/d or IV] and weight categories (< 70 kg, 70 to 90 kg, and > 90 kg) in a 1:1 ratio to receive either Process C or Process D. Overall, 129 subjects were randomized to Arm A (Process C), and 132 subjects were randomized to Arm B (Process D).

All subjects were treated until recurrence of disease, unacceptable toxicity, or subject withdrawal of consent, with a maximum of 1 year of treatment, or study termination by the Sponsor, whichever occurred first. The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



This study was conducted at 32 investigational sites in 13 countries (Argentina, Australia, Brazil, Chile, France, Ireland, Italy, Mexico, New Zealand, Poland, Romania, Spain, and United States).

The study was initiated on 24-Jun-2019 and is still ongoing.

Objectives and outcomes/endpoints

Primary and secondary objectives and endpoints for study CA2098FC are described below.

Table 2: Primary and secondary objectives and endpoints

Objectives	Endpoints
Primary	
To compare the PK of Process D relative to Process C.	AUC(TAU)(0-336h) at Week 1 Day 1 (after first dose) and AUC(TAU)(0-336h) at Week 17 Day 1 (after multiple doses)
Secondary	
To characterize the PK of Process D and Process C.	Cmax and Ctau at Week 1 Day 1 after first dose Cmax, Ctau, clearance, and volume of distribution at Week 17 Day 1 after multiple doses Ctrough
To assess the immunogenicity of Process D and Process C.	Incidence and frequency of anti-nivolumab antibodies and neutralizing antibodies
To assess the safety and tolerability of Process D and Process C.	Safety (including but not limited to): AEs, SAEs, AEs leading to discontinuation, deaths, and clinical laboratory abnormalities per CTCAE, version 5.0

Test and reference products

Subjects received Process C or Process D nivolumab at a dose of 3 mg/kg as a 30-minute infusion on Day 1 of each treatment cycle Q2W for Week 1 to Week 17 and a flat dose of 480 mg Q4W for Week 19 to Week 51 until recurrence, unacceptable toxicity, withdrawal of consent, completion of 1 year of treatment, or the study ends, whichever occurred first. Subjects received 3 mg/kg dose based on body weight, which was assessed at each visit. All doses were rounded up to the nearest milligram per institutional standard.

There were no dose escalations or reductions of nivolumab allowed. Subjects were dosed no less than 12 days from the previous dose during Q2W cycles and no less than 25 days during Q4W cycles. Pre-medications were not recommended for the first dose of nivolumab.

The investigational products used in this study are summarised below.

Table 3: Details on investigational products used in study CA2098FC

Product Description and Dosage Form	Strength
Nivolumab (BMS-936558-01) Solution for Injection (Process C)	100 mg (10 mg/mL)
Nivolumab (BMS-936558-01) Solution for Injection (Process D)	100 mg (10 mg/mL)

Sampling times

Nivolumab PK blood samples were collected at 0:00 (pre-dose), 0:30 (end of infusion), 4:00, 24:00, 48:00, 96:00 and 168:00 hours after start of nivolumab infusion. ADA blood samples were also collected at pre-dose times (Week 1 Day 1 and Week 17 Day 1).

Additionally, pre-dose PK blood samples and ADA blood samples were collected on Week 3 Day 1, Week 19 Day 1, week 35 Day 1 and Week 51 Day 1 (Table below).

Table 4: Pharmacokinetic and ADA sampling schedule

Study Day of Sample Collection	Event	Time Relative to Start of Nivolumab Infusion (hr:min)	Nivolumab PK Blood Sample	Nivolumab ADA Blood Sample
Week 1 Day 1	Predose	0:00	X	X
	EOI[a]	0:30	X	
		4:00	X	
Week 1 Day 2		24:00	X	
Week 1 Day 3		48:00	X	
Week 1 Day 5		96:00	X[b]	
Week 2 Day 1		168:00	X	
Week 3 Day 1	Predose	0:00	X	X
Week 17 Day 1	Predose	0:00	X	X
	EOI[a]	0:30	X	
		4:00	X	
Week 17 Day 2		24:00	X	
Week 17 Day 3		48:00	X	
Week 17 Day 5		96:00	X[b]	
Week 18 Day 1		168:00	X	
Week 19 Day 1	Predose	0:00	X	X
Week 35 Day 1	Predose	0:00	X	X
Week 51 Day 1	Predose	0:00	X	X

[a] EOI=End of Infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion).

[b] If the collection falls on a weekend or on day(s) when sites are closed, samples can be collected on the day before or after, but they must remain as close to the nominal collection day as possible.

Pharmacokinetic parameters

PK parameters for nivolumab were derived by non-compartmental analysis methods using serum concentration versus time data following the first and last dose administration of nivolumab 3 mg/kg IV Q2W (Week 1, Day 1 and Week 17, Day 1, respectively). Actual times were used for all analyses.

Geometric mean, %CV, N, mean, SD, min, max, and median were presented by treatment group for C_{max}, T_{max}, AUC(0-336h) [AUC(TAU)], and Ctau, after the first dose (Week 1) and after multiple doses (Week 17); for CLT, Vz, AI_AUC, and T-HALF-eff, only after multiple doses (Week 17). AI_AUC was based on the ratio of AUC(TAU) after multiple doses (Week 17) to that after the first dose (Week 1). Ctrough values were summarized separately from the other PK parameters using geometric mean, %CV, N, mean, SD, min, max, and median, across all cycles where predose PK samples were collected. In addition, scatterplots of Ctrough vs week were provided overlaid by the geometric mean values, for each treatment.

Within a dosing interval, the C_{max} and T_{max} were recorded directly from experimental observations. The AUC(TAU) was calculated by log- and linear-trapezoidal summations or linear up/log down method in Phoenix WinNonlin™ (version 8.2).

For the purpose of calculating PK parameters, predose concentrations that were less than the assay's LLOQ and concentrations prior to the first quantifiable concentration that were less than the LLOQ were set to zero, and all other concentrations less than LLOQ were set to missing.

Statistical analysis

A linear fixed effect model with treatment, AJCC staging and weight category (as recorded in the IRT) as fixed effects was fitted to the log-transformed PK parameters AUC(0-336h) at Week 1, Day 1 and at Week 17, Day 1 for use in estimation of effects and construction of CIs. To assess biocomparability of Process D to Process C, point estimates and the 2-sided 90% CIs for treatment differences on the log scale was exponentiated to obtain estimates for ratios of geometric means and respective 90% CIs for nivolumab AUC(0-336h) at Week 1, Day 1 and at Week 17, Day 1 on the original scale. Biocomparability of Process D to Process C was concluded if the 90% CIs for the ratios of geometric means for nivolumab AUC(0-336h) at Week 1, Day 1 and at Week 17, Day 1 are contained within 0.8 to 1.25 limits.

Subject disposition

The enrolment period was approximately 15 months from 24-Jun-2019 to 25-Sep-2020. 341 subjects were enrolled, and 261 subjects were randomized and treated (129 to the nivolumab Process C group and 132 to the nivolumab Process D group).

Table 5: Summary of demographic characteristics

	Number of Subjects (%)		
	Process C N = 129	Process D N = 132	Total N = 261
AGE (YEARS)			
N	129	132	261
MEAN	55.8	54.2	55.0
MEDIAN	57.0	57.0	57.0
MIN , MAX	25 , 81	20 , 87	20 , 87
SD	13.6	15.4	14.5
AGE CATEGORIZATION 1 (%)			
< 65 YEARS	88 (68.2)	89 (67.4)	177 (67.8)
>= 65 YEARS	41 (31.8)	43 (32.6)	84 (32.2)
AGE CATEGORIZATION 2 (%)			
< 75 YEARS	123 (95.3)	122 (92.4)	245 (93.9)
>= 75 YEARS	6 (4.7)	10 (7.6)	16 (6.1)
SEX (%)			
MALE	87 (67.4)	78 (59.1)	165 (63.2)
FEMALE	42 (32.6)	54 (40.9)	96 (36.8)
RACE (%)			
WHITE	126 (97.7)	127 (96.2)	253 (96.9)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	1 (0.8)	1 (0.4)
OTHER	3 (2.3)	4 (3.0)	7 (2.7)
WEIGHT (KG)			
N	129	132	261
MEAN	82.1	80.8	81.4
MEDIAN	81.0	78.6	79.7
MIN , MAX	52 , 144	50 , 140	50 , 144
SD	18.5	16.5	17.5
WEIGHT CATEGORIZATION (CRF) (%)			
<70 KG	33 (25.6)	33 (25.0)	66 (25.3)
70 TO 90 KG	65 (50.4)	68 (51.5)	133 (51.0)
>90 KG	31 (24.0)	31 (23.5)	62 (23.8)

Source: Table S.3.2.1

Table 6: Analysis population

Population	Description	Total Number of Subjects
All Enrolled Subjects	All subjects who sign an informed consent form and are registered into the IRT.	341
All Randomized Subjects	All subjects who are randomized to any treatment arm in the study.	261
All Treated Subjects	All subjects who receive at least 1 dose of nivolumab	261
PK Subjects	All treated subjects with available PK concentration-time data.	261
Evaluable PK Subjects	The Evaluable PK Subjects is a subset of the PK Subjects. The Evaluable PK Subjects includes all subjects in the PK Subjects with adequate dosing and adequate PK profiles for accurate estimation of PK parameters. All available derived PK parameter values will be included in the PK data set and reported, but only subjects in the Evaluable PK Population will be included in the summary statistics and statistical analysis.	240[a]
Immunogenicity Evaluable Subjects	All treated subjects who have a baseline and at least 1 post baseline immunogenicity assessment.	241

Source: Table S.2.5 (all enrolled subjects), Table S.2.6A (all randomized subjects), Table S.2.7 (all treated subjects), Appendix 4.6.2 (PK subjects), Table S.9.1 (evaluable PK subjects), Table S.7.10 (ADA Summary)

[a] Numbers of evaluable PK subjects vary for different PK parameters. For primary endpoint AUC(TAU), there are 240 evaluable PK subjects at Week 1, and 195 evaluable PK subjects at Week 17. Numbers of evaluable PK subjects for other PK parameters by treatment group are provided in Table S.9.1.

While 261 patients had available PK concentration-time data, only 240 subjects were considered as PK evaluable patients by the MAH (i.e. subjects with adequate dosing and PK profiles).

Table 7: Summary of reasons for subjects without AUC (TAU) values in the statistical analysis

	Process C N = 127	Process D N = 132	Total N = 259
WEEK 1			
SUBJECTS WITH EVALUABLE AUC(TAU) (%)	121 (95.3)	119 (90.2)	240 (92.7)
SUBJECTS WITHOUT EVALUABLE AUC(TAU) (%)	6 (4.7)	13 (9.8)	19 (7.3)
REASON(%)			
AUC(TAU) EXTRAPOLATION GREATER THAN 30%	4 (3.1)	8 (6.1)	12 (4.6)
INCOMPLETE PROFILE	0	2 (1.5)	2 (0.8)
PROFILE MISSING POTENTIAL Tmax	1 (0.8)	0	1 (0.4)
OTHER*	1 (0.8)	3 (2.3)	4 (1.5)
WEEK 17			
SUBJECTS WITH EVALUABLE AUC(TAU) (%)	93 (73.2)	102 (77.3)	195 (75.3)
SUBJECTS WITHOUT EVALUABLE AUC(TAU) (%)	34 (26.8)	30 (22.7)	64 (24.7)
REASON(%)			
AUC(TAU) EXTRAPOLATION GREATER THAN 30%	11 (8.7)	14 (10.6)	25 (9.7)
INCOMPLETE PROFILE	0	0	0
PROFILE MISSING POTENTIAL Tmax	1 (0.8)	0	1 (0.4)
OTHER*	22 (17.3)	16 (12.1)	38 (14.7)

* Other means not enough PK concentration data for AUC(TAU) to be derived at week 1 or at week 17.
Program Source: BMS_GBS\CA209\WYA33304\Biostatistics\Production\Tables\PA\rt-pk-aucmis.sas 07MAR2023:13:51

Pharmacokinetic results

In the primary analysis performed with treatment, AJCC staging and weight category as fixed effects, AUC(TAU) geometric mean ratios (90% CI) were of 1.012 (0.984, 1.041) and 0.998 (0.951, 1.047) at Week 1, Day 1 and at Week 17, Day 1, respectively (table below).

Table 8: Statistical Analysis of PK parameters

Week 1 Day 1 (N = 240)	PK parameter = AUC(TAU) (ug*h/mL)							
	On Natural Logarithmic Scale						On Original Scale	
TREATMENT AND COMPARISON	ADJUSTED MEAN	STANDARD ERROR	DF	T	Pr > |T|	90% CI	ADJUSTED GEO MEAN	90% CI
Process C (N = 121)	9.464	0.017	235.0	569.76	<.0001	(9.436, 9.491)	12880.910	(12532.409, 13239.101)
Process D (N = 119)	9.476	0.016	235.0	574.50	<.0001	(9.449, 9.503)	13040.487	(12690.088, 13400.561)
Process D vs Process C	0.012	0.017	235.0	0.73	0.4677	(-0.016, 0.040)	1.012	(0.984, 1.041)

Week 17 Day 1 (N = 195)	PK parameter = AUC(TAU) (ug*h/mL)							
	On Natural Logarithmic Scale						On Original Scale	
TREATMENT AND COMPARISON	ADJUSTED MEAN	STANDARD ERROR	DF	T	Pr > |T|	90% CI	ADJUSTED GEO MEAN	90% CI
Process C (N = 93)	10.601	0.031	190.0	347.39	<.0001	(10.551, 10.652)	40184.903	(38208.170, 42263.904)
Process D (N = 102)	10.599	0.028	190.0	378.54	<.0001	(10.553, 10.646)	40104.798	(38290.983, 42004.532)
Process D vs Process C	-0.002	0.029	190.0	-0.07	0.9455	(-0.050, 0.046)	0.998	(0.951, 1.047)

MODEL INFORMATION
Residual Variance Method - Profile
Fixed Effects SE Method - Model-Based
Degrees of Freedom Method - Residual
Fixed Effects - AJCC staging (IRT), Weight category (IRT) and Treatment

Source: refer to CA2098FC Primary CSR Table 9.2-1 and Appendix 8.2.3[6]

An additional analysis was performed with only treatment as a fixed effect. In this analysis, Week 1, Day 1 and Week 17, Day 1 AUC(TAU) geometric mean ratios (90% CI) were of 1.013 (0.983, 1.043) and 1.002 (0.955, 1.051).

Plots of mean (+SD) nivolumab serum concentrations vs time by treatment at Week 1 and Week 17 are presented below.

Figure 2: Mean (+SD) nivolumab serum concentrations vs time by treatment at Week 1

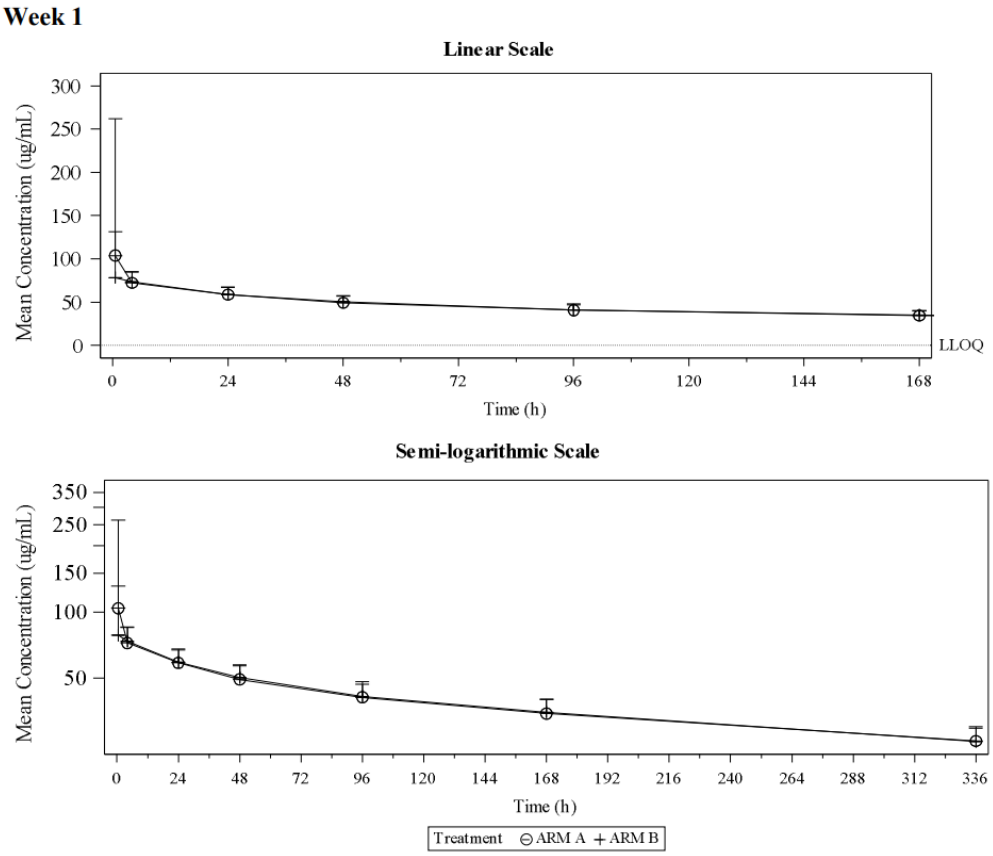


Figure 3: Mean (+SD) nivolumab serum concentrations vs time by treatment at Week 17

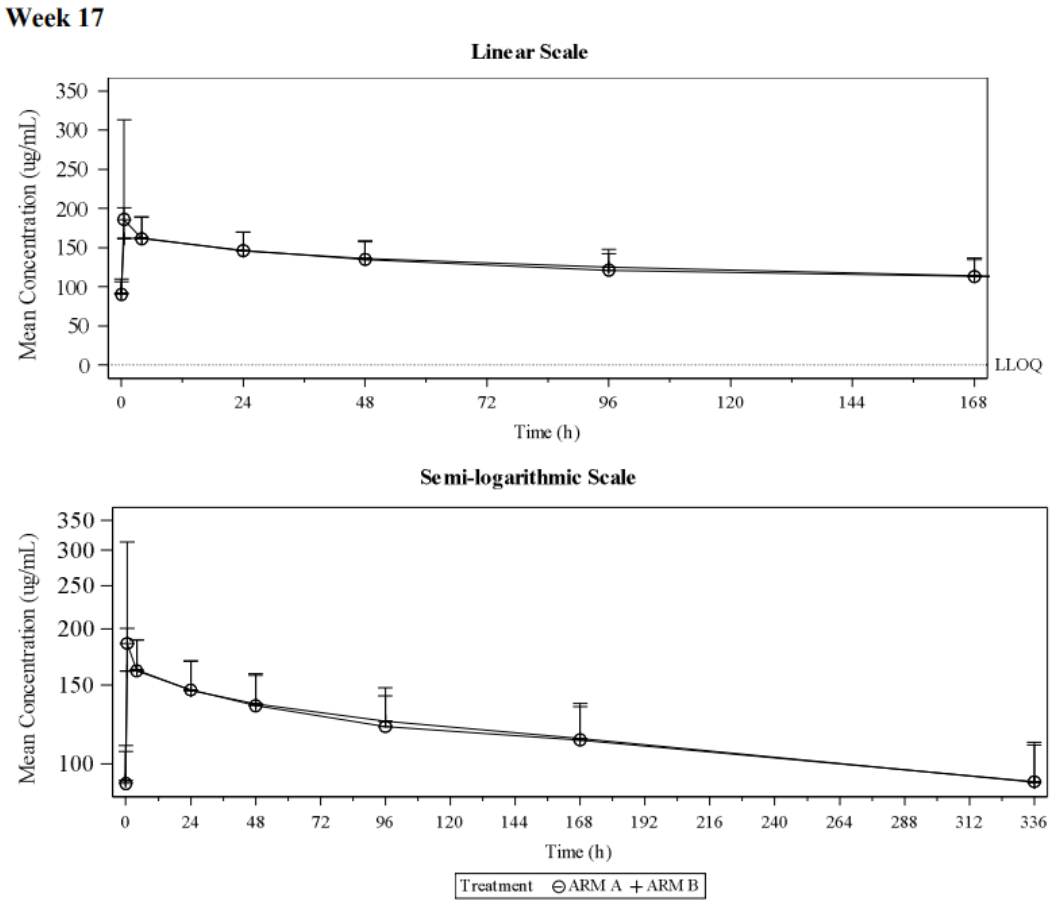


Figure S.4.6.4

Treatment Description: ARM A: Process C, 3 mg/kg Q2W + 480 mg Q4W; ARM B: Process D, 3 mg/kg Q2W + 480 mg Q4W.

Note: < LLOQ = Less than lower limit of quantitation (0.200 µg/mL).

Table 9: Summary of nivolumab PK parameters by treatment on Week 1, Day 1 and Week 17, Day 1

PARAMETER STATISTIC	TREATMENT	
	Process C	Process D
Week 1 Day 1		
Cmax (ug/mL)		
GEO.MEAN [N]	84.6 [125]	78.8 [130]
(%CV)	(139)	(60)
Tmax (h)		
MEDIAN [N]	4.00 [125]	3.92 [130]
(MIN-MAX)	(0.300-21.6)	(0.417-24.1)
AUC(TAU) (ug*h/mL)		
GEO.MEAN [N]	12880 [121]	13046 [119]
(%CV)	(16)	(12)
Ctau (ug/mL)		
GEO.MEAN [N]	25.5 [122]	25.3 [121]
(%CV)	(16)	(16)
Week 17 Day 1		
Cmax (ug/mL)		
GEO.MEAN [N]	178 [105]	167 [117]
(%CV)	(64)	(21)
Tmax (h)		
MEDIAN [N]	4.00 [105]	4.00 [117]
(MIN-MAX)	(0.383-24.7)	(0.450-24.6)
AUC(TAU) (ug*h/mL)		
GEO.MEAN [N]	39282 [93]	39345 [102]
(%CV)	(18)	(19)
Ctau (ug/mL)		
GEO.MEAN [N]	89.4 [94]	88.0 [102]
(%CV)	(21)	(23)
CLT (mL/min)		
GEO.MEAN [N]	0.103 [93]	0.101 [102]
(%CV)	(30)	(35)
T-HALFeff (h)		
MEAN [N]	603 [90]	601 [95]
(SD)	(139.6)	(136.7)
Vz (L)		
GEO.MEAN [N]	4.82 [98]	4.80 [111]
(%CV)	(33)	(55)
AI AUC		
GEO.MEAN [N]	3.04 [88]	2.98 [95]
(%CV)	(20)	(20)

Source: Table S.9.1

Following the first round of assessment, the MAH provided new comparability data including the subjects that were initially excluded due to AUC_{extrap} greater than 30% and profile missing potential T_{max}. A new biocomparability analysis was carried out, which included patients with AUC(TAU) extrapolated greater than 30% (12 patients in Week 1 and 25 patients in Week 17) and profiles with missing T_{max} (1 patient in Week 1 and 1 patient in Week 17). The results of the new biocomparability analysis are shown.

Table 10: Statistical Analysis of BMS-936558 Pharmacokinetic Parameters Expanded PK Participants

Protocol: CA2098FC

Page 1 of 2

Statistical Analysis of BMS-936558 Pharmacokinetic Parameters
Expanded PK Participants

Week 1 Day 1(0-336h)

PK parameter = AUC(TAU) (ug*h/mL)

TREATMENT AND COMPARISON	On Natural Logarithmic Scale						On Original Scale	
	ADJUSTED MEAN	STANDARD ERROR	DF	T	Pr > |T|	90% CI	ADJUSTED GEO MEAN	90% CI
Process C	9.466	0.016	248.0	577.22	<.0001	(9.439, 9.493)	12916.272	(12571.241, 13270.771)
Process D	9.471	0.016	248.0	594.02	<.0001	(9.444, 9.497)	12975.076	(12637.989, 13321.155)
Process D vs Process C	0.005	0.017	248.0	0.27	0.7854	(-0.023, 0.032)	1.005	(0.977, 1.033)

Week 17 Day 1(0-336h) PK parameter = AUC(TAU) (ug*h/mL)

	On Natural Logarithmic Scale						On Original Scale	
TREATMENT AND COMPARISON	ADJUSTED MEAN	STANDARD ERROR	DF	T	Pr > |T|	90% CI	ADJUSTED GEO MEAN	90% CI
Process C	10.602	0.028	216.0	376.78	<.0001	(10.555, 10.648)	40213.616	(38387.142, 42126.994)
Process D	10.597	0.026	216.0	412.58	<.0001	(10.555, 10.639)	40012.666	(38350.448, 41746.930)
Process D vs Process C	-0.005	0.027	216.0	-0.19	0.8528	(-0.050, 0.040)	0.995	(0.952, 1.040)

MODEL INFORMATION
Residual Variance Method - Profile
Fixed Effects SE Method - Model-Based
Degrees of Freedom Method - Residual
Fixed Effects - AJCC staging (IRT), Weight category (IRT) and Treatment

2.6.3. Discussion on clinical pharmacology

Analytical methods ICD 416, ICDIM 140 and VSDCBA were validated to quantitate nivolumab concentrations, detect ADA, and characterise NAb in human serum, respectively. Overall, the applied methods are acceptable according to ICH M10 Guideline, and no major concerns arise.

The MAH was asked to justify why few samples for the quantification of nivolumab and one ADA sample were pending analysis. It was agreed that the overall integrity and validity of the PK analysis for Study CA2098FC are not affected by these few missing data.

Some samples from Study CA2098FC were confirmed positive for ADA and had sufficient volume for the titer assay. Those samples were analysed for neutralising activity, and majority of them were reported as "not neutralising" according to pre-specified criteria. A few samples were not reported due to insufficient sample volume. Thus, there is no evidence of formation of NAb.

Study CA2098FC

Study CA2098FC is a randomized, double-blind, parallel, phase 1 study submitted to assess the biocomparability of Process D vs Process C. Subjects were randomly assigned within stratified AJCC Staging (8th edition) [Stage IIIa/b/c/d or IV] and weight categories (< 70 kg, 70 to 90 kg, and > 90 kg) in a 1:1 ratio to receive either Process C or Process D.

The parallel design is considered adequate due to the long half-life of nivolumab (25 days), as this avoids the long wash-out period of a cross-over design.

The monitoring activities included on-site monitoring visits, un-blinded in-person or remote visits, off-site monitoring visits and central monitoring.

The chosen primary PK parameters were AUC(TAU) after the first dose (Week 1 Day 1) and AUC(TAU) after multiple doses (Week 17 Day 1), and this is in line with the recommendations of the EMA Guideline on similar biological medicinal products containing monoclonal antibodies. Similarly, secondary endpoints were C_{max} and Ctau, and Ctrough. This is acceptable according to the aforementioned Guideline.

Subjects received Process C or Process D nivolumab at a dose of 3 mg/kg as a 30-minute infusion on Day 1 of each treatment cycle Q2W for Week 1 to Week 17 and a flat dose of 480 mg Q4W for Week 19 to Week 51 until recurrence, unacceptable toxicity, withdrawal of consent, completion of 1 year of treatment, or the study ends, whichever occurred first.

Information regarding the manufacturing date, expiry date and certificates of analysis for the investigational products used in study CA2098FC has been provided.

The selection of batches for Process C did not follow a specific criteria, and the choice was based on supply chain availability. Instead, for Process D, a batch that was deemed analytically comparable to Process C was selected. This approach is considered acceptable.

Additionally, in accordance with EMA Clinical pharmacology and pharmacokinetics Q&A Question 7.1, the protein content of the test and reference product should be determined beforehand and analysed using the same bioanalytical method. During the procedure the MAH confirmed that the same analytical method was used.

According to the Guideline on similar biological medicinal products containing monoclonal antibodies, the chosen sampling times should enable the characterisation of the concentration-time profiles both after the first dose and at steady state. Nivolumab was initially infused every 2 weeks, and PK samples were collected up to 336 hours (14 days) after start of nivolumab infusion. Even though these sampling times do not cover the half-life of nivolumab (25 days), this is acceptable considering that they are the longest possible according to the posology of the study treatment.

PK parameters for nivolumab were derived by non-compartmental analysis methods using serum concentration versus time data. Actual times were used for all analyses and this is acceptable according to the EMA Guideline on the Investigation of Bioequivalence. The AUC(TAU) was calculated by log- and linear-trapezoidal summations or linear up/log down method in Phoenix WinNonlin™ (version 8.2).

Population analysed

The enrolment period was approximately 15 months from 24-Jun-2019 to 25-Sep-2020. 341 subjects were enrolled, and 261 subjects were randomized and treated (129 to the nivolumab Process C group and 132 to the nivolumab Process D group).

According to the EMA Guideline on the Investigation of Bioequivalence, for parallel design studies, treatment groups should be comparable in all known variables that may affect the PK of the active substance. This is an essential pre-requisite to give validity to the results from such studies. For this study, demographic characteristics such as sex, age, race and weight were similar between both treatment groups.

Initially, even though 261 patients had available PK concentration-time data, only 240 patients at Week 1 and 195 patients at Week 17 were considered as evaluable PK subject population by the MAH, and thus included in the statistical PK analysis for this bioequivalence study. The reasons for the exclusion of certain patients from the PK analysis were provided by the MAH, however, two reasons for exclusion were considered unacceptable ($AUC_{0\text{-}TAU}$ extrapolated >30% and profile missing potential T_{max}). Therefore, the MAH was asked to repeat the statistical PK analysis, including the aforementioned excluded subjects (see below).

Pharmacokinetic results

In the first analysis, nivolumab Process C and Process D were found to be biocomparable as the AUC(0-336 h) geometric mean ratios (90% CI) were 1.012 (0.984, 1.041) and 0.998 (0.951, 1.047) at Week 1 and Week 17, respectively. However, in order to draw definitive conclusions regarding the bioequivalence of the new nivolumab Process D to the currently approved nivolumab Process C, the MAH was asked to repeat the biocomparability analysis including the subjects with an $AUC_{0\text{-}TAU}$ extrapolated >30% and including profiles missing potential T_{max}.

In this new biocomparability analysis, Process C and Process D were also found to be biocomparable as the AUC(0-336 h) geometric mean ratios (90% CI) were 1.005 (0.977, 1.033) and 0.995 (0.952, 1.040) at Week 1 and Week 17, respectively.

2.6.4. Conclusions on clinical pharmacology

In conclusion, PK results support demonstration of biocomparability between nivolumab Process C and Process D.

2.6.5. Clinical efficacy

2.6.5.1. Main study

Study CA2098FC: A Randomized, Double-Blind, Parallel, Phase 1 Study to Compare the Pharmacokinetics of Nivolumab Process D to Nivolumab Process C after Complete Resection of Stage IIIa/b/c/d or Stage IV Melanoma

Methods

- **Study Participants**

All subjects were required to be ≥ 18 years old of age or age of majority at the time of informed consent and have:

- Either Stage IIIa/b/c/d or Stage IV (AJCC Staging, 8th edition) histologically confirmed melanoma that was completely surgically resected to be eligible. All melanomas, except ocular/uveal melanoma, regardless of primary site of disease were allowed; mucosal melanomas were eligible. Subjects must have been surgically rendered free of disease with negative margins on resected specimens.
  - If Stage III melanoma (whether Stage IIIa, IIIb, IIIc, or IIId) at the time of diagnosis, the subject must have demonstrated clinical or radiographic evidence of regional metastases, either in the regional lymph nodes or locoregional metastases manifesting as satellite or in-transit metastases, or microsatellites discovered at the time of microscopic evaluation of the primary tumor diagnostic biopsy. The pathology report for Stage IIIa, IIIb, IIIc, and IIId must have been reviewed, signed, and dated by the investigator.
  - If Stage IV melanoma, the pathology report confirming negative margins must have been reviewed, dated, and signed by the investigator prior to randomization.
  - For CNS lesion(s) at the time of diagnosis, documentation indicating that there had been complete resection of CNS lesion(s) was sufficient as confirmation of negative margins.
- Complete resection must have been performed within 12 weeks prior to randomization.
- Formalin-fixed paraffin embedded tissue block (preferably obtained within 12 weeks prior to enrollment) or 10 to 20 unstained tumor tissue slides (preferably sectioned within 12 weeks of enrollment). If a minimum of 10 slides was not obtainable, submission of fewer slides was acceptable in some circumstances following discussion with the Sponsor. Slides were sent to a central laboratory for biomarker analysis. Subjects must not have received any intervening systemic anticancer therapy between date that the submitted tumor tissue was obtained and enrollment. Biopsy was excisional, incisional, or core needle.
- Note: Fine needle aspiration was unacceptable for submission. Biopsies of bone lesions that did not have a soft tissue component were also unacceptable for submission.

Imaging studies included CT or MRI scans of the chest, abdomen, pelvis, and all known sites of resected disease in the setting of Stage IIIa/b/c/d or Stage IV disease, and brain MRI or CT (brain CT

was allowable if MRI was contraindicated or if there was no known history of resected brain lesions). Subjects with equivocal lymph nodes (⩾ 10 mm and ≤ 15 mm in a short axis) were eligible if confirmation with histology/cytology was available. If risk of biopsy was too high or biopsy was not feasible, 2 sequential CT or MRI scans, showing no progressive and measurable disease, or PET/CT demonstrating no fluorodeoxyglucose uptake, were acceptable. The second scan must have occurred at least 4 weeks after the initial scan.

- **Treatments**

See section 2.6.2.1

- **Objectives**

See section 2.6.2.1

- **Outcomes/endpoints**

See section 2.6.2.1

Efficacy was assessed using the recurrence-free survival (RFS) endpoint as an exploratory endpoint.

- **Sample size**

Biocomparability of the Process D cell line relative to Process C is concluded if the 90% Cis for the ratio of geometric means for nivolumab AUC(TAU)(0-336h) at Week 1, Day 1 (after first dose) and at Week 17, Day 1 (after multiple doses) are contained within the equivalence interval: 80% to 125%.

If AUC(TAU) of Process D is 11% greater or 10% less than AUC(TAU) of Process C, then 83 participants per treatment arm would provide 97% or 90% power with respect to AUC(TAU)(0-336h) at Week 1, Day 1 (after first dose) and at Week 17, Day 1 (after multiple doses), respectively, to conclude equivalence between the 2 manufacturing processes. The overall power would be at least 87%.

Accounting for 35% of participants data being not evaluable for statistical analysis due to dropouts, dose delays, insufficient sampling, etc., a total of 254 participants (127 per each arm) were estimated to be randomized and dosed to ensure that 83 participants per arm complete all relevant procedures.

- **Randomisation and Blinding (masking)**

This was a double-blind study. Subjects were randomly assigned within stratified AJCC Staging (8th edition) [Stage IIIa/b/c/d or IV] and weight categories (< 70 kg, 70 to 90 kg, and > 90 kg) in a 1:1 ratio to receive either Process C or Process D.

- **Statistical methods**

The efficacy of Process D and Process C in terms of RFS is an exploratory endpoint.

The RFS analyses were conducted in randomized subjects. RFS was programmatically determined based on the disease recurrence date provided by the investigator and is defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma (including melanoma in situ), or death (whatever the cause), whichever occurred first. A subject who died without reported recurrence was considered to have recurred on the date of death. For subjects who remained alive and whose disease had not recurred and without new primary disease, RFS was censored on the date of last evaluable disease assessment. For those subjects who remained alive and had no recorded post-randomization disease assessment, RFS was censored on the day of randomization.

The hazard ratio and corresponding 2-sided 95% CI was estimated using a Cox proportional hazards

model, with treatment group as a single covariate, stratified by AJCC staging and weight category (as recorded in the IRT). RFS curves, RFS medians with 95% CIs, and RFS rates at 6, 12, 18, and 24 months, with 95% CIs were estimated using Kaplan-Meier methodology.

Sensitivity analyses of RFS were also performed:

- RFS stratified analysis using stratification factors as obtained from the baseline CRF pages (instead of IRT). This analysis was performed only if at least one stratification factor (Weight category or AJCC staging) at randomization (as per IRT) and baseline was not concordant for at least 10% of all randomized subjects.
- RFS analysis using a 2-sided, un-stratified Cox proportional hazards model with treatment as the single covariate was conducted.
- RFS analysis for subjects with no relevant deviation. This analysis was conducted only if there were more than 10% subjects with relevant protocol deviations.

For additional details on statistical methods, see section 2.6.2.1.

Results

- **Participant flow**

At the time of DBL, 341 subjects were enrolled, and 261 subjects were randomized and treated (129 to the nivolumab Process C group and 132 to the nivolumab Process D group).

At the time of DBL, there were no subjects continuing treatment in either treatment arm.

Table 11: Subject Disposition - All Enrolled, Randomized, and Treated Subjects

Status (%)	Process C	Process D	Total
ENROLLED			341 (100.0)
RANDOMIZED OR ENTERING TREATMENT PERIOD	129	132	261 (76.5)
NOT RANDOMIZED OR ENTERING TREATMENT PERIOD			80 (23.5)
REASON FOR NOT RANDOMIZED OR ENTERING TREATMENT PERIOD			
SUBJECT WITHDREW CONSENT			12 (3.5)
LOST TO FOLLOW-UP			1 (0.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA			60 (17.6)
OTHER			7 (2.1)
TREATED	129 (100.0)	132 (100.0)	261 (100.0)
CONTINUING IN THE TREATMENT PERIOD	0	0	0
COMPLETED THE TREATMENT PERIOD	79 (61.2)	88 (66.7)	167 (64.0)
NOT CONTINUING IN THE TREATMENT PERIOD	50 (38.8)	44 (33.3)	94 (36.0)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD			
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	2 (1.6)	1 (0.8)	3 (1.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.8)	1 (0.4)
DISEASE PROGRESSION	1 (0.8)	0	1 (0.4)
STUDY DRUG TOXICITY	16 (12.4)	23 (17.4)	39 (14.9)
ADVERSE EVENT UNRELATED TO STUDY DRUG	2 (1.6)	2 (1.5)	4 (1.5)
DISEASE RECURRENCE	27 (20.9)	15 (11.4)	42 (16.1)
OTHER	2 (1.6)	2 (1.5)	4 (1.5)
NOT CONTINUING IN THE TREATMENT PERIOD DUE TO COVID-19	1 (0.8)	1 (0.8)	2 (0.8)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD DUE TO COVID-19			
ADVERSE EVENT UNRELATED TO STUDY DRUG	1 (0.8)	0	1 (0.4)
OTHER	0	1 (0.8)	1 (0.4)
CONTINUING IN THE STUDY	112 (86.8)	118 (89.4)	230 (88.1)
NOT CONTINUING IN THE STUDY	17 (13.2)	14 (10.6)	31 (11.9)
REASON FOR NOT CONTINUING IN THE STUDY			
DEATH	15 (11.6)	14 (10.6)	29 (11.1)
SUBJECT WITHDREW CONSENT	2 (1.6)	0	2 (0.8)
NOT CONTINUING IN THE STUDY DUE TO COVID-19	0	1 (0.8)	1 (0.4)
REASON FOR NOT CONTINUING IN THE STUDY DUE TO COVID-19			
DEATH	0	1 (0.8)	1 (0.4)

Source: Table S.2.5 (pre-randomized subject status), Table S.2.6A (randomized subject status), Table S.2.7 (end of treatment period subject status)
Note: Percentages based on subjects entering period.

- **Recruitment**

The enrolment period was approximately 15 months, from 24-Jun-2019 to 25-Sep-2020.

The study was conducted in 12 countries including: Australia, Brazil, Chile, France, Ireland, Italy, Mexico, New Zealand, Poland, Romania, Spain, and United States. The LPLV and DBL of the study occurred on 14 October 2021 and 18-February 2022, respectively.

Minimum follow-up was 15.7 months, and median follow-up was 25.9 months (range: 15.7, 31.8).

- **Conduct of the study**

Protocol amendments

The original protocol for this study was dated 10 Dec 2018. As of the 18 Feb 2022 DBL, there were 2 global protocol revisions, 6 administrative letters and 1 clarification memo. The protocol amendment revision 02 was dated 24 Sep 2021.

Table 12: Summary of Key Changes to Protocol CA2098FC

Document (Amendment) /Date	Summary of Key Changes	Planned Sample Size	Subjects Randomized at time of Protocol Amendment
Revised Protocol 01 25-Oct-2019	• Modified to remove language requiring complete lymph node dissection with lymph node positive disease to align with practice and guideline changes. • Modified minimum number of slides required • Allowed adjuvant radiation therapy after resection of large nodal metastases or extra nodal extension. • PBMC language was removed from the protocol text and Table 9.8-1. Receptor occupancy test included to compare the biological effect of the nivolumab produced by Process C with the nivolumab produced by Process D. Blood will be drawn at the same time as PK sampling at the following time points: W1D1 pre-dose and 4 hours post-dose and W17D1 pre-dose and 4 hours post-dose. • Changes as per Administrative Letter 01 and 02 and Clarification Memo 01.	254	66
Protocol Amendment 02 24-Sep-2021	• Aligned safety language based on CTCAE v5 safety reporting purposes • Removed male contraception requirements • Clarified the blinding/unblinding section • Made minor wording modifications to secondary endpoint • Included changes as previously communicated in Administrative Letters 03, 04, 05, 06	254	261

Important protocol deviations

Table 13: Summary of important protocol deviations – all enrolled subjects

Protocol Deviation Classification Protocol Deviation Specifications	No. of Subjects
Total IPDs	**35**
Trial Procedures	**23**
Repetitive and/or systemic non-important protocol deviations for tumor assessments not performed within the specified scheduled.	8
Failure to collect PK samples for planned PK time points as specified in the protocol.	4
Failure to collect PK samples for planned PK timepoint due to COVID.	2
Pregnancy Tests not performed as per protocol specified schedule.	2
Tumor assessment scans not performed as per specified schedule.	4
Failure to perform the Survival Follow up visit 1 within the timelines	1
Failure to perform the Follow up visit 2 within the timelines	1
Re-consent containing updated risk language or updated safety information not signed	1
Safety Reporting	**6**
Tumor Assessment not performed as per timelines specified in the protocol	3
Failure to notify BMS of all SAEs (initial report) in accordance with the time period required by the protocol and/or applicable regulation.	2
Follow-up visit 1 and/or 2 not performed.	1
Informed Consent and/or Ethics (IEC/IRB)	**7**
Re-consent containing updated risk language or updated safety information not signed or signed with delay.	7

A protocol deviation (exclusion criterion 3f met. AST/ALT ≥ 3.0 × ULN) was reported in the primary CSR and inadvertently re-entered in the source listing.
Source: Appendix 2.3

Relevant protocol deviations

Relevant Protocol Deviations (RPD) are IPDs that could affect the interpretability of key study results, are programmable deviations from clinical database and are protocol specific.

Table 14: Relevant protocol deviations – all randomized subjects

	Number of Subjects (%)		
	Process C N = 129	Process D N = 132	Total N = 261
SUBJECTS WITH AT LEAST ONE DEVIATION	27 (20.9)	30 (22.7)	57 (21.8)
AT ENTRANCE			
SUBJECTS MISSING AT LEAST ONE INCLUSION OR EXCLUSION CRITERION	5 (3.9)	8 (6.1)	13 (5.0)
ON-TREATMENT			
NIVOLUMAB ADMINISTRATION ERROR <75% OR >125% OF THE PLANNED DOSAGE	6 (4.7)	8 (6.1)	14 (5.4)
LESS THAN 12 DAYS FROM PREVIOUS DOSE DURING Q2W CYCLES	7 (5.4)	3 (2.3)	10 (3.8)
LESS THAN 25 DAYS FROM PREVIOUS DOSE DURING Q4W CYCLES	4 (3.1)	3 (2.3)	7 (2.7)
MORE THAN 42 DAYS FROM PREVIOUS DOSE	7 (5.4)	9 (6.8)	16 (6.1)
MORE THAN 42 DAYS FROM PREVIOUS DOSE DUE TO COVID	1 (0.8)	3 (2.3)	4 (1.5)

Source: Table S.2.4

- **Baseline data**

For a summary of demographic characteristics, see section 2.6.2.1.

Baseline disease characteristics

Table 15: Baseline disease characteristics summary – all randomized subjects

	Number of Subjects (%)		
	Process C N = 129	Process D N = 132	Total N = 261
AJCC 8.0 STAGING			
IIIA/B/C/D	117 (90.7)	115 (87.1)	232 (88.9)
IV	12 (9.3)	17 (12.9)	29 (11.1)
ECOG PERFORMANCE STATUS			
0	122 (94.6)	124 (93.9)	246 (94.3)
1	7 (5.4)	8 (6.1)	15 (5.7)
PRIOR RADIOTHERAPY			
YES	3 (2.3)	4 (3.0)	7 (2.7)
NO	126 (97.7)	128 (97.0)	254 (97.3)
BASELINE LDH LEVEL			
<= 1.5 X ULN	127 (98.4)	132 (100.0)	259 (99.2)
> 1.5 X ULN	2 (1.6)	0	2 (0.8)
REGION			
US/WEST EU	55 (42.6)	49 (37.1)	104 (39.8)
EAST EU	7 (5.4)	10 (7.6)	17 (6.5)
AUS/NZ	38 (29.5)	35 (26.5)	73 (28.0)
CENTRAL/SOUTH AMERICA	29 (22.5)	38 (28.8)	67 (25.7)
BASELINE PD-L1+ STATUS BASED ON A 1% CUT OFF			
>= 1%	61 (47.3)	68 (51.5)	129 (49.4)
< 1%	37 (28.7)	40 (30.3)	77 (29.5)
INDETERMINATE	6 (4.7)	8 (6.1)	14 (5.4)
NOT EVALUABLE	25 (19.4)	16 (12.1)	41 (15.7)
BASELINE PD-L1+ STATUS BASED ON A 5% CUT OFF			
>= 5%	42 (32.6)	44 (33.3)	86 (33.0)
< 5%	56 (43.4)	64 (48.5)	120 (46.0)
INDETERMINATE	6 (4.7)	8 (6.1)	14 (5.4)
NOT EVALUABLE	25 (19.4)	16 (12.1)	41 (15.7)
DISEASE STAGE AT DIAGNOSIS			
IIIA	18 (14.0)	17 (12.9)	35 (13.4)
IIIB/C/D	99 (76.7)	98 (74.2)	197 (75.5)
IV	12 (9.3)	17 (12.9)	29 (11.1)
DISEASE STAGE AT DIAGNOSIS			
IIIA	18 (14.0)	17 (12.9)	35 (13.4)
IIIB	32 (24.8)	32 (24.2)	64 (24.5)
IIIC	64 (49.6)	60 (45.5)	124 (47.5)
IIID	3 (2.3)	6 (4.5)	9 (3.4)
IV	12 (9.3)	17 (12.9)	29 (11.1)

MELANOMA TNM CLASSIFICATION

METASTASIS			
M0	109 (84.5)	113 (85.6)	222 (85.1)
M1A	2 (1.6)	8 (6.1)	10 (3.8)
M1A(0)	2 (1.6)	1 (0.8)	3 (1.1)
M1A(1)	1 (0.8)	1 (0.8)	2 (0.8)
M1B	2 (1.6)	4 (3.0)	6 (2.3)
M1B(0)	2 (1.6)	2 (1.5)	4 (1.5)
M1C(0)	1 (0.8)	0	1 (0.4)
M1D	1 (0.8)	0	1 (0.4)
M1D(1)	0	1 (0.8)	1 (0.4)
MX	4 (3.1)	2 (1.5)	6 (2.3)
UNKNOWN	5 (3.9)	0	5 (1.9)
NODES			
N0	6 (4.7)	9 (6.8)	15 (5.7)
N1	8 (6.2)	9 (6.8)	17 (6.5)
N1A	33 (25.6)	36 (27.3)	69 (26.4)
N1B	23 (17.8)	20 (15.2)	43 (16.5)
N1C	6 (4.7)	5 (3.8)	11 (4.2)
N2	3 (2.3)	2 (1.5)	5 (1.9)
N2A	9 (7.0)	15 (11.4)	24 (9.2)
N2B	16 (12.4)	10 (7.6)	26 (10.0)
N2C	7 (5.4)	4 (3.0)	11 (4.2)
N3	5 (3.9)	7 (5.3)	12 (4.6)
N3A	1 (0.8)	4 (3.0)	5 (1.9)
N3B	4 (3.1)	1 (0.8)	5 (1.9)
N3C	5 (3.9)	6 (4.5)	11 (4.2)
NX	3 (2.3)	4 (3.0)	7 (2.7)
TUMOR			
T0	8 (6.2)	6 (4.5)	14 (5.4)
T1	2 (1.6)	1 (0.8)	3 (1.1)
T1A	7 (5.4)	10 (7.6)	17 (6.5)
T1B	6 (4.7)	3 (2.3)	9 (3.4)
T2	1 (0.8)	1 (0.8)	2 (0.8)
T2A	24 (18.6)	18 (13.6)	42 (16.1)
T2B	4 (3.1)	6 (4.5)	10 (3.8)
T3	1 (0.8)	1 (0.8)	2 (0.8)
T3A	10 (7.8)	19 (14.4)	29 (11.1)
T3B	18 (14.0)	15 (11.4)	33 (12.6)
T4	2 (1.6)	1 (0.8)	3 (1.1)
T4A	12 (9.3)	9 (6.8)	21 (8.0)
T4B	25 (19.4)	30 (22.7)	55 (21.1)
TIS	0	2 (1.5)	2 (0.8)
TX	8 (6.2)	10 (7.6)	18 (6.9)
UNKNOWN	1 (0.8)	0	1 (0.4)
BRAIN METASTASIS			
YES	1 (0.8)	2 (1.5)	3 (1.1)
NO	128 (99.2)	130 (98.5)	258 (98.9)
BRAF STATUS			
MUTANT	43 (33.3)	34 (25.8)	77 (29.5)
WILD-TYPE	17 (13.2)	31 (23.5)	48 (18.4)
NOT REPORTED	69 (53.5)	67 (50.8)	136 (52.1)

Source: Table S.3.2.7

Previous treatments

Table 16: Prior cancer therapy summary – all randomized subjects

	Number of Subjects (%)		
	Process C N = 129	Process D N = 132	Total N = 261
PRIOR SURGERY RELATED TO CANCER			
YES	129 (100.0)	132 (100.0)	261 (100.0)
NO	0	0	0
PRIOR RADIOTHERAPY			
YES	3 (2.3)	4 (3.0)	7 (2.7)
NO	126 (97.7)	128 (97.0)	254 (97.3)
PRIOR SYSTEMIC CANCER THERAPY RELATED TO CANCER			
YES	3 (2.3)	1 (0.8)	4 (1.5)
NO	126 (97.7)	131 (99.2)	257 (98.5)

Source: Table S.3.3.5

- **Numbers analysed**

See section 2.6.2.1.

- **Outcomes and estimation**

As of the 18-Feb-2022 DBL for the Addendum 01 to the CA2098FC Primary CSR (minimum follow-up of 15.7 months), the efficacy profile of nivolumab Process D was comparable to Process C based on RFS results in all randomized subjects as well as RFS results in PD-L1 positive subjects, and subjects with no relevant protocol deviations.

Table 17: Efficacy Results - All Randomized Subjects - CA2098FC (Addendum 01 CSR DBL: 18-Feb-2022)

	Minimum Follow-up: 15.7 months	
	Nivolumab Process C	Nivolumab Process D
RFS - All Randomized Subjects	N = 129	N = 132
Events, n / Subjects, n (%)	47 / 129 (36.4)	43 / 132 (32.6)
Median RFS, months[a] (95% CI)	N.A. (27.27 - N.A.)	N.A. (29.80 - N.A.)
HR[b] (95% CI)	0.81 (0.53 - 1.23)	
RFS - Tumor cell PD-L1 Positive (PD-L1 ≥1%) Subjects[c]	N = 61	N = 68
Events, n / Subjects, n (%)	24 / 61 (39.3)	21 / 68 (30.9)
Median RFS, months[a] (95% CI)	27.60 (16.72 - N.A.)	N.A. (N.A - N.A)
HR[b] (95% CI)	0.75 (0.42 - 1.36)	
RFS - Subjects with no Relevant Protocol Deviation	N = 102	N = 102
Events, n Subjects, n (%)	38 / 102 (37.3%)	31 / 102 (30.4%)
Median RFS, months[a] (95% CI)	N.A (27.27 - N.A)	N.A (N.A - N.A.)
HR[b] (95% CI)	0.75 (0.46 - 1.21)	
RFS - All Randomized Subjects, Unstratified Analysis	N = 129	N = 132
Events, n Subjects, n (%)	47 / 129 (36.4%)	43 / 132 (32.6%)
Median RFS, months[a] (95% CI)	N.A (27.27 - N.A)	N.A (29.80 - N.A)
HR[b] (95% CI)	0.84 (0.56 - 1.28)	
RFS Rate[a] (95% CI) - All Randomized Subjects	N = 129	N = 132
6-Months	80.6 (72.6, 86.4)	87.9 (81.0, 92.4)
12-Months	74.3 (65.8, 81.0)	76.5 (68.3, 82.9)
18-Months	66.7 (57.6, 74.2)	72.1 (63.4, 79.0)
24-Months	64.2 (54.9, 72.1)	66.5 (57.2, 74.3)

[a] Based on Kaplan-Meier Estimates.

[b] Stratified Cox proportional hazard model. Hazard Ratio is Nivolumab Process D over Nivolumab Process C.

[c] 206/261 (78.9%) subjects (98/129 [76.0%] subjects in Process C and 108/132 [81.8%] subjects in Process D) had tumor cell PD-L1 quantifiable at baseline (refer to Table S.10.2 of the addendum to the CA2098FC Primary CSR).

Source: Table 7.1-1 of the Addendum 01 to the CA2098FC Primary CSR

Table 18: Reason for Censoring, Recurrence-Free Survival – All Randomized subjects

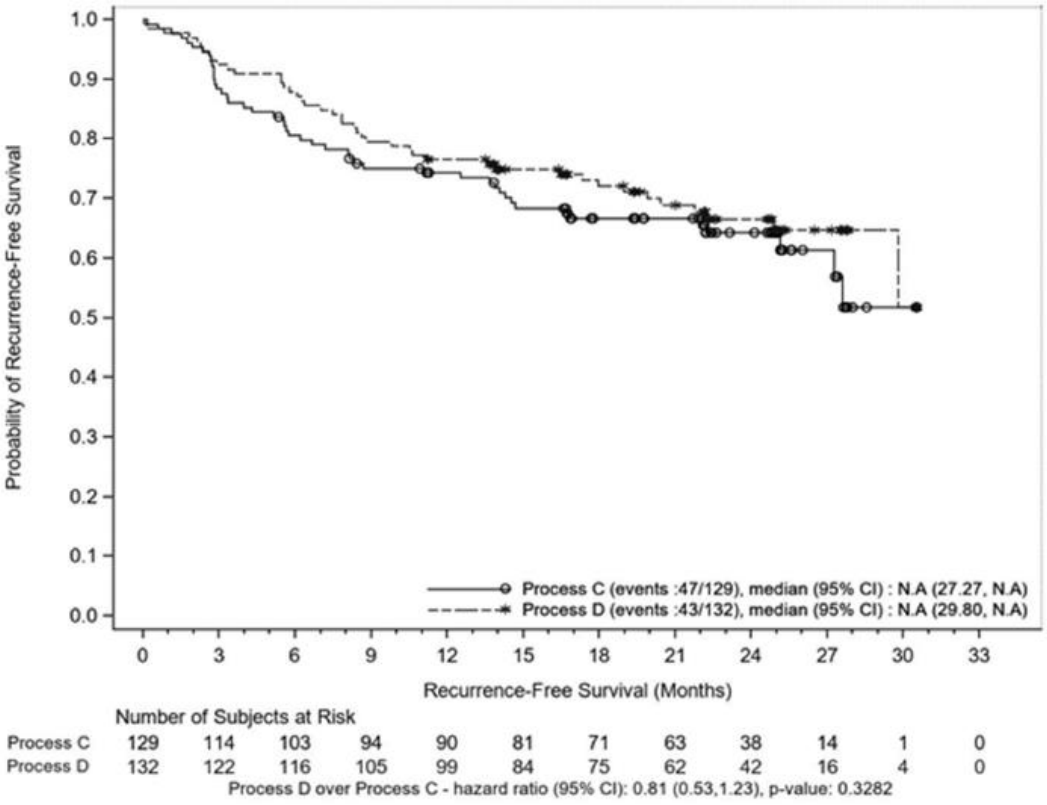
	Process C N = 129	Process D N = 132
NUMBER OF EVENTS (%)	47 (36.4)	43 (32.6)
TYPE OF EVENTS (%)		
RECURRENCE	45 (34.9)	39 (29.5)
DISEASE AT BASELINE	0	1 (0.8)
DISTANT RECURRENCE	23 (17.8)	21 (15.9)
REGIONAL NODE RECURRENCE	5 (3.9)	9 (6.8)
LOCAL RECURRENCE	13 (10.1)	6 (4.5)
NEW PRIMARY MELANOMA IN SITU	4 (3.1)	2 (1.5)
NEW PRIMARY INVASIVE MELANOMA	0	0
DEATH	2 (1.6)	4 (3.0)
NUMBER OF SUBJECTS CENSORED (%)	82 (63.6)	89 (67.4)
CENSORED ON DATE OF RANDOMIZATION	0	0
CENSORED ON DATE OF LAST DISEASE ASSESSMENT ON-STUDY OR LAST ASSESSMENT PRIOR TO SUBSEQUENT ANTI CANCER THERAPY	82 (63.6)	89 (67.4)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (1)	0	0
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	0	0
RECEIVED SUBSEQUENT RADIOTHERAPY	0	0
RECEIVED SUBSEQUENT SURGERY	0	0
SECOND NON-MELANOMA PRIMARY CANCER (2)	2 (1.6)	1 (0.8)
STILL ON-TREATMENT	0	0
IN FOLLOW-UP	79 (61.2)	88 (66.7)
OFF STUDY	1 (0.8)	0
LOST TO FOLLOW-UP	0	0
WITHDREW CONSENT	1 (0.8)	0
OTHER	0	0

Source: Table S.5.3

(1) Disease assessments and death if any, occurring after start of subsequent anti-cancer therapy or second non-melanoma primary cancer are not considered.

(2) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy or experienced second non-melanoma primary cancer without a prior reported RFS event. Those subjects were censored at the last evaluable disease assessment prior to/on start date of subsequent anti-cancer therapy or second non-melanoma primary cancer.

Figure 4: KM plot of Recurrence-Free-Survival – All randomized subjects



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

Immunogenicity results

Nivolumab Process C

Of the 118 nivolumab ADA-evaluable subjects in the nivolumab Process C treatment group, 5 (4.2%) subjects were nivolumab ADA-positive at baseline, and 3 (2.5%) subjects were nivolumab ADA-positive after the start of treatment.

- No subjects were considered persistent positive or developed neutralizing antibody.
- The highest titer value observed among nivolumab ADA-positive subjects was 32, which occurred in 1 subject. All other titers were low, ranging from 1 to 16.

Nivolumab Process D

Of the 123 nivolumab ADA-evaluable subjects in the nivolumab Process D treatment group, 5 (4.1%) subjects were nivolumab ADA-positive at baseline, and 8 (6.5%) subjects were nivolumab ADA-positive after the start of treatment.

- 2 (1.6%) subjects were considered persistent positive, and no subjects developed neutralizing antibodies.
- The highest titer value observed among nivolumab ADA-positive subjects was 8, which occurred in 2 subjects. All other titers were low, ranging from 1 to 4.

Table 19: Anti-Drug Antibody assessments summary - All immunogenicity evaluable subjects with baseline and at least one post-baseline assessment

Subject ADA Status (%)	Process C N = 118	Process D N = 123
BASELINE ADA POSITIVE	5 (4.2)	5 (4.1)
ADA POSITIVE	3 (2.5)	8 (6.5)
PERSISTENT POSITIVE (PP)	0	2 (1.6)
NOT PP LAST SAMPLE POSITIVE	1 (0.8)	1 (0.8)
OTHER POSITIVE	2 (1.7)	5 (4.1)
NEUTRALIZING POSITIVE	0	0
ADA NEGATIVE	115 (97.5)	115 (93.5)

Source: Table S.7.10

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;

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;

ADA Negative: A subject with no ADA-positive sample after initiation of treatment.

Onset and duration of immunogenicity

The assessment of onset and duration of anti-nivolumab ADAs was based on a small number of participants who became nivolumab ADA-positive after the start of treatment with either Process C or

Process D. The median time to first detection of ADAs to nivolumab was similar between nivolumab Process C and Process D. The median duration of ADAs to nivolumab was somewhat longer for nivolumab Process D versus Process C.

Table 20: Onset and duration of Anti-Drug Antibodies to nivolumab – all treated subjects with ADA-positive status for whom ADA is not detected at baseline

Kinetics of ADA	Process C N = 3	Process D N = 8
TIME TO FIRST DETECTION OF ADA TO NIVOLUMAB		
N	3	8
MEDIAN (Q1, Q3), WEEKS	2.29 (2.14, 29.14)	2.14 (2.14, 2.36)
MIN, MAX	2.1, 29.1	2.0, 7.3
DURATION OF ADA TO NIVOLUMAB		
N	3	8
MEDIAN (95% CI), WEEKS	8.07 (2.14, N.A.)	14.29 (13.86, 34.14)
MIN, MAX	0.1*, 14.0	0.1*, 56.3*
NUMBER OF DOSES BEFORE FIRST DETECTION OF ADA TO NIVOLUMAB		
N	3	8
MEDIAN (MIN, MAX)	1.0 (1, 8)	1.0 (1, 1)
NUMBER OF DOSES AFTER FIRST DETECTION OF ADA TO NIVOLUMAB		
N	3	8
MEDIAN (MIN, MAX)	10.0 (2, 17)	13.0 (7, 17)
TOTAL NUMBER OF DOSES OF NIVOLUMAB		
N	3	8
MEDIAN (MIN, MAX)	18.0 (3, 18)	14.0 (8, 18)

Source: Table S.7.12

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 participants with baseline ADA-positive sample and had an increased titer at post-baseline since this type of immune response differs mechanistically.

*Censored observation.

N.A.: Not Applicable.

Effect of immunogenicity on efficacy

Nivolumab Process C

Based on assessment of the presence of ADAs vs RFS, some subjects positive for nivolumab ADAs continued treatment with clinical benefit, and there was no apparent trend showing an effect of positive ADA on the efficacy of nivolumab Process C.

Among the 3 nivolumab ADA-positive subjects, 2 were censored in follow-up with no events reported, and 1 subject had a distant reoccurrence of disease. The ADA titers among the 3 subjects with nivolumab ADAs ranged from 1 to 32.

Nivolumab Process D

Based on assessment of the presence of ADAs vs RFS, some subjects positive for nivolumab ADAs continued treatment with clinical benefit, and there was no apparent trend showing an effect of positive ADA on the efficacy of nivolumab Process D.

Among the 8 nivolumab ADA-positive subjects, 5 were censored in follow-up with no events reported, 1 subject had a distant reoccurrence of disease, 1 subject had a local occurrence of disease, and death was reported for 1 subject after 10.5 months of RFS. The ADA titers among the 8 subjects with nivolumab ADAs ranged from 1 to 8.

- **Summary of main efficacy results**

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

Table 21: Summary of efficacy for trial CA2098FC

Title: A Randomized, Double-Blind, Parallel, Phase 1 Study to Compare the Pharmacokinetics of Nivolumab Process D to Nivolumab Process C after Complete Resection of Stage IIIa/b/c/d or Stage IV Melanoma				
Study identifier	CA2098FC ClinicalTrials.gov Identifier: NCT03980314			
Design	Phase 1, randomized, double-blinded study to compare the PK of Process D nivolumab to Process C nivolumab administered after complete resection of Stage IIIa/b/c/d or Stage IV melanoma in subjects with no evidence of disease.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		From 24-Jun-2019. Ongoing. Not applicable Not applicable	
Hypothesis	Exploratory			
Treatments groups	Process C		Process C nivolumab (3 mg/kg IV Q2W for Week 1 to Week 17 followed by 480 mg IV Q4W for Week 19 to Week 51), up to 1 year. N=129	
	Process D		Process D nivolumab (3 mg/kg IV Q2W for Week 1 to Week 17 followed by 480 mg IV Q4W for Week 19 to Week 51), up to 1 year. N=132	
Endpoints and definitions	Exploratory endpoint	RFS	Time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma (including melanoma in situ), or death (whatever the cause), whichever occurred first.	
Database lock	18 February 2022			
Results and Analysis				
Analysis description	**Exploratory Analysis**			
Analysis population and time point description	All randomized subjects: 261 subjects			
Descriptive statistics and estimate variability	Treatment group		Process C	Process D
	Number of subject		129	132
	RFS (median, months)		NR	NR
	95% CI		(27.27, NR)	(29.80, NR)
Effect estimate per comparison	Exploratory endpoint: RFS		Comparison groups	Process C vs. Process D
			Hazard Ratio (HR)	0.81
			95% CI	0.53, 1.23
			P-value	Not applicable (descriptive)

2.6.5.2. In vitro biomarker test for patient selection for efficacy

Not applicable

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

Not applicable

2.6.5.4. Supportive study(ies)

Not applicable

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The basis of this submission is Study CA2098FC, a randomized, double-blind, parallel, Phase 1 study aimed to demonstrate biocomparability of Process C IV nivolumab to Process D IV nivolumab in 261 patients with stage IIIa/b/c/d or stage IV melanoma after complete resection. The primary endpoints of this study were AUC (tau) (0-336h) at week 1 day 1 (after first dose) and AUC (tau) (0-336h) at week 17 day 1 (after multiple doses).

Subjects were randomized 1:1 to receive nivolumab Process C (Arm A) or nivolumab Process D (Arm B) and randomization was stratified by AJCC Staging (8th edition) [Stage IIIa/b/c/d or IV] and weight categories (< 70 kg, 70 to 90 kg, and > 90 kg).

The target study population included subjects ≥ 18 years old with histologically confirmed completely resected Stage IIIa/b/c/d or Stage IV (AJCC Staging, 8th edition) melanoma with no evidence of disease. The target population was agreed by the CHMP during a SA (EMEA/H/SA/2253/6/2018/III).

The only efficacy endpoint included in this study was "recurrence-free-survival (RFS)", and was an exploratory endpoint. Therefore, the results mentioned below are only descriptive in nature and are considered as supportive.

Median follow-up was 25.9 months (range: 15.7, 31.8), with a minimum follow-up of 15.7 months. Data base lock was 18 February 2022. Although in terms of efficacy assessment a longer follow-up might have been informative, in this context this follow-up is considered acceptable.

Relevant protocol deviations were reported with a similar frequency in both arms: 20.9% in Process C and 22.7% in Process D.

Overall, the design and conduct of the study are considered acceptable. It should be noted that in the CHMP SA provided in 2018 (EMEA/H/SA/2253/6/2018/III) no efficacy issue was addressed.

Efficacy data and additional analyses

A total of 261 patients were randomized, 129 to the Process C arm and 132 to the Process D arm. This number of patients is deemed adequate, considering that the primary objective of this clinical trial was to compare the PK of both processes, and that efficacy was only considered as supportive.

No relevant differences were observed between treatment arms in terms of baseline demographics. Median age was 57 years in both arms, most patients were males (67.4% in Process C and 59.1% in Process D) and white (97.7% in Process C and 96.2% in Process D). Similarly, no differences were observed in baseline disease characteristics. The majority of patients had IIIa/b/c/d stage in both arms (90.7% in Process C and 87.1% in Process D). Only 2.3% of patients in Process C and 3% of patients in Process D received prior radiotherapy and all patients had prior surgery related to cancer (as per protocol). Most patients did not receive prior systemic cancer therapy related to cancer (97.7% in Process C vs. 99.2% in Process D). Overall, treatment arms were also balanced in terms of PDL-1 status: 47.3% of patients in Process C and 51.5% in Process D had PDL-1 expression ≥ 1%. There was

a higher proportion of patients with BRAF mutation in Process C compared to Process D (33.3% vs 25.8%). Apart from that no major differences were identified between treatment arms. Thus, considering all this, it can be concluded that both treatment arms were overall well-balanced in terms of baseline characteristics.

No statistically significant differences were observed between both arms in terms of efficacy. The HR for RFS in all randomized subjects was 0.81 (95% CI: 0.53-1.23), with 47 events (36.4%) reported in Process C vs. 43 events (32.6%) in Process D. Median RFS was not reached in either arm. Similar results were observed in patients with PDL-1 ≥1%: the HR was 0.75 (95% CI: 0.42–1.36), with 24 events (39.3%) reported in Process C vs. 21 events (30.9%) in Process D. In this case median RFS was reached in Process C (27.60 months [95% CI: 16.72 – NR]). The HR in subjects with no relevant protocol deviations was 0.75 (95%CI: 0.46-1.21), with 38 events (37.3%) reported in Process C vs. 31 events (30.4%) in Process D. RFS in all randomized subjects (unstratified analysis) was also similar: the HR was 0.84 (95% CI: 0.56-1.28), with 47 events (36.4%) in Process C vs. 43 events (32.6%) in Process D.

RFS rates in all randomized subjects were similar in both arms, or even slightly higher in Process D when compared with Process C: at 6 months 80.6 (95% CI: 72.6, 86.4) in Process C vs. 87.9 (95% CI: 81.0, 92.4) in Process D; at 12 months 74.3 (95% CI: 65.8, 81.0) in Process C vs. 76.5 (95% CI: 68.3, 82.9) in Process D; at 18 months 66.7 (95% CI: 57.6, 74.2) in Process C vs. 72.1 (95% CI: 63.4, 79.0) in Process D; and at 24 months 64.2 (95% CI: 54.9, 72.1) in Process C vs. 66.5 (95% CI: 57.2, 74.3) in Process D.

Immunogenicity incidence was higher in the Process D arm than in the Process C arm: in Process D there were 8 (6.5%) ADA-positive patients vs. 3 (2.5%) ADA-positive patients in Process C. The median duration of nivolumab ADAs was longer in Process D than in Process C: 14.29 (95% CI: 13.86, 34.14) weeks in Process D vs. 8.07 (95% CI: 2.14, NA) weeks in Process C. No patients in either arm developed neutralizing ADAs (see discussion on clinical safety). Overall, it does not appear that immunogenicity had an impact on efficacy results.

Therefore, based on the above-mentioned results, no relevant differences appear in terms of efficacy between Process C and Process D; although, as previously mentioned, these results are only descriptive and therefore no firm conclusions can be drawn.

2.6.7. Conclusions on the clinical efficacy

No relevant differences have been observed in RFS between patients randomized to Process C and patients randomized to Process D, suggesting that the efficacy between both processes might be similar. However, it should be noted that the efficacy data provided are only descriptive, as the primary endpoints of this study were PK endpoints (see 2.6.4).

2.6.8. Clinical safety

The primary safety data presented to support the nivolumab drug substance manufacturing process change application (from the current approved Process C to a newly optimized Process D) is based on the pivotal clinical biocomparability Study CA2098FC.

The primary safety data, is, therefore, based on 129 subjects treated with nivolumab Process C and 132 subjects treated with nivolumab Process D. To further support the safety data collected from Study CA2098FC, additional exposure-adjusted analyses were conducted for all-causality unique select AEs to contextualize numerically higher incidence of some select AE categories noted in nivolumab Process D compared to nivolumab Process C. Additionally, the MAH has performed a non-exposure

adjusted descriptive analysis of drug-related select AEs within 30 days of last dose, to further address the differences observed in certain select AEs and cardiac disorders events with nivolumab Process D compared with nivolumab Process C.

2.6.8.1. Patient exposure

A majority of subjects treated with nivolumab dosed at 3 mg/kg IV Q2W, received 90% to < 110% of the planned dose intensity, 114 (88.4%) and 113 (85.6%) in Process C and Process D, respectively. A higher proportion was seen during the phase with nivolumab dosed at 480 mg IV Q4W: (100 [95.2%]) and (112 [95.7%]) in Process C and Process D, respectively.

One subject in Process D, treated with nivolumab dosed at 3 mg/kg IV Q2W, had a relative dose intensity greater than or equal to 110%, while none were reported in the Process C arm. The median number of doses received was 9 for both Process C and Process D for subjects during the phase of nivolumab dosed at 3 mg/kg IV Q2W as well as the phase of nivolumab dosed at 480 mg IV Q4W.

The median duration of therapy was 11.53 and 11.55 months for subjects in both Process C and Process D, respectively.

Table 22: Cumulative dose and relative dose intensity summary – all treated subjects

	Process C N = 129	Process D N = 132
Treatment: Nivolumab 3 mg/kg IV Q2W		
NUMBER OF SUBJECTS WHO RECEIVED DOSES	129 (100.0)	132 (100.0)
NUMBER OF DOSES RECEIVED		
MEAN (SD)	8.4 (1.5)	8.5 (1.6)
MEDIAN (MIN - MAX)	9.0 (2 - 9)	9.0 (1 - 9)
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)	25.1 (4.5)	25.5 (4.9)
MEDIAN (MIN - MAX)	27.0 (6 - 27)	27.0 (3 - 34)
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	1 (0.8)
90% TO < 110%	114 (88.4)	113 (85.6)
70% TO < 90%	12 (9.3)	18 (13.6)
50% TO < 70%	3 (2.3)	0
< 50%	0	0
Treatment: Nivolumab 480 mg IV Q4W		
NUMBER OF SUBJECTS WHO RECEIVED DOSES	105 (81.4)	117 (88.6)
NUMBER OF DOSES RECEIVED		
MEAN (SD)	7.9 (2.3)	7.9 (2.2)
MEDIAN (MIN - MAX)	9.0 (1 - 9)	9.0 (1 - 9)
CUMULATIVE DOSE (MG)		
MEAN (SD)	3768.7 (1099.7)	3802.3 (1046.2)
MEDIAN (MIN - MAX)	4320.0 (480 - 4320)	4320.0 (480 - 4320)
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	0
90% TO < 110%	100 (95.2)	112 (95.7)
70% TO < 90%	5 (4.8)	5 (4.3)
50% TO < 70%	0	0
< 50%	0	0

Source: Table S.4.1

Note: Percentages are computed out of the total number of subjects who received doses.

Table 23: Duration of study therapy summary – all treated subjects

	Process C N = 129	Process D N = 132
DURATION OF THERAPY (MONTHS)		
MEAN (MIN, MAX)	9.23 (0.5, 14.8)	9.84 (0.0, 14.8)
MEDIAN	11.53	11.55
> 3 MONTHS (%)	112 (86.8)	121 (91.7)
> 6 MONTHS (%)	99 (76.7)	110 (83.3)
> 9 MONTHS (%)	88 (68.2)	99 (75.0)
> 12 MONTHS (%)	15 (11.6)	20 (15.2)

Source: Table S.4.61

Interruption or delay of study therapy

In both arms of the study, most subjects received all doses of the study medications without an infusion interruption or dose delay.

Dose delays:

The number of subjects with at least one dose delay was 50 (38.8%) and 58 (43.9%) in Process C and Process D, respectively. The most common reason for dose delays of treatment in both arms of the study was due to AEs. The number of subjects with at least one dose delay due to COVID-19 was 9 (7.0%) and 11 (8.3%) in Process C and Process D, respectively.

Infusion interruptions:

The number of subjects with at least one infusion interruption was 2 (1.6%) and 8 (6.1%) in Process C and Process D, respectively.

Table 24: Dose delays and infusion interruptions of study therapy - all treated subjects

	Process C N = 129	Process D N = 132
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	50 (38.8)	58 (43.9)
NUMBER OF DOSE DELAYED PER SUBJECT		
0	79 (61.2)	74 (56.1)
1	38 (29.5)	38 (28.8)
2	8 (6.2)	18 (13.6)
3	3 (2.3)	2 (1.5)
>= 4	1 (0.8)	0
TOTAL NUMBER OF DOSE DELAYED/ TOTAL NUMBER OF DOSES RECEIVED (A)	67/1780 (3.8)	80/1921 (4.2)
REASON FOR DOSE DELAY (B)		
ADVERSE EVENT	42 (62.7)	44 (55.0)
OTHER	24 (35.8)	33 (41.3)
NOT REPORTED	1 (1.5)	3 (3.8)
LENGTH OF DOSE DELAY (B)		
4 - 7 DAYS	22 (32.8)	39 (48.8)
8 - 14 DAYS	30 (44.8)	22 (27.5)
15 - 42 DAYS	11 (16.4)	17 (21.3)
> 42 DAYS	4 (6.0)	2 (2.5)
SUBJECTS WITH AT LEAST ONE DOSE DELAYED DUE TO COVID-19 (%)	9 (7.0)	11 (8.3)
TOTAL NUMBER OF DOSE DELAYED DUE TO COVID-19/ TOTAL NUMBER OF DOSES RECEIVED (A)	9/1780 (0.5)	11/1921 (0.6)
REASON FOR DOSE DELAY DUE TO COVID-19 (C)		
ADVERSE EVENT	2 (22.2)	7 (63.6)
OTHER	7 (77.8)	4 (36.4)
NOT REPORTED	0	0
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%) (D)	2 (1.6)	8 (6.1)
NUMBER OF INFUSIONS INTERRUPTED PER SUBJECT (%) (D)		
0	127 (98.4)	124 (93.9)
1	2 (1.6)	5 (3.8)

2	0	2 (1.5)
3	0	0
>= 4	0	1 (0.8)
TOTAL NUMBER OF INFUSIONS INTERRUPTED/ TOTAL NUMBER OF DOSES RECEIVED (%)	2/1909 (0.1)	15/2053 (0.7)
REASON FOR INFUSION INTERRUPTION (%) (E)		
HYPERSENSITIVITY REACTION	0	8 (53.3)
INFUSION ADMIN ISSUES	0	1 (6.7)
OTHER	2 (100.0)	6 (40.0)
NOT REPORTED	0	0

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

(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) In the Process D arm, one subject with interruption reason of "Other" was actually "INFUSION RELATED HYPERSENSITIVITY REACTION" and remapped to "HYPERSENSITIVITY REACTION"

(E) Percentages are computed out of the total number of doses interrupted by treatment group.

Source: Table S.4.2.1 (dose delay summary) of the CA2098FC Addendum to the Primary CSR[1] and Table S.4.2.2 (dose interruptions) in Appendix 1.

Table 25: "Other reasons" of infusion interruptions in the nivolumab Process D arm – CA2098FC

Subject	Cycle	"Other Reasons" of infusion interruptions[a]
Subject A	Week 3 Day 1	Infusion reaction back pain
Subject B	Week 3 Day 1	Infusion-related hypersensitivity reaction
	Week 7 Day 1	Infusion-related hypersensitivity reaction
	Week 9 Day 1	Infusion-related hypersensitivity reaction
	Week 11 Day 1	Infusion-related hypersensitivity reaction
	Week 13 Day 1	Infusion-related hypersensitivity reaction
Subject C	Week 3 Day 1	Lumbar pain
	Week 17 Day 1	Back pain and rash-maculo papular
Subject D	Week 1 Day 1	Lumbar pain
Subject E	Week 31 Day 1	Cardiac arrythmia
	Week 39 Day 1	Cardiac arrythmia

[a] The verbatim terms reported as other reasons of infusion interruptions were also captured as relevant AE preferred terms on the AE page.

Source: refer to Appendix 4.1 of the CA2098FC Addendum 01 to the Primary CSR[3]

Adverse events leading to dose delays

Any-grade all-causality AEs leading to dose delay (within 30 days of last dose) were reported in 37 (28.7%) subjects in the nivolumab Process C treatment group and 39 (29.5%) subjects in the nivolumab Process D treatment group. Grade 3-4 AEs leading to dose delay were reported in 5 (3.9%) subjects in the nivolumab Process C treatment group and 8 (6.1%) subjects in the nivolumab Process D treatment group.

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

- Nivolumab Process C: ALT increased (4.7%), hyperthyroidism (3.1%), AST increased and diarrhoea (2.3% each), and faecal calprotectin increased and COVID-19 (1.6% each).
- Nivolumab Process D: COVID-19 (3.8%), diarrhoea (3.0%), hyperthyroidism and asthenia (2.3% each), and AST increased, herpes zoster, nausea, and hyperbilirubinemia (1.5% each).

Any-grade drug-related AEs leading to dose delay (within 30 days of last dose) were reported in 25 (19.4%) subjects in the nivolumab Process C treatment group and 21 (15.9%) subjects in the nivolumab Process D treatment group. Grade 3-4 AEs leading to delay were reported in 5 (3.9%) subjects in the nivolumab Process C treatment group and 2 (1.5%) subjects in the nivolumab Process D treatment group.

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

- Nivolumab Process C: ALT increased (4.7%), hyperthyroidism (3.1%), AST increased (2.3%), and diarrhoea (1.6%).
- Nivolumab Process D: diarrhoea (3.0%), ALT increased, hyperthyroidism, and asthenia (2.3% each), and AST increased, nausea, and hyperbilirubinemia (1.5% each).

Table 26: Adverse events leading to dose delay in ≥ 1% of all treated subjects in any treatment

System Organ Class (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	37 (28.7)	5 (3.9)	0	39 (29.5)	8 (6.1)	0
Investigations	12 (9.3)	1 (0.8)	0	4 (3.0)	0	0
Alanine aminotransferase increased	6 (4.7)	1 (0.8)	0	1 (0.8)	0	0
Aspartate aminotransferase increased	3 (2.3)	1 (0.8)	0	2 (1.5)	0	0
Faecal calprotectin increased	2 (1.6)	0	0	0	0	0
Infections and infestations	5 (3.9)	0	0	13 (9.8)	3 (2.3)	0
COVID-19	2 (1.6)	0	0	5 (3.8)	1 (0.8)	0
Herpes zoster	0	0	0	2 (1.5)	0	0
Endocrine disorders	5 (3.9)	0	0	4 (3.0)	1 (0.8)	0
Hyperthyroidism	4 (3.1)	0	0	3 (2.3)	1 (0.8)	0
Gastrointestinal disorders	3 (2.3)	0	0	9 (6.8)	0	0
Diarrhoea	3 (2.3)	0	0	4 (3.0)	0	0
Nausea	0	0	0	2 (1.5)	0	0
General disorders and administration site conditions	4 (3.1)	1 (0.8)	0	4 (3.0)	0	0
Asthenia	1 (0.8)	1 (0.8)	0	3 (2.3)	0	0
Hepatobiliary disorders	0	0	0	3 (2.3)	1 (0.8)	0
Hyperbilirubinaemia	0	0	0	2 (1.5)	0	0

Source: Table S.6.4.2.3

MedDRA Version 24.1. CTC Version 5.0.

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

Table 27: Drug-related adverse events leading to dose delay in ≥ 1% of all treated subjects in any treatment

System Organ Class (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	25 (19.4)	5 (3.9)	0	21 (15.9)	2 (1.5)	0
Investigations	11 (8.5)	1 (0.8)	0	3 (2.3)	0	0
Alanine aminotransferase increased	6 (4.7)	1 (0.8)	0	1 (0.8)	0	0
Aspartate aminotransferase Increased	3 (2.3)	1 (0.8)	0	2 (1.5)	0	0
Endocrine disorders	5 (3.9)	0	0	4 (3.0)	1 (0.8)	0
Hyperthyroidism	4 (3.1)	0	0	3 (2.3)	1 (0.8)	0
Gastrointestinal disorders	2 (1.6)	0	0	8 (6.1)	0	0
Diarrhoea	2 (1.6)	0	0	4 (3.0)	0	0
Nausea	0	0	0	2 (1.5)	0	0
General disorders and administration site conditions	2 (1.6)	1 (0.8)	0	3 (2.3)	0	0
Asthenia	1 (0.8)	1 (0.8)	0	3 (2.3)	0	0
Hepatobiliary disorders	0	0	0	2 (1.5)	0	0
Hyperbilirubinaemia	0	0	0	2 (1.5)	0	0

Source: Table S.6.4.2.4

MedDRA Version 24.1. CTC Version 5.0.

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

2.6.8.2. Adverse events

Table 28: Summary of safety – all treated subjects – CA2098FC

Safety Parameters	Number of Subjects (%)			
	Nivolumab Process C (N = 129)		Nivolumab Process D (N = 132)	
Deaths	15 (11.6)		14 (10.6)	
Primary Reason for Death				
Disease	13 (10.1)		10 (7.6)	
Study Drug Toxicity	0		1 (0.8)	
Unknown	0		1 (0.8)	
Other[a]	2 (1.6)		2 (1.5)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	15 (11.6)	9 (7.0)	20 (15.2)	17 (12.9)
Drug-related SAEs	9 (7.0)	7 (5.4)	7 (5.3)	6 (4.5)
All-causality AEs leading to DC	20 (15.50)	8 (6.2)	20 (15.2)	9 (6.8)
Drug-related AEs leading to DC	15 (11.6)	5 (3.9)	18 (13.6)	8 (6.1)
All-causality AEs	124 (96.1)	23 (17.8)	126 (95.5)	37 (28.0)
Drug-related AEs	114 (88.4)	13 (10.1)	111 (84.1)	17 (12.9)
≥ 15% Drug-related AEs in Any Treatment				
Rash	22 (17.1)	1 (0.8)	28 (21.2)	1 (0.8)
Pruritis	21 (16.3)	0	32 (24.2)	0
Fatigue	31 (24.0)	0	35 (26.5)	0
Diarrhea	15 (11.6)	0	22 (16.7)	2 (1.5)
Hypothyroidism	26 (20.2)	0	24 (18.2)	0
Hyperthyroidism	23 (17.8)	0	21 (15.9)	1 (0.8)
Arthralgia	23 (17.8)	0	18 (13.6)	1 (0.8)
All-causality Select AEs by Category				
Skin	55 (42.6)	2 (1.6)	76 (57.6)	1 (0.8)
Endocrine	45 (34.9)	4 (3.1)	38 (28.8)	4 (3.0)
Gastrointestinal	31 (24.0)	1 (0.8)	40 (30.3)	4 (3.0)
Hepatic	26 (20.2)	1 (0.8)	35 (26.5)	4 (3.0)
Renal	6 (4.7)	0	8 (6.1)	0
Pulmonary	4 (3.1)	0	4 (3.0)	0
Hypersensitivity/Infusion Reactions	2 (1.6)	0	8 (6.1)	0
Drug-related Select AEs by Category				
Skin	52 (40.3)	2 (1.6)	74 (56.1)	1 (0.8)
Endocrine	43 (33.3)	2 (1.6)	37 (28.0)	3 (2.3)

Gastrointestinal	18 (14.0)	1 (0.8)	24 (18.2)	4 (3.0)
Hepatic	18 (14.0)	1 (0.8)	25 (18.9)	3 (2.3)
Pulmonary	4 (3.1)	0	3 (2.3)	0
Renal	3 (2.3)	0	3 (2.3)	0
Hypersensitivity/Infusion Reactions	2 (1.6)	0	8 (6.1)	0
All-causality Non-endocrine IMAEs within 100 days of last dose where Immune Modulating Medication was Initiated by Category				
Rash	13 (10.1)	2 (1.6)	17 (12.9)	2 (1.5)
Diarrhea/Colitis	6 (4.7)	3 (2.3)	7 (5.3)	5 (3.8)
Hepatitis	3 (2.3)	0	8 (6.1)	4 (3.0)
Pneumonitis	3 (2.3)	0	3 (2.3)	1 (0.8)
Nephritis and Renal Dysfunction	2 (1.6)	0	3 (2.3)	0
Hypersensitivity	1 (0.8)	0	2 (1.5)	0
All-causality Endocrine IMAEs within 100 days of last dose by Category				
Adrenal insufficiency	2 (1.6)	1 (0.8)	3 (2.3)	1 (0.8)
Hypothyroidism/Thyroiditis	28 (21.7)	0	27 (20.5)	0
Hypothyroidism	27 (20.9)	0	26 (19.7)	0
Hyperthyroidism	23 (17.8)	0	21 (15.9)	1 (0.8)
Thyroiditis	3 (2.3)	0	1 (0.8)	0
Diabetes Mellitus	2 (1.6)	2 (1.6)	3 (2.3)	2 (1.5)
Hypophysitis	1 (0.8)	0	2 (1.5)	0
All-causality OESIs within 100 days of last dose by Category				
Myositis/Rhabdomyolysis	1 (0.8)	0	1 (0.8)	1 (0.8)
Uveitis	1 (0.8)	0	1 (0.8)	0
Myocarditis	0	0	2 (1.5)	2 (1.5)
Pancreatitis	0	0	2 (1.5)	1 (0.8)

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Note: All events were reported within 30 days after last dose of study therapy unless otherwise indicated.

[a] The verbatim terms reported for the 'other' reasons of death with nivolumab Process C were sepsis secondary to the COVID-19 (147 days after the last dose) and cardiogenic shock (301 days after the last dose); with nivolumab Process D were sudden cardiac death (155 days after the last dose) and cardiogenic shock (477 days after the last dose).

Common adverse events

The overall frequencies of any grade AEs (all causality and drug-related) [within 100 days of last dose] were comparable between the nivolumab Process D and Process C arms. Numerically higher frequencies of all-causality Grade 3-4 AEs were observed in the Process D vs. the Process C arm (44 [33.3%] subjects and 32 [24.8%] subjects, respectively) driven by small differences in some SOCs due to a few event PTs, though no specific patterns were noted with these events.

Table 29: Adverse events by worst CTC grade in ≥ 5% of all treated subjects - CA2098FC

System Organ Class (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**125 (96.9)**	**32 (24.8)**	**0**	**126 (95.5)**	**44 (33.3)**	**0**
General disorders and administration site conditions	69 (53.5)	3 (2.3)	0	71 (53.8)	0	0
Fatigue	38 (29.5)	0	0	43 (32.6)	0	0
Asthenia	14 (10.9)	2 (1.6)	0	18 (13.6)	0	0
Pyrexia	10 (7.8)	0	0	8 (6.1)	0	0
Oedema peripheral	5 (3.9)	0	0	9 (6.8)	0	0
Skin and subcutaneous tissue disorders	69 (53.5)	3 (2.3)	0	86 (65.2)	2 (1.5)	0
Pruritus	26 (20.2)	0	0	35 (26.5)	0	0
Rash	22 (17.1)	1 (0.8)	0	31 (23.5)	1 (0.8)	0
Dry skin	6 (4.7)	0	0	12 (9.1)	0	0
Vitiligo	6 (4.7)	0	0	8 (6.1)	0	0
Rash maculo-papular	3 (2.3)	0	0	13 (9.8)	0	0
Gastrointestinal disorders	63 (48.8)	6 (4.7)	0	75 (56.8)	9 (6.8)	0
Diarrhoea	32 (24.8)	1 (0.8)	0	38 (28.8)	4 (3.0)	0
Nausea	14 (10.9)	0	0	21 (15.9)	2 (1.5)	0
Dry mouth	13 (10.1)	0	0	15 (11.4)	0	0
Constipation	11 (8.5)	0	0	15 (11.4)	0	0
Abdominal pain	10 (7.8)	0	0	6 (4.5)	0	0
Vomiting	10 (7.8)	1 (0.8)	0	9 (6.8)	0	0
Gastrooesophageal reflux disease	3 (2.3)	0	0	7 (5.3)	0	0
Musculoskeletal and connective tissue disorders	61 (47.3)	1 (0.8)	0	63 (47.7)	3 (2.3)	0
Arthralgia	36 (27.9)	0	0	29 (22.0)	1 (0.8)	0
Myalgia	14 (10.9)	0	0	12 (9.1)	0	0
Back pain	11 (8.5)	0	0	17 (12.9)	1 (0.8)	0
Investigations	50 (38.8)	8 (6.2)	0	54 (40.9)	6 (4.5)	0
Alanine aminotransferase increased	18 (14.0)	1 (0.8)	0	21 (15.9)	1 (0.8)	0
Aspartate aminotransferase increased	17 (13.2)	1 (0.8)	0	17 (12.9)	1 (0.8)	0
Blood thyroid stimulating hormone increased	7 (5.4)	0	0	1 (0.8)	0	0
Weight decreased	5 (3.9)	1 (0.8)	0	7 (5.3)	0	0
Nervous system disorders	40 (31.0)	4 (3.1)	0	44 (33.3)	0	0
Headache	20 (15.5)	0	0	23 (17.4)	0	0
Dizziness	10 (7.8)	0	0	5 (3.8)	0	0
Infections and infestations	39 (30.2)	0	0	55 (41.7)	9 (6.8)	0
COVID-19	6 (4.7)	0	0	8 (6.1)	1 (0.8)	0
Endocrine disorders	37 (28.7)	1 (0.8)	0	37 (28.0)	3 (2.3)	0
Hypothyroidism	27 (20.9)	0	0	26 (19.7)	0	0
Hyperthyroidism	23 (17.8)	0	0	22 (16.7)	1 (0.8)	0
Metabolism and nutrition disorders	30 (23.3)	5 (3.9)	0	32 (24.2)	6 (4.5)	0
Decreased appetite	7 (5.4)	0	0	10 (7.6)	0	0
Hyperglycaemia	7 (5.4)	0	0	5 (3.8)	2 (1.5)	0
Hyponatraemia	7 (5.4)	1 (0.8)	0	9 (6.8)	1 (0.8)	0
Respiratory, thoracic and mediastinal disorders	26 (20.2)	0	0	44 (33.3)	3 (2.3)	0
Cough	11 (8.5)	0	0	15 (11.4)	1 (0.8)	0
Psychiatric disorders	17 (13.2)	0	0	20 (15.2)	0	0
Insomnia	10 (7.8)	0	0	11 (8.3)	0	0
Blood and lymphatic system disorders	10 (7.8)	0	0	19 (14.4)	4 (3.0)	0
Anaemia	3 (2.3)	0	0	12 (9.1)	3 (2.3)	0
Vascular disorders	10 (7.8)	1 (0.8)	0	17 (12.9)	3 (2.3)	0
Hypertension	5 (3.9)	1 (0.8)	0	8 (6.1)	3 (2.3)	0

MedDRA Version 24.1. CTC Version 5.0.

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

Source: Table 8.8-1 in Addendum 01 to the CA2098FC Primary CSR[1]

Table 30: Drug-related adverse events by worst CTC grade in ≥ 5% of all treated subjects - CA2098FC

System Organ Class (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**114 (88.4)**	**16 (12.4)**	**0**	**112 (84.8)**	**22 (16.7)**	**0**
Skin and subcutaneous tissue disorders	61 (47.3)	2 (1.6)	0	81 (61.4)	1 (0.8)	0
Rash	22 (17.1)	1 (0.8)	0	28 (21.2)	1 (0.8)	0
Pruritus	21 (16.3)	0	0	34 (25.8)	0	0
Dry skin	5 (3.9)	0	0	9 (6.8)	0	0
Vitiligo	5 (3.9)	0	0	8 (6.1)	0	0
Rash maculo-papular	3 (2.3)	0	0	13 (9.8)	0	0
General disorders and administration site conditions	44 (34.1)	2 (1.6)	0	51 (38.6)	0	0
Fatigue	32 (24.8)	0	0	35 (26.5)	0	0
Asthenia	11 (8.5)	2 (1.6)	0	12 (9.1)	0	0
Gastrointestinal disorders	39 (30.2)	5 (3.9)	0	46 (34.8)	9 (6.8)	0
Diarrhoea	18 (14.0)	1 (0.8)	0	25 (18.9)	4 (3.0)	0
Dry mouth	12 (9.3)	0	0	13 (9.8)	0	0
Nausea	9 (7.0)	0	0	14 (10.6)	1 (0.8)	0
Endocrine disorders	37 (28.7)	1 (0.8)	0	36 (27.3)	2 (1.5)	0
Hypothyroidism	27 (20.9)	0	0	25 (18.9)	0	0
Hyperthyroidism	23 (17.8)	0	0	21 (15.9)	1 (0.8)	0
Musculoskeletal and connective tissue disorders	35 (27.1)	0	0	33 (25.0)	2 (1.5)	0
Arthralgia	25 (19.4)	0	0	19 (14.4)	1 (0.8)	0
Myalgia	9 (7.0)	0	0	10 (7.6)	0	0
Investigations	34 (26.4)	5 (3.9)	0	30 (22.7)	4 (3.0)	0
Alanine aminotransferase increased	12 (9.3)	1 (0.8)	0	17 (12.9)	1 (0.8)	0
Aspartate aminotransferase increased	10 (7.8)	1 (0.8)	0	13 (9.8)	1 (0.8)	0
Nervous system disorders	16 (12.4)	0	0	14 (10.6)	0	0
Headache	3(2.3)	0	0	8 (6.1)	0	0

MedDRA Version 24.1. CTC Version 5.0.

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

Source: Table 8.8-2 in Addendum 01 to the CA2098FC Primary CSR[1]

2.6.8.3. Serious adverse events, deaths, and other significant events

Serious adverse events (SAEs)

Among all treated subjects, the overall proportion of subjects with all-causality SAEs (within 100 days of last dose) was similar between the nivolumab Process C and Process D treatment groups, 24 (18.6%) vs. 28 (21.2%).

Among all treated subjects, the overall proportion of subjects with drug-related SAEs (within 100 days of last dose) was similar between the nivolumab Process C and Process D treatment groups, 11 (8.5%) vs. 9 (6.8%).

There were 2 SAEs of myocarditis attributed to study drug toxicity by the investigator in the nivolumab Process D treatment group. These 2 SAEs were G3 events and resolved in both subjects following steroid therapy instituted per the recommended guidelines.

Table 31: SAEs reported in ≥ 1% of all treated subjects in any treatment

System Organ Class (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**24 (18.6)**	**16 (12.4)**	**0**	**28 (21.2)**	**22 (16.7)**	**0**
Respiratory, thoracic and mediastinal disorders	3 (2.3)	0	0	2 (1.5)	2 (1.5)	0
Pneumonitis	2 (1.6)	0	0	1 (0.8)	1 (0.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.3)	2 (1.6)	0	3 (2.3)	2 (1.5)	0
Metastatic malignant melanoma	2 (1.6)	2 (1.6)	0	2 (1.5)	2 (1.5)	0
Metabolism and nutrition disorders	1 (0.8)	1 (0.8)	0	4 (3.0)	4 (3.0)	0
Diabetic ketoacidosis	1 (0.8)	1 (0.8)	0	3 (2.3)	3 (2.3)	0
Cardiac disorders	1 (0.8)	1 (0.8)	0	4 (3.0)	4 (3.0)	0
Myocarditis	0	0	0	2 (1.5)	2 (1.5)	0

Source: Table S.6.3.1.2.3

MedDRA Version 24.1. CTC Version 5.0.

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

Table 32: Drug-related SAEs reported in ≥ 1% of all treated subjects in any treatment

System Organ Class (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**11 (8.5)**	**8 (6.2)**	**0**	**9 (6.8)**	**9 (6.8)**	**0**
Respiratory, thoracic and mediastinal disorders	2 (1.6)	0	0	1 (0.8)	1 (0.8)	0
Pneumonitis	2 (1.6)	0	0	1 (0.8)	1 (0.8)	0
Cardiac disorders	0	0	0	3 (2.3)	3 (2.3)	0
Myocarditis	0	0	0	2 (1.5)	2 (1.5)	0

Source: Table S.6.3.1.2.4

MedDRA Version 24.1. CTC Version 5.0.

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

Deaths

As of the 18-Feb-2022 DBL, death was reported in 15 (11.6%) subjects in the nivolumab Process C treatment group and 14 (10.6%) subjects in the nivolumab Process D treatment group. Disease progression was the most common cause of death.

Table 33: Death summary – all treated subjects

	Process C N = 129	Process D N = 132	Total N = 261
NUMBER OF SUBJECTS WHO DIED (%)	**15 (11.6)**	**14 (10.6)**	**29 (11.1)**
PRIMARY REASON FOR DEATH (%)			
DISEASE	13 (10.1)	10 (7.6)	23 (8.8)
STUDY DRUG TOXICITY	0	1 (0.8)	1 (0.4)
UNKNOWN	0	1 (0.8)	1 (0.4)
OTHER	2 (1.6)	2 (1.5)	4 (1.5)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	0	0	0
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	0	0	0

Source: Table S.6.15

Deaths attributed to study drug toxicity

There was 1 death attributed to study drug toxicity by the investigator in the nivolumab Process D arm. The subject died (130 days after last dose of nivolumab Process D) due to multiple organ dysfunction considered to be related to treatment by investigator (but deemed not be treatment related by BMS).

Deaths attributed to other reasons

The verbatim terms reported for the "other reasons" were consistent with events expected in the population under study and none were considered related to study drug.

- Nivolumab Process C: sudden cardiac death (155 days after the last dose), cardiogenic shock (477 days after the last dose)
- Nivolumab Process D: sepsis secondary to the COVID-19 (147 days after the last dose), cardiogenic shock (301 days after the last dose)

Select adverse events

The majority of select AEs were Grade 1-2, and most were considered drug-related by the investigator. The numerical difference noted between the two processes in several select AE categories including skin, endocrine, gastrointestinal, hepatic, and hypersensitivity/infusion reactions were primarily driven by low-grade AEs.

The most frequently reported all-causality select AE categories (any grade) [within 100 days of last dose] were as follows in each treatment group:

- Nivolumab Process C: skin (43.4%), endocrine (34.9%), gastrointestinal (25.6%), and hepatic (21.7%).
- Nivolumab Process D: skin (59.1%), endocrine (31.8%), gastrointestinal (31.1%), and hepatic (28.8%).

The most frequently reported all-causality select AE by PT (any grade) [within 100 days of last dose] were as follows in each treatment group:

- Nivolumab Process C: diarrhoea (24.8%), pruritus and hypothyroidism (20.2% each), hyperthyroidism (17.8%), and rash (17.1%).
- Nivolumab Process D: diarrhoea (28.8%), pruritus (26.5%), rash (23.5%), hypothyroidism (19.7%), and hyperthyroidism (16.7%).

The most frequently reported drug-related select AE categories (any grade) [within 100 days of last dose] were as follows in each treatment group:

- Nivolumab Process C: skin (40.3%), endocrine (33.3%), gastrointestinal (14.7%), and hepatic (14.0%).
- Nivolumab Process D: skin (57.6%), endocrine (28.8%), hepatic and gastrointestinal (19.7% each).

The most frequently reported drug-related select AE by PT (any grade) [within 100 days of last dose] were as follows in each treatment group:

- Nivolumab Process C: hypothyroidism (20.9%), hyperthyroidism (17.8%), rash (17.1%), and pruritus (16.3%).

- Nivolumab Process D: pruritus (25.8%), rash (21.2%), hypothyroidism and diarrhea (18.9% each), and hyperthyroidism (15.9%).

All the reported drug-related serious select AEs by PT (any grade) [within 100 days of last dose] were as follows in each treatment group:

- Nivolumab Process C: pneumonitis (1.6%), and colitis, immune-mediated enterocolitis, pemphigus, rash, adrenal insufficiency, and diabetic ketoacidosis (0.8% each).
- Nivolumab Process D: colitis, diarrhoea, enteritis, hepatitis, pneumonitis, adrenal insufficiency, diabetic ketoacidosis, and hyperthyroidism (0.8% each).

Across the select AE categories, the majority of events were manageable using the established algorithms, with resolution occurring when IMMs (mainly systemic corticosteroids) were administered in the nivolumab Process C and Process D treatment groups. At the time of DBL, with the exception of the endocrine category, the majority of subjects' drug-related select AEs had resolved in the nivolumab Process C and Process D treatment groups.

Table 34: Select adverse events by worst CTC grade in ≥ 1% of all treated subjects in any treatment

Select Adverse Event Category Sub Category (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
GASTROINTESTINAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**33 (25.6)**	**3 (2.3)**	**0**	**41 (31.1)**	**6 (4.5)**	**0**
Diarrhoea	32 (24.8)	1 (0.8)	0	38 (28.8)	4 (3.0)	0
Colitis	2 (1.6)	1 (0.8)	0	3 (2.3)	0	0
HEPATIC ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**28 (21.7)**	**2 (1.6)**	**0**	**38 (28.8)**	**5 (3.8)**	**0**
Alanine aminotransferase increased	18 (14.0)	1 (0.8)	0	21 (15.9)	1 (0.8)	0
Aspartate aminotransferase increased	17 (13.2)	1 (0.8)	0	17 (12.9)	1 (0.8)	0
Blood bilirubin increased	5 (3.9)	0	0	4 (3.0)	0	0
Transaminases increased	2 (1.6)	0	0	5 (3.8)	1 (0.8)	0
Hepatitis	1 (0.8)	0	0	5 (3.8)	3 (2.3)	0
Hepatic cytolysis	2 (1.6)	1 (0.8)	0	2 (1.5)	0	0
Hyperbilirubinaemia	0	0	0	3 (2.3)	0	0
PULMONARY ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**4 (3.1)**	**0**	**0**	**5 (3.8)**	**1 (0.8)**	**0**
Pneumonitis	4 (3.1)	0	0	4 (3.0)	1 (0.8)	0
Interstitial lung disease	0	0	0	2 (1.5)	0	0
RENAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**6 (4.7)**	**0**	**0**	**9 (6.8)**	**0**	**0**
Blood creatinine increased	5 (3.9)	0	0	5 (3.8)	0	0
Tubulointerstitial nephritis	1 (0.8)	0	0	2 (1.5)	0	0
SKIN ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**56 (43.4)**	**2 (1.6)**	**0**	**78 (59.1)**	**2 (1.5)**	**0**
Pruritus	26 (20.2)	0	0	35 (26.5)	0	0
Rash	22 (17.1)	1 (0.8)	0	31 (23.5)	1 (0.8)	0
Rash maculo-papular	3 (2.3)	0	0	13 (9.8)	0	0
Vitiligo	6 (4.7)	0	0	8 (6.1)	0	0
Dermatitis	2 (1.6)	0	0	2 (1.5)	0	0
Erythema	4 (3.1)	0	0	0	0	0
Rash macular	2 (1.6)	0	0	2 (1.5)	0	0
Rash papular	1 (0.8)	0	0	3 (2.3)	0	0
Rash pruritic	2 (1.6)	0	0	2 (1.5)	0	0

Skin hypopigmentation	1 (0.8)	0	0	3 (2.3)	0	0
Dermatitis acneiform	1 (0.8)	0	0	2 (1.5)	0	0
Eczema	2 (1.6)	0	0	1 (0.8)	0	0
Psoriasis	1 (0.8)	0	0	2 (1.5)	0	0
HYPERSENSITIVITY/INFUSION REACTION						
TOTAL SUBJECTS WITH AN EVENT	**2 (1.6)**	**0**	**0**	**8 (6.1)**	**0**	**0**
Hypersensitivity	0	0	0	3 (2.3)	0	0
Infusion related hypersensitivity reaction	2 (1.6)	0	0	1 (0.8)	0	0
Infusion related reaction	0	0	0	3 (2.3)	0	0
ENDOCRINE ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**45 (34.9)**	**4 (3.1)**	**0**	**42 (31.8)**	**6 (4.5)**	**0**
THYROID DISORDER	**43 (33.3)**	**0**	**0**	**35 (26.5)**	**1 (0.8)**	**0**
Hypothyroidism	27 (20.9)	0	0	26 (19.7)	0	0
Hyperthyroidism	23 (17.8)	0	0	22 (16.7)	1 (0.8)	0
Blood thyroid stimulating hormone increased	7 (5.4)	0	0	1 (0.8)	0	0
Thyroiditis	2 (1.6)	0	0	1 (0.8)	0	0
DIABETES	**3 (2.3)**	**3 (2.3)**	**0**	**4 (3.0)**	**3 (2.3)**	**0**
Diabetes mellitus	3 (2.3)	3 (2.3)	0	1 (0.8)	1 (0.8)	0
Diabetic ketoacidosis	1 (0.8)	1 (0.8)	0	3 (2.3)	3 (2.3)	0
ADRENAL DISORDER	**2 (1.6)**	**1 (0.8)**	**0**	**4 (3.0)**	**2 (1.5)**	**0**
Adrenal insufficiency	2 (1.6)	1 (0.8)	0	4 (3.0)	2 (1.5)	0
PITUITARY DISORDER	**1 (0.8)**	**0**	**0**	**2 (1.5)**	**0**	**0**
Hypopituitarism	0	0	0	2 (1.5)	0	0

Source: Table S.6.5.1.3.9 (all-causality select AEs), Table S.6.5.1.3.13 (all-causality select endocrine AEs)

MedDRA Version 24.1. CTC Version 5.0.

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

Table 35: Drug-related select adverse events by worst CTC grade in ≥ 1% of all treated subjects in any treatment

Select Adverse Event Category Sub Category (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
GASTROINTESTINAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**19 (14.7)**	**3 (2.3)**	**0**	**26 (19.7)**	**6 (4.5)**	**0**
Diarrhoea	18 (14.0)	1 (0.8)	0	25 (18.9)	4 (3.0)	0
Colitis	2 (1.6)	1 (0.8)	0	2 (1.5)	0	0
HEPATIC ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**18 (14.0)**	**1 (0.8)**	**0**	**26 (19.7)**	**4 (3.0)**	**0**
Alanine aminotransferase increased	12 (9.3)	1 (0.8)	0	17 (12.9)	1 (0.8)	0
Aspartate aminotransferase increased	10 (7.8)	1 (0.8)	0	13 (9.8)	1 (0.8)	0
Blood bilirubin increased	4 (3.1)	0	0	2 (1.5)	0	0
Hepatitis	1 (0.8)	0	0	4 (3.0)	3 (2.3)	0
Hyperbilirubinaemia	0	0	0	3 (2.3)	0	0
Transaminases increased	1 (0.8)	0	0	2 (1.5)	0	0
PULMONARY ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**4 (3.1)**	**0**	**0**	**4 (3.0)**	**1 (0.8)**	**0**
Pneumonitis	4 (3.1)	0	0	4 (3.0)	1 (0.8)	0
RENAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**3 (2.3)**	**0**	**0**	**4 (3.0)**	**0**	**0**
Blood creatinine increased	2 (1.6)	0	0	1 (0.8)	0	0
Tubulointerstitial nephritis	1 (0.8)	0	0	2 (1.5)	0	0
SKIN ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	**52 (40.3)**	**2 (1.6)**	**0**	**76 (57.6)**	**1 (0.8)**	**0**
Pruritus	21 (16.3)	0	0	34 (25.8)	0	0
Rash	22 (17.1)	1 (0.8)	0	28 (21.2)	1 (0.8)	0
Rash maculo-papular	3 (2.3)	0	0	13 (9.8)	0	0
Vitiligo	5 (3.9)	0	0	8 (6.1)	0	0
Rash papular	1 (0.8)	0	0	3 (2.3)	0	0
Skin hypopigmentation	1 (0.8)	0	0	3 (2.3)	0	0
Dermatitis acneiform	1 (0.8)	0	0	2 (1.5)	0	0
Erythema	3 (2.3)	0	0	0	0	0
Psoriasis	1 (0.8)	0	0	2 (1.5)	0	0
Rash pruritic	2 (1.6)	0	0	1 (0.8)	0	0
Rash macular	0	0	0	2 (1.5)	0	0

HYPERSENSITIVITY/INFUSION REACTION						
TOTAL SUBJECTS WITH AN EVENT	2 (1.6)	0	0	8 (6.1)	0	0
Hypersensitivity	0	0	0	3 (2.3)	0	0
Infusion related hypersensitivity reaction	2 (1.6)	0	0	1 (0.8)	0	0
Infusion related reaction	0	0	0	3 (2.3)	0	0
ENDOCRINE ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	43 (33.3)	2 (1.6)	0	38 (28.8)	3 (2.3)	0
THYROID DISORDER	41 (31.8)	0	0	34 (25.8)	1 (0.8)	0
Hypothyroidism	27 (20.9)	0	0	25 (18.9)	0	0
Hyperthyroidism	23 (17.8)	0	0	21 (15.9)	1 (0.8)	0
Blood thyroid stimulating hormone increased	5 (3.9)	0	0	1 (0.8)	0	0
Thyroiditis	2 (1.6)	0	0	1 (0.8)	0	0
ADRENAL DISORDER	2 (1.6)	1 (0.8)	0	3 (2.3)	1 (0.8)	0
Adrenal insufficiency	2 (1.6)	1 (0.8)	0	3 (2.3)	1 (0.8)	0
PITUITARY DISORDER	1 (0.8)	0	0	2 (1.5)	0	0
Hypopituitarism	0	0	0	2 (1.5)	0	0

Source: Table S.6.5.1.3.10 (drug-related select AEs), Table S.6.5.1.3.14 (drug-related select endocrine AEs)
MedDRA Version 24.1. CTC Version 5.0.
Note: Includes events reported between first dose and 100 days after last dose of study therapy.

Table 36: Drug-related serious select adverse events by worst CTC grade in all treated subjects

Select Adverse Event Category Sub Category (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
GASTROINTESTINAL ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	2 (1.6)	2 (1.6)	0	2 (1.5)	2 (1.5)	0
Colitis	1 (0.8)	1 (0.8)	0	1 (0.8)	0	0
Diarrhoea	0	0	0	1 (0.8)	1 (0.8)	0
Enteritis	0	0	0	1 (0.8)	1 (0.8)	0
Immune-mediated enterocolitis	1 (0.8)	1 (0.8)	0	0	0	0
HEPATIC ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	0	0	0	1 (0.8)	1 (0.8)	0
Hepatitis	0	0	0	1 (0.8)	1 (0.8)	0
PULMONARY ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	2 (1.6)	0	0	1 (0.8)	1 (0.8)	0
Pneumonitis	2 (1.6)	0	0	1 (0.8)	1 (0.8)	0
SKIN ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	2 (1.6)	2 (1.6)	0	0	0	0
Pemphigus	1 (0.8)	1 (0.8)	0	0	0	0
Rash	1 (0.8)	1 (0.8)	0	0	0	0
ENDOCRINE ADVERSE EVENT						
TOTAL SUBJECTS WITH AN EVENT	2 (1.6)	2 (1.6)	0	3 (2.3)	3 (2.3)	0
ADRENAL DISORDER	1 (0.8)	1 (0.8)	0	1 (0.8)	1 (0.8)	0
Adrenal insufficiency	1 (0.8)	1 (0.8)	0	1 (0.8)	1 (0.8)	0
DIABETES	1 (0.8)	1 (0.8)	0	1 (0.8)	1 (0.8)	0
Diabetic ketoacidosis	1 (0.8)	1 (0.8)	0	1 (0.8)	1 (0.8)	0
THYROID DISORDER	0	0	0	1 (0.8)	1 (0.8)	0
Hyperthyroidism	0	0	0	1 (0.8)	1 (0.8)	0

Source: Table S.6.5.1.3.12 (drug-related serious select AEs), Table S.6.5.1.3.16 (drug-related serious select endocrine AEs)
MedDRA Version 24.1. CTC Version 5.0.
Note: Includes events reported between first dose and 100 days after last dose of study therapy.

Immune Mediated Adverse Events (IMAEs)

Overall, the majority of IMAEs were Grade 1-2. The most frequently reported IMAE categories (any grade) were as follows in each treatment group:

- Nivolumab Process C: hypothyroidism/thyroiditis (20.9%), hyperthyroidism (17.8%), and rash (10.1%).
- Nivolumab Process D: hypothyroidism/thyroiditis (19.7%), hyperthyroidism (15.9%), and rash (12.9%).

The most frequently (> 1%) reported Grade 3-4 IMAE categories were as follows in each treatment group:

- Nivolumab Process C: diabetes mellitus (1.6%).
- Nivolumab Process D: diarrhoea and hepatitis (2.3%), and diabetes ketoacidosis (1.5% each).

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

Table 37: Onset, management and resolution of all-causality IMAEs within 100 days of last dose – nivolumab Process C treated subjects (N= 129)

IMAE Category	N (%) Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE	Median Time to Resolution (range), wks[a, b]
Pneumonitis	3 (2.3) / 0	12.86 (11.14 - 60.29)	100.0 / 100.0	6.71 (5.14 - 18.71)	100.0	22.29 (6.00 - 31.57)
Diarrhea/Colitis	6 (4.7) / 3 (2.3)	29.79 (3.14 - 56.29)	100.0 / 83.3	12.86 (2.00 - 75.86)	83.3	6.86 (3.43 - 40.71+)
Hepatitis	3 (2.3) / 0	22.29 (7.14 - 24.14)	100.0 / 100.0	12.71 (3.14 - 34.00)	66.7	33.29 (2.14 - 33.29)
Nephritis/Renal Dysfunction	2 (1.6) / 0	15.64 (12.14 - 19.14)	100.0 / 50.0	42.43 (35.43 - 49.43)	0	N.A. (49.71+ - 92.57+)
Rash	13 (10.1)/ 2 (1.6)	5.14 (1.00 - 33.14)	100.0 / 15.4	62.57 (1.00 - 128.29)	61.5	50.29 (1.14 - 106.86+)
Hypersensitivity	1 (0.8) / 0	6.14 (6.14 - 6.14)	100.0 / 0	46.71 (46.71 - 46.71)	100.0	0.14 (0.14 - 0.14)
Adrenal Insufficiency	2 (1.6) / 1 (0.8)	20.71 (16.29 - 25.14)	100.0 / 50.0	85.57 (85.00 - 86.14)	0	N.A. (85.00+ - 86.14+)
Hypothyroidism/ Thyroiditis	28 (21.7) / 0	14.21 (1.71 - 26.86)	0 / 0	N.A.	35.7	N.A. (2.43 - 116.57+)
Diabetes Mellitus	2 (1.6) / 2 (1.6)	38.79 (31.43 - 46.14)	0 / 0	N.A.	0	N.A. (58.29+ - 65.14+)
Hyperthyroidism	23 (17.8) / 0	6.14 (2.14 - 45.71)	13.0 / 0	5.14 (2.29 - 12.00)	87.0	8.14 (2.71 - 88.29+)
Hypophysitis	1 (0.8) / 0	30.71 (30.71 - 30.71)	0 / 0	N.A.	0	N.A. (22.14+ - 22.14+)

Note: Includes events reported after the first dose and within 100 days of last dose of study therapy. Denominator is based on the number of subjects who experienced the event. Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis. Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved. For each subject, the longest duration of immune-mediated AEs is considered.

(A) From Kaplan-Meier estimation.

(B) Symbol + indicates a censored value.

Table 38: Onset, management and resolution of all-causality IMAEs within 100 days of last dose – nivolumab Process D treated subjects (N= 132)

IMAE Category	N (%) Subj. with Any Grade/ Grade 3-4 IMAEs	Median Time to IMAE Onset (range), wks	% Subj. with IMAEs Receiving IMM / High-dose Corticosteroids	Median Duration IMM (range), wks	% Subj. with Resolution of IMAE	Median Time to Resolution (range), wks[a, b]
Pneumonitis	3 (2.3) / 1 (0.8)	24.29 (15.86 - 48.14)	100.0 / 66.7	5.14 (2.00 - 48.00)	66.7	5.57 (2.14 - 52.57+)
Diarrhea/Colitis	7 (5.3) / 5 (3.8)	24.57 (3.29 - 56.71)	100.0 / 100.0	7.57 (0.71 - 21.57)	100.0	5.57 (3.14 - 51.71)
Hepatitis	8 (6.1) / 4 (3.0)	36.14 (6.71 - 63.00)	100.0 / 75.0	6.00 (0.29 - 32.29)	100.0	12.29 (1.00 - 38.14)
Nephritis/Renal Dysfunction	3 (2.3) / 0	34.14 (29.14 - 35.14)	100.0 / 100.0	11.14 (0.57 - 85.29)	33.3	N.A. (2.43 - 88.43+)
Rash	17 (12.9) / 2 (1.5)	14.14 (0.43 - 51.14)	100.0 / 17.6	69.57 (1.71 - 124.29)	82.4	25.71 (7.43 - 124.86+)
Hypersensitivity	2 (1.5) / 0	2.07 (2.0 - 2.14)	100.0 / 0	0.36 (0.14 - 0.57)	100.0	0.14 (0.14 - 0.14)
Adrenal Insufficiency	3 (2.3) / 1 (0.8)	56.57 (9.29 - 63.14)	66.7 / 0	27.57 (6.00 - 49.14)	0	N.A. (6.00+ - 87.29+)
Hypothyroidism/ Thyroiditis	27 (20.5) / 0	14.14 (5.43 - 41.57)	3.7 / 3.7	2.29 (2.9 - 2.9)	26.9	N.A. (0.71 - 114.14+)
Diabetes Mellitus	3 (2.3) / 2 (1.5)	6.43 (5.14 - 42.14)	0 / 0	N.A.	66.7	1.00 (0.57 - 65.43+)
Hyperthyroidism	21 (15.9) / 1 (0.8)	5.14 (1.86 - 42.0)	9.5 / 4.8	4.50 (1.86 - 7.14)	95.2	5.14 (2.14 - 66.43+)
Hypophysitis	2 (1.5) / 0	32.86 (14.29 - 51.43)	50.0 / 0	68.00 (68.0 - 68.0)	0	N.A. (19.86+ - 68.14+)

Note: Includes events reported after the first dose and within 100 days of last dose of study therapy. Denominator is based on the number of subjects who experienced the event. Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis. Events without a stop date or with a stop date equal to the death as well as Grade 5 events are considered unresolved. For each subject, the longest duration of immune-mediated AEs is considered.

(A) From Kaplan-Meier estimation.

(B) Symbol + indicates a censored value.

Source: Table 8.6.1.1-1 (pneumonitis), Table 8.6.1.2-1 (diarrhea/colitis), Table 8.6.1.2-2 (diarrhea/colitis), Table 8.6.1.3-1 (hepatitis), Table 8.6.1.3-2 (hepatitis), Table 8.6.1.4-1 (nephritis/renal dysfunction), Table 8.6.1.4-2 (nephritis/renal dysfunction), Table 8.6.1.5-1 (rash), Table 8.6.1.5-2 (rash), Table 8.6.1.6-1 (hypersensitivity), Table 8.6.1.6-2 (hypersensitivity), Table 8.6.2.1-1 (adrenal insufficiency), Table 8.6.2.2-1 (hypophysitis), Table 8.6.2.2-2 (hypophysitis), Table 8.6.2.3-1 (hypothyroidism/thyroiditis), Table 8.6.2.3-2 (hypothyroidism/thyroiditis), Table 8.6.2.4-1 (hyperthyroidism), Table 8.6.2.4-2 (hyperthyroidism), Table 8.6.2.5-1 (diabetes mellitus), and Table 8.6.2.5-2 (diabetes mellitus) in Addendum 01 to the CA2098FC Primary CSR[1]

Hepatitis

Any-grade hepatitis IMAEs (within 100 days of last dose) were reported in 3 (2.3%) subjects in the nivolumab Process C treatment group and 8 (6.1%) subjects in the nivolumab Process D treatment group. Grade 3-4 hepatitis IMAEs were reported in 4 (3.0%) subjects in the nivolumab Process D treatment group and no subjects in the nivolumab Process C treatment group.

Table 39: Immune-mediated adverse events adverse events by worst CTC grade in the hepatitis category - all treated subjects

Immune-Mediated AE Category Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
HEPATITIS						
TOTAL SUBJECTS WITH AN EVENT	3 (2.3)	0	0	8 (6.1)	4 (3.0)	0
Alanine aminotransferase increased	2 (1.6)	0	0	2 (1.5)	1 (0.8)	0
Hepatitis	0	0	0	4 (3.0)	3 (2.3)	0
Aspartate aminotransferase increased	2 (1.6)	0	0	1 (0.8)	1 (0.8)	0
Hyperbilirubinaemia	0	0	0	2 (1.5)	0	0
Transaminases increased	1 (0.8)	0	0	0	0	0

Source: Table S.6.2.02.2 (non-endocrine immune-mediated AEs)

MedDRA Version 24.1. CTC Version 5.0.

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

Other Events of Special Interest (OESIs)

Among all treated subjects, OESIs (regardless of causality or IMM treatment, with extended follow-up) were infrequent, and all events resolved by the time of DBL:

- Nivolumab Process C: OESIs were reported in 2 subjects (4 events), all of which resolved at the time of the DBL. Two of these events were resolved with IMMs.
- Nivolumab Process D: OESIs were reported in 5 subjects (17 events), of which all events resolved with IMMs at the time of the DBL.

Table 40: 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 Process C				
Uveitis				
Grade 1 drug-related AE uveitis	none	04-Sep-2020 (156)	1	Yes
Grade 2 drug-related AE uveitis	dexamethasone	05-Sep-2020 (157)	21	Yes
Grade 1 drug-related AE uveitis	none	26-Sep-2020 (178)	42	Yes
Rhabdomyolysis				
Grade 2 drug-related AE rhabdomyolysis	prednisone	07-Feb-2020 (31)	124	Yes
Nivolumab Process D				
Pancreatitis				
Grade 2 drug-related AE pancreatitis	pancrelipase, prednisone	13-Oct-2020 (86)	52	Yes
Grade 3 drug-related SAE pancreatitis	prednisone	01-Feb-2021 (134)	26	Yes
Grade 2 drug-related AE pancreatitis	prednisone	27-Feb-2021 (160)	11	Yes
Grade 2 drug-related AE pancreatitis	prednisone	12-Mar-2021 (173)	83	Yes
Uveitis				
Grade 1 drug-related AE uveitis	atropine, dexamethasone, oxytetracycline, sodium phosphate	12-May-2020 (92)	59	Yes
Grade 2 drug-related AE uveitis	dexamethasone, sodium phosphate	09-Jul-2020 (150)	14	Yes
Grade 1 drug-related AE uveitis	dexamethasone, sodium phosphate	22-Jul-2020 (163)	7	Yes
Grade 1 drug-related AE uveitis	dexamethasone	04-Sep-2020 (156)	13	Yes
Grade 2 drug-related AE uveitis	dexamethasone	05-Sep-2020 (157)	4	Yes
Grade 1 drug-related AE uveitis	dexamethasone	26-Sep-2020 (178)	4	Yes
Myocarditis				
Grade 3 drug-related SAE myocarditis	methylprednisolone, prednisone	11-Sep-2019 (38)	14	Yes
Grade 2 drug-related AE myocarditis	mycophenolate mofetil, prednisone	25-Sep-2019 (52)	230	Yes
Grade 3 drug-related SAE myocarditis	methylprednisolone, ramipril	07-Nov-2019 (67)	5	Yes
Myositis				
Grade 3 drug-related SAE myositis	methylprednisolone, mycophenolate mofetil, prednisone	11-Sep-2019 (38)	24	Yes
Grade 2 drug-related AE myositis	mycophenolate mofetil, prednisone	05-Oct-2019 (62)	220	Yes
Grade 2 drug-related SAE myositis	Prednisone	07-Feb-2020 (31)	13	Yes
Grade 1 drug-related AE myositis	prednisone	12-May-2020 (282)	84	Yes

Source: Appendix 6.83.1 (for OESI and IMM), Appendix 6.1.1 (for seriousness and duration of event)
MedDRA Version 24.1. CTC Version 5.0.
Note: Other Events of Special Interest included preferred terms describing specific events reported within 100 days of last dose.

2.6.8.4. Laboratory findings

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were primarily Grade 1 or 2 in severity.

The following Grade 3 hematologic abnormalities were reported in all treated subjects with on-treatment laboratory results:

- Nivolumab Process C: lymphocytes (absolute) decreased (2.7%) and absolute neutrophil count decreased (0.8%)
- Nivolumab Process D: haemoglobin decreased (2.3%), lymphocytes (absolute) decreased (0.9%), and absolute neutrophil count decreased (0.8%).

Serum Chemistry

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 group.

One (0.8%) subject in the nivolumab Process C treatment group and no subjects in the nivolumab Process D treatment group had concurrent ALT or AST > 3 × ULN with total bilirubin > 1.5 × ULN within 30 days, based on laboratory results reported after the first dose and within 30 days of last dose of study therapy.

Table 41: Summary of laboratory abnormalities in specific liver tests (SI Units) – all treated subjects

Abnormality (%)	Process C N = 129	Process D N = 132	Total N = 261
	N = 129	N = 132	N = 261
ALT or AST > 3xULN (%)	8 (6.2)	8 (6.1)	16 (6.1)
ALT or AST > 5xULN (%)	1 (0.8)	4 (3.0)	5 (1.9)
ALT or AST > 10xULN (%)	0	1 (0.8)	1 (0.4)
ALT or AST > 20xULN (%)	0	0	0
	N = 129	N = 132	N = 261
TOTAL BILIRUBIN > 2xULN	1 (0.8)	4 (3.0)	5 (1.9)
	N = 129	N = 132	N = 261
ALP > 1.5xULN	5 (3.9)	5 (3.8)	10 (3.8)
	N = 129	N = 132	N = 261
CONCURRENT ALT OR AST ELEVATION > 3xULN WITH TOTAL BILIRUBIN > 1.5xULN WITHIN ONE DAY (%)	0	0	0
CONCURRENT ALT OR AST ELEVATION > 3xULN WITH TOTAL BILIRUBIN > 1.5xULN WITHIN 30 DAYS (%)	1 (0.8)	0	1 (0.4)
CONCURRENT ALT OR AST ELEVATION > 3xULN WITH TOTAL BILIRUBIN > 2xULN WITHIN ONE DAY (%)	0	0	0
CONCURRENT ALT OR AST ELEVATION > 3xULN WITH TOTAL BILIRUBIN > 2xULN WITHIN 30 DAYS (%)	0	0	0

Source: Table S.7.6.4

Note: Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy. Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.

Kidney function tests

Most subjects with at least 1 on-treatment measurement had normal creatinine values during the treatment reporting period. The abnormalities in creatinine (increases from baseline) were reported as Grade 1 or 2. No subjects in the nivolumab Process C or Process D treatment groups had a Grade 3 or 4 increased creatinine level.

Thyroid function tests

The majority of all treated subjects in each treatment group had normal TSH levels at baseline and throughout the treatment period.

TSH (SI units) increases (> ULN) from baseline (≤ ULN) were reported in 46 (35.7%) and 49 (37.1%) of subjects in the nivolumab Process C and Process D treatment groups, respectively. Decreases (< LLN) from baseline (≥ LLN) were reported in 43 (33.3%) and 44 (33.3%) of subjects in the nivolumab Process C and Process D treatment groups, respectively.

Table 42: Summary of laboratory abnormalities in specific thyroid tests (SI Units) – all treated subjects with at least one on-treatment TSH measurement

Abnormality (%)	Process C N = 129	Process D N = 132	Total N = 261
	N = 129	N = 132	N = 261
TSH > ULN	46 (35.7)	49 (37.1)	95 (36.4)
	N = 129	N = 132	N = 261
WITH TSH <= ULN AT BASELINE	42 (32.6)	40 (30.3)	82 (31.4)
	N = 74	N = 76	N = 150
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	24 (32.4)	23 (30.3)	47 (31.3)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	20 (27.0)	16 (21.1)	36 (24.0)
WITH FT3/FT4 TEST MISSING (A) (B)	2 (2.7)	10 (13.2)	12 (8.0)
	N = 129	N = 132	N = 261
TSH < LLN	43 (33.3)	44 (33.3)	87 (33.3)
	N = 129	N = 132	N = 261
WITH TSH >= LLN AT BASELINE	41 (31.8)	43 (32.6)	84 (32.2)
	N = 74	N = 76	N = 150
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	31 (41.9)	30 (39.5)	61 (40.7)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	11 (14.9)	10 (13.2)	21 (14.0)
WITH FT3/FT4 TEST MISSING (A) (B)	1 (1.4)	4 (5.3)	5 (3.3)

Source: Table S.7.6.3

Note: Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.

(A) Within a 2-week window after the abnormal TSH test date.

(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.

Electrolytes

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:

- Nivolumab Process C: hyperkalaemia (1.6%), hypokalaemia (1.6%), hypoglycaemia (0.8%).
- Nivolumab Process D: hyponatremia (2.3%).

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Not applicable.

2.6.8.7. Immunological events

Effect of immunogenicity on safety

Nivolumab Process C

In the nivolumab Process C treatment group, the incidence of nivolumab ADA was low, and an effect of ADA on the safety of nivolumab Process C treatment was not observed.

Among the nivolumab Process C treated subjects evaluable and positive for nivolumab ADA (N = 3), no subject had hypersensitivity/infusion-related reaction select AEs, compared with 2 of 115 subjects (1.7%) in the nivolumab ADA-negative subgroup. Thus, for the nivolumab Process C treatment, the presence of nivolumab ADA did not appear to be associated with the occurrence of these events.

Nivolumab Process D

Overall, an effect of ADA on the safety of nivolumab Process D treatment was not observed.

Among the nivolumab Process D treated subjects evaluable and positive for nivolumab ADA, 1 of 8 subjects had hypersensitivity/infusion-related reaction select AEs, compared with 7 of 115 subjects in the nivolumab ADA-negative subgroup. The reported hypersensitivity/infusion reaction in the one ADA-positive subject was a Grade 2 infusion-related reaction (infusion reaction back pain) that resolved within 1 day without treatment.

Table 43: Select AEs of hypersensitivity/infusion reaction by ADA status (positive, negative) for AEs – all treated subjects with ADA positive or ADA negative

	Process C		Process D	
Preferred Term (%)	Nivolumab ADA Positive N = 3	Nivolumab ADA Negative N = 115	Nivolumab ADA Positive N = 8	Nivolumab ADA Negative N = 115
TOTAL SUBJECTS WITH AN EVENT	0	2 (1.7)	1 (12.5)	7 (6.1)
Hypersensitivity	0	0	0	4 (3.5)
Infusion related hypersensitivity reaction	0	2 (1.7)	0	1 (0.9)
Infusion related reaction	0	0	1 (12.5)	1 (0.9)
Bronchospasm	0	0	0	1 (0.9)

Source: Table S.7.13.3

MedDRA Version 24.0. CTC Version 5.0.

Note: Includes events between first dose and within the last dose of therapy + 100 days.

For additional details on immunogenicity see section Outcomes and estimation – immunogenicity results.

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

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

2.6.8.9. Discontinuation due to adverse events

Table 44: Adverse events leading to discontinuation in ≥ 1% of all treated subjects in any treatment

System Organ Class (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**22 (17.1)**	**9 (7.0)**	**0**	**25 (18.9)**	**11 (8.3)**	**0**
Gastrointestinal disorders	4 (3.1)	2 (1.6)	0	8 (6.1)	4 (3.0)	0
Colitis	2 (1.6)	0	0	1 (0.8)	0	0
Gastritis	2 (1.6)	1 (0.8)	0	1 (0.8)	1 (0.8)	0
Diarrhoea	0	0	0	2 (1.5)	0	0
Respiratory, thoracic and mediastinal disorders	4 (3.1)	0	0	3 (2.3)	1 (0.8)	0
Pneumonitis	2 (1.6)	0	0	3 (2.3)	1 (0.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.3)	3 (2.3)	0	0	0	0
Metastatic malignant melanoma	2 (1.6)	2 (1.6)	0	0	0	0
Renal and urinary disorders	2 (1.6)	0	0	2 (1.5)	0	0
Tubulointerstitial nephritis	1 (0.8)	0	0	2 (1.5)	0	0
Cardiac disorders	0	0	0	2 (1.5)	2 (1.5)	0
Myocarditis	0	0	0	2 (1.5)	2 (1.5)	0
Hepatobiliary disorders	0	0	0	4 (3.0)	2 (1.5)	0
Hepatitis	0	0	0	4 (3.0)	2 (1.5)	0

Source: Table S.6.4.2.5

MedDRA Version 24.1. CTC Version 5.0.

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

Table 45: Drug-related adverse events leading to discontinuation in ≥ 1% of all treated subjects in any treatment

System Organ Class (%) Preferred Term (%)	Process C N = 129			Process D N = 132		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**16 (12.4)**	**5 (3.9)**	**0**	**23 (17.4)**	**10 (7.6)**	**0**
Gastrointestinal disorders	4 (3.1)	2 (1.6)	0	8 (6.1)	4 (3.0)	0
Colitis	2 (1.6)	0	0	1 (0.8)	0	0
Gastritis	2 (1.6)	1 (0.8)	0	1 (0.8)	1 (0.8)	0
Diarrhoea	0	0	0	2 (1.5)	0	0
Respiratory, thoracic and mediastinal disorders	3 (2.3)	0	0	3 (2.3)	1 (0.8)	0
Pneumonitis	2 (1.6)	0	0	3 (2.3)	1 (0.8)	0
Renal and urinary disorders	2 (1.6)	0	0	2 (1.5)	0	0
Tubulointerstitial nephritis	1 (0.8)	0	0	2 (1.5)	0	0
Cardiac disorders	0	0	0	2 (1.5)	2 (1.5)	0
Myocarditis	0	0	0	2 (1.5)	2 (1.5)	0
Hepatobiliary disorders	0	0	0	4 (3.0)	2 (1.5)	0
Hepatitis	0	0	0	4 (3.0)	2 (1.5)	0

Source: Table S.6.4.2.6

MedDRA Version 24.1. CTC Version 5.0.

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

2.6.8.10. Post marketing experience

Not applicable. Nivolumab manufactured following Process D has not been commercialized yet.

Analyses performed across trials

Exposure-adjusted unique select adverse events in CA2098FC and across pooled nivolumab monotherapy studies

Numerically higher rates of select AEs in several categories including skin, hepatic, gastrointestinal, and hypersensitivity / infusion reactions were observed in the Process D arm compared to the Process C arm. In addition, 3 Grade 3 drug-related/treatment emergent cardiac disorder events (2 myocarditis events and 1 angina pectoris event) were reported in the Process D arm vs none in the Process C arm.

In order to better understand and provide context for these observed numerical differences between treatment arms in CA2098FC, an exposure-adjusted analysis was conducted. Exposure-adjusted safety data from study CA2098FC for nivolumab Process D and Process C were assessed side-by-side with a pooled nivolumab monotherapy group across all tumor types, as well as a pooled melanoma subset.

Table 46: Exposure-adjusted any grade unique select adverse event summary - All treated subjects

	CA2098FC Process C Arm N=129			CA2098FC Process D Arm N=132			Pooled Nivo Mono (multiple studies) N=7327			Pooled Nivo Mono Melanoma Subset (multiple studies) N=1379		
AE Category/PT	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)
Total subjects with an event	94 (72.9)	49.1	191.4 (154.7, 234.3)	107 (81.1)	47.5	225.3 (184.6, 272.2)	5002 (68.3)	2350.4	212.8 (207.0, 218.8)	1081 (78.4)	425.6	254.0 (239.1, 269.6)
Hepatic	28 (21.7)	111.7	25.1 (16.7, 36.2)	38 (28.8)	118.4	32.1 (22.7, 44.1)	1316 (18.0)	5469.4	24.1 (22.8, 25.4)	210 (15.2)	1333.9	15.7 (13.7, 18.0)
Skin	56 (43.4)	86.4	64.8 (49.0, 84.2)	78 (59.1)	77.6	100.5 (79.5, 125.4)	2683 (36.6)	3929.8	68.3 (65.7, 70.9)	739 (53.6)	709.6	104.1 (96.8, 111.9)
Hypersensitivity/ infusion reaction	2 (1.6)	131.6	1.5 (0.2, 5.5)	8 (6.1)	136.2	5.9 (2.5, 11.6)	337 (4.6)	5990.0	5.6 (5.0, 6.3)	71 (5.1)	1400.6	5.1 (4.0, 6.4)
Gastrointestinal	33 (25.6)	108.2	30.5 (21.0, 42.8)	41 (31.1)	112.8	36.3 (26.1, 49.3)	1885 (25.7)	4828.5	39.0 (37.3, 40.8)	501 (36.3)	1007.3	49.7 (45.5, 54.3)

P-Y = person-years of exposure based on time to first onset.

Incidence rate per 100 person-years of exposure (IR/100 P-Y) = event count * 100/person-years of exposure.

MedDRA Version: 24.1.

Studies included in the pooled nivolumab monotherapy dataset - all indications globally: CA209003, CA209004, CA209010, CA209012, CA209017, CA209025, CA209032, CA209037, CA209039, CA209040, CA209057, CA209063, CA209066, CA209067, CA209078, CA209140, CA209141, CA209142, CA209143, CA209205, CA209227, CA209238, CA209274, CA209275, CA209331, CA209451, CA209459, CA209577, ONO-4538-12, ONO-4538-24

Studies included in the pooled nivolumab monotherapy dataset – melanoma, globally: CA209003, CA209004, CA209037, CA209066, CA209067, CA209238.

Includes events reported between first dose and 100 days after last dose of study therapy, except for ONO-4538-12 and ONO-4538-24. ONO-4538-12 and ONO-4538-24 include events reported between first dose and the earlier date between 28 days after the end of treatment period or the start date of the posttreatment observation period.

95% Confidence interval for rate is based on the exact method for Poisson distribution.

Source: Table 2 and Table 4 in Appendix 1

Table 47: Exposure-adjusted grade 3-4 unique select adverse event summary - all treated subjects

AE Category/PT	CA2098FC Process C Arm N=129			CA2098FC Process D Arm N=132			Pooled Nivo Mono (multiple studies) N=7327			Pooled Nivo Mono Melanoma Subset (multiple studies) N=1379		
	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)
Total subjects with an event	12 (9.3)	130	9.2 (4.8, 16.1)	21 (15.9)	138.3	15.2 (9.4, 23.2)	1151 (15.7)	5800.3	19.8 (18.7, 21.0)	207 (15.0)	1370.9	15.1 (13.1, 17.3)
Hepatic	2 (1.6)	133.6	1.5 (0.2, 5.4)	5 (3.8)	143.5	3.5 (1.1, 8.1)	476 (6.5)	6081.1	7.8 (7.1, 8.6)	71 (5.1)	1444.2	4.9 (3.8, 6.2)
Skin	2 (1.6)	133	1.5 (0.2, 5.4)	2 (1.5)	144	1.4 (0.2, 5.0)	135 (1.8)	6218.1	2.2 (1.8, 2.6)	29 (2.1)	1458.9	2.0 (1.3, 2.9)
Hypersensitivity/ infusion reaction	0	134.1	0.0 (0.0, 2.8)	0	144.4	0.0 (0.0, 2.6)	25 (0.3)	6268.7	0.4 (0.3, 0.6)	3 (0.2)	1470.0	0.2 (0.0, 0.6)
Gastrointestinal	3 (2.3)	133.6	2.2 (0.5, 6.6)	6 (4.5)	143.4	4.2 (1.5, 9.1)	181 (2.5)	6219.4	2.9 (2.5, 3.4)	57 (4.1)	1451.3	3.9 (3.0, 5.1)

P-Y = person-years of exposure based on time to first onset.

Incidence rate per 100 person-years of exposure (IR/100 P-Y) = event count * 100/person-years of exposure.

MedDRA Version: 24.1.

Studies included in the pooled nivolumab monotherapy dataset - all indications globally: CA209003, CA209004, CA209010, CA209012, CA209017, CA209025, CA209032, CA209037, CA209039, CA209040, CA209057, CA209063, CA209066, CA209067, CA209078, CA209140, CA209141, CA209142, CA209143, CA209205, CA209227, CA209238, CA209274, CA209275, CA209331, CA209451, CA209459, CA209577, ON-O4538-12, ONO-4538-24

Studies included in the pooled nivolumab monotherapy dataset – melanoma, globally: CA209003, CA209004, CA209037, CA209066, CA209067, CA209238.

Includes events reported between first dose and 100 days after last dose of study therapy, except for ONO-4538-12 and ONO-4538-24. ONO-4538-12 and ONO-4538-24 include events reported between first dose and the earlier date between 28 days after the end of treatment period or the start date of the posttreatment observation period.

95% Confidence interval for rate is based on the exact method for Poisson distribution.

Source: Table 2 and Table 4 in Appendix 1

Table 48: Exposure-adjusted grade 3-4 cardiac disorder adverse event summary - all treated subjects

AE Category/PT	CA2098FC Process C Arm N=129			CA2098FC Process D Arm N=132			Pooled Nivo Mono (multiple studies) N=7327			Pooled Nivo Mono Melanoma Subset (multiple studies) N=1379		
	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)
Cardiac disorders[a]	1 (0.8)	134.1	0.7 (0.0, 4.2)	5 (3.8)	141.8	3.5 (1.1, 8.2)	171 (2.3)	6210.3	2.8 (2.4, 3.2)	26 (1.9)	1459.2	1.8 (1.2, 2.6)
Myocarditis	0	134.1	0.0 (0.0, 2.8)	2 (1.5)	144	1.4 (0.2, 5.0)	4 (<0.1)	6280.5	0.1 (0.0, 0.2)	0	1474.0	0.0 (0.0, 0.3)
Angina pectoris	0	134.1	0.0 (0.0, 2.8)	1 (0.8)	144.1	0.7 (0.0, 3.9)	3 (<0.1)	6280.5	0.0 (0.0, 0.1)	0	1474.0	0.0 (0.0, 0.3)

P-Y = person-years of exposure based on time to first onset.

Incidence rate per 100 person-years of exposure (IR/100 P-Y) = event count * 100/person-years of exposure.

MedDRA Version: 24.1.

Studies included in the pooled nivolumab monotherapy dataset - all indications globally: CA209003, CA209004, CA209010, CA209012, CA209017, CA209025, CA209032, CA209037, CA209039, CA209040, CA209057, CA209063, CA209066, CA209067, CA209078, CA209140, CA209141, CA209142, CA209143, CA209205, CA209227, CA209238, CA209274, CA209275, CA209331, CA209451, CA209459, CA209577, ONO-4538-12, ONO453824

Studies included in the pooled nivolumab monotherapy dataset – melanoma, globally: CA209003, CA209004, CA209037, CA209066, CA209067, CA209238.

Includes events reported between first dose and 100 days after last dose of study therapy, except for ONO-4538-12 and ONO-4538-24. ONO-4538-12 and ONO-4538-24 include events reported between first dose and the earlier date between 28 days after the end of treatment period or the start date of the posttreatment observation period.

95% Confidence interval for rate is based on the exact method for Poisson distribution.

[a]Cardiac Disorders is a SOC of interest instead of a select AE category per BMS definition.

Source: Table 2 and Table 4 in Appendix 1

Table 49: Exposure-adjusted pancreatitis event summary (any grade and G3-4), by category and PT – all treated subjects in CA2098FC

Table 14 Exposure-Adjusted Pancreatitis Event Summary (Any Grade and Grade 3-4), By Category and PT - All Treated Subjects in CA2098FC

Pancreatitis AE Category/PT	CA2098FC Process C Arm N=129			CA2098FC Process D Arm N=132			Pooled Nivo Mono (multiple studies) N=7327			Pooled Nivo Mono Melanoma Subset (multiple studies) N=1379		
	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)	n (%)	P-Y	IR/100 P-Y (95% CI)
Any Grade												
Pancreatitis AE	0	134.5	0.0 (0.0, 2.7)	2 (1.5)	143.9	1.4 (0.2, 5.0)	36 (0.5)	6265.8	0.6 (0.4, 0.8)	14 (1.0)	1467.8	1.0 (0.5, 1.6)
Pancreatitis	0	134.5	0.0 (0.0, 2.7)	2 (1.5)	143.9	1.4 (0.2, 5.0)	30 (0.4)	6267.1	0.5 (0.3, 0.7)	12 (0.9)	1468.2	0.8 (0.4, 1.4)
Autoimmune pancreatitis	NR	NR	NR	NR	NR	NR	3 (<0.1)	6280.5	0.0 (0.0, 0.1)	2 (0.1)	1473.6	0.1 (0.0, 0.5)
Acute pancreatitis	NR	NR	NR	NR	NR	NR	2 (<0.1)	6281.3	0.0 (0.0, 0.1)	0	1474.0	0.0 (0.0, 0.3)
Subacute pancreatitis	NR	NR	NR	NR	NR	NR	1 (<0.1)	6281.4	0.0 (0.0, 0.1)	0	1474.0	0.0 (0.0, 0.3)
Grade 3-4												
Pancreatitis AE	0	134.5	0.0 (0.0, 2.7)	1 (0.8)	144.1	0.7 (0.0, 3.9)	20 (0.3)	6273.9	0.3 (0.2, 0.5)	10 (0.7)	1471.2	0.7 (0.3, 1.2)
Pancreatitis	0	134.5	0.0 (0.0, 2.7)	1 (0.8)	144.1	0.7 (0.0, 3.9)	16 (0.2)	6275.0	0.3 (0.1, 0.4)	8 (0.6)	1471.6	0.5 (0.2, 1.1)
Autoimmune pancreatitis	NR	NR	NR	NR	NR	NR	3 (<0.1)	6280.5	0.0 (0.0, 0.1)	2 (0.1)	1473.6	0.1 (0.0, 0.5)
Acute pancreatitis	NR	NR	NR	NR	NR	NR	1 (<0.1)	6281.4	0.0 (0.0, 0.1)	0	1474.0	0.0 (0.0, 0.3)

Abbreviations: NR: (PT) not reported in the source outputs; P-Y = person-years of exposure based on time to first onset.

Incidence rate per 100 person-years of exposure (IR/100 P-Y) = event count * 100/person-years of exposure.

MedDRA Version: 24.1.

Studies included in the pooled nivolumab monotherapy dataset - all indications globally: CA209003, CA209004, CA209010, CA209012, CA209017, CA209025, CA209032, CA209037, CA209039, CA209040, CA209057, CA209063, CA209066, CA209067, CA209078, CA209140, CA209141, CA209142, CA209143, CA209205, CA209227, CA209238, CA209274, CA209275, CA209331, CA209451, CA209459, CA209577, ONO-453812, ONO453824

Studies included in the pooled nivolumab monotherapy dataset – melanoma, globally: CA209003, CA209004, CA209037, CA209066, CA209067, CA209238.

Includes events reported between first dose and 100 days after last dose of study therapy, except for ONO-4538-12 and ONO-4538-24. ONO-4538-12 and ONO-4538-24 include events reported between first dose and the earlier date between 28 days after the end of treatment period or the start date of the posttreatment observation period.

95% Confidence interval for rate is based on the exact method for Poisson distribution.

Source: Table 1 (Pooled nivo monotherapy studies) and Table 2 (CA2098FC) in Appendix 5

Drug-related select adverse events and all causality cardiac disorder events in CA2098FC versus pooled nivolumab monotherapy and combination therapy studies

Table 50: Drug-related select AEs (by category and PT) within 30 days of last dose reported in CA2098FC versus pooled nivolumab monotherapy and combination therapy studies

Select AE Category Sub-Category/Preferred Term	CA2098FC Nivo Process C N = 129			CA2098FC Nivo Process D N = 132			Nivo Mono[a] N =4122			Nivo+Chemo[b] N = 1268			Nivo+Ipi (±Chemo)[a,c] N =2094			Nivo+Cabo[a] N = 320		
	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5
Gastrointestinal	18 (14.0)	1 (0.8)	0	24 (18.2)	4 (3.0)	0	631 (15.3)	62 (1.5)	0	335 (26.4)	51 (4.0)	0	580 (27.7)	145 (6.9)	1 (<0.1)	189 (59.1)	22 (6.9)	0
Diarrhoea	15 (11.6)	0	0	22 (16.7)	2 (1.5)	0	608 (14.8)	43 (1.0)	0	322 (25.4)	39 (3.1)	0	537 (25.6)	92 (4.4)	1 (<0.1)	187 (58.4)	21 (6.5)	0
Colitis	2 (1.6)	0	0	2 (1.5)	0	0	50 (1.2)	23 (0.6)	0	19 (1.5)	10 (0.8)	0	108 (5.2)	67 (3.2)	0	3 (0.9)	0	0
Autoimmune colitis	0	0	0	1 (0.8)	1 (0.8)	0	2 (<0.1)	1 (0.1)	0	2 (0.2)	2 (0.2)	0	7 (0.3)	4 (0.2)	0	NR	NR	NR
Enteritis	0	0	0	1 (0.8)	1 (0.8)	0	2 (<0.1)	1 (<0.1)	0	2 (0.2)	1 (<0.1)	0	3 (0.1)	1 (<0.1)	0	1 (0.3)	1 (0.3)	0
Frequent bowel movements	1 (0.8)	0	0	0	0	0	9 (0.2)	0	0	NR	NR	NR	2 (<0.1)	0	0	2 (0.6)	0	0
Immune-mediated enterocolitis	1 (0.8)	1 (0.8)	0	0	0	0	2 (<0.1)	2 (<0.1)	0	3 (0.2)	2 (0.2)	0	6 (0.3)	5 (0.2)	0	NR	NR	NR
Hepatic	18 (14.0)	1 (0.8)	0	25 (18.9)	3 (2.3)	0	311 (7.5)	73 (1.8)	0	249 (19.6)	36 (2.8)	0	402 (19.2)	188 (9.0)	0	133 (41.6)	35 (10.9)	0
ALT increased	12 (9.3)	1 (0.8)	0	15 (11.4)	0	0	161 (3.9)	33 (0.8)	0	115 (9.1)	8 (0.6)	0	223 (10.6)	89 (4.3)	0	86 (26.9)	16 (5.0)	0
AST increased	10 (7.8)	1 (0.8)	0	12 (9.1)	0	0	164 (4.0)	27 (0.7)	0	139 (11.0)	14 (1.1)	0	215 (10.3)	66 (3.2)	0	81 (25.3)	11 (3.4)	0
Hepatitis	1 (0.8)	0	0	4 (3.0)	3 (2.3)	0	6 (0.1)	2 (<0.1)	0	2 (0.2)	1 (<0.1)	0	22 (1.1)	19 (0.9)	0	6 (1.9)	4 (1.3)	0
Hyperbilirubinaemia	0	0	0	3 (2.3)	0	0	7 (0.2)	1 (<0.1)	0	10 (0.8)	2 (0.2)	0	14 (0.7)	1 (<0.1)	0	4 (1.3)	1 (0.3)	0
Blood bilirubin increased	4 (3.1)	0	0	2 (1.5)	0	0	30 (0.7)	3 (<0.1)	0	52 (4.1)	4 (0.3)	0	31 (1.5)	3 (0.1)	0	16 (5.0)	1 (0.3)	0
Transaminases increased	1 (0.8)	0	0	2 (1.5)	0	0	24 (0.6)	6 (0.1)	0	14 (1.1)	0	0	42 (2.0)	22 (1.1)	0	13 (4.1)	2 (0.6)	0
Hepatic cytolysis	1 (0.8)	0	0	1 (0.8)	0	0	9 (0.2)	4 (<0.1)	0	1 (<0.1)	0	0	15 (0.7)	8 (0.4)	0	NR	NR	NR
Liver function test increased	0	0	0	1 (0.8)	0	0	5 (0.1)	3 (<0.1)	0	4 (0.3)	1 (<0.1)	0	9 (0.4)	7 (0.3)	0	3 (0.9)	0	0
Blood alkaline phosphatase increased	1 (0.8)	0	0	0	0	0	75 (1.8)	7 (0.2)	0	62 (4.9)	5 (0.4)	0	74 (3.5)	13 (0.6)	0	28 (8.8)	2 (0.6)	0
Pulmonary	4 (3.1)	0	0	3 (2.3)	0	0	148 (3.6)	33 (0.8)	2 (0.1)	61 (4.8)	16 (1.3)	0	145 (6.9)	32 (1.5)	0	18 (5.6)	5 (1.6)	0

Select AE Category Sub-Category/Preferred Term	CA2098FC Nivo Process C N = 129			CA2098FC Nivo Process D N = 132			Nivo Mono[a] N =4122			Nivo+Chemo[b] N = 1268			Nivo+Ipi (±Chemo)[a,c] N =2094			Nivo+Cabo[a] N = 320		
	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5
Pneumonitis	4 (3.1)	0	0	3 (2.3)	0	0	124 (3.0)	26 (0.6)	2 (<0.1)	52 4.1)	13 (1.0)	0	125 (6.0)	26 (1.2)	0	16 (5.0)	5 (1.6)	0
Interstitial lung disease	0	0	0	1 (0.8)	0	0	19 (0.5)	5 (0.1)	0	8 (0.6)	3 (0.2)	0	16 (0.8)	3 (0.1)	0	2 (0.6)	0	0
Renal	3 (2.3)	0	0	3 (2.3)	0	0	112 (2.7)	18 (0.4)	0	112 (8.8)	15 (1.2)	0	128 (6.1)	30 (1.4)	0	32 (10.0)	4 (1.3)	0
Tubulointerstitial nephritis	1 (0.8)	0	0	2 (1.5)	0	0	4 (<0.1)	3 (<0.1)	0	1 (<0.1)	1 (<0.1)	0	3 (0.1)	2 (<0.1)	0	NR	NR	NR
Blood creatinine increased	2 (1.6)	0	0	1 (0.8)	0	0	85 (2.1)	4 (<0.1)	0	69 (5.4)	2 (0.2)	0	91 (4.3)	4 (0.2)	0	21 (6.6)	2 (0.6)	0
Renal failure	0	0	0	1 (0.8)	0	0	9 (0.2)	1 (<0.1)	0	10 (0.8)	4 (0.3)	0	9 (0.4)	2 (<0.1)	0	9 (2.8)	1 (0.3)	0
Nephritis	1 (0.8)	0	0	0	0	0	NR	NR	NR	1 (<0.1)	1 (<0.1)	0	4 (0.2)	1 (<0.1)	0	2 (0.6)	1 (0.3)	0
Skin	52 (40.3)	2 (1.6)	0	74 (56.1)	1 (0.8)	0	1213 (29.4)	56 (1.4)	0	306 (24.1)	31 (2.4)	0	968 (46.2)	99 (4.7)	0	201 (62.8)	34 (10.6)	0
Pruritus	21 (16.3)	0	0	32 (24.2)	0	0	609 (14.8)	6 (0.1)	0	82 (6.5)	1 (<0.1)	0	509 (24.3)	21 (1.0)	0	55 (17.2)	1 (0.3)	0
Rash	22 (17.1)	1 (0.8)	0	28 (21.2)	1 (0.8)	0	520 (12.6)	24 (0.6)	0	121 (9.5)	9 (0.7)	0	462 (22.1)	50 (2.4)	0	65 (20.3)	6 (1.9)	0
Rash maculo-papular	3 (2.3)	0	0	12 (9.1)	0	0	154 (3.7)	11 (0.3)	0	24 (1.9)	6 (0.5)	0	160 (7.6)	26 (1.2)	0	25 (7.8)	1 (0.3)	0
Vitiligo	5 (3.9)	0	0	8 (6.1)	0	0	98 (2.4)	1 (<0.1)	0	1 (<0.1)	0	0	42 (2.0)	0	0	NR	NR	NR
Rash papular	1 (0.8)	0	0	3 (2.3)	0	0	21 (0.5)	1 (<0.1)	0	2 (0.2)	0	0	22 (1.1)	2 (<0.1)	0	5 (1.6)	1 (0.3)	0
Skin hypopigmentation	1 (0.8)	0	0	3 (2.3)	0	0	13 (0.3)	0	0	1 (<0.1)	0	0	13 (0.6)	0	0	5 (1.6)	0	0
Psoriasis	1 (0.8)	0	0	2 (1.5)	0	0	15 (0.4)	2 (<0.1)	0	1 (<0.1)	0	0	10 (0.5)	2 (<0.1)	0	3 (0.9)	0	0
Rash macular	0	0	0	2 (1.5)	0	0	27 (0.7)	3 (<0.1)	0	7 (0.6)	0	0	25 (1.2)	2 (<0.1)	0	3 (0.9)	0	0
Dermatitis acneiform	1 (0.8)	0	0	2 (1.5)	0	0	39 (0.9)	1 (<0.1)	0	7 (0.6)	0	0	36 (1.7)	2 (<0.1)	0	13 (4.1)	0	0
Dermatitis	1 (0.8)	0	0	1 (0.8)	0	0	27 (0.7)	1 (<0.1)	0	7 (0.6)	0	0	14 (0.7)	0	0	8 (2.5)	1 (0.3)	0

Select AE Category Sub-Category/Preferred Term	CA2098FC Nivo Process C N = 129			CA2098FC Nivo Process D N = 132			Nivo Mono[a] N =4122			Nivo+Chemo[b] N = 1268			Nivo+Ipi (±Chemo)[a,c] N =2094			Nivo+Cabo[a] N = 320		
	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5
Pemphigoid	0	0	0	1 (0.8)	0	0	4 (<0.1)	4 (<0.1)	0	NR	NR	NR	2 (<0.1)	1 (<0.1)	0	2 (0.6)	1 (0.3)	0
Erythema	3 (2.3)	0	0	0	0	0	79 (1.9)	0	0	16 (1.3)	2 (0.2)	0	43 (2.1)	1 (<0.1)	0	11 (3.4)	1 (0.3)	0
Rash pruritic	2 (1.6)	0	0	0	0	0	37 (0.9)	1 (<0.1)	0	7 (0.6)	1 (<0.1)	0	33 (1.6)	1 (<0.1)	0	1 (0.3)	0	0
Eczema	1 (0.8)	0	0	0	0	0	44 (1.1)	0	0	3 (0.2)	0	0	18 (1.9)	0	0	1 (0.3)	0	0
Pemphigus	1 (0.8)	1 (0.8)	0	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Photosensitivity reaction	1 (0.8)	0	0	0	0	0	9 (0.2)	0	0	3 (0.2)	0	0	6 (0.3)	0	0	NR	NR	NR
Hypersensitivity/Infusion Reactions	2 (1.6)	0	0	8 (6.1)	0	0	160 (3.9)	12 (0.3)	0	127 (10.0)	21 (1.7)	0	103 (4.9)	6 (0.3)	0	8 (2.5)	0	0
Infusion related reaction	0	0	0	3 (2.3)	0	0	113 (2.7)	6 (0.1)	0	75 (5.9)	12 (0.9)	0	68 (3.2)	5 (0.2)	0	3 (0.9)	0	0
Hypersensitivity	0	0	0	3 (2.3)	0	0	44 (1.1)	2 (<0.1)	0	51 (4.0)	4 (0.3)	0	33 (1.6)	1 (<0.1)	0	4 (1.3)	0	0
Infusion related hypersensitivity reaction	2 (1.6)	0	0	1 (0.8)	0	0	1 (<0.1)	0	0	3 (0.2)	1 (<0.1)	0	3 (0.1)	0	0	1 (0.3)	0	0
Bronchospasm	0	0	0	1 (0.8)	0	0	3 (<0.1)	1 (<0.1)	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Endocrine	43 (33.3)	2 (1.6)	0	37 (28.0)	3 (2.3)	0	556 (13.5)	28 (0.7)	0	155 (12.2)	10 (0.8)	0	582 (27.8)	104 (5.0)	0	142 (44.4)	8 (2.5)	0
THYROID DISORDER	40 (31.0)	0	0	34 (25.8)	1 (0.8)	0	516 (12.5)	7 (0.2)	0	137 (10.8)	0	0	479 (2.9)	21 (1.0)	0	138 (43.1)	3 (0.9)	0
Hypothyroidism	26 (20.2)	0	0	24 (18.2)	0	0	313 (7.6)	2 (<0.1)	0	92 (7.3)	0	0	303 (14.5)	5 (0.2)	00	112 (35.0)	1 (0.3)	0
Hyperthyroidism	23 (17.8)	0	0	21 (15.9)	1 (0.8)	0	166 (4.0)	2 (<0.1)	0	37 (2.9)	0	0	171 (8.2)	7 (0.3)	0	29 (9.1)	2 (0.6)	0
Blood thyroid stimulating hormone increased	5 (3.9)	0	0	1 (0.8)	0	0	58 (1.4)	1 (<0.1)	0	25 (2.0)	0	0	32 (1.5)	0	0	2 (7.5)	0	0
Thyroiditis	2 (1.6)	0	0	1 (0.8)	0	0	32 (0.8)	1 (<0.1)	0	2 (0.2)	0	0	44 (2.1	4 (0.2)	0	2 (0.6)	0	0
Blood thyroid stimulating hormone decreased	1 (0.8)	0	0	0	0	0	25 (0.6)	0	0	7 (0.6)	0	0	23 (1.1)	0	0	1 (0.3)	0	0

Select AE Category Sub-Category/Preferred Term	CA2098FC Nivo Process C N = 129			CA2098FC Nivo Process D N = 132			Nivo Mono[a] N =4122			Nivo+Chemo[b] N = 1268			Nivo+Ipi (±Chemo)[a,c] N =2094			Nivo+Cabo[a] N = 320		
	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5	Any Grade	G3-4	G5
Immune-mediated thyroiditis	1 (0.8)	0	0	0	0	0	1 (<0.1)	0	0	NR	NR	NR	2 (<0.1)	0	0	NR	NR	NR
PITUITARY DISORDER	1 (0.8)	0	0	2 (1.5)	0	0	24 (0.6)	9 (0.2)	0	8 (0.6)	4 (0.3)	0	115 (5.5)	45 (2.1)	0	2 (0.6)	0	0
Hypopituitarism	0	0	0	2 (1.5)	0	0	6 (0.1)	1 (<0.1)	0	7 (0.6)	3 (0.2)	0	30 (1.4)	11 (0.5)	0	NR	NR	NR
Hypophysitis	1 (0.8)	0	0	0	0	0	16 (0.4)	8 (0.2)	0	1 (<0.1)	1 (<0.1)	0	84 (4.0)	33 (1.6)	0	2 (0.6)	0	0
ADRENAL DISORDER	2 (1.6)	1 (0.8)	0	2 (1.5)	1 (0.8)	0	25 (0.6)	8 (0.2)	0	11 (0.9)	3 (0.2)	0	94 (4.5)	37 (.8)	0	15 (4.7)	6 (1.9)	0
Adrenal insufficiency	2 (1.6)	1 (0.8)	0	2 (1.5)	1 (0.8)	0	22 (0.5)	6 (0.1)	0	11 (0.9)	3 (0.2)	0	82 (3.9)	32 (1.5)	0	1 (4.4)	6 (1.9)	0
Diabetes	1 (0.8)	1 (0.8)	0	2 (1.5)	1 (0.8)	0	11 (0.3)	7 (0.2)	0	5 (0.4)	3 (0.2)	0	18 (0.9)	11 (0.5)	0	NR	NR	NR
Diabetic ketoacidosis	1 (0.8)	1 (0.8)	0	1 (0.8)	1 (0.8)	0	3 (<0.1)	3 (<0.1)	0	1 (<0.1)	1 (<0.1)	0	2 (<0.1)	2 (<0.1)	0	NR	NR	NR
Type 1 diabetes mellitus	1 (0.8)	0	0	1 (0.8)	0	0	2 (<0.1)	1 (<0.1)	0	2 (0.2)	1 (<0.1)	0	6 (0.3)	2 (<0.1)	0	NR	NR	NR
Diabetes mellitus	1 (0.8)	1 (0.8)	0	0	0	0	6 (0.1)	2 (<0.1)	0	3 (0.2)	1 (<0.1)	0	10 (0.5)	4 (0.2)	0	NR	NR	NR

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; cabo: cabozantinib; chemo: chemotherapy; ipi: ipilimumab; mono: monotherapy; nivo: nivolumab; NR: (PT) not reported in the source outputs.

MedDRA Version 24.1, CTC Version 5.0 for CA2098FC. MedDRA Version 24.0; CTC Version: 3.0 for CA209004; CTC Version 4.0 for other studies

Includes events between first dose and 30 days (or min 28 days, subsequent therapy) for ONO-4538-24) after last dose of study therapy.

Nivolumab monotherapy studies:[a]

- CA209063, CA209017, CA209057: NSCLC
- CA209037, CA209066, CA209067, CA209238: Melanoma
- CA209025: RCC
- CA209039: cHL
- CA2009141: SCCHN
- CA209275, CA209032, CA209274: UC
- ONO-4538-24 (CA209473): ESCC
- CA209577: Adjuvant EC or GEJC

Nivo + Chemo studies:[b]

- CA209648: ESCC
- CA209649: Gastric, GEJ or esophageal adenocarcinoma
- CA209816: NSCLC

Nivo + Ipi (± Chemo) studies:[a]

- CA209004 (cohort 8), CA209067, CA209069: Melanoma
- CA209142: dMMR or MSI-H CRC
- CA209214: RCC
- CA209648: ESCC
- CA209743: Mesothelioma
- CA2099LA: NSCLC[c]

Nivo + Cabo study:[a]

- CA2099ER: RCC

[a] For nivolumab monotherapy, nivo+ipi (± chemo), and nivo+cabo, the pooled safety data include data from approved regimens, as presented within the currently approved Product Information.[4]

b For nivo+chemo, the pooled dataset included all nivo+chemo regimens approved (Studies CA209648 and CA209649) as well as safety data from Study CA209816 which is currently ongoing review (procedure EMEA/H/C/003985/II/117, submitted in Mar-2022)

[c] Study CA2099LA has chemo included in the regimen.

Source: CA2098FC: Refer to Table S.6.5.1.3.2 and Table S.6.5.1.3.6 of the Addendum 01 to the CA2098FC Primary CSR; Pooled nivo mono and combo data: Table 4.1 (pooled nivo mono and combo; drug-related select AEs) and Table 5.1 (pooled nivo mono and combo; endocrine drug-related select AEs); Table 9.2 and Table 10.2 (pooled nivo mono; drug-related select AEs by Any grade, Grade 3-4, Grade 5); Table 9.9 and Table 10.9 (pooled nivo+ipi±chemo; drug-related select AEs by Any grade, Grade 3-4, Grade 5); Table 9.16 and Table 10.16 (pooled nivo+chemo; drug-related select AEs by Any grade, Grade 3-4, Grade 5) in Appendix 2.

2.6.9. Discussion on clinical safety

The primary safety data of this submission are the results of the biocomparability study CA2098FC; based on 129 subjects treated with nivolumab Process C and 132 subjects treated with nivolumab Process D.

Treatment exposure was similar in both arms, with a majority of patients receiving 90% to < 110% of the planned dose intensity for both the 3 mg/kg IV Q2W and the 480 mg IV Q4 posology; although the percentage of patients who achieved this dose intensity was higher for the flat dose (95.2% in the Process C arm vs. 95.7% in the Process D arm for the 480 mg flat dose; compared with 88.4% in the Process C arm vs. 85.6% in the Process D arm for the 3 mg/kg dose). Median number of doses was 9 in both arms. Median duration of therapy was also similar in both arms: 11.53 months in the Process C arm vs. 11.55 months in the Process D arm. However, it seems that a slightly higher percentage of patients remained on treatment in the Process D arm compared with the Process C arm: 68.2% of patients in Process C and 75.0% of patients in Process D remained on treatment for longer than 9 months; and 11.6% of patients in Process C vs. 15.2% of patients in Process D remained on treatment for longer than 12 months. Overall, it does not seem that there were relevant differences in terms of treatment exposure. Median follow-up was 25.9 months (range: 15.7, 31.8), with a minimum follow-up of 15.7 months. At DBL (18 February 2022) there were no patients still on treatment.

Dose delays were reported with a slightly higher frequency in Process D arm: 38.8% of patients in the Process C arm had at least one dose delay vs. 43.9% of patients in the Process D arm. In both arms the most frequent reason for a dose delay was the occurrence of an adverse event (62.7% of dose delays in the Process C arm vs. 55% of dose delays in the Process D arm). **AEs leading to dose delay** were reported in a similar percentage of patients in both arms (28.7% of patients in the Process C arm vs. 29.5% of patients in the Process D arm), although some slight imbalances were noted. Particularly, this imbalance was observed in the gastrointestinal disorders: in the Process C arm 3 (2.3%) patients had a dose delay due to AEs belonging to the gastrointestinal SOC, vs. 9 (6.8%) patients in the Process D arm. In the Process C arm 2 (1.6%) of those patients had AEs which were considered drug-related, vs. 8 (6.1%) in the Process D arm.

Regarding **infusion interruptions**, there were 2 patients (1.6%) in Process C who had at least one infusion interruption, vs. 8 patients (6.1) in Process D. In Process C the total number of interrupted infusions was 2, whereas in Process D the total number of interrupted infusions was 15. The 2 infusion interruptions in the Process C arm were due to "other reasons"; whereas in the Process D arm there were 3 interruptions due to hypersensitivity reactions, 1 due to "infusion admin issues" and 11 due to "other reasons". Upon request, the MAH provided the "other reasons" for infusion interruptions in Process D, being 5 out of the 11 infusion interruptions due to "infusion-related hypersensitivity reaction" and having been recorded as "other reasons" instead of "hypersensitivity reaction" by mistake. Therefore, there were 8 hypersensitivity reactions in Process D (instead of 3, as initially stated) vs. none in Process C. The reasons for the observed difference, which suggest tolerability differences between arms, remain unclear.

The frequency of **all-causality any-grade AEs** was similar between arms (96.9% of patients in Process C vs. 95.5% of patients in Process D), although the frequency of **all-causality G3-4 AEs** was relevantly higher in Process D than in Process C: there were 32 patients (24.8%) with an event in Process C, vs. 44 patients (33.3%) in Process D. Although it is agreed with the MAH that it does not seem that this difference is driven by any specific PT or SOC, this difference between arms should not be disregarded, since it suggests that Process D might be associated with a worse tolerability profile than Process C. Regarding any-grade AEs, some relevant differences in terms of the frequency of AEs belonging to a particular SOC have been noted. Namely, AEs belonging to the SOC "skin and subcutaneous tissue disorders" were reported in 69 patients (53.5%) in Process C vs. in 96 patients (65.2%) in Process D. This difference seems to be driven by an increase in the frequency of the PT "pruritus" (20.2% vs. 26.5%), "rash" (17.1% vs. 23.5%) and "rash maculo-papular" (2.3% vs. 9.8%). Reassuringly, in this SOC the frequency of G3-4 events was similar between both arms. Another SOC in which a difference is observed is the SOC "gastrointestinal disorders": 63 patients (48.8%) in Process C reported an AE, vs. 75 patients (56.8%) in Process D. This difference seems to be driven by PTs such as "diarrhoea" (24.8% vs. 28.8%; 0.8% vs. 3% G3-4 events) and "nausea" (10.9% vs. 15.9%). AEs belonging to the SOC "infections and infestations" were also reported with a relevantly higher frequency in the Process D arm than in the Process C arm: 55 patients (41.7%) in the Process D arm vs. 39 patients (30.2%) in the Process C arm. Importantly, a difference in the frequency of G3-4 events was also observed: 9 patients (6.8%) in the Process D arm reported a G3-4 event, vs. no patients in the Process C arm; although this difference was not driven by any particular PT: those 9 patients had a different PT and all events were G3 events, except for one event of "sepsis". The most frequently reported PTs in the Process C arm were "COVID-19" (6 events – 4.7%), "urinary tract infection" (4 events – 4.7%) and "upper respiratory tract infection" (5 events – 3.9%); and in the Process D arm were "COVID-19" (8 events – 6.1%), "nasopharyngitis" (6 events – 4.5%) and "rhinitis" (6 events – 4.5%). Similarly, events belonging to the "respiratory, thoracic and mediastinal disorders" SOC were reported with a higher frequency in the Process D arm than in the Process C arm: 33.3% subjects in the Process D vs. 20.2% in the Process C arm; although in this SOC the difference between arms in terms of G3-4 events was not as marked as in the "infections and infestations" SOC: in Process D there were 3 subjects (2.3%) who had a G3-4 event vs. no patients in Process C. A difference between arms was also evident in the "blood and lymphatic system disorders" SOC: in the Process C arm there were 7.8% of patients who had an any-grade AE vs. 14.4% in the Process D arm; being this difference mainly driven by the PT "anaemia" (3 patients (2.3%) in the Process C arm vs. 12 patients (9.1%) in the Process D arm). Most subjects in both arms had **drug-related AEs**: 114 patients (88.4%) in the Process C arm vs. 112 patients (84.8%) in the Process D arm. In the Process C arm 16 patients (12.4%) had a **drug-related G3-4 AE**, vs. 22 patients (16.7%) in the Process D arm. The SOC in which there was a more marked difference between arms was the "skin and subcutaneous tissue disorders" SOC: 61 patients (47.3%) in the Process C arm reported an any-grade event vs. 81 patients (61.4%) in the Process D arm. The PTs that contributed the most to this difference between arms were: "pruritus" (25.8% in Process D vs. 16.3% in Process C), "rash" (21.2% in Process D vs. 17.1% in Process C) and "rash maculo-papular" (9.8% in Process D vs. 2.3% in Process C). AEs belonging to the "gastrointestinal disorders" SOC were also slightly higher in the Process D arm than in the Process C arm: 34.8% in the Process D arm (9 of them [6.8%] had a G3-4 event) vs. 30.2% in the Process C arm (5 of them [3.9%] had a G3-4 event). This difference seems to be driven by the "diarrhoea" PT: 14% patients in the Process C arm (including 1 G3-4 event) vs. 18.9% patients in the Process D arm (including 4 G3-4 events).

Deaths were reported with a similar frequency in both arms: 15 subjects (11.6%) died in the Process C arm vs. 14 subjects (10.6%) in the Process D arm. Primary reason for death was disease progression in both arms, accounting for 13 subjects (10.1%) in the Process C arm vs. 10 subjects (7.6%) in the Process D arm. Notably, in the Process D arm there was 1 death due to study drug

toxicity, vs. no deaths in the Process C. This death occurred 130 days after the last dose of nivolumab, and was due to a multiple organ dysfunction considered to be related to treatment by the investigator, this not being agreed by the MAH. However, the MAH did not provide any discussion on why the investigator's opinion is not agreed by them. Before suffering a "multiple organ dysfunction" and dying on day 320, this patient had previously suffered from several IMAEs ("uveitis", which started on day 92; and "tubulointerstitial nephritis", which started on day 204).

Additionally, there were 4 patients (2 in each arm) who died due to "other" reasons. Those reasons were "sudden cardiac death" and "cardiogenic shock" for the Process C arm, and "sepsis secondary to COVID" and "cardiogenic shock" for the Process D arm. Of note, in the Process D arm there was an additional death due to "unknown reasons". The MAH did not provide any additional information on that death, although it is remarkable that this patient had a cardiovascular history of first-degree artery block, and that during the clinical trial he had a G4 serious cardiac tamponade, a G2 serious pericardial effusion, and a G3 serious pleural effusion.

SAEs were reported with an overall similar frequency between both arms: in Process C any-grade SAEs were reported in 24 (18.6%) patients, 16 (12.4%) of whom were G3-4 SAEs; vs. 28 (21.2%) any-grade SAEs and 22 (16.7%) G3-4 SAEs in Process D. By PT no relevant differences were noted, except for the 2 myocarditis cases reported in the Process D arm. Of note, no myocarditis cases were reported in the Process C arm.

Regarding **all-causality select adverse events,** it should be noted that some differences were observed between arms, although these differences were mainly driven by low-grade select AEs (G1-2). In terms of select adverse events, the categories in which a more marked difference between arms was observed were the "skin AE" category, "hepatic AE" category, "gastrointestinal AE" category, and "hypersensitivity / infusion reaction" category, with a higher incidence in the Process D arm. In terms of **drug-related select AEs**, the differences between arms remained similar to the differences between arms in all-causality select AEs, suggesting that there are no relevant differences in the percentages of all-causality and drug-related AEs.

Immune-mediated adverse events (IMAEs) were reported with a similar frequency in both arms, although it is noted that the category "hepatitis" was reported with a higher frequency in the Process D arm than in the Process C arm: in the Process C arm 3 (2.3%) subjects had an any-grade IMAE, none of them considered a G3-4 event; whereas in the Process D arm there were 8 (6.1%) subjects with an any-grade IMAE and 4 (3%) of them were G3-4 IMAEs. It should be noted that the category "hepatitis" included the following PTs: "alanine aminotransferase increased", "hepatitis", "aspartate aminotransferase increased", "hyperbilirubinemia" and "transaminases increased". It is worth mentioning the higher frequency of hepatic IMAEs in Process D compared with Process C not only in terms of any-grade IMAEs, but also in terms of G3-4 IMAEs. Reassuringly, all the hepatic IMAEs in the Process D arm resolved. No relevant differences were observed in the endocrine IMAEs rates between both arms.

Other events of special interest (OESIs) were infrequent in both arms, although it should be noted that a clear higher frequency was observed in Process D compared with Process C. In Process C there were 4 events (2 patients), while in Process D there were 17 events (5 subjects). Reassuringly, all events in both arms resolved at the time of DBL. In Process D all events resolved with IMMs. In terms of the nature of those events, in Process C there were 3 uveitis and 1 rhabdomyolysis; all of them of grade 1-2; while in Process D there were 4 pancreatitis (two of them were grade 2 and one was grade 3), 6 uveitis (all were grade 1-2), 3 myocarditis (two of them were grade 3) and 4 myositis (one of them was grade 3 and the other three were grade 1-2). Special importance should be given to the events of myocarditis and pancreatitis, which were clearly imbalanced between arms and could be life-threatening. The MAH has provided an exposure-adjusted analysis for the events of myocarditis

(together with an event of angina pectoris); therefore, these events are discussed in the section focused on this analysis (see below). Regarding the events of pancreatitis, it is noted that the 4 events occurred in 2 subjects and that all were reported as recovered without sequalae. One patient had a G3 pancreatitis on day 134, which was considered as related and led to the discontinuation of nivolumab on day 135. The other patient had G2 pancreatitis on day 86, followed by G2 pancreatic failure on day 144, which also was considered as related and led to the discontinuation of nivolumab. Upon request, an exposure-adjusted analysis for this PT was provided, in which an increase in terms of any-grade events was observed in comparison with the mononotherapy pool (N=7327) and with the monotherapy pool in melanoma (N=1379). In terms of G3-4 events the difference between Process D and the pools is subtler. Considering that there were only 4 events and that all events were reported as recovered without sequalae, no further regulatory action is deemed necessary.

Laboratory findings were overall similar in both arms, with no major differences observed. However, it should be noted that some imbalances were observed in the liver tests: ALT or AST > 5xULN was reported in 4 (3%) patients in the Process D arm vs. in 1 (0.8%) patient in the Process C arm; and total bilirubin > 2xULN was also reported in 4 (3%) patients in the Process D arm vs. in 1 (0.8%) in the Process C arm. Reassuringly, no patient met Hy's law in the Process D arm. These findings were in line with the slightly higher frequency of hepatic AEs (i.e. hepatitis) in the Process D arm compared with the Process C arm.

As mentioned in the clinical efficacy discussion, **immunogenicity** incidence was higher in the Process D arm than in the Process C arm: in Process C there were 3 (2.5%) ADA-positive subjects, vs. 8 (6.5%) ADA-positive subjects in Process D. Median duration of ADAs was notably longer in Process D than in Process C, although the small number of patients who developed ADAs is acknowledged. Of note, this increased immunogenicity in Process D compared with Process C was already highlighted in the FU SA provided in 2022 (EMA/SA/0000074196). Although the fact that in Process D the immunogenicity incidence was more than twice the incidence in Process C is not reassuring, it should be noted that the immunogenicity incidence of nivolumab in monotherapy included in the SmPC is 9%; that is, the reported incidence in the Process D arm, although higher than in the Process C arm, is lower than the reported incidence for the pool of studies of nivolumab in monotherapy. Additionally, it does not seem that safety is impacted by ADAs, since in Process D only 1 patient having developed ADAs had an AE ("infusion related reaction"), although the number of patients is too low.

AEs leading to discontinuation were reported with a similar frequency in both arms: in the Process C arm any-grade AEs were reported in 22 subjects (17.1%) and G3-4 AEs in 9 subjects (7.0%); vs. 25 subjects (18.9%) with any grade AEs and 11 subjects (8.3%) with G3-4 AEs in the Process D arm. However, although the overall frequencies are similar, some imbalances in some SOCs/PTs have been noted. Namely, in the gastrointestinal SOC 4 (3.1%) patients in the Process C arm had any-grade AEs leading to discontinuation; 2 (1.6%) of whom were G3-4; vs. 8 (6.1%) any-grade AEs and 4 (3.0%) G3-4 in the Process D arm. There were 2 (1.5%) patients with myocarditis in Process D (both of them were G3-4 events) vs. no patients in Process C. Importantly, in Process D there were 4 (3%) any-grade hepatitis, 2 (1.5%) of whom were G3-4 events; vs. no patients in Process C. The frequencies of the above-mentioned PTs and SOCs were unchanged after establishing the causality: all the mentioned events (gastrointestinal disorders' SOC, myocarditis PT and hepatitis PT) were considered drug-related.

The MAH has presented **exposure-adjusted analyses for all-causality unique select AEs** to contextualize numerically higher incidences of some select AE categories noted in nivolumab Process D compared to nivolumab Process C. The analysis presented compares side-by-side the number and percentage of patients with a select any-grade and G3-4 AE category ("hepatic", "skin", "hypersensitivity/infusion reaction", "gastrointestinal" and "cardiac disorders" [including myocarditis and angina pectoris]), the person-years of exposure based on time to first onset and the incidence rate per 100 person-years of exposure of the Process C arm, the Process D arm, a pool of studies of

nivolumab in monotherapy for all indications (hereinafter referred as "all-indications pool"), and a pool of studies of nivolumab in monotherapy for the melanoma indications (hereinafter referred as "melanoma pool"). Regarding the analysis on any-grade AEs it is noted that for both the "hypersensitivity/infusion reaction" category and the "gastrointestinal" category the IR/100 P-Y in the Process D arm is similar to the IR/100 P-Y in the all-indications pool and in the melanoma pool. Therefore, although a difference in the incidences of those events is observed between Process C and Process D, it does not seem that the incidence in Process D is considerably higher than in the all-indications pool and in the melanoma pool. In the case of the "skin" category, it is noted that the IR/100 P-Y appears markedly higher in the Process D arm than in the all-indications pool (100.5 [95% CI:79.5, 125.4] in the Process D arm vs. 68.3 [95%CI: 65.7, 70.9] in the all-indications pool). However, when the IR/100 P-Y in Process D is compared with the IR/100 P-Y in the melanoma pool the difference is considerably subtler (100.5 [95% CI: 79.5, 125.4] in the Process D arm vs. 104.1 [95% CI: 96.8, 111.9] in the melanoma pool), which is reassuring since it suggests that the incidence observed in the Process D arm is similar to the incidence previously reported for other studies of nivolumab in the melanoma setting. However, this trend is not observed in the case of the "hepatic" category: for the hepatic category the IR/100 P-Y seems higher in the Process D arm (32.1 [95% CI: 22.7, 44.1]) than in either the all-indications pool (24.1 [95% CI: 22.8, 25.4)) or the melanoma pool (15.7 [95%CI: 13.7, 18.0]). This observation is not reassuring, since it suggests that the administration of nivolumab manufactured following Process D could somehow translate into a higher incidence of any-grade hepatic AEs. Nevertheless, in the exposure-adjusted G3-4 analysis it is noted that the IR/100 P-Y of G3-4 hepatic events in the Process D arm appears lower than in the all-indications pool and in the melanoma pool. This trend is also observed for the skin and the hypersensitivity / infusion reaction categories, although in the gastrointestinal category the IR/100 P-Y seems to be slightly higher in the Process D arm (4.2 [95% CI: 1.5, 9.1]) compared with the all-indications pool (2.9 [95% CI:2.5, 3.4]) and the melanoma pool (3.9 [95% CI: 3.0, 5.1]). As previously mentioned, the MAH has also analysed the G3-4 AEs belonging to the "cardiac disorders" SOC. It should be noted that the total percentage of events seemed higher in the Process D arm than in either of the pools: 5 events (3.8%) in the Process D arm vs. 171 events (2.3%) in the all-indications pool and 26 events (1.9%) in the melanoma pool. Among the reported PTs there were 2 myocarditis events (1.5%) in the Process D arm, vs. 4 events (<0.1%) in the all-indications pool and 0 events in the melanoma pool. The IR/100 P-Y was also higher in the Process D arm than in the pools: 1.4 (95% CI: 0.2, 5.0) in the Process D arm vs. 0.1 (95% CI: 0.0, 0.2) in the all-indications pool and 0.0 (95% CI: 0.0, 0.3) in the melanoma pool. Although the number of G3-4 myocarditis events is very low and therefore it is difficult to draw conclusions, it is noted that there were 2 events reported in the Process D arm, in which there were 132 patients included; vs. 4 events in the all-indications pool, in which there were 7327 patients included. This suggests that with Process D there is a higher incidence of these events compared with the safety pool of studies of nivolumab in the approved indications. There was 1 event (0.8%) of "angina pectoris" in the Process D arm vs. 3 events (<0.1%) in the all-indications pool and 0 events in the melanoma pool. The IR/100 P-Y in the Process D arm is 0.7 (95% CI: 0.0, 3.9), vs. 0.0 (95% CI: 0.0, 0.1) in the all-indications pool and 0.0 (95% CI: 0.0, 0.3) in the melanoma pool. Considering that there was only 1 event in the Process D arm and that therefore this could have been a random finding, no conclusions can be drawn on the existence of potential differences between the Process D arm and the pools.

Additionally, the MAH has performed a **non-exposure adjusted descriptive analysis of drug-related select AEs** within 30 days of last dose, to further address the differences observed in certain select AEs and cardiac disorders events with nivolumab Process D compared with nivolumab Process C. In this analysis the MAH presents side-by-side the total number and percentages of any-grade, G3-4 and G5 events in the Process C arm, in the Process D arm, in the monotherapy all-indications pool (hereinafter referred as "monotherapy pool"), in the pool of studies of nivolumab in combination with

chemotherapy, in the pool of studies of nivolumab in combination with ipilimumab ± chemotherapy, and in a study of nivolumab in combination with cabozantinib. Since nivolumab was administered as monotherapy in the study CA2098FC, the comparison which has been considered more relevant is the one referring to the pool of monotherapy studies, which included 4122 patients. It should be noted that, as previously mentioned, the frequency of events in some categories seems to be increased in the Process D arm in comparison with the monotherapy pool. This increase was observed in the "hepatic" category, with 25 (18.9%) any-grade events in Process D vs. 311 (7.5%) in the monotherapy pool. Overall, all PTs in this category were reported with a higher frequency in the Process D arm than in the monotherapy pool. Similarly, events in the "skin" category were reported with a higher frequency in the Process D arm than in the monotherapy pool: 74 (56.1%) any-grade events vs. 1213 (29.4%) in the monotherapy pool. In this category all PTs were also overall increased in the Process D arm with respect to the monotherapy pool, although the differences were more marked in some PTs (pruritus: 24.2% vs. 14.8%; rash: 21.2% vs. 12.6% and rash maculo-papular: 9.1% vs. 3.7%). Additionally, the "endocrine" category was also increased in the Process D arm compared with the monotherapy pool: 28% vs. 13.5%. However, in this case the difference between Process C and Process D is subtler (28% in Process D vs. 33.3% in Process C) and, therefore, the differences observed between Process D and the monotherapy pool are not considered as worrisome. Reassuringly, all the mentioned differences in any-grade events are overall not observed (or are subtler) for G3-4 events, except for the "hepatitis" PT, in which 3 (2.3%) events were reported in the Process D arm vs. 2 (<0.1%) in the monotherapy pool.

Considering the results of the pivotal study (CA2098FC), together with both the exposure-adjusted and the non-exposure adjusted analyses, the frequency of some PTs seems to be slightly higher with nivolumab manufactured following Process D than with nivolumab manufactured following Process C. Although it is acknowledged that these differences were mainly due to G1-2 events, it is unclear why such differences (which in some cases are appreciably higher) were observed; considering that no differences between arms were supposed to be observed. The MAH was requested to further elaborate on the potential reasons why there seems to exist some differences in the safety profile of nivolumab between both processes, and a thorough justification on the differences between both manufacturing processes was provided. After reviewing the provided data, it does not seem that any of the implemented changes could have led to the observed differences in the safety profile of Process D nivolumab vs. Process C nivolumab. Therefore, there is no apparent explanation for the observed differences. A close monitoring on those events is needed in the following PSURs.

2.6.10. Conclusions on the clinical safety

The administration of nivolumab manufactured following Process C and following Process D was associated with the same AEs in nature, not being identified any new signal with Process D. However, it has been noted that the frequency of some AEs was unexpectedly higher in the Process D arm than in the Process C arm. Notably, this increase has been noted in AEs belonging to the following categories: hypersensitivity/infusion reactions, skin, hepatic, cardiac and gastrointestinal; as well as the PT of pancreatitis. The MAH has presented two additional analyses comparing the results obtained in the Process D arm with different safety pools of nivolumab administered in other settings. The results of those analyses provide reassurance for some AEs, but uncertainties remain for others (i.e. hepatic events). The MAH also provided a thorough review on the differences between both manufacturing processes, with the aim of identifying the potential reasons for the observed differences in terms of safety. However, it does not seem that any of the implemented changes could have led to the observed differences in the safety profile of Process D vs. Process C. Considering there is no apparent explanation for these observed differences and taking into account the small data size, no

changes in the SmPC or RMP are warranted, although those events should be closely monitored in the following PSURs.

2.7. Risk Management Plan

No changes in the safety concerns, PhV plan and RMM were included in this procedure.

2.7.1. Safety concerns

Table 51: 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 ARs, and other irARs) Severe infusion reactions
Important potential risks	Embryofetal toxicity Immunogenicity Risk of GVHD with nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment Patients with autoimmune disease Patients already receiving systemic immunosuppressants before starting nivolumab Long-term safety in adolescent patients ≥ 12 years of age

2.7.2. Pharmacovigilance plan

Table 52: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	**Summary of objectives**	**Safety concerns addressed**	**Milestone(s)**	**Due Date(s)**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Postmarketing use safety profile, management and outcome of immune-related ARs (including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other irARs [uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and Vogt-Koyanagi-Harada disease]), and severe infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Long-term follow-up of ipilimumab, nivolumab and nivolumab in combination with ipilimumab treated paediatric patients enrolled in the DMTR (CA184557)[a] Voluntary PASS	To assess safety and long-term outcomes in children and adolescents.	Long-term safety in adolescent patients > 12 years of age	1. Submission of protocol[a] 2. Interim Study Report 3. Final report of study results	4Q 2023 4Q 2026 4Q 2033

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

2.7.3. Risk minimisation measures

Table 53: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, skin ARs, and other irARs)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: Patient Alert Card	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Postmarketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimisation measures: SmPC Section 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Long-term safety in adolescent patients ≥ 12 years of age	Routine risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: MAH to sponsor the extension of the DMTR to include paediatric subjects treated with nivolumab monotherapy and nivolumab + ipilimumab to collect their safety data (CA184557).

2.7.4. Conclusion

The CHMP considered that the risk management plan version 34.1 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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable based on the fact that no changes were made to the package leaflet.

3. Benefit-Risk Balance

The object of this submission is to support the nivolumab drug substance manufacturing process change from the current approved Process C to newly optimized Process D, developed using a new nivolumab cell line. No changes in the already approved indications or, in general, to the SmPC were introduced.

3.1.1. Main clinical studies

The basis of this submission is Study CA2098FC, a randomized, double-blind, parallel, Phase 1 study aimed to demonstrate biocomparability of Process C IV nivolumab to Process D IV nivolumab in 261 patients with Stage IIIa/b/c/d or Stage IV melanoma after complete resection. The primary endpoints of the study were PK endpoints, AUC(TAU) (0-336 h) at Week 1 Day 1 (after first dose) and AUC(TAU) (0-336 h) at Week 17 Day 1 (after multiple doses). Secondary endpoints included safety and tolerability, together with immunogenicity. Efficacy, measured as recurrence-free-survival (RFS) was an exploratory endpoint.

3.2. Favourable effects

In terms of PK, which was the main objective of the study, nivolumab Process C and Process D were found to be biocomparable as the AUC(0-336 h) geometric mean ratios (90% CI) were 1.012 (0.984, 1.041) and 0.998 (0.951, 1.047) at Week 1 and Week 17, respectively.

In terms of efficacy, which was an exploratory endpoint, the HR for RFS in all randomized subjects was 0.81 (95% CI: 0.53-1.23), with 47 events (36.4%) reported in Process C vs. 43 events (32.6%) in Process D. Median RFS was not reached in either arm. In subjects with no relevant protocol deviations the HR was 0.75 (95% CI: 0.46-1.21), with 38 events (37.3%) reported in Process C vs. 31 events (30.4%) in Process D.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

Dose delays were reported with a similar frequency in both arms: 38.8% of patients in the Process C arm had at least one dose delay vs. 43.9% of patients in the Process D arm. In both arms the most frequent reason for a dose delay was the occurrence of an adverse event (62.7% of dose delays in the Process C arm vs. 55% of dose delays in the Process D arm).

Regarding **infusion interruptions**, there were 2 patients (1.6%) in Process C who had at least one infusion interruption, vs. 8 patients (6.1%) in Process D. In Process C the total number of interrupted infusions was 2, whereas in Process D the total number of interrupted infusions was 15.

The frequency of **all-causality any-grade AEs** was similar between arms (96.9% of patients in Process C vs. 95.5% of patients in Process D), although the frequency of all-causality G3-4 AEs was higher in Process D than in Process C: there were 32 patients (24.8%) with an event in Process C, vs. 44 patients (33.3%) in Process D. AEs belonging to some SOCs were reported with a higher frequency in the Process D than in the Process C: "skin and subcutaneous tissue disorders" (53.5% vs. 65.2%), "gastrointestinal disorders" (48.8% vs. 56.8%), "infections and infestations" (30.2% vs. 41.7%), "respiratory, thoracic and mediastinal disorders" (20.2% vs. 33.3%) and "blood and lymphatic system disorders" (7.8% vs. 14.4%).

Most subjects in both arms had **drug-related AEs**: 114 patients (88.4%) in the Process C arm vs. 112 patients (84.8%) in the Process D arm. In the Process C arm 16 patients (12.4%) had a drug-related G3-4 AE, vs. 22 patients (16.7%) in the Process D arm.

Regarding **deaths,** 15 subjects (11.6%) died in the Process C arm vs. 14 subjects (10.6%) in the Process D arm. Primary reason for death was disease progression in both arms, accounting for 13 subjects (10.1%) in the Process C arm vs. 10 subjects (7.6%) in the Process D arm.

In Process C any-grade **SAEs** were reported in 24 (18.6%) patients compared with 28 (21.2%) patients in Process D.

Regarding **all-causality select adverse events**, some differences were observed between arms, although these differences were mainly driven by low-grade select AEs (G1-2). The categories in which a more marked difference between arms was observed were the "skin AE" category, "hepatic AE" category, "gastrointestinal AE" category, and "hypersensitivity / infusion reaction" category.

Immune-mediated adverse events (IMAEs) were reported with a similar frequency in both arms, although the category "hepatitis" was reported with a higher frequency in the Process D arm than in the Process C arm: in the Process C arm 3 (2.3%) subjects had an any-grade IMAE, none of them considered a G3-4 event; whereas in the Process D arm there were 8 (6.1%) subjects with an any-grade IMAE and 4 (3%) of them were G3-4 IMAEs. All hepatic IMAEs in the Process D resolved.

Other events of special interest (OESIs) were infrequent in both arms, although a higher frequency was observed in Process D compared with Process C: in Process C there were 4 events (2 patients), while in Process D there were 17 events (5 subjects). All events in both arms resolved at the time of DBL. In Process D there were 4 pancreatitis (two of them were grade 2 and one was grade 3), and 3 myocarditis (two of them were grade 3), whereas in Process C there were no events of pancreatitis or myocarditis.

Immunogenicity incidence was higher in the Process D arm than in the Process C arm: in Process C there were 3 (2.5%) ADA-positive subjects, vs. 8 (6.5%) ADA-positive subjects in Process D. The median duration of nivolumab ADAs was longer in Process D than in Process C: 14.29 (95% CI: 13.86, 34.14) weeks in Process D vs. 8.07 (95% CI: 2.14, NA) weeks in Process C. No patients in either arm developed neutralizing ADAs.

AEs leading to discontinuation were reported with a similar frequency in both arms: in the Process C arm any-grade AEs were reported in 22 subjects (17.1%) vs. 25 subjects (18.9%) in the Process D arm.

3.5. Uncertainties and limitations about unfavourable effects

The frequency of some AEs was unexpectedly higher in the Process D arm than in the Process C arm; notably in AEs belonging to the following categories: hypersensitivity / infusion reactions, skin, hepatic, cardiac and gastrointestinal; together with the PT of pancreatitis. The MAH presented two additional analyses comparing the results obtained in the Process D arm with different safety pools of nivolumab administered in other settings. The results of those analyses provided reassurance for some AEs, but uncertainties remain for others (i.e., hepatic events). Although thorough explanations were provided on the differences between both manufacturing processes with the aim of identifying the potential reasons for the observed safety differences, the reasons for these differences remain unknown. Considering there is no apparent explanation for these observed differences and taking into account the small data size, no changes in the SmPC or RMP are warranted.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Nivolumab Process C and Process D were found to be biocomparable as the AUC(0-336 h) geometric mean ratios (90% CI) were 1.012 (0.984, 1.041) and 0.998 (0.951, 1.047) at Week 1 and Week 17, respectively.

No relevant differences were observed in terms of RFS; although it should be noted that efficacy was included as an exploratory endpoint, and, therefore, these results are only descriptive.

While the overall safety profile of nivolumab Process D was comparable and consistent with nivolumab Process C in Study CA2098FC and reflective of the historical experience with nivolumab, the frequency of some AEs was unexpectedly higher in Process D than in Process C. Although the reasons for this observed imbalanced between arms are unclear, it should be noted that these differences were mainly driven by G1-2 AEs, and that those events resolved. Additionally, no differences in the number of deaths or treatment discontinuations were observed between arms, suggesting that the differences observed did not translate into major safety problems. The additional analyses performed by the MAH provided reassurance for some AEs categories such as the skin category, but are not enough to provide reassurance for some other categories, such as the hepatic category or the cardiac disorders category. Although it seems that somehow nivolumab Process D translate into a slightly worse tolerability profile than Process C, the limitations of study CA2098FC, which included only 261 patients, are acknowledged.

Immunogenicity of Process D appears to be higher than Process C although it seems lower than the reported incidence in the pool of studies of nivolumab as monotherapy.

From a quality point of view, comparability of both Process C and Process D is demonstrated. The quality dossier provides comprehensive information regarding the new development of manufacturing Process D and only one minor issue is still pending.

3.7.2. Balance of benefits and risks

Comparability of Process D with Process C can be considered demonstrated from a quality point of view. From a clinical point of view, the basis of this submission is the comparability of PK results between Process C and Process D in Study CA2098FC. In this regard, the primary endpoints of the study were met and therefore biocomparability is considered demonstrated. In terms of safety, no new signals have been identified with Process D compared to Process C, although the frequency of some AEs was unexpectedly higher in Process D than in Process C. Considering there is no apparent explanation for these observed differences and taking into account the small data size, no changes in the SmPC or RMP are warranted.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of OPDIVO is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Opdivo is not similar to Adcetris within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of, OPDIVO 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 melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

Non-small cell lung cancer (NSCLC)

OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

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

Malignant pleural mesothelioma (MPM)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

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.

Classical Hodgkin lymphoma (cHL)

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

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 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 $\geqslant$ 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 metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Oesophageal squamous cell carcinoma (OSCC)

OPDIVO in combination with ipilimumab 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 $\geqslant$ 1%.

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 $\geqslant$ 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) $\geqslant$ 5.

The CHMP therefore recommends the extension(s) 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.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where OPDIVO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use OPDIVO have access to/are provided with the patient alert card.

- The patient alert card shall contain the following key messages:
  - That OPDIVO treatment may increase the risk of:
    - Immune related pneumonitis
    - Immune related colitis

- Immune related hepatitis
- Immune related nephritis and renal dysfunction
- Immune related endocrinopathies
- Immune related skin adverse reactions
- Other immune related ARs

- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the OPDIVO prescriber

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.