20 July 2023
EMA/358599/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO

International non-proprietary name: nivolumab

Procedure No. EMEA/H/C/003985/II/0130

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADA	anti-drug antibodies
AE	adverse event
AJCC	American Joint Committee on Cancer
CI	confidence interval
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CT	computerized tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA	cytotoxic T-lymphocyte-associated protein
DBL	database lock
DCO	data cut-off
BICR	blinded independent central review
DMFS	distant metastasis-free survival
DMTR	Dutch Melanoma Treatment Registry
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
E-R	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
EQ-5D-5L	Euro Quality of Life 5-dimensional 5-level index
FACIT	Functional Assessment of Chronic Illness Therapy
FFR	freedom from relapse
GC	gastric cancer
GCP	good clinical practice
GEJC	gastroesophageal junction cancer
HR	hazard ratio
IMAE	immune-mediated adverse event
IRT	Interactive Response Technology
ITT	intent-to-treat
IV	intravenous
mAb	monoclonal antibody
MAH	Marketing Authorisation Holder
MID	minimally important difference
MRI	Magnetic resonance imaging
N/A, NA, N.A.	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OC	Oesophageal cancer

OESI	other events of special interest
ORR	objective response rate
OS	overall survival
OSCC	Oesophageal squamous cell carcinoma
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand-1
PFS2	progression-free survival through next-line therapy
PK	Pharmacokinetic(s)
PRO	patient reported outcome
PS	performance status
PSUR	Periodic Safety Update Report
PT	Preferred term
QLQ-C30	Quality of Life Questionnaire Core-30
QoL	Quality of Life
QxW	every x weeks
RCC	renal cell carcinoma
RFS	recurrence-free survival
RNA	ribonucleic acid
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TFI	treatment free interval
TMB	tumor mutational burden
UI	utility index
ULN	upper limit of normal
VAS	visual analogue scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 7 February 2023 an application for a variation.

The following variation was requested:

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

Extension of indication to include OPDIVO for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma who have undergone complete resection, based on results from study CA20976K; This is a phase III, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus placebo after complete resection of stage IIB/C melanoma. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 33.0 of the RMP has also been submitted.

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

Information on paediatric requirements

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

At the time of submission of the application, the PIP P/0432/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0432/2020.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: N/A Co-Rapporteur: Johann Lodewijk Hillege (acting as Rapporteur)

Timetable	Actual dates
Submission date	7 February 2023
Start of procedure	25 February 2023
CHMP-Co Rapporteur's preliminary assessment report circulated on	21 April 2023
PRAC Rapporteur Assessment Report's preliminary assessment report circulated on	27 April 2023
PRAC RMP advice and assessment overview adopted by PRAC on	12 May 2023
CHMP-Co Rapporteur's updated assessment report circulated on	17 May 2023
Request for supplementary information adopted by the CHMP on	25 May 2023
MAH's responses submitted to the CHMP on	26 May 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 June 2023
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on	23 June 2023
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	4 July 2023
PRAC RMP advice and assessment overview adopted by PRAC on	6 July 2023
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	13 July 2023
CHMP opinion adopted on	20 July 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH submitted a variation to the marketing authorisation to extend the indication to include:

"OPDIVO as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma who have undergone complete resection.".

The finally approved wording is (new text in **bold**):

"OPDIVO as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with ***Stage IIB or IIC melanoma, or*** *melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see SmPC section 5.1).".*

Epidemiology and risk factors

The European annual incidence of malignant melanoma varies from 3–5/100 000 in Mediterranean countries to 12–35/100 000 in Nordic countries. The incidence of melanoma has been rising steadily over the last 40 years, with a trend towards stabilization of mortality, except in elderly males[1]. Melanoma incidence peaks at 65 years, though any age can be affected[2]. Paediatric melanoma, usually defined as melanoma occurring in patients younger than 20 years, represents approximately 1% to 4% of all melanomas.[7,8] While rare in the adolescent population, the incidence of melanoma rises sharply to over 10 per million in the second decade, and 15-19 year old account for between 70% and 80% of all melanoma cases diagnosed in individuals < 20 years of age[3,4] The major environmental risk factor for melanoma is ultraviolet (UV) radiation and the best prevention is physical protection with adapted garments. Risk factors for melanoma in pediatric and adult patients are similar. Genetic predisposing conditions for developing melanoma, specifically in the pediatric population, do more frequently manifest in early childhood than in adolescence.

Biologic features, aetiology and pathogenesis

Most melanomas arise as superficial, indolent tumours that are confined to the epidermis, where they remain for several years. At some point, probably in response to the stepwise accumulation of genetic abnormalities, the melanoma is transformed into an expansile nodule that extends beyond the biologic boundary of the basement membrane and invades the dermis. Frequently observed mutations in order of decreasing frequency are BRAF, RAS and NF1[5]. Melanoma is a heterogeneous and complex disease with various clinical factors and molecular defects playing a key role in outcomes. Cutaneous melanoma is by far the most common melanoma subtype, accounting for in excess of 90% of cases of melanoma. The 2018 World Health Organization classification of cutaneous melanoma takes into account the site of origin (epithelium associated versus non-epithelium associated), role of cumulative sun damage (CSD; high CSD related, low CSD related, or non-CSD related), mole phenotype (high versus low nevus count), and frequency of BRAF, NRAS, and other relevant mutations. Based on morphologic features, there are four main types of cutaneous melanoma: superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanoma, and nodular melanoma. Less common variants include amelanotic melanoma, spitzoid melanoma, and desmoplastic melanoma. Paediatric melanoma is conventionally distinguished into three main categories, including conventional melanoma (CM), melanoma arising in congenital nevi (CNM), and spitzoid melanoma. CMs show a high rate of single nucleotide variations (SNVs) that are characteristic of UV damage and displays a high rate of genetic similarities with adult melanoma. On the contrarily, there is evidence that melanoma arising in CNMs shows a lower frequency of UV-related mutations, possibly due to a higher baseline risk.

The 8th Edition AJCC Cancer Staging Manual also applies to paediatric melanoma. The comparison between adult and paediatric melanoma is challenging given the poorly investigated biology and pathogenesis of disease in the paediatric setting. Controversial findings have been reported in terms of prognostic values in the young age categories for histopathological hallmarks such as ulceration and

[1] Hollestein LM, van den Akker SAW, Nijsten T et al. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann Oncol 2012; 23(2): 524–530
[2] National Cancer Registration and Analysis Service, Public Health England, https://www.cancerresearchuk.org (15 October 2019, date last accessed).
[3] Jen M, Murphy M, Grant-Kels JM. Childhood melanoma. Clin Dermatol 2009;27:529–36.
[4] Brecht IB, De Paoli A, Bisogno G et al, Pediatric patients with cutaneous melanoma: A European study. Pediatr Blood Cancer. 2018 Jun;65(6):e26974.
[5] Shain AH, Yeh I, Kovalyshyn I, et al. The Genetic Evolution of Melanoma from Precursor Lesions. N Engl J Med 2015; 373:1926

thickness (see below section), differences in primary site of lesions between adults and adolescents have been described, as well as stage at diagnosis and tumour subtypes. Primary melanoma tumour characteristics are considered to be comparable between adolescent and adult melanoma patients, in contrast to the disease in prepubescent children. In an analysis of 1255 paediatric and young adults (age less than 20 years), the 10 to 19 year-old group had similar baseline characteristics compared with the group of 20 to 24 year-old young adults, while there were significant differences in baseline characteristics of young children (age less than 10 years) as compared with adolescents and young adults. Young children were more likely to be non-white and to have metastases, nodular or other histology, head, face, or neck primaries, thicker lesions, and history of cancer.[6]

Clinical presentation, diagnosis and stage/prognosis

Suspicious pigmented lesions are usually clinically analysed with the 'ugly duckling' concept and the 'ABCD' rule: Asymmetry, Border irregularities, Colour heterogeneity, Dynamics, (Dynamics or evolution in colours, elevation or size). The eighth version of the American Joint Committee on Cancer (AJCC) staging and classification system, which includes sentinel node staging, is the preferred classification system[7].

The target population is confined to adults and adolescents 12 years of age and older with stage IIB and stage IIC melanoma (patients with T3b-T4b N0 disease per AJCC 8th edition) who have undergone complete resection. These patients have a primary tumour that is thick and/or ulcerated (>4 mm thick with or without ulceration, or >2 to 4 mm thick with ulceration), but no lymph node involvement. Patients with Stage IIB/C resected melanoma are at high risk of melanoma recurrence (approximately one third of Stage IIB and one half of Stage IIC patients will recur within 5 years). Melanoma-specific survival of Stage IIB and IIC patients is generally similar to melanoma-specific survival of Stage IIIA and IIIB patients, respectively. 5-year and 10-year melanoma-specific survival is estimated to be 83%-87% and 72%-82%, respectively, for Stage IIB patients and 70%-82% and 58%-75%, respectively, for Stage IIC patients.[2,4]

Management

Standard of care for patients with clinical Stage II melanoma of all substages consists of wide surgical excision of the primary melanoma with the option to perform a sentinel lymph node biopsy. For Stage IIB/C melanomas (tumor thickness > 2.0 mm), the evaluation of the sentinel lymph node for disease involvement and a wide excision of the primary melanoma with 2-cm margins is recommended. Patients who have a positive sentinel lymph node are upstaged to Stage III and can undergo either surveillance of the nodal basin with ultrasound or complete lymph node dissection. Per current guidelines, patients with node positive disease may be offered nivolumab, pembrolizumab, dabrafenib/trametinib (for patients with a BRAF V600 activating mutation), or observation in the adjuvant setting. Current treatment recommendations for patients with a negative sentinel lymph node biopsy or for patients in whom a sentinel lymph node biopsy was not conducted for any reason is observation with periodic surveillance to detect disease recurrence. In addition to observation for patients with Stage IIB or IIC melanoma, adjuvant pembrolizumab is also a recommended treatment option in the National Comprehensive Cancer Network (NCCN) guidelines after a clinician has a detailed discussion with a patient taking into consideration treatment benefits and risks[8].

[6] Strouse JJ, Fears TR, Tucker MA, et al. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol 2005;23:4735-41.
[7] Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging:evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67(6):472–492.
[8] National Comprehensive Cancer Network (NCCN). NCNN Clinical Practive Guidelines in Oncology (NCCN Guidelines®). Melanoma: Cutaneous. Version 3. 2022. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf.

Pembrolizumab has not yet been listed in the European Society for Medical Oncology (ESMO) guidelines for treatment of Stage IIB/C adjuvant melanoma[9].

Currently, only 1 approved treatment option, pembrolizumab, exists for Stage IIB/C resected melanoma patients. In Jun-2022, pembrolizumab (Keytruda) was approved for the adjuvant treatment of adult and paediatric (≥ 12 years of age) patients with Stage IIB or IIC melanoma following complete resection and is the only approved treatment option available for these patients (Keytruda II/111 EPAR). Approval was based on the registrational study KEYNOTE-716, a multicentre, randomised, double-blind, placebo-controlled study in patients with resected Stage IIB or IIC melanoma who received pembrolizumab 200 mg every three weeks (or the paediatric [12 to 17 years old] dose of 2 mg/kg intravenously [up to a maximum of 200 mg] every three weeks) or placebo, for up to one year or until disease recurrence or unacceptable toxicity. The study initially demonstrated a statistically significant improvement in RFS (HR 0.65; 95% CI 0.46, 0.92), supported by a statistically significant effect of pembrolizumab relative to placebo on DMFS at the first interim analysis.

Melanoma in adolescents and adults is generally regarded as an analogous disease and is treated similarly using multimodal therapy including surgery, systemic therapy, and in some cases, radiation. As such, current treatment strategies for paediatric and adolescent melanoma are based on clinical guidelines for adult patients[10], and there are limited clinical studies evaluating treatment outcomes in these age groups. Despite the small number of patients, results of these studies suggest that safety profiles and treatment effects in adolescents are comparable with adult patients.

The efficacy and safety of nivolumab has been reviewed for use in adolescent patients (≥ 12 to < 18 years old) in the Type II variation for extension of the indication for nivolumab as a single agent or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adolescents and for nivolumab as monotherapy for the adjuvant treatment of adolescents with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (EMEA/H/C/003985/II/0125/G, positive opinion April 2023).

2.1.2. About the product

Opdivo (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. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Nivolumab monotherapy is currently approved in the EU for the treatment of patients with advanced/metastatic melanoma, NSCLC, RCC, classical Hodgkin lymphoma, squamous cell cancer of the head and neck, urothelial carcinoma, and OSCC (Opdivo SmPC).

In the adjuvant setting, nivolumab is approved for treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, muscle invasive urothelial carcinoma, and oesophageal cancer or GEJC, and in the neoadjuvant treatment of adult patients with resectable Stage IB-IIIA non-small cell lung cancer.

[9] Michielin O, van Akkooi ACJ, Ascierto PA, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol 2019;30:1884-1901.
[10] Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2019;80(1):208-50.

Nivolumab is also approved in combination therapy for the treatment of patients with melanoma, RCC, mismatch repair deficient/microsatellite instability-high colorectal cancer, malignant pleural mesothelioma, NSCLC, GC, GEJC or OC, and OSCC.

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

Scientific advice was not sought for the proposed indication.

2.1.4. General comments on compliance with GCP

The pivotal study CA20976K was conducted in accordance with the principles of Good Clinical Practice (GCP) as defined by the International Council for Harmonisation and was conducted to meet the ethical requirement of European Directive 2001/20/EC. For Study CA20976K, the protocol, amendments, administrative letters, and subject informed consent form received Institutional Review Board/Independent Ethics Committee approval prior to implementation.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Nivolumab is a protein, which is expected to be metabolised in the body and biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), nivolumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not expect to pose a significant risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

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

Nivolumab is a monoclonal antibody and is not expected to pose a significant risk to the environment, thus the lack of ERA studies is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Summary of clinical efficacy studies

Study number	Design	Study Population	Number randomized/ treated	Dosing regimen	Primary efficacy endpoint
CA20976K	Phase 3, randomized double blind study	Adults and adolescent subjects ≥12 years old with resected Stage IIB/C melanoma and no evidence of disease (stage T3b, T4a and T4b)	N = 790 randomized (526 to nivolumab and 264 to placebo) N = 788 treated (524 with nivolumab and 264 with placebo)	Blinded phase: Nivolumab 480 mg Q4W or Placebo Q4W Maximum duration of 12 months Open-label phase crossover or re-challenge with nivolumab: Nivolumab 480 mg Q4W	Recurrence free survival (investigator)
CA209238	Phase 3, randomized double blind study	Completely resected Stage IIIB/C or Stage IV melanoma in adults and adolescents ≥15 years of age	N = 906 randomized (453 to nivolumab and 453 to ipilimumab) N = 905 treated (452 with nivolumab and 453 with ipilimumab)	Nivolumab: 3 mg/kg IV every 2 weeks Ipilimumab: 10 mg/kg IV Q3W for 4 doses, then 10 mg/kg IV Q12W starting at Week 24 Maximum duration of 12 months	Recurrence free survival (investigator)

2.3.2. Pharmacokinetics

Nivolumab doses of 240 mg Q2W or 480 mg Q4W are currently approved in adults in the EU for multiple indications, including advanced melanoma and for the adjuvant treatment of resected Stage III/IV melanoma. The approved dosing regimens for melanoma were based on population pharmacokinetics and exposure-response (E-R) safety and efficacy analyses. This is supported by similar nivolumab exposures across subjects with Stage III/IV resected melanoma and similar recurrence free survival (RFS) across Stage III/IV for the 3 mg/kg Q2W dosing regimen from Study CA209238 and for the 480 mg Q4W dosing regimen from Study CA209915 (see procedures EMEA/H/C/003985/0003, II/0036, II/0041, and II/0069).

In the recently adopted procedure EMEA/H/C/003985/II/0125/G, extensive pharmacokinetic and exposure-response safety analyses across adolescent and adult studies were conducted to recommend an adolescent (≥ 12 to < 18 years) dosing regimen in advanced and resected Stage III/IV melanoma based on paediatric extrapolation principles.

Predicted pharmacokinetic exposure parameters of nivolumab for the proposed posology in adolescents and adults with melanoma are summarised in Table 2 and Table 3. For treatment of adults with melanoma, dosing of 240 mg Q2W or 480 mg Q4W is approved. For adolescents, currently a body-weight based dosing is proposed for patients 30-40 kg i.e. 3 mg/kg Q2W or 6 mg/kg Q4W, and a flat dosing regimen for patients> 40 kg i.e. 240 mg Q2W or 480 mg Q4W. As can be seen in Table 2 and Table 3, adolescents with body-weights 40-60 kg have on average slightly higher exposures than those observed in adults. Since a body weight dosing is proposed for adolescents with body weight < 40 kg,

nivolumab exposures are within the range of adults for adolescents weighing 30-40 kg. Average nivolumab exposures in adolescents > 60 kg are within the range of adults.

Table 2 Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 3 mg/kg (< 40 kg) or 240 mg (≥ 40 kg) Q2W and Adults with Adjuvant Treatment of Melanoma at 240 mg Q2W

Exposure (µg/mL)	Body Weight (kg)	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]	Adult 10 mg/kg Geo. Mean
Cavgss	30-40	95.4 (30.8)	Yes	NA	89.7-167	261
	40-50	183 (29.5)	No (9.58%)	167 (32.3)		
	50-60	170 (32.5)	No (1.8%)	152 (32.1)		
	60-70	147 (29.5)	Yes	136 (28.5)		
	70-80	138 (30.7)	Yes	120 (29.6)		
	80-90	123 (29.3)	Yes	107 (28)		
	90-100	116 (30.7)	Yes	102 (32.4)		
	100-110	116 (31.5)	Yes	91.7 (25.6)		
	≥ 110	90.6 (36.2)	Yes	89.7 (29.7)		
Cminss	30-40	78 (35.9)	Yes	NA	74.1-137	200
	40-50	150 (33.9)	No (9.49%)	137 (38)		
	50-60	141 (37)	No (2.92%)	128 (36)		
	60-70	121 (34.3)	Yes	113 (32.8)		
	70-80	115 (35.4)	Yes	99.2 (34.4)		
	80-90	102 (33.2)	Yes	87.9 (32.8)		
	90-100	95.5 (35.5)	Yes	84.5 (36.8)		
	100-110	96.4 (36.4)	Yes	75.2 (29.8)		
	≥ 110	74.2 (41.5)	Yes	74.1 (34.2)		
Cmaxss	30-40	137 (26.1)	Yes	NA	123-231	385
	40-50	260 (27.2)	No (12.6%)	231 (27.7)		
	50-60	235 (28.9)	No (1.73%)	202 (30.3)		
	60-70	208 (25.5)	Yes	189 (24.4)		
	70-80	191 (26.9)	Yes	166 (25.4)		
	80-90	171 (26.3)	Yes	149 (23.7)		
	90-100	163 (26.9)	Yes	142 (28.3)		
	100-110	163 (28)	Yes	127 (22.5)		
	≥ 110	128 (32.5)	Yes	123 (26.9)		

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/
R-Program Source: Analysis-Directory/R/scripts/5-simulation-nivo.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-mono-240.csv
[a] The range of lowest to highest geometric mean exposure in adults across body weight groups.

Table 3 Predicted Nivolumab Exposures for Adolescents with Adjuvant Treatment of Melanoma at 6 mg/kg (< 40 kg) or 480 mg (≥ 40 kg) Q4W and Adults with Adjuvant Treatment of Melanoma at 480 mg Q4W

Exposure (µg/mL)	Body Weight (kg)	Adolescent Geo. Mean (%CV)	If in Adult Range	Adult Geo. Mean (%CV)	Adult Low - High Geo. Mean[a]	Adult 10 mg/kg Geo. Mean
	30-40	104 (32.3)	Yes	NA		
	40-50	198 (35.1)	No (15.1%)	172 (30.4)		
	50-60	176 (31.5)	No (2.33%)	149 (29.7)		
	60-70	162 (33.1)	Yes	136 (31.9)		
Cavgss	70-80	146 (30.5)	Yes	115 (29.3)	83.2-172	261
	80-90	129 (33.9)	Yes	101 (29.4)		
	90-100	116 (29.5)	Yes	96.5 (26.5)		
	100-110	108 (30.1)	Yes	93.9 (34.2)		
	≥ 110	96 (30.8)	Yes	83.2 (29.3)		
	30-40	73.8 (40.4)	Yes	NA		
	40-50	141 (44.2)	No (14.6%)	123 (38.6)		
	50-60	129 (39)	No (4.88%)	104 (39.3)		
	60-70	115 (41.3)	Yes	94.6 (41.5)		
Cminss	70-80	105 (38.3)	Yes	81.4 (36.9)	57.4-123	200
	80-90	92.2 (43.7)	Yes	69.1 (39.2)		
	90-100	81.4 (38.7)	Yes	66.4 (36.4)		
	100-110	75.2 (39.5)	Yes	64.6 (46.2)		
	≥ 110	66.9 (40.3)	Yes	57.4 (37.5)		
	30-40	190 (30.4)	Yes	NA		
	40-50	371 (30.5)	No (24.5%)	298 (26.8)		
	50-60	311 (29.9)	No (4.36%)	263 (25.1)		
	60-70	302 (29.1)	No (1.34%)	245 (27)		
Cmaxss	70-80	266 (26.5)	Yes	204 (26.3)	153-298	385
	80-90	235 (26.4)	Yes	184 (26.7)		
	90-100	218 (27.5)	Yes	176 (22.7)		
	100-110	205 (25.2)	Yes	172 (27.3)		
	≥ 110	182 (26.6)	Yes	153 (28.6)		

Analysis-Directory: /global/pkms/data/CA/209/adjmel-ped/prd/ppk/final/
R-Program Source: Analysis-Directory/R/scripts/5-simulation-nivo.Rmd
Source: Analysis-Directory/R/export/expo-all-sto-mel-mono-480.csv

[a] The range of lowest to highest geometric mean exposure in adults across body weight groups.

2.3.3. Discussion on clinical pharmacology

No new pharmacokinetic and exposure-response data were submitted for this application. This is acceptable based on the well known pharmacology of nivolumab in patients with melanoma.

Extension of the indication to include adolescent patients aged 12 years and older in treatment of advanced (unresectable or metastatic) melanoma (nivolumab monotherapy), treatment of advanced (unresectable or metastatic) melanoma (nivolumab in combination with ipilimumab) and adjuvant treatment of melanoma (nivolumab monotherapy) for Opdivo has been evaluated in procedure EMEA/H/C/003985/II/0125/G. Since there were no new data in adolescents in the current procedure,

the posology of Opdivo for adolescents with stage IIB or IIC melanoma who have undergone complete resection was harmonised with the approved posology in procedure EMEA/H/C/003985/II/0125/G, where for treatment of adults with melanoma, dosing of 240 mg Q2W or 480 mg Q4W is proposed and for adolescents, a body-weight based dosing is proposed for patients 30-40 kg i.e. 3 mg/kg Q2W or 6 mg/kg Q4W, and a flat dosing regimen for patients> 40 kg i.e. 240 mg Q2W or 480 mg Q4W (see SmPC 4.2).

2.3.4. Conclusions on clinical pharmacology

No new pharmacology data were provided for this extension of indication. This is considered acceptable. The posology for Opdivo monotherapy in adolescents with melanoma has been established during evaluation of EMEA/H/C/003985/II/0125/G.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Nivolumab is approved at the 240 mg Q2W and 480 mg Q4W dose for numerous indications.

The proposed posology of nivolumab 480 mg Q4W and 240 mg Q2W are recommended based on the totality of clinical data from Study CA20976K dosing 480 mg Q4W as a 30-minute IV infusion, as well as the collective clinical experience of nivolumab monotherapy in melanoma. The following provide a summary of the dose justification for nivolumab in adults and adolescents:

- Clinical efficacy and safety data from pivotal Study CA20976K confirmed the favourable benefit-risk of nivolumab 480 mg Q4W as adjuvant treatment in subjects with completely resected Stage IIB/C melanoma.
- The stage of resected melanoma prior to treatment is not expected to impact nivolumab PK given the similarity of PK across different stages of resected III/IV from study CA209238 for 3 mg/kg Q2W dosing and from study CA209915 for 480 mg Q4W dosing. Therefore, nivolumab PK is expected to be similar in resected Stage IIB/C to that of resected Stage III/IV.
- Previous population pharmacokinetics and exposure-response safety and efficacy analyses confirmed a favourable benefit-risk profile for adults in the adjuvant treatment of resected Stage III/IV melanoma and advanced melanoma for the 240 mg Q2W or 480 mg Q4W dosing regimens.
- Previous population pharmacokinetics and exposure-response safety analyses, showed a favourable benefit-risk profile for adolescents in adjuvant treatment of melanoma Stage III/IV across adult and adolescent studies for the 240 mg Q2W or 480 mg Q4W dosing regimens for adolescents ≥40 kg and 3 mg/kg Q2W or 6 mg/kg Q4W for adolescents < 40 kg (EMEA/H/C/003985/II/125/G).
- Exposure differences between 240 mg Q2W and 480 mg Q4W have been extensively evaluated in advanced and adjuvant settings. Clinical equivalence of the posology is supported by modelling and simulation with the same benefit-risk expected to apply across resected Stage IIB/C and III/IV melanoma.

- An alternative nivolumab dosing option of 240 mg Q2W provides patients and clinicians with dosing flexibility and is consistent with the current approved dosing regimens of 240 mg Q2W or 480 mg Q4W in advanced melanoma and the adjuvant treatment of resected Stage III/IV melanoma.
- No dose modifications are needed for any patient subgroups.

The posology of Opdivo for adolescents with stage IIB or IIC melanoma who have undergone complete resection has been harmonized with the agreed posology in the previous procedure EMEA/H/C/003985/II/0125/G.

2.4.2. Main study(ies)

CA20976K: A Phase 3, Randomized, Double-Blind Study of Adjuvant Immunotherapy with Nivolumab versus Placebo after Complete Resection of Stage IIB/C Melanoma

Methods

Study CA20976K (NCT04099251) is a Phase 3, randomized, double-blind study designed to evaluate the use of adjuvant immunotherapy with nivolumab versus placebo after complete resection of Stage IIB/C melanoma in adults and adolescent subjects ≥ 12 years old. Subjects with resected Stage IIB/C melanoma and no evidence of disease were randomized to treatment with either nivolumab or placebo for a duration of 12 months. In the event of disease recurrence, subjects had the option to receive on-study open-label nivolumab treatment or receive treatment per local standard of care. Placebo-treated subjects who experienced disease recurrence within 3 years after the last dose of placebo, and nivolumab-treated subjects who experienced recurrence greater than 6 months and within 3 years after completing treatment, were eligible to receive on-study open-label nivolumab treatment. Subjects with recurrent resectable disease were offered nivolumab for a maximum duration of 12 months, whereas subjects with recurrent unresectable or metastatic disease were offered nivolumab for a maximum of 24 months (Figure 1).

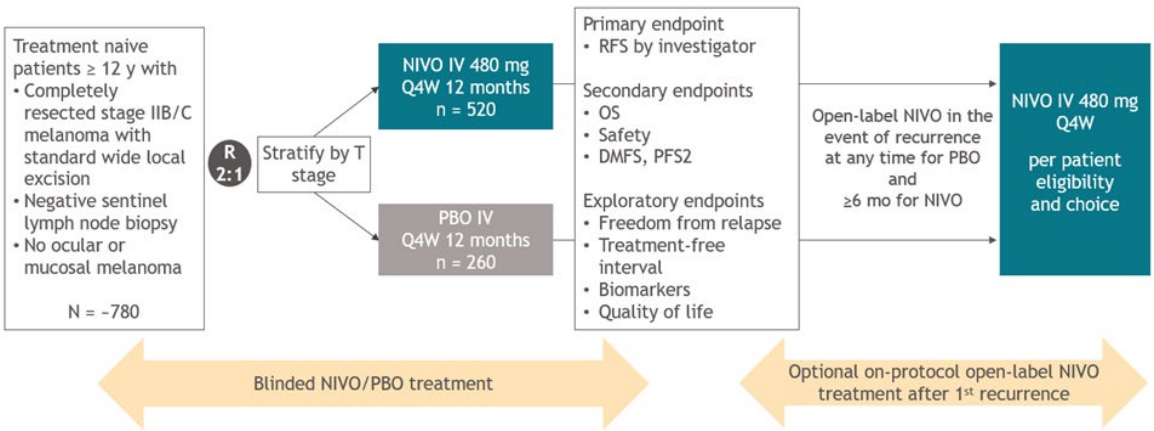


Figure 1 Schematic study design CA20976K

Tumor assessments were performed every 26 weeks (± 14 days) during the treatment phase of 12 months using CT and CT/MRI. Participants with signs or symptoms consistent with brain metastases should have an MRI of the brain (CT if MRI was contraindicated) as clinically indicated.

Participants must be followed for at least 100 days after the last dose of study treatment. FU1 should occur 30 days from the last dose (± 7 days) and FU2 occurs approximately 100 days (± 7 days) from the last dose of study treatment.

Long term follow-up: Imaging was performed every 26 weeks (± 14 days) during years 1, 2, and 3 and every 52 weeks (± 28 days) during years 4 and 5. Participants who develop a loco-regional recurrence only, must be followed by surveillance imaging until the development of distant metastases.

Survival status was determined every 12 weeks (±14 days) from FU2 until the OS final analysis.

In the current application (thus also in this document), only data from the blinded part are presented.

Study participants

Male and female participants (≥ 12 years of age) with completely resected Stage IIB or IIC melanoma, with no evidence of disease (NED). Note: Where local regulations and/or institutional policies do not allow for participants < 18 years of age, the eligible participant population is ≥ 18 years of age.

Inclusion criteria

Key inclusion criteria included the following:

- Participants must have been diagnosed with Stage IIB/C cutaneous melanoma (AJCC Staging, 8th edition) and have histologically confirmed melanoma that is completely surgically resected, with documented negative margins (per local standard) for disease on resected specimens. All melanomas, except ocular and mucosal melanoma, regardless of primary site of disease will be allowed.
- Complete resection with documented negative margins (per local standard) and sentinel lymph node assessment for presence/absence of disease, must be performed within 12 weeks prior to randomization. Note: In case of delays exceeding 12 weeks due to unforeseen circumstances, the eligibility should be discussed with the Medical Monitor or designee.
- Participants must have had a negative sentinel lymph node biopsy. Participants in whom a sentinel lymph node biopsy procedure could not be done or a sentinel lymph node was not detected are not eligible.
- Participants must have disease-free status documented by a complete physical examination (within 14 days) and imaging studies within 4 weeks (28 days) prior to randomization. Imaging studies must include computerized tomography (CT) scans of the chest/abdomen/pelvis or CT scan of the chest and magnetic resonance imaging (MRI) scans of the abdomen and pelvis, and all known sites of resected disease (imaging of extremities for resected melanomas located in the extremities is not a requirement). The evaluation of extremities may be conducted, and documented, per local standard of care. Participants with signs and symptoms consistent with brain metastases should have imaging studies done to rule out the presence of brain metastases.
- Participant has not been previously treated for melanoma beyond complete surgical resection of the melanoma lesion.

- Participant has recovered adequately from toxicity and/or complications from surgery prior to study start.
- ECOG performance status (PS) of 0 or 1 at the time of enrolment.
- Tumour tissue (minimum of 15 unstained slides, preferably freshly cut, or 1 formalin-fixed paraffin-embedded block to contain sufficient tissue for at least 15 sections) from the primary diagnostic biopsy must be shipped to the central laboratory prior to randomization. If the required tumour tissue content cannot be provided, the eligibility should be discussed with the Medical Monitor or designee.

Exclusion criteria

Key exclusion criteria included the following:

Medical Conditions

- History of ocular and mucosal melanoma.
- Participants with active, known, or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
- Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Women who are pregnant or breastfeeding.
- Participants with serious or uncontrolled medical disorders. Additionally, in the case of prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, symptoms must have completely resolved and based on investigator assessment in consultation with the MAH Medical Monitor or designee, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

Prior/Concomitant Therapy

- Use of an investigational agent or an investigational device within 28 days before administration of first dose of study drug.
- Treatment directed against the resected melanoma (eg, chemotherapy, radiation therapy, targeted agents, biotherapy, or limb perfusion) that is administered after the complete resection.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or agents that target IL-2 pathway any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. Exception: Prior adjuvant treatment with interferon (for melanoma other than study entry melanoma) is allowed if completed ≥ 6 months prior to randomization.

- Treatment with complementary medications (e.g., herbal supplements or traditional Chinese medicines) to treat the disease under study within 2 weeks prior to randomization/treatment. Such medications are permitted if they are used as supportive care.
- Participants who have received a live / attenuated vaccine within 30 days of first treatment.

Physical and laboratory test findings

- WBC < 2000/µL
- Neutrophils < 1500/µL
- Platelets < 100×103/µL
- Hemoglobin < 9.0 g/dL
- Serum creatinine > 1.5 x upper limit of normal (ULN), unless creatinine clearance ≥ 40 mL/min (measured or calculated using the Cockroft-Gault formula)

  Female creatinine clearance (CrCl) = [(140 - age in years) x weight in kg x 0.85] ÷ [72 x serum creatinine in mg/dL]

  Male CrCl = [(140 - age in years) x weight in kg x 1.00] ÷ [72 x serum creatinine in mg/dL]
- AST/ALT: > 3.0 x ULN
- Total bilirubin > 1.5 x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0 x ULN)
- Any positive test result for hepatitis B virus or hepatitis C virus indicating presence of virus, eg, Hepatitis B surface antigen (HBsAg, Australia antigen) positive, or Hepatitis C antibody (anti-HCV) positive (except if HCV-RNA negative).
- Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Note: Testing for HIV must be performed at sites where mandated locally.

Allergies and adverse drug reactions

- Known history of allergy or hypersensitivity to study drug components.
- Known history of severe hypersensitivity reaction (Grade ≥ 3) to any monoclonal antibody.

Treatments

Blinded part - Nivolumab/placebo treated subjects: Adult subjects and paediatric subjects (≥ 12 years old) who weighed ≥ 40 kg received nivolumab (or matching placebo) at a dose of 480 mg as an approximately 30-minute infusion on Day 1 of each 4-week treatment cycle until unacceptable toxicity, withdrawal of consent, completion of 12 months of treatment (from first dose of study treatment), disease recurrence, or the study ends, whichever occurred first. Paediatric subjects weighing < 40 kg received nivolumab (or matching placebo) 6 mg/kg once every 4 weeks (Q4W) up to a maximum of 240 mg. Subjects began study treatment (Cycle 1) within 3 calendar days of randomization. Subsequent cycles were initiated within ± 3 days of the target visit date.

Open-Label Nivolumab Treatment: Nivolumab treatment details for adults and paediatric subjects in the open label phase were the same as in the blinded phase.

Dose modifications

Dose escalation or reduction is not recommended for nivolumab. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Objectives/endpoints

Table 4 Objectives and endpoints for study CA20976K

Primary objective	Primary endpoint	Included in this report?
To compare investigator-assessed recurrence-free survival (RFS) between treatment arms	RFS: 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 (due to any cause), whichever occurred first.	Yes
Secondary objectives	**Secondary endpoint**	
To compare the overall survival (OS) between treatment arms	OS was defined as the time between the date of randomization and the date of death, from any cause.	No
To assess safety and toxicity of nivolumab monotherapy	The assessment of safety was based on the incidence of adverse events (AEs). The use of immune modulating medications were also summarized. In addition, clinical laboratory tests and immunogenicity were analyzed. Toxicities were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.	Yes
To evaluate investigator-assessed distant metastases-free survival (DMFS)	DMFS was defined as the time between the date of randomization and the date of first distant recurrence or the date of death (due to any cause), whichever occurred first.	Yes
To evaluate investigator-assessed outcomes on next-line therapies	The definition of next line therapy is any systemic anti-cancer therapy for melanoma with a start date on or after the date of first dose of study drug (randomization date if subject was never treated). **Progression-free survival through next-line therapy** (PFS2) was defined as the time from randomization to recurrence/objective disease progression after the start of next-line of systemic anti-cancer therapy, or to the start of second next-line systemic therapy, or to death from any cause, whichever occurred first.	Yes
	In case PFS2 cannot be reliably determined, an alternative **end-of-next-line-treatment** will be defined as the time from randomization to recurrence/objective disease progression after start of next-line systemic anti-cancer therapy, or to discontinuation of next-line therapy, or death from any cause, whichever occurred first.	No
	Duration of treatment on next-line therapy was defined as the time from first dose date of next-line therapy to last dose date of next-line therapy. Subjects who did not stop the next-line therapy were censored.	Yes
	Objective Response Rate (ORR) was defined as the number of randomized subjects who achieve a best overall response of complete response or partial response after next-line therapy based on investigator assessments (using RECIST v1.1) divided by the number of all randomized subjects.	No

Exploratory endpoints

- To evaluate freedom from relapse (FFR) defined as the time from randomization to recurrence, with censoring of data for participants who had died from causes other than melanoma or treatment-related toxic effects.

- To evaluate treatment-free interval (TFI) defined as the time from last dose of study treatment to the start of subsequent systemic therapy or the last known alive date (for those who never received subsequent cancer therapy).
- To assess the participant's cancer-related Quality of Life (QoL) using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.
- To assess the participant's quality of life and overall health status using the EQ-5D-5L utility index (UI) and visual analogue scale, respectively.
- To characterize participant perceptions of the bothersomeness of symptomatic AEs based on functional assessment of chronic illness therapy (FACIT) GP5 item.
- To characterize the immunogenicity of nivolumab.
- To explore potential association of biomarkers (e.g., PD-L1 expression) with clinical efficacy (RFS, DMFS and OS) and/or incidence of adverse events of nivolumab by analyzing biomarker measures within the tumour microenvironment and periphery (e.g., blood, serum, plasma, tumour tissue and PBMCs) in comparison to clinical outcomes.
- To explore potential association of tumour mutational burden (TMB) with clinical efficacy (RFS, DMFS and OS).

No data were provided on TMB and biomarkers, other than PD-L1.

Sample size

The sample size of the study was based on a comparison of the RFS distribution between subjects randomized to nivolumab and subjects randomized to placebo. Approximately 154 RFS events were required for a two-sided experiment-wise alpha = 0.05 log-rank test, to show a statistically significant difference in RFS between the treatment arms with at least 90% power when the average HR of the nivolumab arm to the placebo arm is 0.573. Given an estimated accrual rate, the accrual of 780 subjects (i.e., 520 subjects in the nivolumab arm and 260 subjects in the placebo arm) would take approximately 29.6 months. Under the assumptions for accrual, an assumed delayed treatment effect of 6 months as per the Sunbelt Melanoma Trial (McMasters KM, et al. J Clin Oncol. 2016;34:1079-1086) and assumed HR as stated above (HR = 1 for the first 6 months, HR = 0.537 after 6 months, HR = 1 from Year 10 [plateau effect]), it would take approximately 68.1 months from the randomization of the first subject to observe the required number of RFS events. An observed HR of 0.707 or less would result in a statistically significant improvement at the final analysis of RFS.

Randomisation

Eligible patients were randomised 2:1 to nivolumab or placebo though the interactive response technology (IRT). Randomization was stratified by AJCC 8th edition tumour category (T3b vs. T4a vs. T4b).

Blinding (masking)

During the double-blind treatment phase, the sponsor, participants, investigator, and site staff were blinded to the study drug administered during the study.

Statistical methods

Efficacy endpoints

The primary endpoint of **RFS** based on the disease recurrence date provided by the investigator 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 (due to any cause), whichever occurs first. For participants who remain alive and whose disease has not recurred, RFS will be censored on the date of last evaluable disease assessment. For those participants who remained alive and had no recorded post-randomization tumour assessment, RFS will be censored on the day of randomization. Censoring rules for the primary definition of RFS are presented in the table below.

Table 5 Censoring scheme for primary definition of RFS

Situation	Date of Event or Censoring	Outcome
Recurrence (local, regional, distant, new primary melanoma, including melanoma in situ)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
Disease at baseline	Date of randomization	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death*	Date of last evaluable disease assessment	Censored
New anticancer therapy**, tumor-directed radiotherapy, or tumor-directed surgery received without recurrence reported prior to or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-melanoma primary cancer (excluding BCC) reported prior or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of diagnosis of second non-melanoma primary cancer	Censored

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

** Open-label nivolumab treatment will be considered as a new anticancer therapy

Abbreviations: BCC, basal cell carcinoma.

The final analysis of RFS was to be conducted when approximately 154 RFS events have occurred. In case the events occurred slower than anticipated, final analysis of RFS would be conducted when at least 139 events (90% of planned number of events for the final analysis) have been observed. In that case, the power would be at least 86% (and the critical hazard ratio (HR) would be 0.692).

An interim analysis of RFS was planned when approximately 123 RFS events (80% information fraction) had been reached among all randomized subjects. The stopping boundaries at the interim and final analyses were derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. With an interim RFS analysis at approximately 123 RFS events, the type I error was 0.024 (two-sided), the power 62.8%, and an observed HR of 0.65 or less would result in a statistically significant improvement. The type I error used for final RFS analysis was 0.0043 (two-sided).

The primary RFS analysis was conducted using a stratified two-sided log-rank test. The stratification factor that was used in the analysis was AJCC tumour category at study entry (as recorded per IRT). The two-sided stratified log-rank p-value was reported. The estimate of the RFS hazard ratio of nivolumab to placebo was calculated using a stratified Cox proportional hazards model, with treatment as the sole covariate, stratified by the above stratification factor. Ties were handled using the exact method. A two sided 100x(1-adjusted α)% and 95% confidence intervals (CI's) for the hazard ratio was also presented, along with the two-sided stratified log-rank p-value.

Sensitivity analyses RFS
In a supportive analysis, a treatment policy strategy was employed for the intercurrent events 'new anti-cancer therapy' and 'second non-melanoma primary cancer'. Further supportive analyses included analyses using an alternative RFS definition (accounting for two or more consecutively missing disease assessments prior to RFS events), analyses accounting for the possibility of delayed effects, analyses to evaluate the proportional hazards assumption and treatment by strata interactions, and analyses using different modelling options (e.g. models without stratification, or including stratification factors as covariates in the model).

The first secondary endpoint **OS** is defined as the time between the date of randomization and the date of death, from any cause. For subjects that are alive, their survival time will be censored at the date of last contact (or "last known alive date"). Overall survival will be censored at the date of randomization for subjects who were randomized but had no follow-up. For the comparison of OS between nivolumab and placebo in all randomized subjects, approximately 277 deaths would be required for a two-sided experiment-wise alpha = 0.05 logrank test, to show a statistically significant difference in OS with at least 76.6% power when the average HR of the nivolumab arm to the placebo arm is 0.7. It is projected that an observed HR of 0.777 or less would result in a statistically significant improvement at the final analysis of OS. In case OS events occur too slowly, final analysis may be triggered when a minimum follow-up of 9 years (i.e., 108 months) is reached.

To ensure sufficient maturity of the OS data at the time formal analysis is performed, one formal OS interim analysis will be conducted when approximately 166 deaths (60% information fraction) have been reached among all randomized subjects, which is expected to occur after the final analysis of RFS. We estimate this would occur when all subjects have a minimum follow-up of approximately 63 months from the randomization of the last subject. The estimated timing for this interim analysis is at 93 months. The stopping boundaries at the interim and final analyses will be derived based on the exact number of OS events using Lan DeMets alpha spending function with O'Brien-Fleming boundaries. With an interim OS analysis at approximately 166 deaths, the type I error would be 0.008 (two-sided), the power 30.7%, and an observed HR of 0.644 or less would result in a statistically significant improvement. The type I error to be used for final OS analysis would be 0.048 (two-sided).

No formal OS interim analysis was planned at the time of either RFS interim or final analysis due to anticipated immaturity of the OS data. Descriptive statistics for OS will be prepared at RFS IA and/or RFS FA upon regulatory requests. If OS results (beyond the frequency of deaths per arm) including Kaplan Meier curves are requested, an administrative alpha of 0.0001 will be spent as alpha penalty. Should such analyses be conducted, only a MAH restricted team will have access to OS descriptive results.

OS will be compared between the treatment groups at the OS interim and final analyses, using stratified two-sided log-rank test stratified by AJCC T category at study entry (as recorded per IRT).

Multiplicity
Multiplicity over RFS and OS was handled by a fixed sequence testing procedure (RFS then OS) and the interim and final analyses were handled using group-sequential methodology as described above.

No formal hypothesis testing was planned besides RFS and OS.

DMFS (secondary) will be determined based on the first date of distant metastasis provided by the investigator and is defined as the time between the date of randomization and the date of first recurrence (distant metastasis) or the date of death (due to any cause), whichever occurs first. Censoring rules for the analysis of DMFS are presented in the table below.

Table 6 Censoring scheme for primary definition of DMFS

Situation	Date of Event or Censoring	Outcome
Recurrence (distant metastasis)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
Disease at baseline	Date of randomization	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored

DMFS will be analyzed using similar analyses methods as for RFS. Analysis results (including p values) are considered descriptive, as no multiplicity adjustment was applied.

PFS2 (secondary): The definition of **next line therapy** is any systemic anti-cancer therapy for the cancer under study with a start date on or after the date of first dose of study drug (randomization date if subject was never treated). Accordingly, progression-free survival through next-line therapy (PFS2) is defined as the time from randomization to recurrence/objective disease progression after the start of the next line of systemic anti-cancer therapy, or to the start of second next-line systemic therapy, or to death from any cause, whichever occurs first. Analysis results (including p values) are considered descriptive, as no multiplicity adjustment was applied.

The following censoring rules will be applied for PFS2:

- For subjects who did not receive subsequent systemic anti-cancer therapy (ie, next-line therapy):
    - Subjects who died will be considered as having the event on the date of death. Subjects who did not die will be censored at the last known alive date.
- For subjects who received subsequent systemic anti-cancer therapy (ie, next-line therapy):
    - Subjects who had a disease progression after the start of subsequent systemic anti-cancer therapy will be considered as having the event on the date of disease progression. Otherwise, if a subject died or started second next-line therapy, the date of death or start date of second next-line therapy will be the event date, whichever is earlier. Subjects who did not experience disease progression, death, or second next-line therapy will be censored on the last known alive date.

Exploratory analyses will be performed for Patient Report Outcome (**PRO)'s** based on EORTC QLQ-C30 and EQ-5D-5L, only descriptive data will be provided.

Pre-planned **subgroup analyses** (descriptive) included age, gender, race, region, disease category, and tumour category.

Biomarker analyses will be exploratory only.

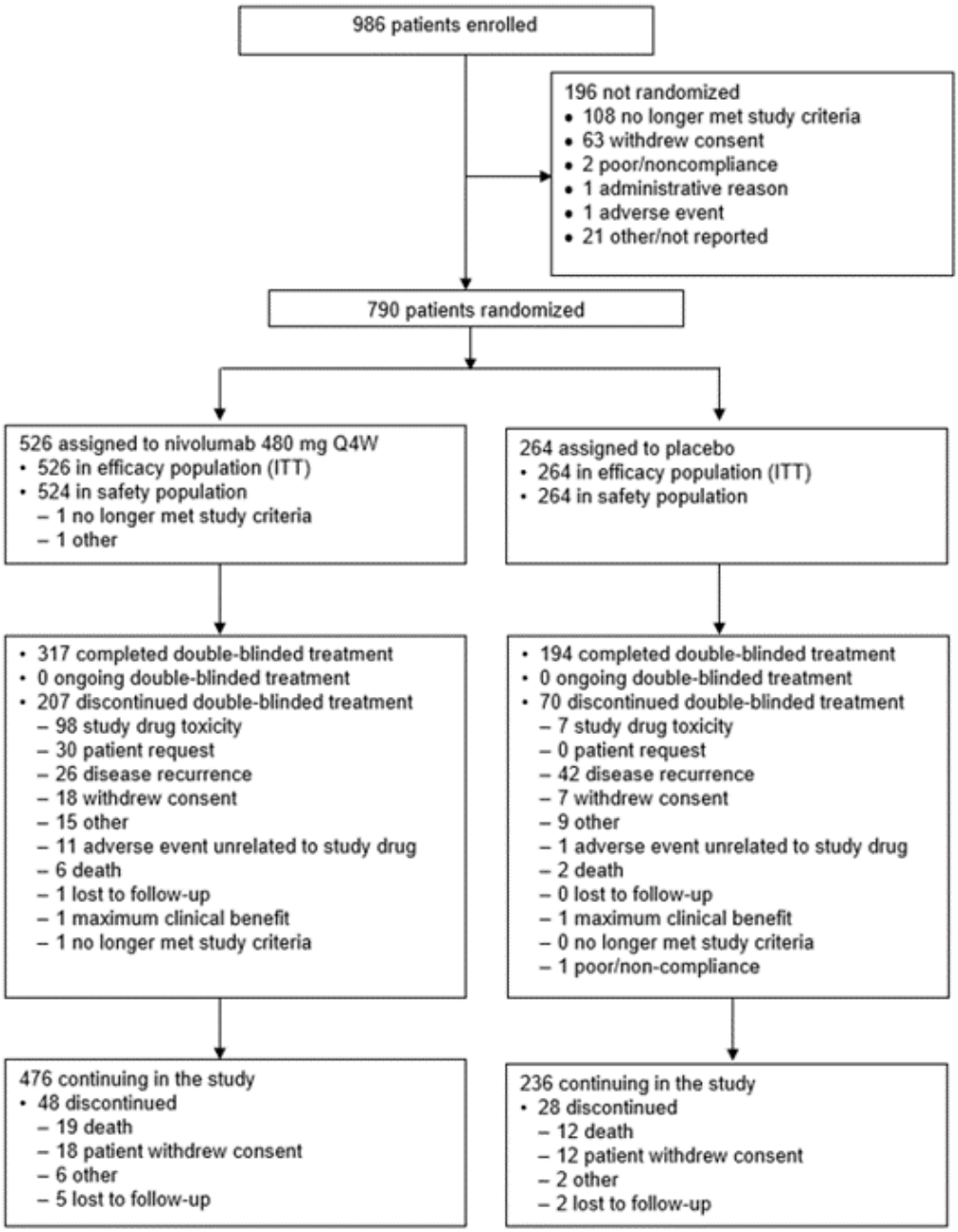
Results

Participant flow

A total of 986 subjects were enrolled, 790 were randomized, and 788 were treated: 524 with nivolumab and 264 with placebo. The most common reason for discontinuation of treatment was study drug toxicity in the nivolumab arm and disease progression in the placebo arm (below table). Thirty subjects were treated with nivolumab in the open-label phase; 28 who received placebo during the blinded phase and 2 who received nivolumab.

At the time of the data cut-off (DCO) (28-Jun-2022), there were 486 (92.7%) subjects in the nivolumab arm and 247 (93.6%) subjects in the placebo arm continuing in the study overall. The median follow-up (date of randomization to the last known date alive or death date) for all randomized subjects was 15.84 months for the nivolumab arm and 15.93 months for the placebo arm. Overall minimum follow-up was 7.8 months.

Figure 2 Ca20976K Participant Flow Chart



Source: Table S.2.7.3.1.

Recruitment

The study was open for enrolment at 129 sites in 20 countries. Enrolment rates were: Australia (11.4%), Austria (3.5%), Belgium (1.1%), Canada (2.1%), Czech Republic (3.4%), Denmark (0.6%),

Finland (0.5%), France (13.2%), Germany (11.5%), Greece (2.4%), Italy (16.3%), Netherlands (2.7%), Norway (1.3%), Poland (5.0%), Romania (2.4%), Spain (4.8%), Sweden (0.2%), Switzerland (0.7%), United Kingdom (0.2%), and the USA (16.5%).

The first patient was enrolled in October 2019 and the last patient in October 2021. The clinical database lock (DBL) for the provided results was 17-Aug-2022.

Conduct of the study

Protocol amendments

The original protocol for this study was dated 13-May-2019. As of the 17-Aug-2022 DBL, there had been a total of 3 global protocol amendments, 3 site specific amendments, and 3 administrative letters. Key changes to Study CA20976K after the original protocol are provided below.

Table 7 Summary of key changes to protocol CA20976K

Document (Amendment)/Date	Summary of Key Changes	Planned Sample Size	Subjects Randomized at time of Protocol Amendment
Protocol Amendment 01/ 16-Oct-2020	The interim analysis (IA) plan for the primary endpoint, recurrence-free survival (RFS), was changed to be conducted at 80% information fraction, following feedback from Health Authorities (HA) that the RFS IA at 67% information fraction may not provide an accurate estimate of the treatment effect size due to immature data. Sample size is reduced from 1000 to 780 to allow adequate projected minimum follow-up time (expected ~24 months) at the interim analysis of primary endpoint.	780	230
Protocol Amendment 02/ 15-Oct-2021	Protocol updated to align the management of adverse events (AEs) in trial subjects, as well as the reporting of such AEs, per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Language was inserted to provide descriptive OS data at the time of positive read out of the primary endpoint (recurrence-free survival [RFS]), as well as the projected number of deaths at the time of interim and final RFS analysis.	780	789
Protocol Amendment 03/ 28-Apr-2022	Added formal interim analysis for Overall Survival (OS) at 60% Information Fraction. OS events are expected to accrue over a long period of time (approximately 11 years since the first patient was treated) in stage IIB-C melanoma patients. The interim OS analysis is expected to occur approximately eight (8) years since the first patient was treated and may help provide preliminary survival data in a timely manner.	780	790

Source: protocol, protocol amendments, and administrative letters in Appendix 1.1 and Appendix 1.1a

Changes to planned analysis: There were no major changes to the planned analysis. Additional post-hoc analyses included ethnicity analysis added to baseline demographic characteristics and a subsequent cancer therapy summary for all randomized subjects.

Protocol deviations

Important Protocol Deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. A review of the deviations determined that there was no detriment to subject safety and no significant impact on the interpretability of study results. A summary of important protocol deviations is presented below.

Table 8 Important protocol deviations summary – All enrolled subjects based on RFS interim analysis 2 database lock (DCO 21-Feb-2023)

	Not Randomized N = 196	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 986
SUBJECTS WITH AT LEAST ONE DEVIATION	2 (1.0)	197 (37.5)	116 (43.9)	315 (31.9)
INCLUSION/EXCLUSION CRITERIA	0	26 (4.9)	14 (5.3)	40 (4.1)
INFORMED CONSENT AND/OR INDEPENDENT ETHICS COMMITTEE AND INSTITUTIONAL REVIEW BOARD (IEC/IRB)	2 (1.0)	71 (13.5)	44 (16.7)	117 (11.9)
PROHIBITED CONCOMITANT MEDICATION	0	3 (0.6)	0	3 (0.3)
SAFETY REPORTING	0	9 (1.7)	10 (3.8)	19 (1.9)
STUDY INTERVENTION (I.E., STUDY TREATMENT)	0	22 (4.2)	12 (4.5)	34 (3.4)
TRIAL PROCEDURES	0	122 (23.2)	61 (23.1)	183 (18.6)

Number of subjects (%)
Source: Table 4.2

GCP deviations and serious breaches

On 02-Sep-2021, the MAH discovered that an automated process for republishing documents from the document management system/PRISM to the shared investigator platform experienced delays due to intermittent system failures. Upon investigation (QE-030565), 21% of suspected unexpected serious adverse reactions (SUSAR) were delayed (1553/7478), of which 18% (278/1553) were initial SUSARs. In addition, 15 blinded SASUSAR reports and 10 executive summaries of development safety update reports that had not been communicated in a timely manner to clinical investigators. Based on assessment, the MAH determined there was no impact to patient safety as the processes to timely report to health authorities and ethics committees were not affected. Also, the signal detection and mechanisms to inform investigators and subjects of changes to the risk benefit profile through updates to the Investigator Brochure and the Informed Consent remained unchanged. This incident was reported as a potential serious breach due to the systemic nature and the potential to impact patient safety as the CA20976K investigators may not have received timely notification of SUSARs and SASUSARs; however, it was confirmed not to be a serious breach.

Baseline data

Baseline demographic (Table 9) and disease (Table 10) characteristics were balanced between treatment arms. Among all randomized subjects, the median age was 62.0 years (range 19 to 92). The majority of subjects were White (98.4%) and male (61.1%). The predominant melanoma subtypes were nodular (50.5%) and superficial spreading (29.5%). Per case record form (CRF), 60.6% of subjects had Stage IIB disease. The tumour category was T3b in 39.0%, T4a in 21.5%, and T4b in 39.5% of all randomized subjects. Discrepancy between IRT and CRF was 1.6% (n=12 the nivolumab arm).

Table 9 Baseline demographic characteristics – All randomized subjects

	Number of Subjects (%)		
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 790
AGE (YEARS)			
MEAN	59.9	59.3	59.7
MEDIAN	62.0	61.0	62.0
MIN , MAX	21 , 87	19 , 92	19 , 92
Q1 , Q3	51.0 , 71.0	51.0 , 69.0	51.0 , 70.0
SD	13.9	13.6	13.8
AGE CATEGORIZATION 1 (%)			
< 65	305 (58.0)	155 (58.7)	460 (58.2)
>= 65	221 (42.0)	109 (41.3)	330 (41.8)
AGE CATEGORIZATION 2 (%)			
< 18	0	0	0
>= 18 AND < 65	305 (58.0)	155 (58.7)	460 (58.2)
>= 65 AND < 75	140 (26.6)	77 (29.2)	217 (27.5)
>= 75 AND < 85	77 (14.6)	30 (11.4)	107 (13.5)
>= 85	4 (0.8)	2 (0.8)	6 (0.8)
SEX (%)			
MALE	322 (61.2)	161 (61.0)	483 (61.1)
FEMALE	204 (38.8)	103 (39.0)	307 (38.9)
RACE (%)			
WHITE	515 (97.9)	262 (99.2)	777 (98.4)
BLACK OR AFRICAN AMERICAN	2 (0.4)	1 (0.4)	3 (0.4)
ASIAN	1 (0.2)	0	1 (0.1)
OTHER	7 (1.3)	1 (0.4)	8 (1.0)
NOT REPORTED	1 (0.2)	0	1 (0.1)
ETHNICITY (%)			
HISPANIC OR LATINO	11 (2.1)	6 (2.3)	17 (2.2)
NOT HISPANIC OR LATINO	317 (60.3)	140 (53.0)	457 (57.8)
NOT REPORTED	198 (37.6)	118 (44.7)	316 (40.0)
COUNTRY BY GEOGRAPHIC REGION (%)			
US AND CANADA	97 (18.4)	46 (17.4)	143 (18.1)
CANADA	11 (2.1)	7 (2.7)	18 (2.3)
UNITED STATES	86 (16.3)	39 (14.8)	125 (15.8)
WESTERN EUROPE	303 (57.6)	160 (60.6)	463 (58.6)
EASTERN EUROPE	58 (11.0)	28 (10.6)	86 (10.9)
AUSTRALIA	68 (12.9)	30 (11.4)	98 (12.4)

Source: Table S.3.2.1b

Table 10 Baseline disease characteristics – All randomized subjects

	Number of Subjects (%)		
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 790
BASELINE ECOG PS			
0	495 (94.1)	245 (92.8)	740 (93.7)
1	31 (5.9)	19 (7.2)	50 (6.3)
BASELINE LDH I			
<= ULN	470 (89.4)	232 (87.9)	702 (88.9)
> ULN	50 (9.5)	25 (9.5)	75 (9.5)
NOT REPORTED	6 (1.1)	7 (2.7)	13 (1.6)
BASELINE LDH II			
<= 2*ULN	520 (98.9)	257 (97.3)	777 (98.4)
> 2*ULN	0	0	0
NOT REPORTED	6 (1.1)	7 (2.7)	13 (1.6)
WEIGHT (KG)			
N	525	264	789
MEAN	84.21	85.58	84.67
MEDIAN	82.10	83.35	82.50
MIN - MAX	43.0 - 162.7	47.1 - 187.7	43.0 - 187.7
Q1 - Q3	71.00 - 95.60	72.10 - 96.30	71.90 - 95.90
SD	18.91	19.93	19.26
TIME FROM WIDE LOCAL EXCISION SURGERY TO RANDOMIZATION (WEEKS)			
N	525	264	789
MEAN	10.34	10.20	10.30
MEDIAN	10.00	10.21	10.14
MIN - MAX	1.3 - 34.0	3.6 - 28.9	1.3 - 34.0
Q1 - Q3	8.14 - 11.86	8.00 - 11.71	8.00 - 11.86
SD	3.67	3.57	3.63
< 3	3 (0.6)	0	3 (0.4)
3 - < 6	35 (6.7)	27 (10.2)	62 (7.8)
6 - < 9	141 (26.8)	69 (26.1)	210 (26.6)
9 - < 12	234 (44.5)	114 (43.2)	348 (44.1)
12 - < 15	70 (13.3)	34 (12.9)	104 (13.2)
15 - < 18	17 (3.2)	7 (2.7)	24 (3.0)
18 - < 21	16 (3.0)	9 (3.4)	25 (3.2)
>= 21	9 (1.7)	4 (1.5)	13 (1.6)
NOT REPORTED	1 (0.2)	0	1 (0.1)

TIME FROM SENTINEL LYMPHADENECTOMY SURGERY TO RANDOMIZATION (WEEKS)			
N	526	263	789
MEAN	9.45	9.09	9.33
MEDIAN	9.71	9.14	9.57
MIN - MAX	2.9 - 18.7	0.4 - 22.0	0.4 - 22.0
Q1 - Q3	7.71 - 11.43	7.29 - 11.00	7.57 - 11.29
SD	2.35	2.51	2.41
< 3	1 (0.2)	1 (0.4)	2 (0.3)
3 - < 6	40 (7.6)	28 (10.6)	68 (8.6)
6 - < 9	171 (32.5)	94 (35.6)	265 (33.5)
9 - < 12	244 (46.4)	118 (44.7)	362 (45.8)
12 - < 15	65 (12.4)	20 (7.6)	85 (10.8)
15 - < 18	4 (0.8)	1 (0.4)	5 (0.6)
18 - < 21	1 (0.2)	0	1 (0.1)
>= 21	0	1 (0.4)	1 (0.1)
NOT REPORTED	0	1 (0.4)	1 (0.1)
DISEASE STAGE AT STUDY ENTRY (PER CRF)			
STAGE IIB	316 (60.1)	162 (61.4)	478 (60.5)
STAGE IIC	210 (39.9)	102 (38.6)	312 (39.5)
STAGE OTHER	0	0	0
STAGE UNKNOWN	0	0	0
T STAGE AT STUDY ENTRY (PER CRF)			
STAGE II PATIENTS	526 (100.0)	264 (100.0)	790 (100.0)
T3B	204 (38.8)	104 (39.4)	308 (39.0)
T4A	112 (21.3)	58 (22.0)	170 (21.5)
T4B	210 (39.9)	102 (38.6)	312 (39.5)
MELANOMA SUB-TYPE			
SUPERFICIAL SPREADING MELANOMA	151 (28.7)	82 (31.1)	233 (29.5)
NODULAR MELANOMA	266 (50.6)	133 (50.4)	399 (50.5)
LENTIGO MALIGNA	13 (2.5)	3 (1.1)	16 (2.0)
ACRAL LENTIGINOUS MELANOMA	28 (5.3)	15 (5.7)	43 (5.4)
DESMOPLASTIC MELANOMA	21 (4.0)	8 (3.0)	29 (3.7)
OTHER	44 (8.4)	22 (8.3)	66 (8.4)
NOT REPORTED	3 (0.6)	1 (0.4)	4 (0.5)

	Number of Subjects (%)		
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	Total N = 790
BASELINE TUMOR CELL PD-L1 STATUS (%)			
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE	307 (58.4)	137 (51.9)	444 (56.2)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE	191 (36.3)	111 (42.0)	302 (38.2)
N	191	111	302
MEAN	8.8	7.5	8.3
MEDIAN	1.0	1.0	1.0
MIN - MAX	0 - 98	0 - 80	0 - 98
Q1 - Q3	0.0 - 5.0	0.0 - 5.0	0.0 - 5.0
SD	19.1	15.3	17.7
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	109/191 (57.1)	58/111 (52.3)	167/302 (55.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	82/191 (42.9)	53/111 (47.7)	135/302 (44.7)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	59/191 (30.9)	33/111 (29.7)	92/302 (30.5)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	132/191 (69.1)	78/111 (70.3)	210/302 (69.5)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE	0	0	0
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE	28 (5.3)	16 (6.1)	44 (5.6)
BASELINE BRAF V600 STATUS			
MUTATION	148 (28.1)	81 (30.7)	229 (29.0)
WILD TYPE	293 (55.7)	136 (51.5)	429 (54.3)
NOT REPORTED/NOT EVALUABLE	85 (16.2)	47 (17.8)	132 (16.7)

Data cutoff: 21-Feb-2023

Source: Table 5.2

Numbers analysed

Efficacy analyses were based on the intention-to-treat (ITT) population, which consisted of all 790 randomized participants.

Table 11 Analysis populations presented in the primary clinical study report

Population	Nivolumab	Placebo	Total
Enrolled subjects: All subjects who signed the informed consent form and obtained a subject number	-	-	986
Randomized subjects: All subjects who were randomized through the IRT. Analyses used the treatment arm as randomized, unless otherwise specified.	526	264	790
Treated subjects: All randomized subjects who received at least one dose of any study medication. Analysis will use the treatment arm as treated, unless otherwise specified.	524	264	788
Immunogenicity evaluable subjects: Nivolumab ADA evaluable subjects. All treated subjects with baseline and at least 1 post baseline pre-infusion nivolumab immunogenicity assessment.	378	-	378

Source: Table S.3.2.3.1 (enrolled), Table S.2.6A.1 (randomized and treated), Table S.7.10.1 (Anti-drug Antibody assessments summary - all nivolumab treated subjects with baseline and 1 post-baseline assessment)

Outcomes and estimation

As of the DCO for this planned interim analysis (28-Jun-2022), 135 RFS events had occurred (87.7% information fraction). Based on a Lan-DeMets alpha spending function with O'Brien-Fleming boundaries, the alpha stopping boundary is 0.03334. The median duration of therapy was 11.04 months in the nivolumab arm and 11.07 months in the placebo arm. Minimum follow-up time was 7.8 months and 8.7 months for nivolumab and placebo, respectively.

An efficacy summary is presented below.

Table 12 Efficacy summary – All randomized subjects

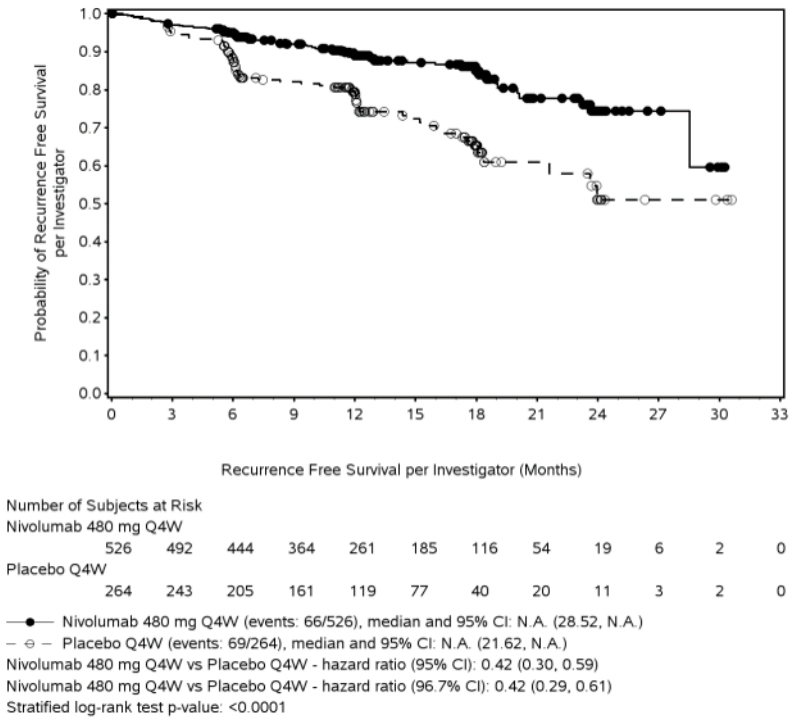
	Nivolumab N=526	Placebo N=264
PRIMARY ENDPOINT		
Recurrence-Free Survival per Investigator		
Events, n/N (%)	66/526 (12.5)	69/264 (26.1)
Recurrence[a]	56 (10.6)	66 (25.0)
Distant recurrence	26 (4.9)	31 (11.7)
Regional node recurrence	11 (2.1)	20 (7.6)
Local recurrence	8 (1.5)	7 (2.7)
Malignant melanoma in situ	7 (1.3)	5 (1.9)
New primary invasive melanoma	4 (0.8)	3 (1.1)
In transit metastasis recurrence	0	0
HR[b] (95% CI) (96.7% CI)	0.42 (0.30, 0.59) (0.29, 0.61)	
Log-rank p-value[c]	< 0.0001	
Median RFS[d] (95% CI), months	N/A (28.52, N/A)	N/A (21.62, N/A)
Rate at 6 months[d], % (95% CI)	95.1 (92.8, 96.6)	88.1 (83.4, 91.5)
Rate at 12 months[d], % (95% CI)	89.0 (85.6, 91.6)	79.4 (73.5, 84.1)
SECONDARY ENDPOINTS		
Distant Metastasis-Free Survival per Investigator		
Events/number of subjects, n/N (%)	42/526 (8.0)	41/264 (15.5)
Median DMFS[d] (95% CI), months	N/A (28.52, N/A)	N/A
HR[b] (95% CI)	0.47 (0.30, 0.72)	
Descriptive p-value	0.0004	
Rate at 6 months[d], % (95% CI)	97.6 (95.9, 98.6)	93.5 (89.7, 96.0)
Rate at 12 months[d], % (95% CI)	92.3 (89.3, 94.5)	86.7 (81.4, 90.5)

	Nivolumab N=526	Placebo N=264
Progression-free Survival on Next-Line Systemic Therapy per Investigator		
Events/number of subjects, n/N (%)	23/526 (4.4)	17/264 (6.4)
Median[d] (95% CI), months	N/A	N/A
HR[b] (95% CI)	0.68 (0.36, 1.27)	

Primary Efficacy Endpoint: Recurrence-free Survival

Study CA20976K met its primary endpoint of RFS; adjuvant nivolumab 480 mg Q4W demonstrated a statistically significant improvement in RFS compared with placebo (HR = 0.42 [95% CI: 0.30, 0.59]; log-rank p-value < 0.0001). The Kaplan-Meier curve shows a separation of curves starting around 3 months which increases over time (Figure 2). RFS rates were higher in the nivolumab arm compared with the placebo arm: 95.1% and 88.1% at 6 months, 89.0% and 79.4% at 12 months.

Figure 3 Kaplan-Meier plot of recurrence-free survival per investigator – All randomized subjects.



Hazard Ratio is Nivolumab over Placebo from Cox proportional hazard model stratified by AJCC T Stage at Study Entry (T3b vs T4a vs T4b) as entered into the IRT.
P-value from 2-sided Log-rank test stratified by the same factor as used in the Cox proportional hazard model.
Symbols represent censored observations
Source: Figure S.5.30.1

At the time of DCO, 12.5% and 26.1% of all randomized subjects in the nivolumab and placebo arm, respectively, had suffered an event for RFS, 87.5% and 73.9% were thus censored for RFS (Table 11), and 425 (80.8%) and 180 (68.2%) subjects were either continuing on-treatment or in follow-up in the nivolumab and placebo arms, respectively.

Table 13 Reason for censoring, recurrence-free survival per investigator – All randomized subject

	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264
NUMBER OF EVENTS (%)	66 (12.5)	69 (26.1)
TYPE OF EVENTS (%)		
RECURRENCE	56 (10.6)	66 (25.0)
DISEASE AT BASELINE	0	0
DISTANT RECURRENCE	26 (4.9)	31 (11.7)
REGIONAL NODE RECURRENCE	11 (2.1)	20 (7.6)
IN TRANSIT METASTASIS RECURRENCE	0	0
LOCAL RECURRENCE	8 (1.5)	7 (2.7)
NEW PRIMARY INVASIVE MELANOMA	4 (0.8)	3 (1.1)
MALIGNANT MELANOMA IN SITU	7 (1.3)	5 (1.9)
DEATH	10 (1.9)	3 (1.1)
NUMBER OF SUBJECTS CENSORED (%)	460 (87.5)	195 (73.9)
CENSORED ON DATE OF RANDOMIZATION	14 (2.7)	3 (1.1)
INCOMPLETE OR NO BASELINE TUMOR ASSESSMENT (1)	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY DISEASE ASSESSMENT WITH EITHER NO RECURRENCE/DEATH OR RECURRENCE/DEATH WITH PRIOR SUBSEQUENT THERAPY/SECOND NON-MELANOMA PRIMARY CANCER (1)	14 (2.7)	3 (1.1)
RECURRENCE/DEATH WITH PRIOR SUBSEQUENT ANTI CANCER THERAPY	0	0
RECURRENCE/DEATH WITH PRIOR SECOND NON-MELANOMA PRIMARY CANCER	0	0
NO RECURRENCE/DEATH	14 (2.7)	3 (1.1)
CENSORED ON DATE OF LAST DISEASE ASSESSMENT ON-STUDY OR LAST ASSESSMENT PRIOR TO SUBSEQUENT ANTI CANCER THERAPY/ SECOND NON-MELANOMA PRIMARY CANCER*	446 (84.8)	192 (72.7)
RECEIVED SUBSEQUENT ANTI-CANCER THERAPY (2)	0	0
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	0	0
RECEIVED SUBSEQUENT RADIOTHERAPY	0	0
RECEIVED SUBSEQUENT SURGERY	0	0
SECOND NON-MELANOMA PRIMARY CANCER (2)	9 (1.7)	8 (3.0)
ON STUDY	425 (80.8)	180 (68.2)
ON-TREATMENT	61 (11.6)	39 (14.8)
IN FOLLOW-UP	364 (69.2)	141 (53.4)
OFF STUDY	12 (2.3)	4 (1.5)
LOST TO FOLLOW-UP	2 (0.4)	2 (0.8)
PARTICIPANT WITHDRAW CONSENT	7 (1.3)	2 (0.8)
OTHER	3 (0.6)	0

*Basel cell carcinomas were excluded from the censoring definition for new-non melanoma primary malignancies.
(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.
Some subjects may have been treated with more than 1 type of subsequent anti-cancer therapy.
Open-label nivolumab treatment will be considered as a new anticancer therapy.
Source: Table S.5.24.

All sensitivity analyses support the primary RFS analysis (Table 14).

Table 14 Recurrence-free survival per investigator, sensitivity analyses – All randomized subjects

	# EVENTS / # SUBJECTS (%) MEDIAN RFS (MONTHS) (1) (95% CI)			
SENSITIVITY ANALYSIS	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264	HR(2) (95% CI)	P-Value (3)
UNSTRATIFIED RFS	66/526 (12.5) N.A. (28.52, N.A.)	69/264 (26.1) N.A. (21.62, N.A.)	0.43 (0.31, 0.61)	<0.0001
UNSTRATIFIED RFS WITH STRATIFICATION FACTOR USED AS COVARITATE	66/526 (12.5) N.A. (28.52, N.A.)	69/264 (26.1) N.A. (21.62, N.A.)	0.43 (0.30, 0.60)	
RFS ACCOUNTING FOR ASSESSMENT ON/AFTER SUBSEQUENT THERAPY / SECOND NON-MELANOMA PRIMARY CANCER	66/526 (12.5) N.A. (28.52, N.A.)	71/264 (26.9) N.A. (21.62, N.A.)	0.41 (0.29, 0.58)	<0.0001
RFS ACCOUNTING FOR MISSING DISEASE ASSESSMENTS PRIOR TO RFS EVENT	66/526 (12.5) N.A. (28.52, N.A.)	69/264 (26.1) N.A. (21.62, N.A.)	0.42 (0.30, 0.59)	<0.0001

(1) Based on Kaplan-Meier Estimates.
(2) Stratified (unless otherwise specified) Cox proportional hazard model. Hazard Ratio is Nivolumab over Placebo.
(3) Log-rank Test stratified by AJCC T Stage at Study Entry (T3b vs T4a vs T4b) as entered into the IRT (unless otherwise specified).

Updated analysis of RFS (DCO: 21-Feb-2023)

An updated RFS analysis was performed with DCO 21-Feb-2023 resulting in an increase of follow-up of about 6 months. Median follow-up was about 24 months and minimum follow-up was 15.6 months. All patients were off blinded treatment. Event rate increased with 5% - 7% in both treatment arms;

19.4% of patients receiving nivolumab and 31.8% of patients receiving placebo had experienced a recurrence event; HR: 0.53 (95% CI: 0.40, 0.71) (Table 15). The reduction in recurrence events was primarily driven by fewer distant recurrences (8.4% vs 14.8%) and regional recurrences (3.0% vs 8.7%) in favor of nivolumab (Table 16). An updated KM plot is presented as well, showing separation of curves up till at least 24 months (Figure 4).

Table 15 Recurrence-free survival summary – All randomized subjects (DCO 21-Feb-2023)

	Nivolumab	**Placebo**
	N = 526	**N = 264**
Recurrence-free Survival per Investigator		
Events, n/N (%)	102/526 (19.4)	84/264 (31.8)
HR [a]	0.53	
(95% CI)	(0.40, 0.71)	
Median RFS [b] (95% CI), months	N.R.	36.14 (24.77, N.R.)
Rate at 6 months [b], % (95% CI)	95.1 (92.8, 96.6)	88.3 (83.7, 91.7)
Rate at 12 months [b], % (95% CI)	88.8 (85.6, 91.2)	81.1 (75.7, 85.4)
Rate at 18 months [b], % (95% CI)	83.9 (80.3, 86.9)	70.7 (64.5 76.1)
Rate at 24 months [b], % (95% CI)	76.5 (71.7, 80.6)	60.6 (52.6, 67.6)
Rate at 30 months [b], % (95% CI)	71.2 (64.4, 76.9)	58.3 (49.4, 66.2)
Rate at 36 months [b], % (95% CI)	69.1 (61.2, 75.7)	58.3 (49.4, 66.2)

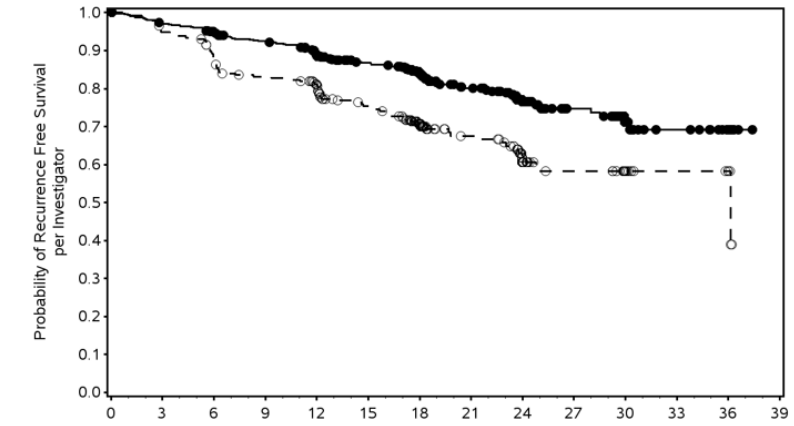
Minimum follow-up: 15.6 months; median follow-up ~24 months.
[a] HR is nivolumab over placebo from Cox proportional hazard model stratified by AJCC T stage at study entry (T3b vs T4a vs T4b) as entered into the IRT.
[b] Based on Kaplan-Meier estimates.

Table 16 Reason for censoring, recurrence free survival per investigator- All randomized subjects (DCO 21-Feb-2023)

	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264
NUMBER OF EVENTS (%)	102 (19.4)	84 (31.8)
TYPE OF EVENTS (%)		
RECURRENCE	88 (16.7)	81 (30.7)
DISEASE AT BASELINE	0	0
LOCAL RECURRENCE	10 (1.9)	10 (3.8)
IN TRANSIT METASTASIS RECURRENCE	4 (0.8)	1 (0.4)
REGIONAL NODE RECURRENCE	16 (3.0)	23 (8.7)
DISTANT RECURRENCE	44 (8.4)	39 (14.8)
NEW PRIMARY INVASIVE MELANOMA	6 (1.1)	3 (1.1)
MALIGNANT MELANOMA IN SITU	8 (1.5)	5 (1.9)
DEATH	14 (2.7)	3 (1.1)
NUMBER OF SUBJECTS CENSORED (%)	424 (80.6)	180 (68.2)
CENSORED ON DATE OF RANDOMIZATION	14 (2.7)	3 (1.1)
INCOMPLETE OR NO BASELINE TUMOR ASSESSMENT (1)	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY DISEASE ASSESSMENT WITH EITHER NO RECURRENCE/DEATH OR RECURRENCE/DEATH WITH PRIOR SUBSEQUENT THERAPY/SECOND NON-MELANOMA PRIMARY CANCER (1)	14 (2.7)	3 (1.1)
RECURRENCE/DEATH WITH PRIOR SUBSEQUENT ANTI CANCER THERAPY	0	0
RECURRENCE/DEATH WITH PRIOR SECOND NON-MELANOMA PRIMARY CANCER	0	0
NO RECURRENCE/DEATH	14 (2.7)	3 (1.1)
CENSORED ON DATE OF LAST DISEASE ASSESSMENT ON-STUDY OR LAST ASSESSMENT PRIOR TO SUBSEQUENT ANTI CANCER THERAPY/ SECOND NON-MELANOMA PRIMARY CANCER	410 (77.9)	177 (67.0)
RECEIVED SUBSEQUENT ANTI-CANCER THERAPY (2)	0	0
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	0	0
RECEIVED SUBSEQUENT RADIOTHERAPY	0	0
RECEIVED SUBSEQUENT SURGERY	0	0
SECOND NON-MELANOMA PRIMARY CANCER (2)	10 (1.9)	8 (3.0)
ON STUDY	385 (73.2)	164 (62.1)
ON-TREATMENT	0	0
IN FOLLOW-UP	385 (73.2)	164 (62.1)
OFF STUDY	15 (2.9)	5 (1.9)
LOST TO FOLLOW-UP	4 (0.8)	2 (0.8)
PARTICIPANT WITHDRAW CONSENT	8 (1.5)	3 (1.1)
OTHER	3 (0.6)	0

(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.
Some subjects may have been treated with more than 1 type of subsequent anti-cancer therapy.
Open-label nivolumab treatment will be considered as a new anticancer therapy.
Program Source: /opt/zfs001/prd/bms247316/stats/rfsia2/prog/tables/rt-ef-rfsinvreascens-sas.sas 04MAY2023:13:02:24

Figure 4 Kaplan-Meier plot of recurrence-free survival per investigator – All randomized subjects (DCO 21-Feb-2023)



Number of Subjects at Risk

Nivolumab 480 mg Q4W	526	492	474	456	422	386	291	210	122	74	40	22	13	0
Placebo Q4W	264	244	224	208	193	165	120	77	44	25	12	7	4	0

Nivolumab 480 mg Q4W (events: 102/526), median and 95% CI: N.A.
Placebo Q4W (events: 84/264), median and 95% CI: 36.14 (24.77, N.A.)
Nivolumab 480 mg Q4W vs Placebo Q4W - hazard ratio (95% CI): 0.53 (0.40, 0.71)

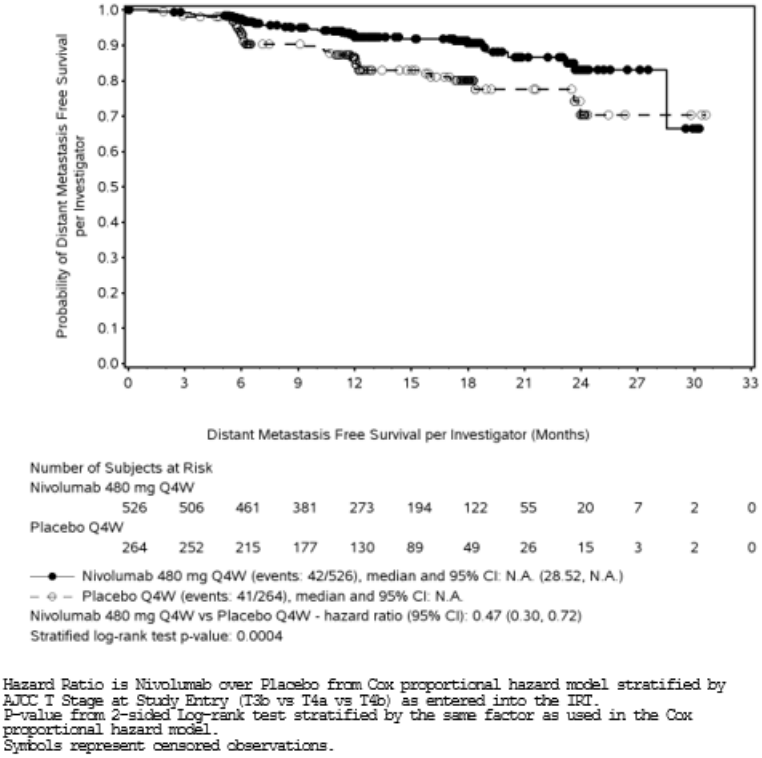
Hazard ratio is nivolumab over placebo from Cox proportional hazard model stratified by AJCC T stage at study entry (T3b vs T4a vs T4b) as entered into the IRT.
Symbols represent censored observations

Secondary endpoints

- **Distant metastasis-free survival**

Adjuvant nivolumab was associated with an improvement in DMFS per Investigator compared with placebo (HR = 0.47 [95% CI: 0.30, 0.72], descriptive result). Overall, 8% of subjects receiving nivolumab and 15.5% receiving placebo experienced a distant recurrence. DMFS rates were numerically higher in the nivolumab arm compared with the placebo arm: 97.6% and 93.5% at 6 months, and 92.3% and 86.7% at 12 months (Table 12 and Figure 5).

Figure 5 Kaplan-Meier plot of distant metastases-free survival per investigator – All randomized subjects



Updated analysis of DMFS (DCO: 21-Feb-2023)

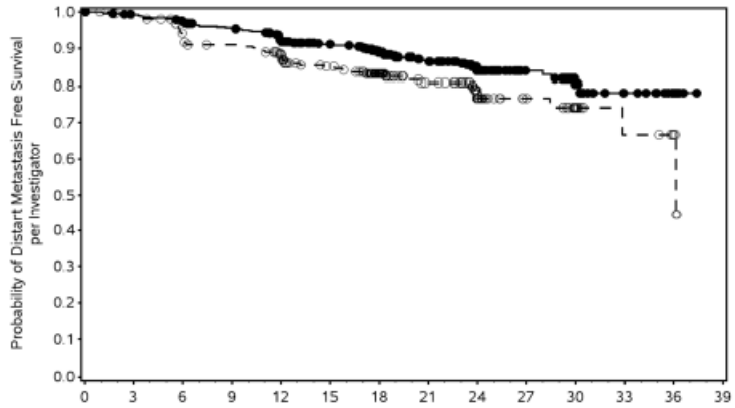
As of the 21-Feb-2023 DCO, 13.1% of patients receiving nivolumab and 19.3% of patients receiving placebo had experienced a DMFS event (4% - 5% increase compared to previous DCO) (HR: 0.62, 95% CI: 0.43, 0.89) (Table 17). DMFS rates over time were numerically higher in the nivolumab arm compared with the placebo arm and the KM curves separate from 6 months onwards (Figure 6). As of the data cut-off, 457 (86.9%) and 213 (80.7%) of all randomized patients in the nivolumab and placebo arms, respectively, were censored for DMFS. The majority of patients were censored on the date of their last disease assessment on study.

Table 17 Distant metastasis-free survival summary – All randomized subjects (DCO 21-Feb-2023)

	Nivolumab	**Placebo**
	N = 526	**N = 264**
Distant Metastasis-free Survival per Investigator		
Events/number of subjects, n/N (%)	69/526 (13.1)	51/264 (19.3)
Median DMFS [a] (95% CI), months	N.R.	36.14 (32.85, N.R.)
HR [b]	0.62	
(95% CI)	(0.43, 0.89)	
Rate at 6 months [a], % (95% CI)	97.6 (95.9, 98.7)	93.7 (90.0, 96.1)
Rate at 12 months [a], % (95% CI)	92.0 (89.3, 94.1)	88.5 (83.9, 91.9)
Rate at 18 months [a], % (95% CI)	89.0 (85.8, 91.5)	83.2 (77.9, 87.4)
Rate at 24 months [a], % (95% CI)	84.0 (79.7, 87.5)	76.5 (69.3, 82.3)
Rate at 30 months [a], % (95% CI)	80.4 (74.1, 85.3)	74.1 (65.2, 81.0)
Rate at 36 months [a], % (95% CI)	78.1 (70.1, 84.2)	66.7 (48.7, 79.6)

Minimum follow-up: 15.6 months; median follow-up ~24 months.
a Based on Kaplan-Meier estimates.
b HR is nivolumab over placebo from Cos proportional hazard model stratified by AJCC T stage at study entry (T3b vs T4a vs T4b) as entered into the IRT.
Source: Table S.5.31.1 (DMFS), Table S.5.32.1 (RFS rates).

Figure 6 Kaplan-Meier plot of distant metastasis-free survival per investigator – All randomized subjects (DCO 21-Feb-2023)



Number of Subjects at Risk

Nivolumab 480 mg Q4W	526	505	493	478	441	408	308	225	134	82	44	22	13	0
Placebo Q4W	264	253	236	226	210	186	143	96	57	32	16	9	4	0

Nivolumab 480 mg Q4W (events: 69/526), median and 95% CI: N.A.
Placebo Q4W (events: 51/264), median and 95% CI: 36.14 (32.85, N.A.)
Nivolumab 480 mg Q4W vs Placebo Q4W - hazard ratio (95% CI): 0.62 (0.43, 0.89)

Hazard ratio is nivolumab over placebo from Cox proportional hazard model stratified by AJCC T stage at study entry (T3b vs T4a vs T4b) as entered into the IRT.

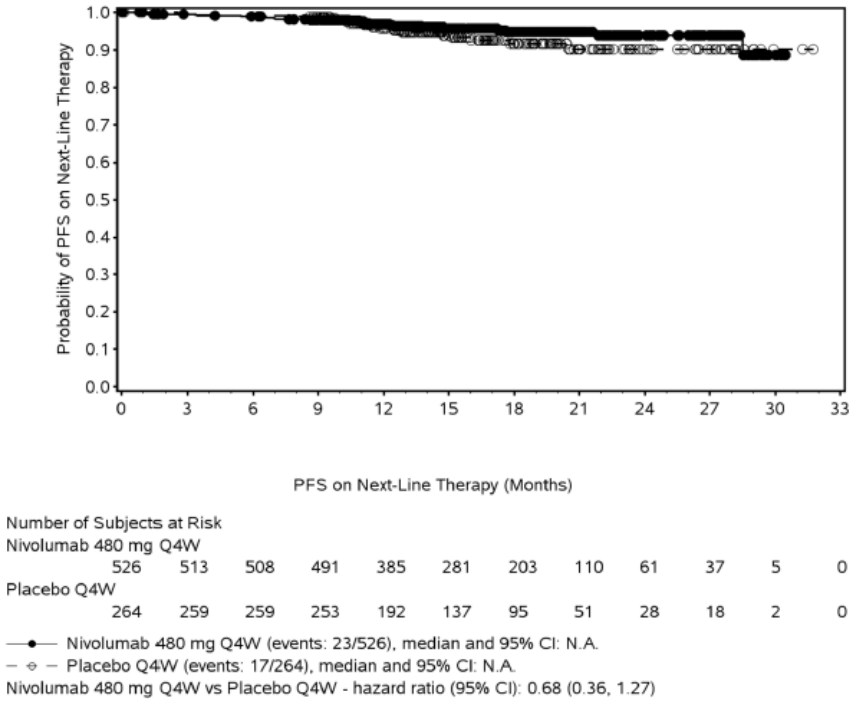
Symbols represent censored observations.

Source: Figure S.5.33.1

- **PFS2**

As of the data cutoff, relatively few PFS2 events (n=40) occurred. In all randomized subjects, 23 (4.4%) PFS2 events occurred in the nivolumab arm and 17 (6.4%) events occurred in the placebo arm. The PFS2 HR favoured nivolumab over placebo: 0.68 (95% CI: 0.36, 1.27), though results are descriptive only (Figure 7).

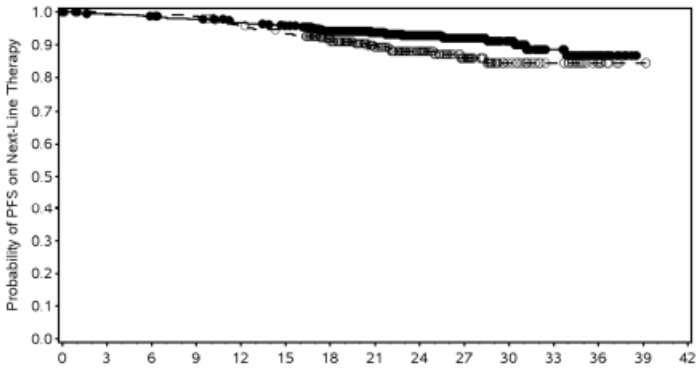
Figure 7 Kaplan-Meier plot of progression-free survival per investigator through next-line systemic therapy – Primary definition – All randomized subjects



Updated analysis of PFS2 (DCO: 21-Feb-2023)

As of the 21-Feb-2023 DCO, 40 (7.6%) PFS2 events had occurred in the nivolumab arm and 31 (11.7%) PFS2 events had occurred in the placebo arm (HR: 0.63; 95% CI: 0.40, 1.01). The updated KM plot is shown below (Figure 8).

Figure 8 Kaplan-Meier plot of progression-free survival per investigator through next-line systemic therapy – primary definition – All randomized subjects (DCO 21-Feb-2023)



Number of Subjects at Risk

Nivolumab 480 mg Q4W	526	517	512	505	495	486	431	333	240	160	85	48	19	0	0
Placebo Q4W	264	259	259	258	247	240	208	151	111	73	36	24	8	2	0

Nivolumab 480 mg Q4W (events: 40/526), median and 95% CI: N.A.
Placebo Q4W (events: 31/264), median and 95% CI: N.A.
Nivolumab 480 mg Q4W vs Placebo Q4W - hazard ratio (95% CI): 0.63 (0.40, 1.01)

Hazard ratio is nivolumab over placebo from Cox proportional hazard model stratified by AJCC T stage at study entry (T3b vs T4a vs T4b) as entered into the IRT.

Symbols represent censored observations.

PFS2 is defined as the time from randomization to second recurrence/objective disease progression after next-line systemic therapy, or to death from any cause or to start of second next-line systemic therapy, whichever occurs first.

Source: Figure S.5.36.1

Subsequent cancer therapy

More than 90% of all patients experiencing a recurrence received subsequent therapy (Table 18). More patients in the placebo arm than in the nivolumab arm received subsequent systemic therapy (74.1% vs 50.0%). Nivolumab monotherapy was the most commonly reported subsequent systemic therapy in the placebo arm (45.7% vs. 9.1% in the nivolumab arm), whereas a combination of ipilimumab and nivolumab was the most common subsequent systemic therapy in the nivolumab arm (22.7% vs. 24.7% in the placebo arm).

Table 18 Subsequent cancer therapy summary – All randomized subjects (DCO: 21-Feb-2023)

	Number of Subjects (%)	
	Nivolumab 480 mg Q4W N = 88	Placebo Q4W N = 81
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	81 (92.0)	76 (93.8)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	16 (18.2)	7 (8.6)
CURATIVE	8 (9.1)	3 (3.7)
PALLIATIVE	9 (10.2)	4 (4.9)
OTHER	0	0
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	55 (62.5)	47 (58.0)
TUMOR RESECTION CURATIVE	47 (53.4)	37 (45.7)
TUMOR RESECTION PALLIATIVE	1 (1.1)	6 (7.4)
OTHER	9 (10.2)	4 (4.9)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%) (2)	44 (50.0)	60 (74.1)
ANTI-CTLA4	2 (2.3)	1 (1.2)
IPILIMUMAB	2 (2.3)	1 (1.2)
ANTI-PD1 OR ANTI-PDL1	10 (11.4)	41 (50.6)
BEMPEGALDESLEUKIN;NIVOLUMAB	0	2 (2.5)
NIVOLUMAB (2)	8 (9.1)	37 (45.7)
PEMBROLIZUMAB	3 (3.4)	2 (2.5)
COMBO ANTI-CTLA4 + ANTI-PD1 OR COMBO ANTI-CTLA4 + ANTI-PDL1	20 (22.7)	20 (24.7)
IPILIMUMAB;NIVOLUMAB	20 (22.7)	20 (24.7)
COMBO BRAF MEK NRAS INHIBITOR	9 (10.2)	6 (7.4)
BINIMETINIB;ENCORAFENIB	5 (5.7)	5 (6.2)
DABRAFENIB;TRAMETINIB	5 (5.7)	3 (3.7)
COMBO PD1 AND LAG-3	1 (1.1)	3 (3.7)
NIVOLUMAB;RELATLIMAB	1 (1.1)	3 (3.7)
INVESTIGATIONAL ANTINEOPLASTIC	1 (1.1)	0
INVESTIGATIONAL DRUG	1 (1.1)	0
INVESTIGATIONAL ANTINEOPLASTIC AGENTS	1 (1.1)	1 (1.2)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	0	1 (1.2)
NL 201	1 (1.1)	0
MEK NRAS INHIBITOR	1 (1.1)	0
TRAMETINIB	1 (1.1)	0
OTHER SYSTEMIC ANTICANCER AGENTS	1 (1.1)	0
IMATINIB MESILATE	1 (1.1)	0
OTHER SYSTEMIC ANTICANCER THERAPY	1 (1.1)	3 (3.7)
CYCLOPHOSPHAMIDE	1 (1.1)	0
DACARBAZINE	1 (1.1)	2 (2.5)
DACARBAZINE CITRATE	0	1 (1.2)
FOTEMUSTINE	1 (1.1)	0
PACLITAXEL	0	1 (1.2)
PLATINUM COMPOUNDS	2 (2.3)	0
CARBOPLATIN;PACLITAXEL	1 (1.1)	0
CISPLATIN;ETOPOSIDE	1 (1.1)	0
UNASSIGNED	7 (8.0)	2 (2.5)
CABOZANTINIB S-MALATE;IPILIMUMAB;NIVOLUMAB	0	1 (1.2)
DABRAFENIB MESILATE;TRAMETINIB DIMETHYL SULFOXIDE	3 (3.4)	0
IMATINIB	1 (1.1)	0
INCAGN 02385;INCAGN 02390;RETIFANLIMAB	1 (1.1)	0
INTERLEUKIN INHIBITORS;IPILIMUMAB;NIVOLUMAB	1 (1.1)	0
INVESTIGATIONAL DRUG;IPILIMUMAB;NIVOLUMAB	1 (1.1)	0
NILOTINIB	1 (1.1)	0
NIVOLUMAB;TRAMETINIB	0	1 (1.2)

Only the subjects who had a recurrence after the randomization date and before the subsequent anti-cancer therapy/second non-melanoma primary cancer are included.

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).

(2) Open label treatment (Nivo Monotherapy) is considered a subsequent systemic therapy in this summary. Subsequent therapy data for the whole study, both blinded and open label phases, is reported.

Source: Table 3.2

Among all randomized subjects, a lower proportion of subjects received subsequent cancer therapy in the nivolumab arm than in the placebo arm (9.5% vs 23.5%), driven by fewer subjects receiving subsequent systemic therapy (5.7% vs 18.6%) and subsequent surgery (6.8% vs 14.8%).

Table 19 Subsequent cancer therapy summary – All randomized subjects

	Number of Subjects (%)	
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	50 (9.5)	62 (23.5)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	10 (1.9)	3 (1.1)
CURATIVE	5 (1.0)	0
PALLIATIVE	6 (1.1)	3 (1.1)
OTHER	0	0
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	36 (6.8)	39 (14.8)
TUMOR RESECTION CURATIVE	32 (6.1)	33 (12.5)
TUMOR RESECTION PALLIATIVE	0	3 (1.1)
OTHER	4 (0.8)	3 (1.1)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%) (2)	30 (5.7)	49 (18.6)
ANTI-CTLA4	9 (1.7)	13 (4.9)
IPILIMUMAB	9 (1.7)	13 (4.9)
ANTI-PD1 OR ANTI-PDL1	15 (2.9)	44 (16.7)
NIVOLUMAB (2)	13 (2.5)	43 (16.3)
PEMBROLIZUMAB	3 (0.6)	1 (0.4)
RETIFANLIMAB	1 (0.2)	0
BRAF INHIBITOR	5 (1.0)	2 (0.8)
DABRAFENIB	2 (0.4)	1 (0.4)
DABRAFENIB MESILATE	1 (0.2)	0
ENCORAFENIB	2 (0.4)	2 (0.8)
COMBO ANTI-CTLA4 + ANTI-PD1 OR COMBO ANTI-CTLA4 + ANTI-PDL1	5 (1.0)	3 (1.1)
IPILIMUMAB;NIVOLUMAB	5 (1.0)	3 (1.1)
COMBO BRAF MEK NRAS INHIBITOR	2 (0.4)	1 (0.4)
BINIMETINIB;ENCORAFENIB	0	1 (0.4)
DABRAFENIB;TRAMETINIB	2 (0.4)	1 (0.4)
COMBO ANTI-PD1 AND ANTI-LAG-3	1 (0.2)	2 (0.8)
NIVOLUMAB;RELATLIMAB	1 (0.2)	2 (0.8)
INVESTIGATIONAL ANTINEOPLASTIC	1 (0.2)	0
INVESTIGATIONAL DRUG	1 (0.2)	0
INVESTIGATIONAL ANTINEOPLASTIC AGENTS	2 (0.4)	2 (0.8)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	2 (0.4)	1 (0.4)
NEMVALEUKIN ALFA	0	1 (0.4)
ANTI-LAG-3	0	1 (0.4)
RELATLIMAB	0	1 (0.4)
MEK NRAS INHIBITOR	6 (1.1)	3 (1.1)
BINIMETINIB	2 (0.4)	2 (0.8)
TRAMETINIB	3 (0.6)	2 (0.8)
TRAMETINIB DIMETHYL SULFOXIDE	1 (0.2)	0
OTHER SYSTEMIC ANTICANCER AGENTS	1 (0.2)	0
IMATINIB MESILATE	1 (0.2)	0
OTHER SYSTEMIC ANTICANCER CHEMOTHERAPY	1 (0.2)	1 (0.4)
CYCLOPHOSPHAMIDE	1 (0.2)	0
DACARBAZINE	1 (0.2)	0
DACARBAZINE CITRATE	0	1 (0.4)
FOTEMUSTINE	1 (0.2)	0
PACLITAXEL	0	0 (0.4)
PLATINUM COMPOUNDS	1 (0.2)	0
CISPLATIN;ETOPOSIDE	1 (0.2)	0
VEGFR TARGETED THERAPY	0	1 (0.4)
CABOZANTINIB S-MALATE	0	1 (0.4)

(1) Subject may have received more than one type of subsequent therapy. Subsequent therapy was defined as therapy started on or after first dosing date (randomization date if subject never treated).
(2) Open label treatment (Nivo Monotherapy) is considered a subsequent therapy in this summary. Subsequent therapy data for the whole study, both blinded and open label phases, is reported.

Next line systemic cancer therapy is specified in below Table 20.

Table 20 Next-line systemic cancer therapy summary – Primary definition – All randomized subjects (DCO: 21-Feb-2023)

	Number of Subjects (%)	
	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264
SUBJECTS WHO RECEIVED OPEN LABEL NIVOLUMAB TREATMENT (%)	3 (0.6)	30 (11.4)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	42 (8.0)	32 (12.1)
BEMPEGALDESLEUKIN;NIVOLUMAB	0	2 (0.8)
BINIMETINIB;ENCORAFENIB	2 (0.4)	0
CISPLATIN;ETOPOSIDE	1 (0.2)	0
DABRAFENIB MESILATE;TRAMETINIB DIMETHYL SULFOXIDE	3 (0.6)	0
DABRAFENIB;TRAMETINIB	3 (0.6)	1 (0.4)
DACARBAZINE	1 (0.2)	0
IMATINIB MESILATE	1 (0.2)	0
INTERLEUKIN INHIBITORS;IPILIMUMAB;NIVOLUMAB	1 (0.2)	0
INVESTIGATIONAL DRUG	1 (0.2)	0
INVESTIGATIONAL DRUG;IPILIMUMAB;NIVOLUMAB	1 (0.2)	0
IPILIMUMAB	1 (0.2)	0
IPILIMUMAB;NIVOLUMAB	18 (3.4)	17 (6.4)
NIVOLUMAB	5 (1.0)	7 (2.7)
NIVOLUMAB;RELATLIMAB	0	3 (1.1)
NL 201	1 (0.2)	0
PEMEROLIZUMAB	2 (0.4)	2 (0.8)
TRAMETINIB	1 (0.2)	0

The primary definition of next line therapy is defined as any systemic anti-cancer therapy for the cancer under study with a start date on or after the date of first dose of study drug (randomization date if subject was never treated), or, starts open label treatment

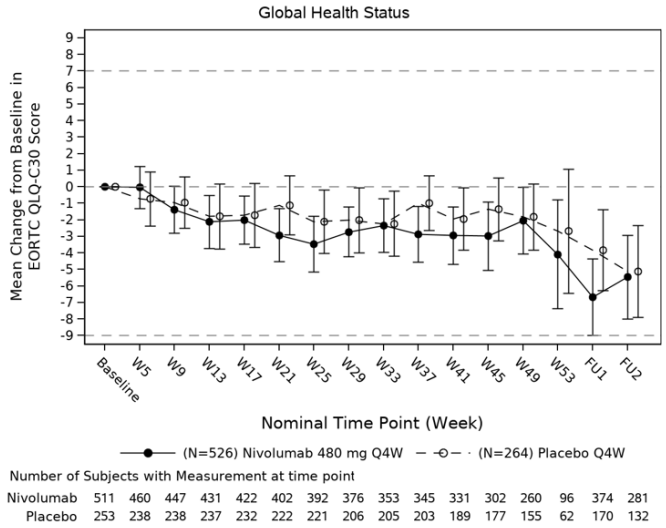
- **Duration of treatment on next-line systemic therapy**

Median duration of treatment on next-line systemic therapy was numerically lower in the nivolumab arm (n=30) compared to placebo (3.94 months vs 11.07 months). This was based on a limited number of patients (nivolumab: n=45, and placebo: n=62).

- **QoL/PRO**

Quality of life on treatment through Week 53 was measured by EORTC QLQ-C30 subscales and showed no clinically meaningful deterioration in any arm (descriptive analysis). Mean change in EORTC QLQ-C30 global health status/QoL score from baseline is shown in Figure 9. Compliance rates were high throughout treatment (above 90%). Similar results were observed for EORTS QLQ-C30 Role Functioning subscale. Also scores for other subscales remained stable in both treatment arms, with no group mean score from baseline reaching the minimally important difference (MID).

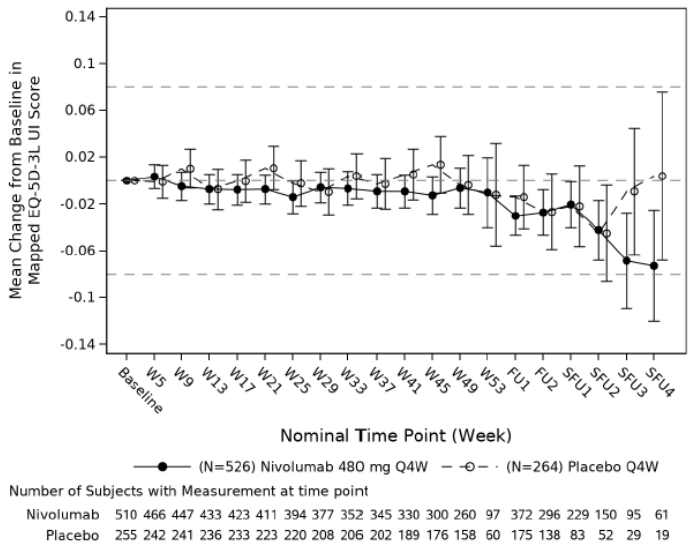
Figure 9 Mean change in EORTC QLQ-C30 Global health status/QOL score from baseline – All randomized adult subjects



Error bars represent standard error for the mean.
Only time points where data available for >=10 subjects in each treatment group are plotted.
The MID for the subscales of the EORTC QLQ-C30 as recommended by Musoro et al.
Baseline is defined as the latest assessment within a 3 day window on or prior to first dose date (randomization date if not treated).
Data prior to the open label first dose date is being reported
Note: FU1 occurs 30 days after last dose and not necessarily after W53

In addition, no clinically meaningful deterioration was observed based on the EQ-5D-3L utility index (Figure 10) and mean visual analogue scale (VAS) scores in either arm (data not shown; descriptive analysis for both). High questionnaire completion rates (>90%) were obtained in each arm during treatment.

Figure 10 Mean changes in mapped EQ-5S-3L utility index from baseline – All randomized subjects



Error bars represent standard error for the mean.
Only time points where data available for >=10 subjects in each treatment group are plotted.
Horizontal reference line indicates minimum important difference (MID), considered a change of >= 0.08 points from baseline.
Mapped EQ-5D-3L Utility Index Score based on Support Unit (DSU) EuroQoL (EQG) model developed by Hernandez-Alava et. al.
Baseline is defined as the latest assessment within a 3 day window on or prior to first dose date
(randomization date if not treated).
Data prior to the open label first dose date is being reported.

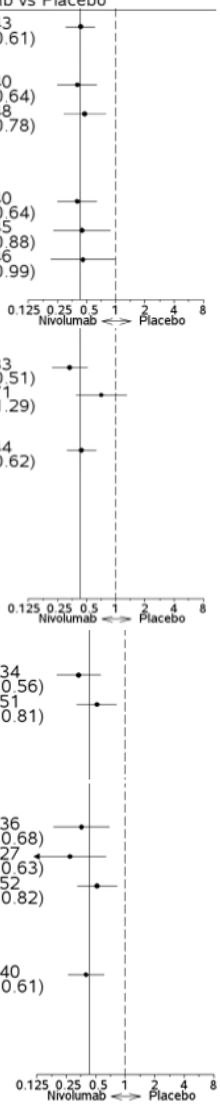
Ancillary analyses

Subgroup analyses of RFS

Subgroup analyses are shown in Table 21. These support a beneficial effect of adjuvant nivolumab over placebo (HR<1) in all subgroups.

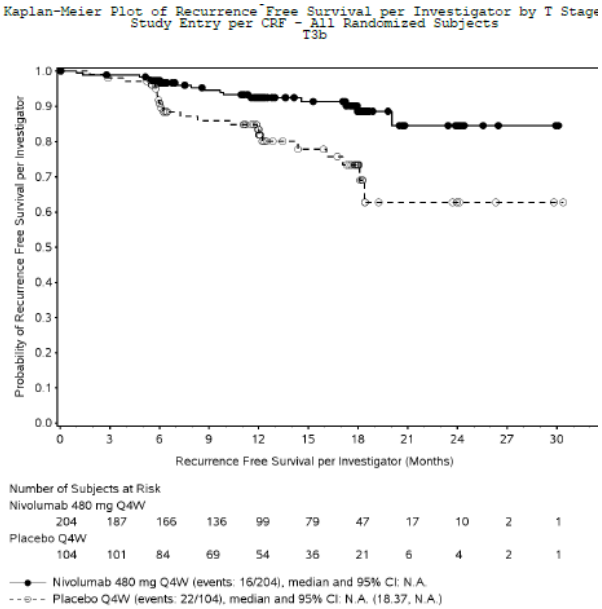
Table 21 Forest plot of treatment effect on recurrence-free survival per investigator in pre-defined subsets – All randomized subjects

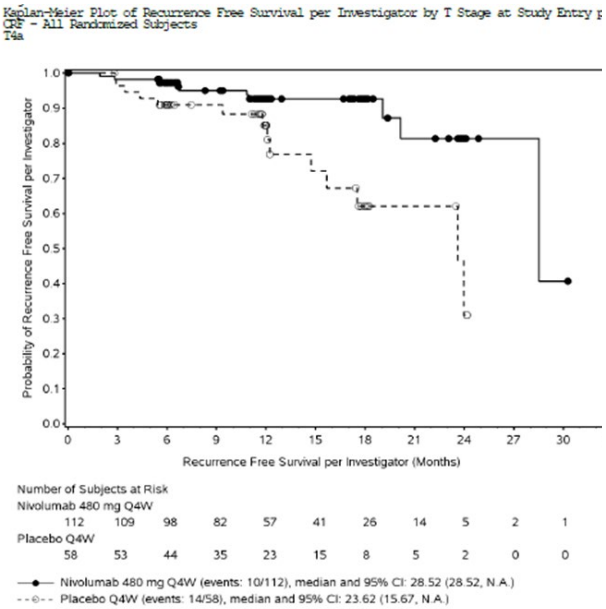
	N	Nivolumab 480 mg Q4W N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Placebo Q4W N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
Overall	790	66 (526)	N.A. (28.52, N.A.)	89.0 (85.6, 91.6)	69 (264)	N.A. (21.62, N.A.)	79.4 (73.5, 84.1)	0.43 (0.31, 0.61)
Age Category I								
< 65	460	33 (305)	N.A. (28.52, N.A.)	91.5 (87.4, 94.4)	39 (155)	N.A. (21.62, N.A.)	81.2 (73.5, 86.9)	0.40 (0.25, 0.64)
>= 65	330	33 (221)	N.A.	85.4 (79.3, 89.8)	30 (109)	23.62 (18.07, N.A.)	76.8 (66.8, 84.2)	0.48 (0.29, 0.78)
Age Category II								
< 18	0	0 (0)			0 (0)			
>= 18 and < 65	460	33 (305)	N.A. (28.52, N.A.)	91.5 (87.4, 94.4)	39 (155)	N.A. (21.62, N.A.)	81.2 (73.5, 86.9)	0.40 (0.25, 0.64)
>= 65 and < 75	217	16 (140)	N.A.	89.2 (81.9, 93.6)	18 (77)	N.A. (18.07, N.A.)	79.7 (67.9, 87.5)	0.45 (0.23, 0.88)
>= 75 and < 85	107	17 (77)	N.A.	78.2 (65.6, 86.6)	11 (30)	16.03 (10.28, N.A.)	68.4 (46.1, 83.0)	0.46 (0.21, 0.99)
>= 85	6	0 (4)	N.A.	N.A.	1 (2)	17.08 (N.A., N.A.)	100.0 (100.0, 100.0)	
Sex								
Male	483	39 (322)	N.A.	89.9 (85.6, 93.0)	51 (161)	23.62 (18.07, N.A.)	76.5 (68.6, 82.7)	0.33 (0.22, 0.51)
Female	307	27 (204)	28.52 (28.52, N.A.)	87.6 (81.6, 91.7)	18 (103)	N.A.	83.9 (74.1, 90.2)	0.71 (0.39, 1.29)
Race								
White	777	65 (515)	N.A. (28.52, N.A.)	88.7 (85.3, 91.4)	68 (262)	N.A. (21.62, N.A.)	79.7 (73.8, 84.4)	0.44 (0.31, 0.62)
Black	3	1 (2)	23.66 (N.A., N.A.)	100.0 (100.0, 100.0)	0 (1)	N.A.	N.A.	
Asian	1	0 (1)	N.A.	N.A.	0 (0)			
Other	8	0 (7)	N.A.	100.0 (100.0, 100.0)	1 (1)	1.08 (N.A., N.A.)	0.0 (N.A., N.A.)	
Not Reported	1	0 (1)	N.A.	N.A.	0 (0)			
Disease stage category								
Stage IIb	479	26 (316)	N.A. (28.52, N.A.)	92.6 (88.6, 95.2)	36 (163)	23.95 (18.37, N.A.)	84.1 (76.8, 89.3)	0.34 (0.20, 0.56)
Stage IIc	311	40 (210)	N.A. (23.66, N.A.)	83.8 (77.5, 88.4)	33 (101)	N.A. (16.03, N.A.)	72.0 (61.6, 80.0)	0.51 (0.32, 0.81)
Stage Other	0	0 (0)			0 (0)			
Stage Unknown	0	0 (0)			0 (0)			
T stage								
T3b	308	16 (204)	N.A.	92.6 (87.2, 95.7)	22 (104)	N.A. (18.37, N.A.)	83.4 (73.8, 89.7)	0.36 (0.19, 0.68)
T4a	170	10 (112)	28.52 (28.52, N.A.)	92.6 (85.1, 96.4)	14 (58)	23.62 (15.67, N.A.)	85.2 (70.7, 92.8)	0.27 (0.12, 0.63)
T4b	312	40 (210)	N.A. (23.66, N.A.)	83.8 (77.5, 88.4)	33 (102)	N.A. (16.03, N.A.)	72.3 (61.9, 80.2)	0.52 (0.33, 0.82)
Region								
US and Canada	143	8 (97)	N.A. (20.04, N.A.)	92.7 (84.2, 96.7)	8 (46)	N.A. (15.67, N.A.)	84.2 (67.8, 92.7)	
Western Europe	463	41 (303)	N.A. (28.52, N.A.)	89.0 (84.5, 92.3)	46 (160)	23.62 (17.91, N.A.)	78.0 (70.0, 84.0)	0.40 (0.26, 0.61)
Eastern Europe	86	8 (58)	N.A.	84.5 (71.3, 92.0)	9 (28)	23.95 (16.10, N.A.)	80.2 (58.6, 91.3)	
Australia	98	9 (68)	N.A.	87.9 (76.2, 94.1)	6 (30)	N.A.	78.8 (58.7, 89.9)	
ROW	0	0 (0)			0 (0)			

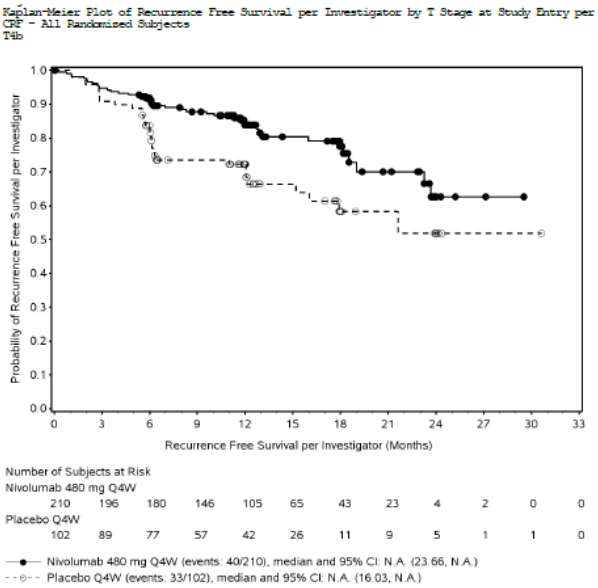


HR is not computed for subset category with less than 10 events per treatment group. The solid vertical reference line presents overall HR value. Note: One subject with T4b melanoma was incorrectly entered as IIB instead of IIC.

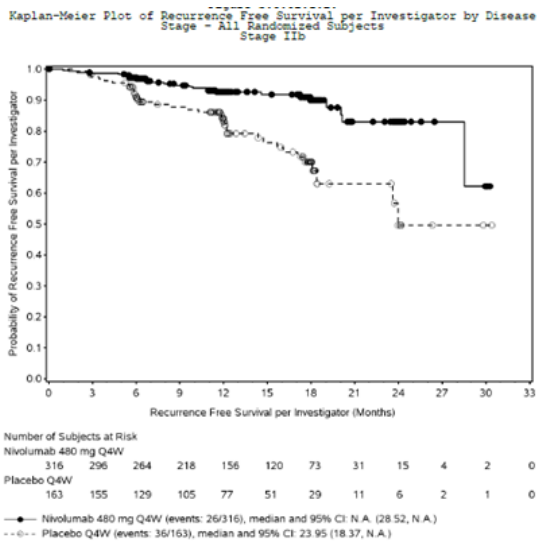
Kaplan-Meier curves of RFS by tumour category (T3b, T4a, or T4b) at study entry

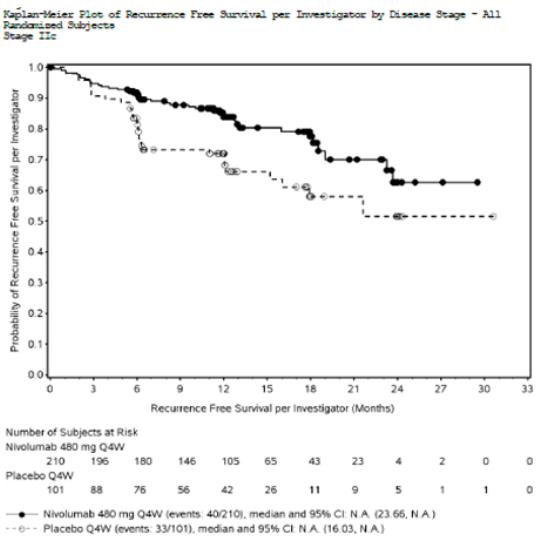






Kaplan Meier curves of RFS by disease stage (IIB or IIC) at study entry



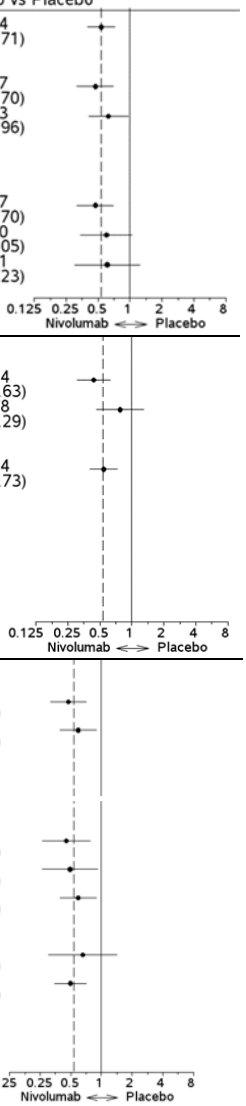


Updated subgroup analysis of RFS (DCO 21-Feb-2023)

In a pre-specified subgroup analysis for all randomized patients, RFS HRs (95% CI) for all subgroups were below 1 for nivolumab vs placebo (Figure 11).

Figure 11 Forest plot of treatment effect on recurrence-free survival per investigator in pre-defined subsets – All randomized subjects (DCO 21-Feb-2023)

		Nivolumab 480 mg Q4W			Placebo Q4W			Unstratified
	N	N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Hazard Ratio (95% CI) Nivolumab vs Placebo
Overall	790	102 (526)	N.A.	88.8 (85.6, 91.2)	84 (264)	36.14 (24.77, N.A.)	81.1 (75.7, 85.4)	0.54 (0.40, 0.71)
Age Category I								
< 65	460	51 (305)	N.A.	92.1 (88.3, 94.7)	48 (155)	36.14 (36.14, N.A.)	82.9 (75.9, 88.0)	0.47 (0.32, 0.70)
>= 65	330	51 (221)	N.A.	84.1 (78.3, 88.4)	36 (109)	N.A. (23.03, N.A.)	78.5 (69.2, 85.3)	0.63 (0.41, 0.96)
Age Category II								
< 18	0	0 (0)			0 (0)			
>= 18 and < 65	460	51 (305)	N.A.	92.1 (88.3, 94.7)	48 (155)	36.14 (36.14, N.A.)	82.9 (75.9, 88.0)	0.47 (0.32, 0.70)
>= 65 and < 75	217	27 (140)	N.A.	88.1 (81.2, 92.5)	23 (77)	N.A. (23.79, N.A.)	81.1 (70.2, 88.3)	0.60 (0.34, 1.05)
>= 75 and < 85	107	23 (77)	N.A.	77.3 (65.6, 85.5)	12 (30)	23.62 (10.28, N.A.)	70.5 (49.5, 84.0)	0.61 (0.30, 1.23)
>= 85	6	1 (4)	N.A. (11.50, N.A.)	50.0 (0.6, 91.0)	1 (2)	17.08 (N.A., N.A.)	100.0 (100.0, 100.0)	
Sex								
Male	483	63 (322)	N.A.	89.2 (85.1, 92.2)	60 (161)	36.14 (23.62, N.A.)	78.2 (70.9, 83.9)	0.44 (0.31, 0.63)
Female	307	39 (204)	N.A.	88.1 (82.6, 91.9)	24 (103)	N.A.	85.8 (77.2, 91.3)	0.78 (0.47, 1.29)
Race								
White	777	100 (515)	N.A.	88.5 (85.3, 91.0)	83 (262)	36.14 (24.77, N.A.)	81.4 (76.0, 85.7)	0.54 (0.40, 0.73)
Black	3	1 (2)	23.66 (N.A., N.A.)	100.0 (100.0, 100.0)	0 (1)	N.A.	100.0 (100.0, 100.0)	
Asian	1	1 (1)	17.58 (N.A., N.A.)	100.0 (100.0, 100.0)	0 (0)			
Other	8	0 (7)	N.A.	100.0 (100.0, 100.0)	1 (1)	1.08 (N.A., N.A.)	0.0 (N.A., N.A.)	
Not Reported	1	0 (1)	N.A.	100.0 (100.0, 100.0)	0 (0)			
Disease stage category								
Stage IIB	478	47 (316)	N.A.	91.5 (87.6, 94.2)	46 (162)	36.14 (24.77, N.A.)	86.0 (79.5, 90.5)	0.47 (0.31, 0.71)
Stage IIC	312	55 (210)	N.A. (30.23, N.A.)	84.8 (79.1, 89.1)	38 (102)	N.A. (19.81, N.A.)	73.2 (63.2, 80.9)	0.59 (0.39, 0.89)
Stage Other	0	0 (0)			0 (0)			
Stage Unknown	0	0 (0)			0 (0)			
T stage								
T3b	308	26 (204)	N.A.	91.9 (86.9, 95.0)	28 (104)	36.14 (24.77, N.A.)	85.3 (76.8, 90.9)	0.45 (0.26, 0.77)
T4a	170	21 (112)	N.A.	90.8 (83.6, 94.9)	18 (58)	N.A. (23.03, N.A.)	87.2 (75.0, 93.7)	0.49 (0.26, 0.92)
T4b	312	55 (210)	N.A. (30.23, N.A.)	84.8 (79.1, 89.1)	38 (102)	N.A. (19.81, N.A.)	73.2 (63.2, 80.9)	0.59 (0.39, 0.89)
Region								
US and Canada	143	16 (97)	N.A.	89.8 (81.4, 94.6)	11 (46)	N.A. (23.03, N.A.)	86.0 (71.4, 93.4)	0.65 (0.30, 1.41)
Western Europe	463	63 (303)	N.A.	89.7 (85.6, 92.7)	56 (160)	36.14 (23.62, N.A.)	80.0 (72.7, 85.5)	0.49 (0.34, 0.71)
Eastern Europe	86	9 (58)	N.A.	83.5 (70.6, 91.0)	10 (28)	N.A. (21.62, N.A.)	82.1 (62.3, 92.1)	
Australia	98	14 (68)	N.A. (25.00, N.A.)	87.4 (76.4, 93.5)	7 (30)	N.A.	79.3 (59.6, 90.1)	
ROW	0	0 (0)			0 (0)			



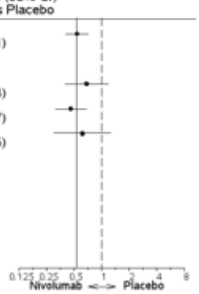
HR is not computed for subset category with less than 10 events per treatment group.
"ROW" stands for Rest of World.
The dashed vertical reference line presents overall HR value of ITT population.
Source: Figure S.5.31.1.1.

BRAF mutation

A total of 790 patients were randomized in the study, out of which 658 (83.3%) had evaluable BRAF V600 samples and 132 were not evaluable. BRAF status was determined by whole DNA exome sequencing of the submitted tumor samples. Subgroup analysis by BRAF mutation status is shown below.

Figure 12 Forest plot of treatment effect on recurrence-free survival per investigator – Baseline BRAF V600 status subsets – All randomized subjects (DCO 21-Feb-2023)

	N	Nivolumab 480 mg Q4W N of Events (N of subjects)	Nivolumab 480 mg Q4W mRFS (95% CI)	Nivolumab 480 mg Q4W 12-month RFS (95% CI)	Placebo Q4W N of Events (N of subjects)	Placebo Q4W mRFS (95% CI)	Placebo Q4W 12-month RFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
Overall	790	102 (526)	N.A.	88.8 (85.6, 91.2)	84 (264)	36.14 (24.77, N.A.)	81.1 (75.7, 85.4)	0.54 (0.40, 0.71)
Subjects with Baseline B-RAF V600 Status								
Mutation	229	31 (148)	N.A. (30.23, N.A.)	88.0 (81.4, 92.3)	22 (81)	N.A. (24.77, N.A.)	83.2 (72.8, 89.9)	0.68 (0.39, 1.18)
Wild Type	429	55 (293)	N.A.	90.2 (86.1, 93.2)	48 (136)	36.14 (23.62, N.A.)	78.5 (70.4, 84.6)	0.46 (0.31, 0.67)
Not Reported/Not Evaluable	132	16 (85)	N.A.	84.9 (75.0, 91.1)	14 (47)	N.A. (18.37, N.A.)	85.1 (71.3, 92.6)	0.61 (0.30, 1.26)



Hazard ratio is Nivolumab over Placebo from unstratified Cox proportional hazards model by dichotomized biomarker defined by median/cutoff. Hazard ratio is not computed for subset category with less than 10 events per treatment group.
The straight solid vertical reference line presents overall HR value. The dashed vertical reference line presents an HR of 1.
Source: Figure 1.2.2.

PD-L1 subgroups

Biomarker assay

The PD-L1 immunohistochemistry 28-8 pharmDx assay co-developed by the MAH and DAKO North America (Carpinteria, CA US) using a rabbit anti-human PD-L1 antibody (clone 28-8; Epitomics Inc, Burlingame, CA US) was used to assess PD-L1 expression in tumour samples. The Dako 28-8 assay has acceptable cut slide stability validated up to 4 months and has not generated data beyond this time point; thus only freshly sectioned samples from tumour blocks were used for this retrospective analysis.

Please note the following definitions:

PD-L1 expression missing: no available tumour biopsy specimen for PD-L1 evaluation.

PD-L1 expression: the percentage of tumour cells demonstrating plasma membrane PD-L1 staining of any intensity in a minimum of 100 evaluable tumour cells using the Dako PD-L1 immunohistochemistry 28-8 pharmDx assay.

Quantifiable: an available tumour biopsy specimen and the number of viable tumour cells is ≥100 and percentage of tumour PD-L1 expression is ≥ 0%.

Indeterminate: tumour cell membrane staining hampered for reasons attributed to the biology of the tumour biopsy specimen and not because of improper sample preparation or handling.

Not evaluable: tumour biopsy specimen was not optimally collected or prepared (eg, PD-L1 expression is neither quantifiable nor indeterminate).

Baseline characteristics patients with PD-L1 status

Determination of PD-L1 status was not mandatory for inclusion in the trial and any comparisons are therefore exploratory. Pre-treatment tumour tissue from 346 of the 790 (43.8%) randomized participants (nivolumab, n=219 [41.6%]; placebo, n=127 [48.1%]) was available for PD-L1 analysis. Among these participants, 300 participants (86.7%) were evaluable for PD-L1 expression, including

189 and 111 participants in the nivolumab and placebo arms, respectively. In the nivolumab arm, tumour cell PD-L1 expression ≥ 1% and ≥ 5% were identified in 109 (57.7%) and 59 (31.2%) participants, respectively. In the placebo arm, tumour cell PD-L1 expression ≥ 1% and ≥ 5% were identified in 58 (52.3%) and 33 (29.7%) participants, respectively (Table 22).

Table 22 Frequency of PD-L1 tumour cell expression status: All randomized subjects

Population PD-L1 Expression Category	Nivolumab 480 mg Q4W N = 526	Placebo Q4W N = 264
SUBJECTS WITH PD-L1 EXPRESSION MISSING AT BASELINE (N(%))	307 (58.4)	137 (51.9)
SUBJECTS WITH PD-L1 QUANTIFIABLE AT BASELINE (N(%))	189 (35.9)	111 (42.0)
PD-L1 EXPRESSION (%)		
MEAN	8.9	7.5
MEDIAN	1.0	1.0
MIN , MAX	0 , 98	0 , 80
Q1 , Q3	0.0 , 5.0	0.0 , 5.0
STANDARD DEVIATION	19.1	15.3
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 1%	109/189 (57.7)	58/111 (52.3)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 1%	80/189 (42.3)	53/111 (47.7)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION >= 5%	59/189 (31.2)	33/111 (29.7)
SUBJECTS WITH BASELINE PD-L1 EXPRESSION < 5%	130/189 (68.8)	78/111 (70.3)
SUBJECTS WITH INDETERMINATE PD-L1 EXPRESSION AT BASELINE (N(%))	0	0
SUBJECTS WITH PD-L1 EXPRESSION AT BASELINE NOT EVALUABLE (N(%))	30 (5.7)	16 (6.1)

Note: Not evaluable - Tumor tissue sample was not optimally collected or prepared and PD-L1 expression was neither quantifiable nor indeterminate. Not evaluable may be determined from H&E process before the tumor biopsy specimen was sent for PD-L1 evaluation or from the H&E process during PD-L1 evaluation.

Indeterminate - Tumor cell membrane staining hampered for reasons attributed to the biology of the tumor tissue sample and not because of improper sample preparation or handling.

Baseline characteristics were generally balanced in PD-L1 quantifiable and non-quantifiable subgroups and the all-randomized subjects, although some imbalances were observed in tumour category, geographic region, and melanoma subtype. A higher percentage of subjects in the PD-L1 quantifiable group were enrolled from Eastern Europe than the all-randomized subjects (23.0% vs 10.9%). A lower percentage of subjects in the PD-L1 quantifiable group had a T stage of T4A at study entry than the all-randomized subjects (15.3% vs 21.5%). A higher percentage of subjects in the PD-L1 quantifiable group had a melanoma sub-type of nodular melanoma than the all-randomized subjects (59.0% vs 50.5%). These numerical differences between the PD-L1 quantifiable group and the all-randomized subjects were similarly observed within both treatment arms.

Table 23 Baseline demographic and disease characteristics summary by PD-L1 assessment population: All randomized subjects

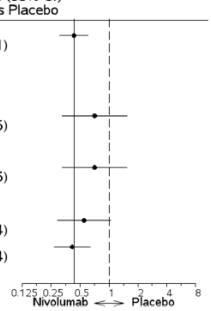
	All Randomized Subjects with Quantifiable PD-L1 at Baseline N = 300	All Randomized Subjects with PD-L1 Indeterminate/Not Reported/ Not Evaluable at Baseline N = 490	All Randomized Subjects N = 790
AGE (YEARS)			
N	300	490	790
MEAN	59.6	59.8	59.7
MEDIAN	62.0	62.0	62.0
MIN , MAX	19 , 92	21 , 87	19 , 92
Q1 , Q3	50.0 , 70.0	51.0 , 70.0	51.0 , 70.0
SD	14.1	13.6	13.8
AGE CATEGORIZATION 1 (%)			
< 65	175 (58.3)	285 (58.2)	460 (58.2)
>= 65	125 (41.7)	205 (41.8)	330 (41.8)
AGE CATEGORIZATION 2 (%)			
< 18	0	0	0
>= 18 AND < 65	175 (58.3)	285 (58.2)	460 (58.2)
>= 65 AND < 75	85 (28.3)	132 (26.9)	217 (27.5)
>= 75 AND < 85	35 (11.7)	72 (14.7)	107 (13.5)
>= 85	5 (1.7)	1 (0.2)	6 (0.8)
SEX (%)			
MALE	172 (57.3)	311 (63.5)	483 (61.1)
FEMALE	128 (42.7)	179 (36.5)	307 (38.9)
REGION (%)			
US AND CANADA	33 (11.0)	110 (22.4)	143 (18.1)
WESTERN EUROPE	183 (61.0)	280 (57.1)	463 (58.6)
EASTERN EUROPE	69 (23.0)	17 (3.5)	86 (10.9)
AUSTRALIA	15 (5.0)	83 (16.9)	98 (12.4)
BASELINE ECOG PS			
0	278 (92.7)	462 (94.3)	740 (93.7)
1	22 (7.3)	28 (5.7)	50 (6.3)
BASELINE LDH I			
<= ULN	263 (87.7)	439 (89.6)	702 (88.9)
> ULN	31 (10.3)	44 (9.0)	75 (9.5)
NOT REPORTED	6 (2.0)	7 (1.4)	13 (1.6)
BASELINE LDH II			
<= 2*ULN	294 (98.0)	483 (98.6)	777 (98.4)
> 2*ULN	0	0	0
NOT REPORTED	6 (2.0)	7 (1.4)	13 (1.6)
DISEASE STAGE AT STUDY ENTRY (PER CRF)			
STAGE IIB	169 (56.3)	310 (63.3)	479 (60.6)
STAGE IIC	131 (43.7)	180 (36.7)	311 (39.4)
STAGE OTHER	0	0	0
STAGE UNKNOWN	0	0	0
T STAGE AT STUDY ENTRY (PER CRF)			
STAGE II PATIENTS	300 (100.0)	490 (100.0)	790 (100.0)
T3B	123 (41.0)	185 (37.8)	308 (39.0)
T4A	46 (15.3)	124 (25.3)	170 (21.5)
T4B	131 (43.7)	181 (36.9)	312 (39.5)
MELANOMA SUB-TYPE			
SUPERFICIAL SPREADING MELANOMA	78 (26.0)	155 (31.6)	233 (29.5)
NODULAR MELANOMA	177 (59.0)	222 (45.3)	399 (50.5)
LENTIGO MALIGNA	7 (2.3)	9 (1.8)	16 (2.0)
ACRAL LENTIGINOUS MELANOMA	11 (3.7)	32 (6.5)	43 (5.4)
DESMOPLASTIC MELANOMA	2 (0.7)	27 (5.5)	29 (3.7)
OTHER	22 (7.3)	44 (9.0)	66 (8.4)
NOT REPORTED	3 (1.0)	1 (0.2)	4 (0.5)
LOCATION OF PRIMARY MELANOMA			
HEAD AND NECK	61 (20.3)	105 (21.4)	166 (21.0)
ARM	51 (17.0)	116 (23.7)	167 (21.1)
LEG	70 (23.3)	105 (21.4)	175 (22.2)
TRUNK	118 (39.3)	164 (33.5)	282 (35.7)

RFS by PD-L1 subgroup

The relative benefit of biomarker-defined subgroups was assessed as an exploratory endpoint. Evaluation of treatment effect (nivolumab vs. placebo) on RFS in PD-L1 positive subgroups (≥ median, ≥ 1%, and ≥ 5%) was limited by the low number of RFS events, precluding the estimation of HRs (Table 24). In the PD-L1 negative subgroups (< median, < 1%, and < 5%), treatment benefit from nivolumab compared to placebo was observed with HRs below one and wide confidence intervals overlapping the ITT HR. For PD L1 analysis as a continuous variable, treatment benefit from nivolumab compared to placebo was observed in both the PD-L1 high (HR=0.43, 95% CI: 0.24, 0.76) and low subgroups (HR=0.52, 95% CI: 0.28, 0.94).

Table 24 Forest plot of treatment effect on recurrence free survival per investigator in baseline PD-L1 subsets (Cut-offs: median, 1%, and 5%) – All randomized subjects

	N	Nivolumab 480 mg Q4W N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Placebo Q4W N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
Overall	790	66 (526)	N.A. (28.52, N.A.)	89.0 (85.6, 91.6)	69 (264)	N.A. (21.62, N.A.)	79.4 (73.5, 84.1)	0.43 (0.31, 0.61)
Subjects with Baseline PD-L1 (%) Status								
>= Median (>= 1.0)	167	8 (109)	N.A.	93.9 (86.9, 97.2)	17 (58)	N.A. (16.03, N.A.)	75.4 (61.2, 85.0)	
< Median (< 1.0)	133	14 (80)	28.52 (N.A., N.A.)	83.7 (72.4, 90.7)	12 (53)	23.95 (21.62, N.A.)	83.1 (69.0, 91.2)	0.71 (0.33, 1.55)
>= 1%	167	8 (109)	N.A.	93.9 (86.9, 97.2)	17 (58)	N.A. (16.03, N.A.)	75.4 (61.2, 85.0)	
< 1%	133	14 (80)	28.52 (N.A., N.A.)	83.7 (72.4, 90.7)	12 (53)	23.95 (21.62, N.A.)	83.1 (69.0, 91.2)	0.71 (0.33, 1.55)
>= 5%	92	3 (59)	N.A.	96.4 (86.3, 99.1)	9 (33)	N.A. (14.36, N.A.)	73.1 (52.9, 85.7)	
< 5%	208	19 (130)	28.52 (N.A., N.A.)	86.8 (78.9, 91.9)	20 (78)	23.95 (21.62, N.A.)	81.7 (70.5, 89.0)	0.55 (0.29, 1.04)
PD-L1 INDT/NR/NE	490	44 (337)	N.A.	88.6 (84.2, 91.9)	40 (153)	N.A. (17.91, N.A.)	79.7 (71.7, 85.7)	0.41 (0.27, 0.64)



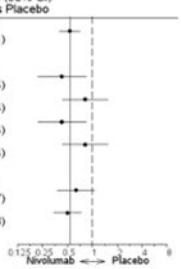
Hazard ratio is Nivolumab over Placebo from unstratified Cox proportional hazards model by dichotomized biomarker defined by median/cutoff. Hazard ratio is not computed for subset category with less than 10 events per treatment group.
The straight vertical reference line presents overall HR value. INDT: Indeterminate; NR: Not Reported; NE: Not Evaluable

Updated RFS by PD-L1 subgroup (DCO 21-Feb-2023)

Updated RFS analyses by PD-L1 subgroup are shown below (Figure 13).

Figure 13 Forest plot of treatment effect on recurrence-free survival per investigator – Baseline PD=L1 subsets (Cutoffs: Median, 1%, and 5%) – All randomized subjects (DCO 21-Feb-2023)

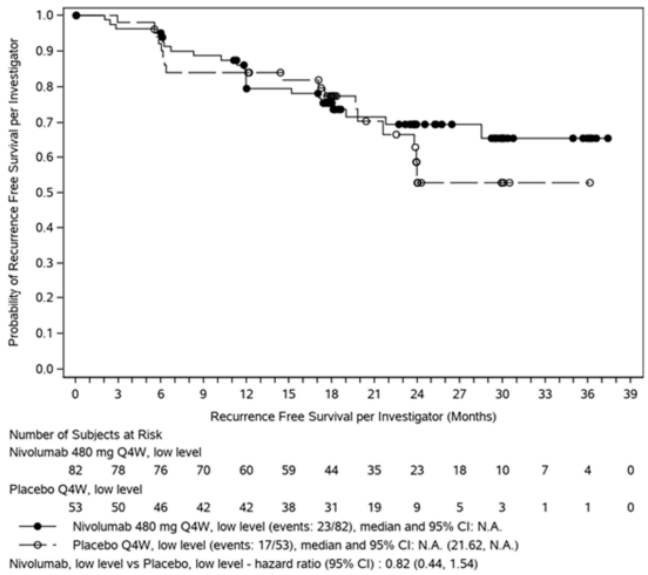
	N	Nivolumab 480 mg Q4W N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Placebo Q4W N of Events (N of subjects)	mRFS (95% CI)	12-month RFS (95% CI)	Unstratified Hazard Ratio (95% CI) Nivolumab vs Placebo
Overall	790	102 (526)	N.A.	88.8 (85.6, 91.2)	84 (264)	36.14 (24.77, N.A.)	81.1 (75.7, 85.4)	0.54 (0.40, 0.71)
Subjects with Baseline PD-L1 (%) Status								
>= Median (>= 1.0)	167	16 (109)	N.A.	93.3 (86.4, 96.7)	19 (58)	36.14 (36.14, N.A.)	77.0 (63.7, 85.9)	0.43 (0.22, 0.84)
< Median (< 1.0)	135	23 (82)	N.A.	79.5 (68.8, 86.9)	17 (53)	N.A. (21.62, N.A.)	84.1 (70.7, 91.7)	0.82 (0.44, 1.54)
>= 1%	167	16 (109)	N.A.	93.3 (86.4, 96.7)	19 (58)	36.14 (36.14, N.A.)	77.0 (63.7, 85.9)	0.43 (0.22, 0.84)
< 1%	135	23 (82)	N.A.	79.5 (68.8, 86.9)	17 (53)	N.A. (21.62, N.A.)	84.1 (70.7, 91.7)	0.82 (0.44, 1.54)
>= 5%	92	8 (59)	N.A.	94.6 (84.1, 98.2)	10 (33)	36.14 (N.A., N.A.)	74.6 (55.5, 86.4)	
< 5%	210	31 (132)	N.A.	84.2 (76.6, 89.5)	26 (78)	N.A. (23.79, N.A.)	82.6 (72.0, 89.5)	0.64 (0.38, 1.07)
PD-L1 INDT/NR/NE	488	63 (335)	N.A.	89.5 (85.6, 92.5)	48 (153)	N.A. (24.77, N.A.)	81.7 (74.4, 87.1)	0.50 (0.34, 0.73)



Hazard ratio is Nivolumab over Placebo from unstratified Cox proportional hazards model by dichotomized biomarker defined by median/cutoff. Hazard ratio is not computed for subset category with less than 10 events per treatment group. The straight solid vertical reference line presents overall HR value and the vertical dashed reference line presents an HR of 1.
Source: Figure 1.2.1.1

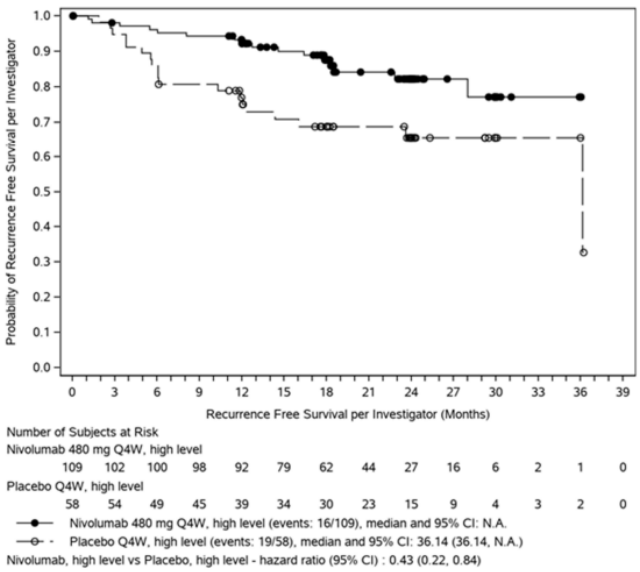
The corresponding KM-curves are shown below for the PD-L1 subgroups (cut-off 1%) and for subjects with indeterminate/not reported/not evaluable PD-L1 at baseline.

Figure 14 Kaplan-Meier Plot of effect on recurrence-free survival per investigator – PD-L1 expression <1% subgroup (All randomized subjects with quantifiable PD-L1 at baseline DCO: 21-Feb-2023)



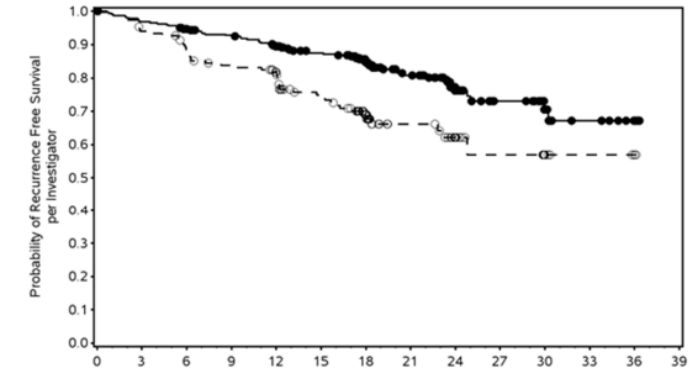
Symbols represent censored observations.
High level is baseline PD-L1 >= 1%; low level is baseline PD-L1 < 1%.
Unstratified Cox proportional hazard model has been applied.
Program Source: /opt/zfs001/prd/bms247316/stats/rfsia2/prog/figures
Program Name: rg-bm-rfsinv-cut-v2-sas.sas 10MAY2023:21:06:58

Figure 15 Kaplan-Meier Plot of effect on recurrence-free survival per investigator – PD-L1 expression ≥1% subgroup (All randomized subjects with quantifiable PD-L1 at baseline DCO: 21-Feb-2023)



Symbols represent censored observations.
High level is baseline PD-L1 >= 1%; low level is baseline PD-L1 < 1%.
Unstratified Cox proportional hazard model has been applied.
Program Source: /opt/zfs001/prd/bms247316/stats/rfsia2/prog/figures
Program Name: rg-bm-rfsinv-cut-v2-sas.sas 10MAY2023:21:06:58

Figure 16 Kaplan-Meier Plot of effect on recurrence-free survival per investigator (All randomized subjects with indeterminate/not reported/not evaluable PD-L1 at baseline DCO: 21-Feb-2023)



Number of Subjects at Risk

Nivolumab 480 mg Q4W	335	312	298	288	270	248	185	131	72	40	24	13	8	0
Placebo Q4W	153	140	129	121	112	93	59	35	20	11	5	3	1	0

Nivolumab 480 mg Q4W (events: 63/335), median and 95% CI: N.A.
Placebo Q4W (events: 48/153), median and 95% CI: N.A. (24.77, N.A.)
Nivolumab 480 mg Q4W vs Placebo Q4W - hazard ratio (95% CI): 0.50 (0.34, 0.73)

Symbols represent censored observations.
Unstratified Cox proportional hazard model has been applied.
Hazard ratio is not computed for subset category with less than 10 events per population of interest.
Program Source: /opt/zfs001/prd/bms247316/stats/rfsia2/prog/figures
Program Name: rg-bm-kmpdlind-sas.sas 06JUL2023:13:06:21

Baseline characteristics between the nivolumab and placebo arms of the PD-L1 expression evaluated population are presented in Table 25 and Table 26. Some imbalances were seen, the largest differences in the PD-L1 expression <1% subgroup were observed for age (48% of nivolumab patients and 36% of placebo patients were ≥ 65 years old) and gender (40% of nivolumab patients and 51% of placebo patients were female). The opposite was seen in the PD-L1 expression ≥ 1% subgroup.

Table 25 Demographic characteristics summary by PD-L1 status at baseline, 1% Cutoff- All randomized subjects (DCO 21-Feb-2023).

	PD-L1 < 1%		PD-L1 >= 1%		PD-L1 Indeterminate/ Not Reported/ Not Evaluable	
	Nivolumab 480 mg Q4W N = 82	Placebo Q4W N = 53	Nivolumab 480 mg Q4W N = 109	Placebo Q4W N = 58	Nivolumab 480 mg Q4W N = 335	Placebo Q4W N = 153
AGE (YEARS)						
N	82	53	109	58	335	153
MEAN	62.2	59.2	57.4	60.8	60.2	58.7
MEDIAN	64.0	61.0	59.0	63.5	63.0	60.0
MIN , MAX	29 , 87	21 , 92	21 , 85	19 , 81	23 , 87	21 , 83
Q1 , Q3	53.0 , 73.0	51.0 , 67.0	48.0 , 69.0	51.0 , 71.0	51.0 , 71.0	51.0 , 69.0
SD	13.2	13.5	15.3	13.2	13.5	13.8
AGE CATEGORIZATION 1 (%)						
< 65	43 (52.4)	34 (64.2)	67 (61.5)	31 (53.4)	195 (58.2)	90 (58.8)
>= 65	39 (47.6)	19 (35.8)	42 (38.5)	27 (46.6)	140 (41.8)	63 (41.2)
AGE CATEGORIZATION 2 (%)						
< 18	0	0	0	0	0	0
>= 18 AND < 65	43 (52.4)	34 (64.2)	67 (61.5)	31 (53.4)	195 (58.2)	90 (58.8)
>= 65 AND < 75	24 (29.3)	14 (26.4)	29 (26.6)	20 (34.5)	87 (26.0)	43 (28.1)
>= 75 AND < 85	13 (15.9)	3 (5.7)	12 (11.0)	7 (12.1)	52 (15.5)	20 (13.1)
>= 85	2 (2.4)	2 (3.8)	1 (0.9)	0	1 (0.3)	0
SEX (%)						
MALE	49 (59.8)	26 (49.1)	56 (51.4)	41 (70.7)	217 (64.8)	94 (61.4)
FEMALE	33 (40.2)	27 (50.9)	53 (48.6)	17 (29.3)	118 (35.2)	59 (38.6)
REGION (%)						
US AND CANADA	6 (7.3)	4 (7.5)	14 (12.8)	9 (15.5)	77 (23.0)	33 (21.6)
WESTERN EUROPE	51 (62.2)	34 (64.2)	60 (55.0)	39 (67.2)	192 (57.3)	87 (56.9)
EASTERN EUROPE	22 (26.8)	15 (28.3)	27 (24.8)	6 (10.3)	9 (2.7)	7 (4.6)
AUSTRALIA	3 (3.7)	0	8 (7.3)	4 (6.9)	57 (17.0)	26 (17.0)

Source: Table S.3.2.1bio

Table 26 Baseline disease characteristics summary by PD-L1 status at baseline, 1% cutoff- All randomized patients (DCO 21-Feb-2023)

	PD-L1 < 1%		PD-L1 >= 1%		PD-L1 Indeterminate/ Not Reported/ Not Evaluable	
	Nivolumab 480 mg Q4W N = 82	Placebo Q4W N = 53	Nivolumab 480 mg Q4W N = 109	Placebo Q4W N = 58	Nivolumab 480 mg Q4W N = 335	Placebo Q4W N = 153
BASELINE ECOG PS						
0	72 (87.8)	49 (92.5)	101 (92.7)	57 (98.3)	322 (96.1)	139 (90.8)
1	10 (12.2)	4 (7.5)	8 (7.3)	1 (1.7)	13 (3.9)	14 (9.2)
BASELINE LDH I						
<= ULN	74 (90.2)	46 (86.8)	97 (89.0)	48 (82.8)	299 (89.3)	138 (90.2)
> ULN	8 (9.8)	6 (11.3)	11 (10.1)	6 (10.3)	31 (9.3)	13 (8.5)
NOT REPORTED	0	1 (1.9)	1 (0.9)	4 (6.9)	5 (1.5)	2 (1.3)
BASELINE LDH II						
<= 2*ULN	82 (100.0)	52 (98.1)	108 (99.1)	54 (93.1)	330 (98.5)	151 (98.7)
> 2*ULN	0	0	0	0	0	0
NOT REPORTED	0	1 (1.9)	1 (0.9)	4 (6.9)	5 (1.5)	2 (1.3)
WEIGHT (KG)						
N	82	53	109	58	334	153
MEAN	81.17	85.56	82.39	86.93	85.54	85.07
MEDIAN	78.25	84.80	80.00	83.70	83.15	83.00
MIN - MAX	51.1 - 132.0	50.0 - 123.0	44.7 - 143.1	47.1 - 136.0	43.0 - 162.7	47.5 - 187.7
Q1 - Q3	70.00 - 90.00	73.00 - 97.00	70.00 - 92.10	74.00 - 98.60	72.10 - 98.00	71.00 - 94.50
SD	16.36	18.45	18.60	19.15	19.51	20.80
TIME FROM WIDE LOCAL EXCISION SURGERY TO RANDOMIZATION (WEEKS)						
N	82	53	109	58	334	153
MEAN	11.08	10.96	11.09	10.33	9.92	9.89
MEDIAN	10.86	10.71	10.71	10.07	9.86	10.14
MIN - MAX	1.3 - 23.4	4.1 - 22.9	3.9 - 29.9	3.6 - 20.4	2.3 - 34.0	3.7 - 28.9
Q1 - Q3	9.14 - 12.00	8.29 - 13.43	8.86 - 12.00	7.71 - 12.00	7.86 - 11.57	8.00 - 11.57
SD	3.83	4.07	4.22	3.75	3.37	3.28
< 3	1 (1.2)	0	0	0	2 (0.6)	0
3 - < 6	3 (3.7)	4 (7.5)	6 (5.5)	6 (10.3)	26 (7.8)	17 (11.1)
6 - < 9	16 (19.5)	14 (26.4)	22 (20.2)	16 (27.6)	103 (30.7)	39 (25.5)
9 - < 12	38 (46.3)	19 (35.8)	53 (48.6)	21 (36.2)	143 (42.7)	74 (48.4)
12 - < 15	12 (14.6)	7 (13.2)	15 (13.8)	9 (15.5)	43 (12.8)	18 (11.8)
15 - < 18	6 (7.3)	5 (9.4)	4 (3.7)	1 (1.7)	7 (2.1)	1 (0.7)
18 - < 21	5 (6.1)	3 (5.7)	6 (5.5)	5 (8.6)	5 (1.5)	1 (0.7)
>= 21	1 (1.2)	1 (1.9)	3 (2.8)	0	5 (1.5)	3 (2.0)
NOT REPORTED	0	0	0	0	1 (0.3)	0
TIME FROM SENTINEL LYMPHADENECTOMY SURGERY TO RANDOMIZATION (WEEKS)						
N	82	53	109	58	335	152
MEAN	9.59	9.09	9.50	8.91	9.40	9.15
MEDIAN	10.00	8.71	9.71	9.14	9.71	9.14
MIN - MAX	4.3 - 13.1	4.1 - 15.1	3.9 - 16.6	3.0 - 14.0	2.9 - 18.7	0.4 - 22.0
Q1 - Q3	7.71 - 11.57	7.29 - 11.00	7.86 - 11.57	6.86 - 10.86	7.71 - 11.29	7.57 - 11.00
SD	2.26	2.48	2.40	2.48	2.37	2.55
< 3	0	0	0	0	1 (0.3)	1 (0.7)
3 - < 6	6 (7.3)	4 (7.5)	8 (7.3)	7 (12.1)	26 (7.8)	17 (11.1)
6 - < 9	21 (25.6)	23 (43.4)	34 (31.2)	20 (34.5)	116 (34.6)	51 (33.3)
9 - < 12	41 (50.0)	22 (41.5)	55 (50.5)	25 (43.1)	148 (44.2)	71 (46.4)
12 - < 15	14 (17.1)	3 (5.7)	10 (9.2)	6 (10.3)	41 (12.2)	11 (7.2)
15 - < 18	0	1 (1.9)	2 (1.8)	0	2 (0.6)	0
18 - < 21	0	0	0	0	1 (0.3)	0
>= 21	0	0	0	0	0	1 (0.7)
NOT REPORTED	0	0	0	0	0	1 (0.7)
DISEASE STAGE AT STUDY ENTRY (PER CRF)						
STAGE IIB	50 (61.0)	30 (56.6)	59 (54.1)	32 (55.2)	207 (61.8)	100 (65.4)
STAGE IIC	32 (39.0)	23 (43.4)	50 (45.9)	26 (44.8)	128 (38.2)	53 (34.6)
STAGE OTHER	0	0	0	0	0	0
STAGE UNKNOWN	0	0	0	0	0	0
T STAGE AT STUDY ENTRY (PER CRF)						
STAGE II PATIENTS	82 (100.0)	53 (100.0)	109 (100.0)	58 (100.0)	335 (100.0)	153 (100.0)
T3B	30 (36.6)	22 (41.5)	46 (42.2)	26 (44.8)	128 (38.2)	56 (36.6)
T4A	20 (24.4)	8 (15.1)	13 (11.9)	6 (10.3)	79 (23.6)	44 (28.8)
T4B	32 (39.0)	23 (43.4)	50 (45.9)	26 (44.8)	128 (38.2)	53 (34.6)
MELANOMA SUB-TYPE						
SUPERFICIAL SPREADING MELANOMA	21 (25.6)	13 (24.5)	32 (29.4)	12 (20.7)	98 (29.3)	57 (37.3)
NODULAR MELANOMA	46 (56.1)	30 (56.6)	64 (58.7)	39 (67.2)	156 (46.6)	64 (41.8)
LENTIGO MALIGNA	4 (4.9)	0	3 (2.8)	0	6 (1.8)	3 (2.0)
ACRAL LENTIGINOUS MELANOMA	2 (2.4)	6 (11.3)	3 (2.8)	0	23 (6.9)	9 (5.9)
DESMOPLASTIC MELANOMA	2 (2.4)	0	0	0	19 (5.7)	8 (5.2)
OTHER	5 (6.1)	4 (7.5)	7 (6.4)	6 (10.3)	32 (9.6)	12 (7.8)
NOT REPORTED	2 (2.4)	0	0	1 (1.7)	1 (0.3)	0
LOCATION OF PRIMARY MELANOMA						
HEAD AND NECK	18 (22.0)	13 (24.5)	16 (14.7)	15 (25.9)	74 (22.1)	30 (19.6)
ARM	13 (15.9)	7 (13.2)	19 (17.4)	12 (20.7)	77 (23.0)	39 (25.5)
LEG	21 (25.6)	16 (30.2)	26 (23.9)	8 (13.8)	69 (20.6)	35 (22.9)
TRUNK	30 (36.6)	17 (32.1)	48 (44.0)	23 (39.7)	115 (34.3)	49 (32.0)

Source: Table S.3.2.7bio

Summary of main study(ies)

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

Table 27 **Summary of Efficacy for trial CA20976K**

Title: A Phase 3, Randomized, Double-Blind Study of Adjuvant Immunotherapy with Nivolumab versus Placebo after Complete Resection of Stage IIB/C Melanoma			
Study identifier	CA20976K		
Design	Randomized, double blind		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28-Oct-2019 – 28-Jun-2022 (clinical data cut-off) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Nivolumab		Adults and adolescents ≥40 kg: 480 mg IV Q4W, 12 months, n=526 Adolescents <40 kg: 6 mg/kg IV Q4W up to 240 mg, 12 months, n=0
	Placebo		Adults and adolescents ≥40 kg: IV infusion Q4W, 12 months, n=264 Adolescents <40 kg: IV infusion Q4W, 12 months, n=0
Endpoints and definitions	Primary endpoint	RFS	Time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death (due to any cause), whichever occurred first
	Secondary endpoint	OS	Time between the date of randomization and the date of death, from any cause
Database lock	17-Aug-2022		

Results and Analysis			
Analysis description	**Primary Analysis (interim analysis of RFS)**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Nivolumab	Placebo
	Number of subject	526	264
	RFS (n events, %)	66 (12.5)	69 (26.1)
	Median Months (95% CI)	NR (28.52, NR)	NR (21.62, NR)
Effect estimate per comparison	Primary endpoint RFS	Comparison groups	Nivolumab vs Placebo
		HR	0.42
		95% CI	0.30, 0.59
		P-value	<0.0001
Notes	DMFS: Distant metastasis free survival; OS: Overall survival; RFS: Recurrence free survival. Median follow-up approximately 16 months and minimal follow-up of 8 months. No OS analysis planned due to immaturity data		

Clinical studies in special populations

Paediatric population

The currently applied for extension of the indication includes adolescents aged 12 years and older. Another procedure to extent the indication of nivolumab for treatment of adolescent patients aged 12 years and older with advanced (unresectable or metastatic) melanoma (nivolumab as monotherapy or in combination with ipilimumab) and adjuvant treatment of melanoma (nivolumab monotherapy) has been recently finalised (EMEA/H/C/003985/II/0125/G). No adolescents were included in study CA20976K which is the pivotal clinical study to support the current extension of the indication.

The applied for indication for adolescents is based on extrapolation of efficacy from adults to adolescents. The MAH justifies the extrapolation based on similarity of disease, understanding of adolescent PK and E R safety, and predicted similar E-R efficacy based on expected similar pharmacology of drug effect (see also section 2.1.1.).

Similarity of melanoma between adults and adolescents:

- The frequency of histological subtypes in adolescent melanoma, as well as the biology, is comparable to melanoma in adults.
- Phenotypic traits that are associated with an increased risk of melanoma are similar in adults and adolescents with melanoma. The staging system for paediatric and adult melanoma is the same.
- The treatment of childhood and adolescent melanoma is based on the same principles as for adult patients including surgical excision, immune checkpoint inhibitors or BRAF/MEK inhibitors.
- As in adults, survival is correlated with the disease stage at diagnosis and overall survival (OS) is similar between the two age groups.

By adult melanoma studies, biomarkers that are associated with patient treatment responses on CPI have been identified, those include tumour mutation burden (TMB), expression of PD-L1, and CD8 T-cell infiltration into tumours. Despite these activity in adult melanoma patients, predictions of patient responses with high confidence is, according to the MAH, not yet possible. Further efforts are ongoing to understand the biology and biomarkers that predict response in adults with high probability. The very small number of adolescents with melanoma, if any, included in clinical trials with check point inhibitors (CPIs) makes it extremely difficult to evaluate predictive biomarkers accurately.

A literature review of relative TMB levels in adolescents and non-adolescent melanoma patients was provided (data not shown). In the review it is stated that a positive association of TMB, a surrogate measure for immunogenic tumour neoantigens arising from UV-irradiation and other genetic instabilities, is associated with adult cutaneous melanoma patient CPI treatment response. In total seven publications were discussed by the MAH.

Although some studies have shown that the presence of somatic mutations in BRAF and PTEN were higher in the group of adolescents and young adults (15-30 years old) in comparison with older adults, overall findings across studies found that conventional melanomas in the adolescent-young adults (AYA) patients had a generally similar profile of genetic changes as those of older adults, including UV-induced SNVs, TMB, CNAs, structural variations and oncogene activating mutations. Genomic profiling of other melanoma tumours found in younger patients, included Spitz melanoma (SM), atypical Spitz tumours (ATS), were all found to have some features of CMs, albeit a unique subset of features for

each type and variations in prevalence by study. None had the high level of somatic mutations (TMB) of CM.

The study of van der Kooij et al., found similar profiles of treatment outcomes for CPI or BRAF/MEK inhibitor therapies for both AYA and older adult advanced melanoma patients from The Dutch Melanoma Treatment Registry (van der Kooij et al. Cancers [Basel]. 2020).

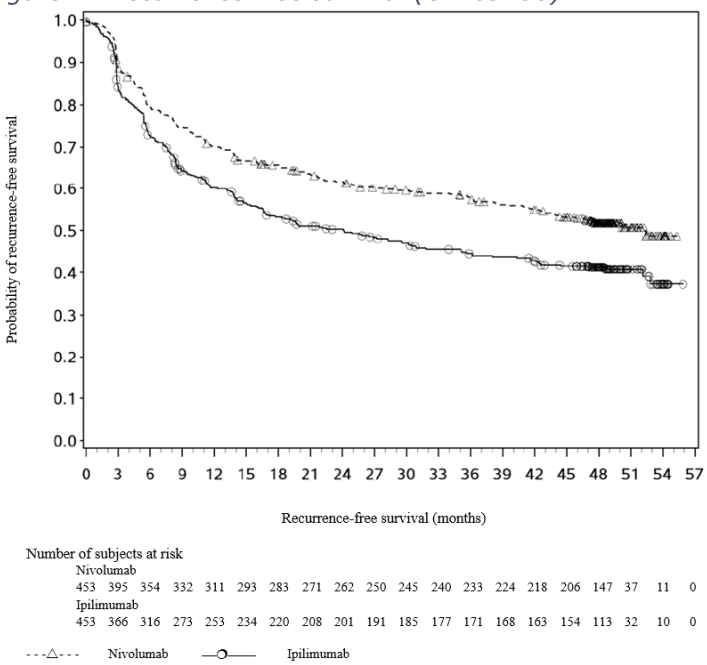
Supportive study

As supportive study the MAH presented Study CA209238,a randomized, double-blind, Phase 3 study investigating adjuvant therapy with nivolumab 3mg/kg versus ipilimimab 10 mg/kg after complete resection of high-risk Stage IIIB/C or IV melanoma (AJCC 7th ed). Patients were enrolled regardless of their PD-L1 status. Randomisation was stratified by tumour PD L1 expression (≥ 5% vs. < 5%/indeterminate), and stage of disease per the AJCC staging system (Stage IIIB/C vs Stage IV M1a-M1b vs Stage IV M1c). The majority of patients had AJCC Stage III disease (81%).

At a primary pre-specified interim analysis (minimum follow up 18 months) a statistically significant improvement in RFS with nivolumab compared to ipilimumab with HR of 0.65 (97.56% CI: 0.51, 0.83; stratified log-rank p<0.0001) was demonstrated (Figure 17). Results from 48-month RFS and DMFS analyses were consistent with analyses at 12, 24, and 36 months. Nivolumab showed improvements in RFS and DMFS rates by 10.5% and 5.9%, respectively at 48-months compared to ipilimumab, (HRs: 0.71, 95% CI [0.60, 0.86] and HR: 0.79, 95% CI [0.63, 0.99], respectively). OS rates at 48 months were high in both groups (78% and 77%), with no significant difference observed between the two groups (HR 0.87, 95% CI 0.66-1.14).

RFS benefit was consistently demonstrated across subgroups, including tumour PD L1-expression, BRAF status, and stage of disease (data not shown).

Figure 17 Recurrence-free survival (CA209238)



Quality of life (QoL) with nivolumab remained stable and close to baseline values during treatment, as assessed by valid and reliable scales like the European Organization for Research and Treatment of Cancer (EORTC) QLQ C30 and the EQ 5D utility index and VAS.

2.4.3. Discussion on clinical efficacy

The MAH is seeking an extension of indication to include:

"OPDIVO as monotherapy is indicated for the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma who have undergone complete resection."

The application is based on results from the pivotal study CA20976K. Inclusion of the adolescent indication is based on extrapolation of efficacy from adults to adolescents.

Design and conduct of clinical studies

Study CA20976K is a phase III, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus placebo after complete resection of stage IIB/C melanoma (NCT04099251). Within Part I, subjects with resected Stage IIB/C melanoma and no evidence of disease were randomized 2:1 to treatment with either nivolumab or placebo for a duration of 12 months. In the event of disease recurrence, subjects had the option to receive on-study open-label nivolumab treatment or receive treatment per local standard of care (Part 2). Only results from Part 1 were presented in the current submission.

Target population: The study enrolled subjects with Stage IIB and IIC cutaneous melanoma based on the eighth edition of the AJCC melanoma staging system. Eligible patients had tumour category T3b, T4a, or T4b, with no regional nodal metastases (N0) confirmed by a negative sentinel lymph node biopsy and no evidence of distant metastasis (M0). Prior systemic therapy for Stage II melanoma was not allowed, except prior adjuvant treatment with interferon if completed ≥ 6 months prior to randomization. All patients had an ECOG PS of 0 or 1. Overall, the eligibility criteria adequately define the target population, with the general remark that the clinical trial population is relatively fit compared with the patient population treated in clinical practice.

Comparator: Randomization to nivolumab or placebo (2:1) was stratified by AJCC tumour category (T3b vs. T4a vs. T4b) which is agreed upon given the prognostic value. The choice of the comparator (placebo) is acceptable, as observation with periodic surveillance to detect disease recurrence was generally recommended at the time of the start of the study. Adjuvant treatment with pembrolizumab has been approved by the CHMP (June 2022; Keytruda II/111 EPAR).

PD-L1 was not included as a stratification factor based on expected tissue limitations in this early-stage patient population at the time of study design and the lack of predictive benefit of PD-L1 expression observed in resected Stage III melanoma. Exploratory analyses were planned between PD-L1 expression and RFS for the subset of patients with tumour specimens available for retrospective analysis (different tumour cell PD-L1 cut-offs (i.e., 1% and 5%) and PD-L1 as a continuous variable). However, uncertainties remained on the beneficial effect of adjuvant treatment in patients with PD-L1 expression <1% in patients with stage III/IV Melanoma (study CA209238, Opdivo II/41 EPAR). Furthermore, the CHMP concluded that the role of PD-L1 expression and/or other biomarkers on efficacy remains to be elucidated and the MAH has been encouraged to further include prospective biomarker studies in melanoma subjects (EMEA/H/C/3985/ANX/030).

Treatment: Adult patients received 480 mg every 4 weeks over 30 minutes up till 12 months. This is in line with the approved dose and treatment duration for nivolumab for adjuvant stage IIIC/IV

melanoma. A 60 minutes infusion time is proposed by the MAH in line with the infusion rate for adjuvant treatment of stage II/IV melanoma. The MAH also included an additional 30-miutes infusion time as used in the pivotal trial (see SmPC). The treatment duration is similar to that of Keytruda approved in the same setting. Whether the optimal treatment duration could be shorter than currently proposed is unknown as no data are available.

Tumour assessments were conducted every 26 weeks during years 1-3 and every 52 weeks from 3 years to 5 years. This is at a similar frequency as in the pivotal study for Keytruda (Keytruda II/111 EPAR). Tumour assessment was performed by the investigator and central blinded independent central review (BICR) was not mandatory. This may be acceptable in the context of a blinded trial, although true blinding may be questioned given the known side effects of nivolumab and placebo being the comparator. The MAH confirmed that no scans were assessed by a BICR committee. Given that immune-related adverse events were also reported in the placebo arm, though at lower frequencies, the risk of unblinding may be limited. In addition, given the observed strength of the effect, it is considered unlikely that potential misclassification of recurrences would have altered the conclusion of the trial. Though acceptable, the rather long, 26-week interval between scans entails that maturation of the RFS KM-curves may take long (e.g., all patients with follow-up between 6 months and 12 months are currently censored at 6 months).

Clinical endpoints: The primary endpoint investigator-assessed RFS can be considered acceptable for the adjuvant setting, provided data are of sufficient maturity and supported by additional endpoints enabling a sound conclusion on efficacy and a proper evaluation of the benefit of early (adjuvant) versus late treatment (at recurrence). This has been previously accepted for Keytruda in the same setting (Keytruda II/111 EPAR). Main secondary endpoints were OS (alpha-controlled) and DMFS (descriptive). An interim OS analysis is only expected to occur 8 years after the first patient was treated and no OS data were currently provided. As the ultimate goal of adjuvant treatment is cure and OS data are needed to better understand whether adjuvant nivolumab increases OS or only delays the progression of disease, these data are considered key to the benefit-risk. The MAH committed to submit interim OS results for study CA20976K with a current estimated timeline of 1Q 2029 for submission (as an Annex II condition to the marketing authorisation). An impact analysis of Part 2 on OS and any other time-dependent endpoints is expected at the time these data become available, taking into account available guidance (https://www.ema.europa.eu/en/documents/scientific-guideline/question-answer-adjustment-cross-over-estimating-effects-oncology-trials_en.pd). DMFS is considered supportive for RFS and may be considered a more clinically relevant representative for long-term benefit, as melanoma is generally considered to be incurable when distant metastasis is present. PFS2 may also provide some information on the long-term benefit in the absence of OS data. Overall, the primary and secondary endpoints are considered established in the adjuvant setting and thus acceptable.

Statistical methods: For the primary analysis (RFS), two intercurrent events are identified ('new anticancer therapy […]' and 'second non-melanoma primary cancer […]'), and subjects are censored at the last assessment date prior to their occurrence. A treatment policy strategy for the intercurrent events was included as a sensitivity analysis in line with the EMA guideline (Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (europa.eu). In addition, the selected strategy to handle missing data due to missed disease assessments, i.e. censoring at baseline, may introduce a bias in the effect estimates. This is further discussed with the results.

The primary analysis for the time-to-event RFS outcome is a log-rank test and Cox proportional hazards model, both stratified by AJCC tumour category (corresponding to the randomization procedure), which is acceptable. The currently presented interim analysis of RFS was planned when approximately 123 RFS events (80% information fraction) had been reached among all randomized

subjects. The statistical methods are considered overall adequate. However, interim analyses on PFS-like endpoints are not recommended (EMA/CHMP/27994/2008/Rev.1).

Baseline characteristics

A total of 986 subjects were enrolled, 790 were randomized, and 788 were treated: 524 with nivolumab and 264 with placebo. Baseline characteristics were generally balanced between the two groups. The median age was 62 years (range 19 to 92), 61% were men, and 98% were white. About 14% of patients were ≥75 years of age, whereas no adolescents were included in the study. Baseline ECOG PS score was 0 (94%) or 1 (6%). Sixty percent had stage IIB and 40% had stage IIC disease, 39% of patients had tumour category T3b or T4b, and 21% had T4a. PD-L1 expression data were evaluable for 189 (35.9%) patients in the nivolumab arm and 111 (42.0%) patients in the placebo arm. BRAF mutation status was available for 658 (83.3%) patients, 429 patients had BRAF Wild Type.

In general, the conduct of the study does not seem to raise any serious concerns which could have introduced any important biases in the analyses of the primary efficacy parameters. Important protocol deviations were balanced between treatment groups and were mostly in the category of trial procedures.

Adolescents

No adolescents were included in the pivotal study. The applied for indication for adolescents is based on extrapolation of efficacy from adults to adolescents. The MAH justifies the extrapolation based on similarity of disease, understanding of adolescent PK and E-R safety, and predicted similar E-R efficacy based on expected similar pharmacology of drug effect. Extrapolation of adult efficacy data, is already accepted for several products intended for the treatment of advanced melanoma and for the treatment of melanoma in the adjuvant setting (Yervoy II/44 EPAR; Opdualag MAA EPAR; Keytruda II/0111 EPAR).

Efficacy data and additional analyses

At the time of DCO (28 June 2022) for the planned interim RFS analysis, the median duration of treatment was 11 months. Median follow-up time was approximately 16 months and minimum follow-up time was 8 months. Approximately 50% and 60% of patients completed treatment in the nivolumab and placebo arm, respectively, whereas 12-15% of patients are ongoing on treatment. More patients discontinued nivolumab compared to placebo (38.7% vs. 25.4%), and mostly due to study drug toxicity (17.9% nivolumab vs. 2.7% placebo) as expected. Minimum follow-up is much shorter than the anticipated minimum follow-up of approximately 24 months for the IA of RFS, limiting the conclusions that can be drawn from these data.

Primary endpoint – Recurrence-Free survival

The study met its primary endpoint as a statistically significant improvement in RFS for patients randomised to the nivolumab arm compared with placebo was observed at the time of the RFS IA: HR 0.42 (95% CI: 0.30, 0.59; log-rank p-value < 0.0001). RFS rates were higher in the nivolumab arm than in the placebo arm at 6 months (97.6% vs 93.5%), and at 12 months (92.3% vs 86.7%). Both regional and distant metastases occurred less frequently with nivolumab. However, follow-up time was too limited and no conclusions could be drawn on the (long-term) clinical benefit in the target population. Upon request, the MAH presented updated efficacy analyses based on a DCO of 21 February2023, resulting in a median follow-up of approximately 24 months and a minimum follow-up of 15.6 months. The results with longer follow-up support the initial efficacy analysis with a HR of 0.53

(95% CI: 0.40-0.71) based on an event rate of 19.4% vs. 31.8% in the nivolumab and placebo arm, respectively. RFS rates were 88.8% in the nivolumab arm and 81.1% in the placebo arm at 12 months of follow-up. Corresponding RFS rates at 18 months were 83.9% in the nivolumab arm and 70.7% in the placebo arm. Results in subgroups were in general consistent with the ITT, with all RFS HR point estimates <1. The RFS rates and median follow-up resemble that available at the time of approval of Keytruda in the same indication (IA3 RFS rates of 19.5% for Keytruda vs 28.5% for placebo at IA3 with a median follow-up 26.9 months; Keytruda II/111 EPAR). Due to the long interval between imaging assessments (6 months), the impact of the limited follow-up is aggravated resulting in censoring focused on 6, 12, 18, etc months. Also, separation of the curves seems only to occur (as anticipated by the MAH) after 6 months and separation thereafter is uncertain due to the censoring in both treatment arms. With longer follow-up, there were no indications of imbalances in reasons for censoring over time. Most patients were censored on the date of their last tumour assessment and remained in the study. Few patients were censored due to "off study" at 6 and 12 months which could have been potential informative censoring. However, given the low numbers this is not likely to impact the obtained results. With the updated results, the RFS events (186) exceed the number of 154 events planned for the final RFS analysis. Overall, updated results on event and censoring rates support the benefit in terms of RFS observed at the IA RFS analysis. The current data allow a robust estimation of the KM-curves up till 12 months, data thereafter are uncertain given the high censoring rates. Updated results with a median follow-up of 36 months could provide robust data up till around 27 months. These are considered of relevance as current data do not allow a conclusion on a potential plateau around 36 months of follow-up. Plus, OS data will only become available in the long term. These updated results with a median follow-up of 36 months can be provided post-marketing and the applicant already committed to provide these data with an estimated timeline of 4Q 2024 as a recommendation (REC).

Sensitivity analyses, including the analysis in which a treatment policy strategy was employed for the intercurrent events ('new anticancer therapy […]' and 'second non-melanoma primary cancer […]'), supported the primary RFS analysis, although their relevance is limited by the limited number of events observed. Relatively few subjects (14 out of 526 and 3 out of 264) have been censored at baseline due to missing disease assessments, which, in light of the observed difference in the KM curves, is not expected to alter the conclusions regarding the primary analysis.

Subgroup analyses in pre-specified subgroups showed similar effects for adjuvant nivolumab as seen for the ITT population, including the subgroups according to disease stage and tumour category. PD L1 subgroup analyses were presented separately and performed in a subset of patients only. There were some imbalances in baseline characteristics with more patients from Eastern Europe, more nodular disease and less T4a tumours in patients with available PD-L1 data versus the ITT. Event rates were low and no HR could be obtained in patients with high PD-L1 expression (≥1% or ≥5%), hampering the interpretation of the results. For patients with low PD-L1 expression (<1% or < 5%), point estimates of HR were below one although higher than for the ITT (PD-L1<1%: HR=0.71 vs ITT: HR=0.43), however the 95% CIs overlap considerably. Given the low event rate and the exploratory comparisons, results are difficult to interpret. No restrictions with regard to PD-L1 expression were made in the adjuvant stage III/IV setting despite some concerns on the benefit in patients with low PD-L1 expression (Opdivo II/41 EPAR), and uncertainty remains on PD-L1 as a predictive marker. An update of RFS per PD-L1 expression subgroup based on the DCO 21-Feb-2023 was provided. Point estimates of the HR in both subgroups were below 1, which was reassuring. The RFS rate at 12 months in the PD-L1 expression ≥ 1% subgroup was numerically higher in the nivolumab arm compared to the placebo arm, 93.3% vs 77.0% (HR: 0.43; 95% CI: 0.22, 0.84) supporting a beneficial effect. On the other hand, the RFS rate at 12 months in the PD-L1 expression < 1% subgroup was numerically lower for nivolumab compared to placebo, 79.5% vs 84.1% (HR: 0.82; 95% CI: 0.44, 1.54). KM curves

show no beneficial effect of nivolumab over placebo up till 24 months in the PD-L1 expression <1% subgroup, thereafter curves separate in favor of nivolumab but censoring rates are high. A clear separation of KM curves in favor of nivolumab is shown in the PD-L1 ≥1% subgroup, whereas the KM curve in subjects with indeterminate/not reported/not evaluable PD-L1 at baseline resemble that of the ITT as may be expected. Overall, uncertainty remains on a beneficial effect in the PD-L1 <1% subgroup. However, given the low event rate, non-stratified comparisons and data available for only a subset of the ITT (<40%) no firm conclusions can be drawn. Updated results are expected with the 36 month update (REC).

Secondary endpoints

An improvement in **distant metastasis-free survival** (DMFS) was seen with adjuvant nivolumab compared to placebo (HR = 0.47 [95% CI: 0.30, 0.72]) and DMFS rates were numerically higher (92.3% vs. 86.7% at 12 months). Although the results for DMFS are not part of the formal testing procedure, it is considered unlikely that these results constitute a chance finding due to the consistency with the results of the primary analysis, the clear separation of the KM curves, the estimate of the HR, and the result of the log-rank test. The results were confirmed with longer follow-up with 13.1% and 19.3% of events in the nivolumab vs the placebo arm (HR: 0.62, 95% CI: 0.43, 0.89), DMFS rates were 92.0% and 88.5% at 12 months, respectively. The results of all DMFS sensitivity analyses were consistent with the DMFS primary analysis (data not shown).

Progression on next line treatment can provide some information on the likelihood for sustained clinical benefit for patients with recurrence after adjuvant melanoma. More patients with recurrence in the nivolumab arm received radiation therapy and surgery compared to the placebo arm where patients in the placebo arm more often received systemic treatment and especially anti-PD-(L)1 therapy, as may be expected. Duration of treatment on next-line systemic cancer treatment was lower for nivolumab compared to placebo, which may be explained by the differences in type of subsequent therapy. Relatively few PFS2 events were currently observed, the HR numerically favoured nivolumab over placebo (HR: 0.68, 95% CI: 0.36, 1.27). Comparable results were observed with longer follow-up in favour of nivolumab (HR: 0.63; 95% CI: 0.40, 1.01), however event rates were still limited (7.6% and 11.7% in the nivolumab and placebo arm, respectively).

The results from the **exploratory endpoints freedom from relapse and treatment-free interval** are in line with the other efficacy data showing a beneficial effect of adjuvant nivolumab treatment (data not shown).

Exploratory analyses of quality of life using the questionnaires EORTC QLQ-C30 and EQ-5D showed a trend for a reduction in mean change score from baseline over time in both treatment arms and numerically somewhat larger for the nivolumab arm. Nevertheless, CIs largely overlap and the MID was not reached at any time for either treatment group. PRO's from blinded trials may be considered for inclusion in the SmPC, provided they are pre-specified in the statistical analysis plan, unbiased and reliable, and type 1 error controlled. Even though CA209076K was a double-blind study, blinding may be questioned given the known side effects of nivolumab and placebo being the comparator. Therefore, it is uncertain whether the QoL results were truly unbiased and reliable. Moreover, the QoL results were not type 1 error controlled. As a result, the above QoL data do not qualify for inclusion in section 5.1. of the SmPC.

Supportive study

Study CA209238 was the registrational study for the adjuvant treatment of nivolumab vs ipilimumab after complete resection of high-risk Stage IIIB/C or IV melanoma (AJCC 7th ed). A pre-specified interim analysis (minimum follow-up 18 months) showed a statistically significant improvement in RFS that was confirmed with longer follow-up time up to 48 months and supported by DMFS. No effect was

seen on OS. These data underline the immaturity of the current data with a minimum follow-up of only 8 months in an earlier setting. It is reassuring that no "rebound" effect for nivolumab was seen in the later stage setting after the adjuvant treatment-phase. Whether this applies to the earlier setting needs to be seen based on longer follow-up time.

Assessment of paediatric data on clinical efficacy

No adolescents were included in study CA20976K, therefore efficacy of Opdivo as adjuvant treatment in adolescents needs to be supported by full extrapolation of efficacy data from the adult population to the adolescent population. Recently, the indication of nivolumab was extended for treatment of adolescent patients aged 12 years and older with advanced (unresectable or metastatic) melanoma (nivolumab as monotherapy or in combination with ipilimumab) and adjuvant treatment of melanoma (nivolumab monotherapy) (EMEA/H/C/003985/II/0125/G).

The extrapolation of the efficacy of nivolumab treatment to the adolescent part of the applied-for target population is considered acceptable.

2.4.4. Conclusions on the clinical efficacy

In study CA20976K, adjuvant treatment with nivolumab showed a statistically significant effect on recurrence-free survival compared to placebo in the target population. Results were supported by a numerical reduction in distant metastases. With the updated results with a median follow-up of approximately 24 months, the current data are considered sufficient to conclude on a beneficial effect on RFS. Moreover, it is considered likely that the obtained results translate into a long-term beneficial effect of adjuvant nivolumab. Some uncertainty exists on the RFS KM-curves beyond 12 months though, due to the censoring rate. Therefore, further long-term efficacy data should be provided post-approval, including OS data. As the ultimate goal of adjuvant treatment is cure, OS data are needed to better understand whether adjuvant nivolumab increases OS or only delays the progression of disease, these data are considered key to the benefit/risk. The OS analysis was not available during this procedure and is included as an Annex II condition.

Therefore, the MAH will provide the following results from study CA20976K post-marketing:

- 4Q 2024 - Updated RFS analysis including subgroup analysis as well as DMFS (REC)
- 1Q 2029 – Interim OS analysis (Annex II.D)

The proposed bridging strategy in support of a paediatric indication is considered acceptable.

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

Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma, the MAH should submit the OS data from the first interim OS analysis of the Phase III study CA20976K (1Q 2029).

2.5. Clinical safety

Introduction

Safety data from the pivotal Phase 3 Study CA20976K was submitted to support the use of nivolumab as monotherapy in the adjuvant setting of Stage IIb/C melanoma following complete resection. The safety data from study CA20976K included 524 patients that were treated with nivolumab. The safety results of Study CA20976K were compared with pooled safety data (n=4646 treated patients) of all studies conducted in different tumour types with nivolumab monotherapy.

Patient exposure

Adult melanoma patients randomized to the nivolumab arm received 480 mg Q4W as a 30 min-infusion.

The planned dosing for adolescents 12 years of age and older weighing ≥40 kg was the same as the adult dose. The planned dose for adolescents (12 years of age and older and weighing < 40 kg) 6 mg/kg Q4W over 60 min. However, no adolescents were included in the study.

The planned treatment duration in the study was 12 months.

The median number of nivolumab doses received was 12 (range: 1 – 14) and the median number of placebo doses received was 13 (range: 1-14) (*Table 28*). The proportion of treated patients who received ≥ 90% of the planned nivolumab dose intensity was 89.7%.

The median duration of therapy was 11.04 months in the nivolumab arm and 11.07 months in the placebo arm (*Table 29*).

Table 28 Cumulative dose and relative Dose Intensity summary-blinded phase- all treated patients

	Nivolumab 480 mg Q4W N = 524	Placebo Q4W N = 264
NUMBER OF DOSES RECEIVED		
MEAN (SD)	10.3 (4.01)	11.5 (3.06)
MEDIAN (MIN - MAX)	12.0 (1 - 14)	13.0 (1 - 14)
CUMULATIVE DOSE (MG)		
MEAN (SD)	4919.0 (1924.41)	N.A.
MEDIAN (MIN - MAX)	5760.0 (480 - 6720)	N.A.
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	N.A.
90% TO < 110%	470 (89.7)	N.A.
70% TO < 90%	51 (9.7)	N.A.
50% TO < 70%	3 (0.6)	N.A.
< 50%	0	N.A.

Last dose date and start dose date are dose dates relative to study phase.
The following subjects received unknown dose(s): 129-963 in Cycle 10, 46-536 in Cycle 12,5-354 in Cycle 13, 77-662 in Cycle 14, 88-737 in Cycle 7, 94-758 in Cycle 14.
The following subjects received either 1 cycle of the wrong treatment (30-444 in cycle 2,138-671 in cycle 5) or site manually dispensed nivolumab from a different study but considered as Placebo in database(39-702, 58-696, 58-787)
or subject skipped one treatment cycle but considered as Placebo in database (7-708).
All above doses are not counted in dosing summary in the Nivolumab arm nor in the Placebo arm.

Source: Table S.4.1.1 in the CA20976K Primary CSR[2]

Table 29 Duration of study therapy summary- all treated patients

	Nivolumab 480 mg Q4W N = 524	Placebo Q4W N = 264
DURATION OF THERAPY (MONTHS)		
MEAN (MIN, MAX)	8.80 (0.0, 12.1)	9.89 (0.0, 12.7)
MEDIAN	11.04	11.07
> 3 MONTHS (%)	454 (86.6)	249 (94.3)
> 6 MONTHS (%)	406 (77.5)	233 (88.3)
> 9 MONTHS (%)	352 (67.2)	206 (78.0)
> 12 MONTHS (%)	17 (3.2)	10 (3.8)

Last dose date and start dose date are dose dates relative to study phase.
The following subjects received unknown dose(s): 129-963 in Cycle 10, 46-536 in Cycle 12, 5-354 in Cycle 13, 77-662 in Cycle 14, 88-737 in Cycle 7, 94-758 in Cycle 14.
All above doses are not counted in dosing summary in the Nivolumab arm nor in the Placebo arm.

Source: Table S.4.61.1 in the CA20976K Primary CSR[2]

Dose Modifications and Dose Delays

Of all treated patients in the blinded phase, the majority received all doses of study drug without dose delays, infusion interruptions, or infusion rate reductions.

Dose reductions were not permitted with nivolumab or placebo.

Dose delays of study drug (proportion of patients with at least 1 dose delay) were reported in 36.3% patients in the nivolumab arm and 33.3% patients in the placebo arm. The majority of dose delays lasted 4-7 days. The most common cause of dose delay in the nivolumab arm was 'adverse event'. 26 (5.0%) and 14 (5.3%) patients had at least one dose delayed due to COVID-19 in the nivolumab and placebo arms, respectively.

The most frequently reported drug-related AEs of any grade leading to dose delay were as follows:

- Nivolumab arm: diarrhea (1.7%), arthralgia (1.5%), ALT increased and blood CPK increased (1.3% each)
- Placebo arm: diarrhea (1.1%), ALT increased, blood CPK increased and AST increased (0.8% each)

For 6.7% of patients a nivolumab infusion interruption was reported. Of the patients who were reported with infusion interruption, the majority were reported with 1 interrupted infusion. Reasons for infusion interruption included hypersensitivity reaction and administration issues.

Infusion rate reductions were reported in 3.1% patients in the nivolumab arm. Reasons for infusion rate reductions included hypersensitivity reaction and administration issues.

Adverse events

Adverse Events (Regardless of Causality)

Any-grade AEs (regardless of causality) were reported in 502 (95.8%) patients in the nivolumab arm, and 229 (86.7%) patients in the placebo arm (Table 30).

Table 30 Summary of safety Results

Safety Parameters	No. of Subjects (%) Nivolumab 480 mg Q4W N = 524	Placebo Q4W N = 264
Deaths[a]	13 (2.5)	8 (3.0)
Primary Reason for Death		
Disease[a]	3 (0.6)	4 (1.5)
Study Drug Toxicity[b]	1 (0.2)	0
Unknown	1 (0.2)	1 (0.4)
Other[c]	8 (1.5)	3 (1.1)

	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	74 (14.1)	55 (10.5)	29 (11.0)	20 (7.6)
Drug-related SAEs	25 (4.8)	23 (4.4)	3 (1.1)	2 (0.8)

	Adverse Events Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality AEs leading to DC	91 (17.4)	37 (7.1)	9 (3.4)	2 (0.8)
Drug-Related AEs leading to DC	77 (14.7)	29 (5.5)	7 (2.7)	2 (0.8)
All-causality AEs	502 (95.8)	115 (21.9)	229 (86.7)	32 (12.1)
≥ 10% of Subjects in Any Treatment Arm				
Fatigue	137 (26.1)	1 (0.2)	66 (25.0)	1 (0.4)
Diarrhea	118 (22.5)	6 (1.1)	40 (15.2)	0
Pruritus	105 (20.0)	1 (0.2)	29 (11.0)	0
Arthralgia	86 (16.4)	2 (0.4)	30 (11.4)	1 (0.4)
Nausea	74 (14.1)	0	29 (11.0)	0
Rash	65 (12.4)	4 (0.8)	25 (9.5)	1 (0.4)
Headache	60 (11.5)	1 (0.2)	33 (12.5)	2 (0.8)
Hypothyroidism	60 (11.5)	0	0	0
Asthenia	59 (11.3)	1 (0.2)	25 (9.5)	0
Blood creatine phosphokinase increased	55 (10.5)	10 (1.9)	31 (11.7)	1 (0.4)
Drug-related AEs	433 (82.6)	54 (10.3)	142 (53.8)	6 (2.3)
≥ 10% of Subjects in Any Treatment Arm				
Fatigue	106 (20.2)	0	53 (20.1)	1 (0.4)
Pruritus	97 (18.5)	1 (0.2)	25 (9.5)	0
Diarrhea	80 (15.3)	4 (0.8)	25 (9.5)	0
Rash	57 (10.9)	4 (0.8)	18 (6.8)	0
Arthralgia	54 (10.3)	1 (0.2)	15 (5.7)	0
Hypothyroidism	54 (10.3)	0	0	0

All-causality Select AEs				
Endocrine	116 (22.1)	9 (1.7)	14 (5.3)	0
Gastrointestinal	122 (23.3)	8 (1.5)	41 (15.5)	0
Hepatic	86 (16.4)	18 (3.4)	35 (13.3)	3 (1.1)
Pulmonary	10 (1.9)	2 (0.4)	1 (0.4)	0
Renal	30 (5.7)	2 (0.4)	10 (3.8)	0
Skin	217 (41.4)	6 (1.1)	64 (24.2)	1 (0.4)
Hypersensitivity/Infusion Reactions	33 (6.3)	0	2 (0.8)	0

Drug-Related Select AEs				
Endocrine	108 (20.6)	9 (1.7)	13 (4.9)	0
Gastrointestinal	85 (16.2)	6 (1.1)	25 (9.5)	0
Hepatic	59 (11.3)	14 (2.7)	16 (6.1)	2 (0.8)
Pulmonary	7 (1.3)	1 (0.2)	1 (0.4)	0
Renal	9 (1.7)	2 (0.4)	0	0
Skin	181 (34.5)	6 (1.1)	47 (17.8)	0
Hypersensitivity/Infusion Reactions	31 (5.9)	0	2 (0.8)	0

Table 31 Adverse Events by Worst CTC Grade in ≥ 5% of All Treated Patients – Blinded Phase

System Organ Class n(%) Preferred Term n(%)	Nivolumab 480 mg Q4W N = 524		Placebo Q4W N = 264	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	502 (95.8)	115 (21.9)	229 (86.7)	32 (12.1)
Skin and subcutaneous tissue disorders	261 (49.8)	8 (1.5)	83 (31.4)	1 (0.4)
Pruritus	105 (20.0)	1 (0.2)	29 (11.0)	0
Rash	65 (12.4)	4 (0.8)	25 (9.5)	1 (0.4)
Rash maculo-papular	28 (5.3)	2 (0.4)	6 (2.3)	0
Gastrointestinal disorders	255 (48.7)	12 (2.3)	107 (40.5)	3 (1.1)
Diarrhea	118 (22.5)	6 (1.1)	40 (15.2)	0
Nausea	74 (14.1)	0	29 (11.0)	0
Constipation	45 (8.6)	0	16 (6.1)	0
Dry mouth	39 (7.4)	0	10 (3.8)	0
General disorders and administration site conditions	253 (48.3)	3 (0.6)	116 (43.9)	1 (0.4)
Fatigue	137 (26.1)	1 (0.2)	66 (25.0)	1 (0.4)
Asthenia	59 (11.3)	1 (0.2)	25 (9.5)	0
Pyrexia	33 (6.3)	0	9 (3.4)	0
Musculoskeletal and connective tissue disorders	190 (36.3)	8 (1.5)	81 (30.7)	3 (1.1)
Arthralgia	86 (16.4)	2 (0.4)	30 (11.4)	1 (0.4)
Myalgia	39 (7.4)	0	16 (6.1)	0
Back pain	26 (5.0)	0	18 (6.8)	0
Investigations	184 (35.1)	36 (6.9)	81 (30.7)	7 (2.7)
Blood creatine phosphokinase increased	55 (10.5)	10 (1.9)	31 (11.7)	1 (0.4)
Alanine aminotransferase increased	48 (9.2)	8 (1.5)	18 (6.8)	1 (0.4)
Aspartate aminotransferase increased	41 (7.8)	8 (1.5)	8 (3.0)	1 (0.4)
Infections and infestations	163 (31.1)	15 (2.9)	67 (25.4)	3 (1.1)
COVID-19	42 (8.0)	2 (0.4)	21 (8.0)	1 (0.4)
Metabolism and nutrition disorders	124 (23.7)	8 (1.5)	46 (17.4)	2 (0.8)
Decreased appetite	36 (6.9)	0	7 (2.7)	0
Nervous system disorders	121 (23.1)	11 (2.1)	61 (23.1)	3 (1.1)
Headache	60 (11.5)	1 (0.2)	33 (12.5)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	108 (20.6)	4 (0.8)	37 (14.0)	0
Cough	38 (7.3)	0	12 (4.5)	0

System Organ Class n(%) Preferred Term n(%)	Nivolumab 480 mg Q4W N = 524		Placebo Q4W N = 264	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Endocrine disorders	102 (19.5)	5 (1.0)	8 (3.0)	0
Hypothyroidism	60 (11.5)	0	0	0
Hyperthyroidism	38 (7.3)	1 (0.2)	3 (1.1)	0
Injury, poisoning and procedural complications	64 (12.2)	2 (0.4)	26 (9.8)	0
Infusion related reaction	28 (5.3)	0	2 (0.8)	0
Vascular disorders	51 (9.7)	11 (2.1)	31 (11.7)	1 (0.4)
Hypertension	30 (5.7)	8 (1.5)	20 (7.6)	1 (0.4)
Psychiatric disorders	41 (7.8)	0	30 (11.4)	1 (0.4)
Insomnia	15 (2.9)	0	14 (5.3)	0

MedDRA Version: 25.0
CTC Version: 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Last dose date and start dose date are dose dates relative to study phase.

Source: Table S.6.1.31.1 in the CA20976K Primary CSR[2]

Drug-Related Adverse Events

Any-grade drug-related AEs were reported in 433 (82.6%) patients in the nivolumab arm and 142 (53.8%) patients in the placebo arm.

The most frequently reported drug-related AEs were as follows:

- Nivolumab arm: fatigue (20.2%), pruritus (18.5%), and diarrhoea (15.3%)
- Placebo arm: fatigue (20.1%), pruritus, and diarrhoea (9.5% each)

Grade 3-4 drug-related AEs were reported in 54 (10.3%) patients in the nivolumab arm, and 6 (2.3%) patients in the placebo arm.

The most frequently reported Grade 3-4 drug-related AEs were as follows:

- Nivolumab arm: AST increased and blood creatine phosphokinase increased (1.1% each)
- Placebo arm: lipase increased (1.1%)

Selected Adverse Events

Selected Adverse Events included AEs in the categories; endocrine, gastrointestinal, hepatic, pulmonary, renal, skin and hypersensitivity/infusion reactions (Table 23).

Selected AEs were reported more frequently in the nivolumab arm than the placebo arm. Most selected AEs reported were Grade 1-2 and most were considered drug-related by the investigator. The most frequently reported drug-related selected AE categories (any grade) in each treatment arm were as follows:

- Nivolumab arm: skin (34.5%), endocrine (20.6%), and gastrointestinal (16.2%)
- Placebo arm: skin (17.8%), gastrointestinal (9.5%), and hepatic (6.1%)

The five most frequently reported drug-related selected AEs by preferred term (PT) (any grade) in each treatment arm were as follows:

- Nivolumab arm: pruritus (18.5%); diarrhoea (15.3%); rash (10.9%), hypothyroidism (10.3%), ALT increased (6.3%)

- Placebo arm: pruritus (9.5%); diarrhoea (9.5%); rash (6.8%), ALT increased (4.9%); AST increased (2.3%)

There were few drug-related serious selected AEs (any grade) reported in either arm, with no more than 2 patients with the same event.

Across the selected AE categories, with the exception of endocrine events, most events in the nivolumab arm resolved using the established algorithms. Less than half (41.7%) of patients with endocrine selected AEs were reported to have event resolution at data cut-off.

Table 32 Onset, Management, and Resolution of Drug-Related Selected AEs – Blinded Phase – Nivolumab Treated Patients (N=524)

Category	% Treated Subjects with Any-grade/ Grade 3-4	Median Time to Onset of (range), wks	% Treated Subjects Leading to DC	% Subjects Treated with IMM/High-Dose Corticosteroids[a]	Median[b] Time to Resolution (range[c]), wks[d,e]	% Subjects with Drug-related Select AE that Resolved[d,e]
Endocrine	20.6/1.7	11.93 (2.3 - 44.1)	1.9	19.4/2.8	N.A. (0.4 - 126.9+)	41.7
Gastrointestinal	16.2/1.1	12.43 (0.1 - 54.4))	2.3	27.1/16.5	3.86 (0.1 - 64.0)	88.1
Hepatic	11.3/2.7	12.43 (0.3 - 56.1)	2.3	28.8/25.4	5.86 (0.3 - 88.7+)	91.4
Pulmonary	1.3/0.2	25.14 (11.3 - 49.6)	0.8	57.1/57.1	8.14 (1.6 - 15.1+)	85.7
Renal	1.7/0.4	28.14 (13.1 - 53.3)	0.8	22.2/22.2	10.14 (0.7 - 38.3+)	66.7
Skin	34.5/1.1	9.00 (0.1 - 48.1)	1.7	38.1/2.2	32.00 (0.1 - 116.0+)	64.1
Hypersensitivity/ Infusion Reaction	5.9/0	3.71 (0.1 - 42.1)	0	25.8/16.1	0.14 (0.1 - 107.0+)	87.1

MedDRA Version 25.0 CTC Version: 5.0

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

[b] From Kaplan-Meier

[c] Symbol + indicates a censored value

[d] Subjects who experienced select AEs without worsening from baseline grade were excluded from time to resolution analysis

[e] Events without a stop date or with a stop date equal to the death, as well as grade 5 events, are considered unresolved

Includes events reported between first dose and 30 days after last dose of study therapy. Last dose date and start dose date are dose dates relative to study phase. The time to resolution of an AE belonging to a select AE category was defined as the longest time from onset to complete resolution or improvement to the grade at baseline among all clustered select AEs belonging to a select AE category experienced by the subject.

Source: Table S.6.5.1.3.2.1 (drug-related select AEs), Table S.6.5.1.3.2 (drug-related select endocrine AEs), Table S.6.117.1 (time to onset of drug-related select AEs), Table S.6.117.2 (time to onset of drug-related select endocrine AEs), Table S.6.5.1.3.2.8 (drug-related select AEs leading to discontinuation), Table S.6.5.1.3.2.9 (drug-related select endocrine AEs leading to discontinuation), Table S.6.12.9.1 (drug-related select AEs treated with IMM/High-dose CS), Table S.6.121.1 (time to resolution of drug-related select AEs), Table S.6.121.2 (time to resolution of drug-related select endocrine AEs), Table S.6.121.3 (time to resolution of drug-related select AEs treated with IMM), Table S.6.121.4 (time to resolution of drug-related select endocrine AEs treated with IMM)

Adverse Events in CA20976K and Across Pooled Monotherapy Studies

The frequencies of any grade, all-causality, and drug-related AEs were comparable in nivolumab treated subjects in CA20976K when compared with the pooled nivolumab monotherapy studies excluding CA20976K and all pooled nivolumab monotherapy studies (including CA20976K).

- Any grade all-causality AEs frequencies were similar in nivolumab monotherapy treated patients in CA20976K vs pooled studies excluding CA20976K and vs pooled studies including CA20976K.
- Drug-related AEs frequencies for any grade were higher in nivolumab monotherapy treated patients in CA20976K vs pooled studies excluding CA20976K vs pooled studies including CA20976K (82.6% vs 74.4% vs 75.3%, respectively). Frequencies for the most of PTs were similar between CA20976K nivolumab monotherapy and pooled studies, excluding few frequencies with an absolute difference of minimum 2% and maximum 4% (*Table 33*).

Overall, the safety data of the CA20976K safety data is considered comparable with the safety data of the nivolumab monotherapy pool.

Table 33 Summary of Drug-Related Adverse Events (re-mapped Terms) by Worst CTC grade (any Grade, Grade 3-4, Grade 5) with 5% Cutoff All Treated Patients with Nivolumab monotherapy Types

System Organ Class (%) Preferred Term (%)	CA20976K Nivolumab Monotherapy N = 524			Pooled Nivolumab Monotherapy Excluding CA20976K N = 4122			Pooled Nivolumab Monotherapy Including CA20976K N = 4646		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	433 (82.6)	54 (10.3)	0	3065 (74.4)	651 (15.8)	7 (0.2)	3498 (75.3)	705 (15.2)	7 (0.2)
General disorders and administration site conditions	160 (30.5)	0	0	1489 (36.1)	72 (1.7)	0	1649 (35.5)	72 (1.5)	0
Fatigue	106 (20.2)	0	0	960 (23.3)	49 (1.2)	0	1066 (22.9)	49 (1.1)	0
Asthenia	38 (7.3)	0	0	278 (6.7)	11 (0.3)	0	316 (6.8)	11 (0.2)	0
Skin and subcutaneous tissue disorders	194 (37.0)	8 (1.5)	0	1363 (33.1)	60 (1.5)	0	1557 (33.5)	68 (1.5)	0
Pruritus	97 (18.5)	1 (0.2)	0	609 (14.8)	6 (0.1)	0	706 (15.2)	7 (0.2)	0
Rash	57 (10.9)	4 (0.8)	0	520 (12.6)	24 (0.6)	0	577 (12.4)	28 (0.6)	0
Gastrointestinal disorders	158 (30.2)	8 (1.5)	0	1242 (30.1)	91 (2.2)	0	1400 (30.1)	99 (2.1)	0
Diarrhoea	80 (15.3)	4 (0.8)	0	608 (14.8)	43 (1.0)	0	688 (14.8)	47 (1.0)	0
Nausea	39 (7.4)	0	0	449 (10.9)	6 (0.1)	0	488 (10.5)	6 (0.1)	0
Dry mouth	36 (6.9)	0	0	123 (3.0)	0	0	159 (3.4)	0	0
Investigations	113 (21.6)	20 (3.8)	0	758 (18.4)	202 (4.9)	0	871 (18.7)	222 (4.8)	0
Alanine aminotransferase increased	33 (6.3)	4 (0.8)	0	161 (3.9)	33 (0.8)	0	194 (4.2)	37 (0.8)	0
Aspartate aminotransferase increased	30 (5.7)	6 (1.1)	0	164 (4.0)	27 (0.7)	0	194 (4.2)	33 (0.7)	0
Blood creatine phosphokinase increased	30 (5.7)	6 (1.1)	0	16 (0.4)	10 (0.2)	0	46 (1.0)	16 (0.3)	0
Musculoskeletal and connective tissue disorders	102 (19.5)	5 (1.0)	0	580 (14.1)	33 (0.8)	0	682 (14.7)	38 (0.8)	0
Arthralgia	54 (10.3)	1 (0.2)	0	276 (6.7)	7 (0.2)	0	330 (7.1)	8 (0.2)	0
Myalgia	28 (5.3)	0	0	173 (4.2)	7 (0.2)	0	201 (4.3)	7 (0.2)	0
Endocrine disorders	92 (17.6)	5 (1.0)	0	499 (12.1)	22 (0.5)	0	591 (12.7)	27 (0.6)	0
Hypothyroidism	54 (10.3)	0	0	313 (7.6)	2 (<0.1)	0	367 (7.9)	2 (<0.1)	0
Hyperthyroidism	36 (6.9)	1 (0.2)	0	166 (4.0)	2 (<0.1)	0	202 (4.3)	3 (<0.1)	0
Metabolism and nutrition disorders	35 (6.7)	4 (0.8)	0	492 (11.9)	57 (1.4)	1 (<0.1)	527 (11.3)	61 (1.3)	1 (<0.1)
Decreased appetite	18 (3.4)	0	0	312 (7.6)	7 (0.2)	0	330 (7.1)	7 (0.2)	0
Injury, poisoning and procedural complications	27 (5.2)	0	0	132 (3.2)	6 (0.1)	0	159 (3.4)	6 (0.1)	0
Infusion related reaction	27 (5.2)	0	0	112 (2.7)	6 (0.1)	0	139 (3.0)	6 (0.1)	0

Immune-Mediated Adverse Events (IMAEs)

IMAEs were reported more frequently in the nivolumab arm than the placebo arm. Overall, most IMAEs were Grade 1-2, excluding hepatitis, nephritis, hypophysitis, and diabetes mellitus (*Table 34*). The most frequently reported IMAEs (any grade) by category in each treatment arm were as follows:

- Nivolumab arm: hypothyroidism/thyroiditis (12.2%), rash (8.6%), and hyperthyroidism (7.6%)
- Placebo arm: hyperthyroidism (1.5%), rash (1.5%), and adrenal insufficiency (1.1%)

Across IMAE categories, most non-endocrine IMAEs were manageable using established algorithms, with resolution occurring when immune-modulating medication (commonly systemic corticosteroids) was administered. Except for hyperthyroidism, many endocrine IMAEs were not considered resolved at the time of DBL due to the continuing need for hormone replacement therapy.

Table 34 Onset, Management, and Resolution of All-Causality IMAEs within 100 days of Last Dose – Blinded Phase – Nivolumab Treated Patients (N = 524)

IMAE Category Subcategory	% Subj. with Any-grade/ Grade 3-4 IMAEs, %/ %	Median Time to Any-grade IMAE Onset (range), wks	% Subj. with Any-grade IMAE leading to DC / Dose Delay	% Subj.[a] with Any-grade IMAEs Receiving IMM / High-dose Corticosteroids[b]	Median Duration of IMM (range[c]), wks	% Subj. with Resolution of IMAE[d,e,f,g]	Median[h] Time to Resolution (range[c]), wks[d,e,f,g]	% Subj.[i] with Recurrence after Reinitiation[j]
Pneumonitis	0.8/ 0.2	26.64 (15.1 - 31.0)	0.4/ 0.2	100/ 100	7.07 (1.7 - 9.7)	75.0	11.21 (7.6 - 15.1+)	0
Diarrhea/ Colitis	4.6/ 1.1	22.86 (0.3 - 54.4)	1.7/ 1.3	100/ 62.5	5.71 (0.3 - 89.3)	73.9	7.86 (1.1 - 40.0+)	50.0%
Hepatitis	4.2/ 2.7	13.43 (2.1 - 49.1)	1.7/ 1.1	100/ 90.9	4.14 (0.6 - 93.6)	86.4	6.50 (0.7 - 46.4+)	33.3
Nephritis/ Renal Dysfunction	0.6/ 0.4	15.71 (9.9 - 20.4)	0.6/ 0	100/ 100	17.57 (10.0 - 25.6)	66.7	7.71 (0.7 - 7.9+)	0
Rash	8.6/ 0.8	9.00 (0.1 - 48.1)	0.8/ 1.0	100/ 11.1	17.57 (0.4 - 118.7)	60.0	30.57 (0.4 - 86.6+)	100
Hypersensitivity	1.3/ 0	7.86 (4.0 - 42.1)	0/ 0	100/ 42.9	0.14 (0.1 - 0.1)	100	0.14 (0.1 - 0.1)	0
Adrenal Insufficiency	2.3/ 0.6	32.14 (7.6 - 66.1)	1.0/ 0.2	100/ 0	33.71 (11.1 - 61.6)	25.0	N.A. (0.4 - 61.7+)	0
Hypophysitis	1.7/ 1.0	31.00 (7.9 - 42.1)	0.8/ 0.6	100/ 22.2	24.86 (1.3 - 76.1)	33.3	N.A. (1.0 - 76.1+)	0
Hypothyroidism/ Thyroiditis	12.2/ 0	12.36 (2.3 - 63.7)	0.4/ 1.3	3.1/ 3.1	1.64 (0.4 - 2.9)	23.4	N.A. (1.4 - 126.9+)	0
Hyperthyroidism	7.6/ 0.2	7.86 (3.6 - 40.1)	0.2/ 1.1	10.0/ 7.5	6.86 (3.7 - 23.1)	92.5	4.43 (1.6+ - 95.1+)	0
Diabetes Mellitus	0.6/ 0.6	28.14 (3.9 - 38.1)	0.4/ 0.2	0/ 0	N.A.	0	N.A. (21.3+ - 77.9+)	0

MedDRA Version: 25.0 CTC Version 5.0

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

Last dose date and start dose date are dose dates relative to study phase.

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

b At a dose ≥ 40 mg prednisone or equivalent.

c Symbol + indicates a censored value.

d Subjects who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis.

e Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.

f For each subject, the longest duration of immune-mediated AEs where immune modulating medication was initiated is considered.

g Time-to-resolution analysis, resolution date was defined as the investigator-assessed IMAE resolution date.

h From Kaplan-Meier estimation.

i Percentages are based on subjects who were re-challenged.

j Subjects who were re-challenged: Subjects with study therapy re-initiated on or after symptom improvement/resolution. Percentages are based on subjects with study therapy withheld. A positive re-challenge/recurrence is defined as any occurrence of new event(s) or worsening of any severity grade IMAE on or after study therapy re-initiation.

Source: Table S.6.2.02.1 (endocrine IMAEs), Table S.6.2.02.4 (non-endocrine IMAEs), Table S.6.217.1 (time to onset endocrine IMAEs), Table S.6.217.2 (time to onset of non-endocrine IMAEs), Table S.6.2.02.2 (endocrine IMAEs leading to DC), Table S.6.2.02.5 (non-endocrine IMAEs leading to DC), Table S.6.2.02.3 (endocrine IMAEs leading to dose delay), Table S.6.2.02.6 (non-endocrine IMAEs leading to dose delay), Table S.6.12.91.1 (duration of IMM for IMAE management), Table S.6.219.1 (time to resolution endocrine IMAEs), Table S.6.219.2 (time to resolution non-endocrine IMAEs), Table S.6.223.1 (recurrence).

Other Events of Special Interest (OESIs)

OESIs were reported in 21/524 patients in the nivolumab arm, including pancreatitis, uveitis, myocarditis, and myositis/rhabdomyolysis categories. The frequency of all OESI categories (any grade; any causality) with nivolumab was < 1%, except for myositis/rhabdomyolysis (1.5%) and pancreatitis (1.5%). Most of the OESIs in the nivolumab arm were considered drug-related by the investigator.

Drug-related OESIs in the nivolumab arm included myositis/rhabdomyolysis (1.5%), pancreatitis (1.3%), myocarditis (0.6%), and uveitis (0.2%).

In the placebo arm, OESIs were reported in 2 (0.8%) patients. The events were rhabdomyolysis in both patients and were considered to be drug-related by the investigator.

Serious adverse event/deaths/other significant events

Any-grade SAEs (regardless of causality) were reported in 74 (14.1%) patients in the nivolumab arm vs 29 (11.0%) patients in the placebo arm (Table 25). Grade 3-4 SAEs were reported in 55 (10.5%) patients in the nivolumab arm and 20 (7.6%) patients in the placebo arm.

The frequency of all reported SAEs were < 1% in both the nivolumab and placebo arms.

The most frequently reported SAEs (regardless of causality) were as follows (*Table 35*):

- Nivolumab arm: COVID-19 (0.8%), ALT increased, AST increased, and pulmonary embolism (0.6% each)
- Placebo arm: melanoma recurrent and invasive breast carcinoma (0.8% each)

Table 35 Serious Adverse Events by Worst CTC Grade Reported in ≥ 0.4% of All Treated Patients – Blinded Phase

System Organ Class n(%) Preferred Term n(%)	Nivolumab 480 mg Q4W N = 524		Placebo Q4W N = 264	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
TOTAL SUBJECTS WITH AN EVENT	74 (14.1)	55 (10.5)	29 (11.0)	20 (7.6)
Infections and infestations	16 (3.1)	13 (2.5)	2 (0.8)	2 (0.8)
COVID-19	4 (0.8)	2 (0.4)	1 (0.4)	1 (0.4)
Diverticulitis	2 (0.4)	2 (0.4)	0	0
Infected seroma	2 (0.4)	2 (0.4)	0	0
Cellulitis	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)
Gastrointestinal disorders	10 (1.9)	9 (1.7)	2 (0.8)	2 (0.8)
Colitis	2 (0.4)	2 (0.4)	0	0
Diarrhea	2 (0.4)	2 (0.4)	0	0
Pancreatitis	2 (0.4)	2 (0.4)	0	0
Inguinal hernia	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)
Lower gastrointestinal hemorrhage	0	0	1 (0.4)	1 (0.4)
Cardiac disorders	8 (1.5)	6 (1.1)	1 (0.4)	1 (0.4)
Acute myocardial infarction	2 (0.4)	2 (0.4)	1 (0.4)	1 (0.4)
Myocarditis	2 (0.4)	2 (0.4)	0	0
Musculoskeletal and connective tissue disorders	8 (1.5)	5 (1.0)	5 (1.9)	3 (1.1)
Osteoarthritis	2 (0.4)	1 (0.2)	0	0
Arthralgia	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)
Bone lesion	0	0	1 (0.4)	0
Osteolysis	0	0	1 (0.4)	0
Rhabdomyolysis	0	0	1 (0.4)	1 (0.4)
Spondylolisthesis	0	0	1 (0.4)	1 (0.4)
Investigations	6 (1.1)	6 (1.1)	1 (0.4)	1 (0.4)
Alanine aminotransferase increased	3 (0.6)	3 (0.6)	0	0
Aspartate aminotransferase increased	3 (0.6)	3 (0.6)	1 (0.4)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	6 (1.1)	4 (0.8)	1 (0.4)	0
Pulmonary embolism	3 (0.6)	2 (0.4)	0	0
Interstitial lung disease	0	0	1 (0.4)	0
Endocrine disorders	5 (1.0)	4 (0.8)	0	0
Adrenal insufficiency	2 (0.4)	2 (0.4)	0	0
Injury, poisoning and procedural complications	5 (1.0)	2 (0.4)	1 (0.4)	0
Fall	0	0	1 (0.4)	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.0)	3 (0.6)	9 (3.4)	6 (2.3)
Basal cell carcinoma	1 (0.2)	0	1 (0.4)	0
Malignant neoplasm progression	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)
Melanoma recurrent	1 (0.2)	1 (0.2)	2 (0.8)	1 (0.4)
Metastatic malignant melanoma	1 (0.2)	0	1 (0.4)	0
Invasive breast carcinoma	0	0	2 (0.8)	2 (0.8)
Malignant melanoma	0	0	1 (0.4)	1 (0.4)
Meningioma	0	0	1 (0.4)	1 (0.4)
Metabolism and nutrition disorders	4 (0.8)	3 (0.6)	2 (0.8)	2 (0.8)
Hyponatremia	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)
Hypophosphatemia	0	0	1 (0.4)	1 (0.4)
Nervous system disorders	4 (0.8)	4 (0.8)	3 (1.1)	2 (0.8)
Syncope	2 (0.4)	2 (0.4)	0	0
Headache	0	0	1 (0.4)	1 (0.4)
Dizziness	0	0	1 (0.4)	1 (0.4)
Transient ischemic attack	0	0	1 (0.4)	0

	Nivolumab 480 mg Q4W N = 524		Placebo Q4W N = 264	
System Organ Class n(%) Preferred Term n(%)	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Renal and urinary disorders	4 (0.8)	3 (0.6)	1 (0.4)	1 (0.4)
Acute kidney injury	2 (0.4)	1 (0.2)	0	0
Urinary retention	0	0	1 (0.4)	1 (0.4)
General disorders and administration site conditions	3 (0.6)	1 (0.2)	1 (0.4)	0
Sudden death	0	0	1 (0.4)	0
Hepatobiliary disorders	2 (0.4)	2 (0.4)	1 (0.4)	1 (0.4)
Hepatitis	0	0	1 (0.4)	1 (0.4)
Reproductive system and breast disorders	2 (0.4)	0	1 (0.4)	1 (0.4)
Benign prostatic hyperplasia	0	0	1 (0.4)	1 (0.4)
Eye disorders	1 (0.2)	0	1 (0.4)	1 (0.4)
Glaucoma	0	0	1 (0.4)	1 (0.4)
Psychiatric disorders	0	0	1 (0.4)	1 (0.4)
Suicidal ideation	0	0	1 (0.4)	1 (0.4)

MedDRA Version: 25.0
CTC Version: 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Last dose date and start dose date are dose dates relative to study phase.
Source: Table S.6.3.1.2.1

Any-grade drug-related SAEs were reported in 25 (4.8%) patients in the nivolumab arm, and 3 (1.1%) patients in the placebo arm. Grade 3-4 drug related SAEs were reported in 23 (4.4%) patients in the nivolumab arm, and 2 (0.8%) patients in the placebo arm.

The most frequently reported drug-related SAEs were as follows:

- Nivolumab arm: colitis, diarrhoea, adrenal insufficiency, and myocarditis (0.4% each)
- Placebo arm: rhabdomyolysis, hepatitis and AST increased (0.4% each)

Deaths

As of the 28-June-2022 data cutoff, 13 (2.5%) treated patients in the nivolumab arm and 8 (3.0%) in the placebo arms had died (*Table 36*). One additional death occurred in the nivolumab arm prior to the data cut-off, but was reported after the database lock for a total of 14 (2.7%) deaths.

There was 1 patient (0.2%) who died due to study drug toxicity in the nivolumab arm. The patient developed a Grade 3 vasculitic skin rash 3 days after the first dose of nivolumab, as well as cervical lymphadenopathy that was confirmed as non-metastatic, with fibrous and lymphadenitic changes only.

The rash resolved with topical steroids, however the patient developed rising creatinine levels and was hospitalized due to Grade 4 acute kidney injury (requiring haemodialysis and intravenous steroids), Grade 3 anaemia and thrombocytopenia (all events related to therapy). Study therapy was discontinued. The patient continued to deteriorate with gastrointestinal bleeding, and cardiac failure; coronary angiography reported re-stenosis of coronary vessels (the subject had past medical history of cardiac bypass). The patient was resuscitated after a cardiac arrest, however continued to deteriorate with Grade 4 sepsis, multiorgan failure and culminating in death, 123 days after the first and only dose of nivolumab. The cause of death was reported as heart failure and acute kidney failure.

There was one Grade 5 event in each treatment arm that was not a drug-related SAE; myocardial ischemia was reported in the nivolumab arm and sudden death in the placebo arm. Only events that led to death within 24 hours were documented as Grade 5. Events leading to death > 24 hours after onset were reported with the worst grade before death and captured in the death listing.

Table 36 Death Summary – Blinded Phase – All Treated Patients

	Nivolumab 480 mg Q4W N = 524	Placebo Q4W N = 264
NUMBER OF SUBJECTS WHO DIED (%)	13* (2.5)	8 (3.0)
PRIMARY REASON FOR DEATH (%)		
DISEASE	3* (0.6)	4 (1.5)
STUDY DRUG TOXICITY	1 (0.2)	0
UNKNOWN	1 (0.2)	1 (0.4)
OTHER	8 (1.5)	3 (1.1)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	1 (0.2)	1 (0.4)
PRIMARY REASON FOR DEATH (%)		
DISEASE	0	0
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER	1 (0.2)	1 (0.4)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	7 (1.3)	2 (0.8)
PRIMARY REASON FOR DEATH (%)		
DISEASE	0	0
STUDY DRUG TOXICITY	0	0
UNKNOWN	0	0
OTHER	7 (1.3)	2 (0.8)

*One additional death due to disease occurred prior to data cutoff, but was reported after DBL, in the nivolumab arm for a total of 14 deaths with 4 deaths due to disease. This subject had a disease recurrence prior to death and this was captured as an RFS event prior to data cutoff.
Last dose is relative to study phase.
Source: Table S.6.15.1

Pulmonary embolism was reported in three patients (0.6%) (Table 27), none of these events were considered related to study drug treatment. One of the patients died due to pulmonary embolism (*Table 37*).

Table 37 Deaths Attributed to Cause of "Other"

Study Treatment	PT (per Investigator)[a]	No. of Subjects
Nivolumab 480 mg Q4W	COVID-19 lung infection	1
	Diverticulitis	1
	Circulatory failure	1
	Suicide	1
	Pulmonary embolism	1
	HSV-1 encephalitis	1
	Potential allergic reaction during TEP scanner	1
	Acute cardiac ischemic event not related to therapy	1
Placebo Q4W	Multi-organ failure	1
	Sudden death	1
	COVID-19 infection	1

[a] Deaths may be captured on death, AE, ECOG performance status, status and follow-up CRF pages.
The verbatim terms for death attributed to "other" were consistent with events expected in the population under study and none were considered related to study drug

Source: Table S.6.17 (death listing)

Laboratory findings

Haematology

Abnormalities in haematology tests performed during treatment or within 30 days of last dose of study drug were as anticipated and were primarily Grade 1 2 in the nivolumab and placebo arms. No Grade 3 4 haematologic abnormalities were reported in ≥2% of patients in either arm.

Liver Tests

During the treatment period, abnormalities in hepatic parameters (increases) were as anticipated and were primarily Grade 1 2. Grade 3 4 hepatic abnormalities were reported in 4.3% in the nivolumab arm and 0.8% of patients in the placebo arm. No patients in either arm were reported with concurrent elevated ALT or AST and elevated total bilirubin.

Thyroid Tests

Most patients were reported with normal thyroid stimulating hormone (TSH) levels at baseline and throughout the treatment period. TSH increases (> ULN) from baseline (≤ ULN) and TSH decreases (< LLN) from baseline (≥ LLN) were reported more frequently in the nivolumab arm than in the placebo arm, as expected.

Kidney Function Tests

Most patients with at least one on-treatment measurement were reported with normal creatinine values during the treatment reporting period. Abnormalities in creatinine (increases) were as anticipated and were primarily Grade 1 2. Grade 3 increases in creatinine were reported in 2 (0.4%) patients in the nivolumab arm and no patients in the placebo arm. No Grade 4 increases in creatinine were reported.

Safety in special populations

In the blinded phase, the frequencies of all-causality and drug-related AEs in the nivolumab and placebo arms for subgroups of gender, race, and age, were similar to AE frequencies reported for the overall study population by treatment (*Table 38*).

By Age:

- Frequencies of all-causality AEs and drug-related AEs were comparable by age category (< 65, ≥ 65 - < 75, and ≥ 75 - < 85) within each treatment arm.
- Due to a very small sample size of patients in the ≥ 85 age category in nivolumab and placebo arms, the interpretability is limited.

By Sex:

- Frequencies of all-causality AEs and Grade 3-4 AEs were slightly higher in males than females in the nivolumab arm.
- The drug-related AE rates were generally similar by sex in both nivolumab and placebo arms.

By Race:

- For subgroups based on race, most of the patients were classified as "White" with frequencies of all-causality AEs and drug-related AEs of any grade and Grade 3-4 consistent with that reported in the overall study population.
- Very low sample sizes in other categories of race, such as "Black" or "African American", "Asian" and "Other", limit the interpretability of potential differences.

By Region:

- Subgroup analyses by region showed that most of the patients were located in Western Europe with frequencies of all-causality AEs and drug-related AEs of any grade and Grade 3-4 consistent with that reported in the overall study population.

Table 38 All-Causality AEs Classified by the Worst CTC Grade and by Age, Sex, Race, and Region – Blinded Phase – All Treated patients

Drug-related AEs (n [%])								
	Nivolumab Arm 480 mg Q4W				Placebo Arm Q4W			
	N	Any Grade	Grade 3-4	Grade 5	N	Any Grade	Grade 3-4	Grade 5
Total	524	433 (82.6)	54 (10.3)	0	264	142 (53.8)	6 (2.3)	0
By Age (years)								
< 65	305	253 (83.0)	29 (9.5)	0	155	94 (60.6)	3 (1.9)	0
≥ 65 and < 75	139	115 (82.7)	17 (12.2)	0	77	36 (46.8)	3 (3.9)	0
≥ 75 and < 85	77	62 (80.5)	8 (10.4)	0	30	11 (36.7)	0	0
≥ 85	3	3 (100.0)	0	0	2	1 (50.0)	0	0
≥ 65	219	180 (82.2)	25 (11.4)	0	109	48 (44.0)	3 (2.8)	0
By Sex								
Male	320	264 (82.5)	39 (12.2)	0	161	87 (54.0)	4 (2.5)	0
Female	204	169 (82.8)	15 (7.4)	0	103	55 (53.4)	2 (1.9)	0
By Race								
White	513	422 (82.3)	53 (10.3)	0	262	140 (53.4)	6 (2.3)	0
Black or African American	2	2 (100.0)	0	0	1	1 (100.0)	0	0
Asian	1	1 (100.0)	0	0	0	0	0	0
Other	7	7 (100.0)	1 (14.3)	0	1	1 (100.0)	0	0
By Region								
US and Canada	97	90 (92.8)	16 (16.5)	0	46	35 (76.1)	2 (4.3)	0
Western Europe	301	241 (80.1)	30 (10.0)	0	160	80 (50.0)	4 (2.5)	0
Eastern Europe	58	39 (67.2)	3 (5.2)	0	28	8 (28.6)	0	0
Australia	68	63 (92.6)	5 (7.4)	0	30	19 (63.3)	0	0

MedDRA Version: 25.0; CTC Version 5.0; Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Table S.6.1.32.1 (any drug-related AEs) Table S.6.1.5.6 (sex), Table S.6.1.5.7 (race), Table S.6.1.5.8 (age), Table S.6.1.5.9 (age), Table S.6.1.5.10 (region)

Safety to Support Use in Adolescents

The safety of nivolumab has been evaluated in adolescent patients (≥ 12 to < 18 years old) in the extension of the indication for nivolumab as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older, and for nivolumab as monotherapy for the adjuvant treatment of adults and adolescents 12 years of age and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (EMEA/H/C/003985/II/0125/G).

Melanoma in adolescents and adults is generally regarded as an analogous disease and is treated similarly using multimodal therapy including surgery, systemic therapy, and in some cases, radiation.

As such, current treatment strategies for pediatric and adolescent melanoma are based on clinical guidelines for adult patients and there are limited clinical studies evaluating treatment outcomes in these age groups. Despite the small number of patients, results of these studies suggested that safety profiles and treatment effects in pediatric patients are comparable with adult patients.

Within the aforementioned procedure (EMEA/H/C/003985/II/0125/G), safety data for the use of nivolumab monotherapy and in combination with ipilimumab in adolescents have been provided from study CA209070, a phase I/II study of nivolumab in children, adolescents, and young adults with recurrent or refractory solid tumours as a single agent and in combination with ipilimumab (NCT02304458). This study did not enroll any adolescent melanoma patient to be treated with the combination and the dosing used is not the same, as approved for melanoma adult patients, which is also the one proposed for the extension of the indication to treat adolescents.

For these reasons, the safety assessment in the current application relies mainly in a full extrapolation approach based on clinical data in adults from the already assessed studies CA209067 (NCT01844505) and CA209238 (NCT02388906), in addition to study CA209915 which was conducted in the adjuvant setting and included two adolescents treated with nivolumab monotherapy (NCT03068455).

Discontinuation due to adverse events

Discontinuation due to adverse events

Any-grade AEs leading to discontinuation (regardless of causality) were reported in 91 (17.4%) patients in the nivolumab arm, and 9 (3.4%) patients in the placebo arm (Table 39). Most AEs leading to discontinuation were Grade 1-2. Grade 3 4 AEs leading to discontinuation were reported in 37 (7.1%) patients in the nivolumab arm, and 2 (0.8%) patients in the placebo arm.

The most common AEs leading to discontinuation (regardless of causality) were as follows:

- Nivolumab arm: arthralgia (1.7%) and diarrhoea, ALT increased, and AST increased (1.1% each)
- Placebo arm: ALT increased and AST increased (0.8% each)

Any-grade drug-related AEs leading to discontinuation were reported in 77 (14.7%) patients in the nivolumab arm, and 7 (2.7%) patients in the placebo arm. Most drug-related AEs leading to discontinuation were Grade 1-2. Grade 3, 4 AEs leading to discontinuation were reported in 29 (5.5%) patients in the nivolumab arm, and 2 (0.8%) patients in the placebo arm.

The most common drug-related AEs leading to discontinuation were as follows:

- Nivolumab arm: arthralgia (1.7%) and diarrhoea (1.1%)
- Placebo arm: ALT increased and AST increased (0.8% each)

Table 39 Adverse Events Leading to Discontinuation by Worst CTC Grade in ≥ 1% of Patients – Blinded Phase – All Treated Patients

System Organ Class n(%) Preferred Term n(%)	Nivolumab 480 mg Q4W N = 524		Placebo Q4W N = 264	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
TOTAL SUBJECTS WITH AN EVENT	91 (17.4)	37 (7.1)	9 (3.4)	2 (0.8)
Musculoskeletal and connective tissue disorders	18 (3.4)	3 (0.6)	1 (0.4)	1 (0.4)
Arthralgia	9 (1.7)	0	0	0
Gastrointestinal disorders	16 (3.1)	5 (1.0)	0	0
Diarrhea	6 (1.1)	3 (0.6)	0	0
Colitis	5 (1.0)	2 (0.4)	0	0
Investigations	14 (2.7)	7 (1.3)	3 (1.1)	1 (0.4)
Alanine aminotransferase increased	6 (1.1)	3 (0.6)	2 (0.8)	0
Aspartate aminotransferase increased	6 (1.1)	4 (0.8)	2 (0.8)	1 (0.4)
Skin and subcutaneous tissue disorders	9 (1.7)	4 (0.8)	0	0
Rash	5 (1.0)	3 (0.6)	0	0

MedDRA Version: 25.0
CTC Version: 5.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Last dose date and start dose date are dose dates relative to study phase.
Source: Table S.6.4.2.2.1

Immunogenicity

Immunogenicity samples were collected at regular intervals in pivotal Study CA20976K. In subjects who were evaluable for anti-drug antibodies (ADA), the incidence of nivolumab ADA was 3.2% (12/378) at baseline and 2.6% (10/378) after the start of treatment. Among the post-treatment ADA positive subjects, 0.5% (2/378) of the ADA evaluable subjects were considered persistently positive (had an ADA positive sample at two or more consecutive timepoints, where the first and last ADA-positive samples are at least 16 weeks apart), and 0.5% (2/378) of the ADA evaluable subjects were neutralizing ADA positive. Data on neutralizing antibodies for Study CA20976K were provided in an addendum to the CA20976K clinical study report (CSR). ADA positivity did not appear to impact hypersensitivity and infusion-related reactions of adjuvant nivolumab treatment in subjects with completely resected Stage IIB/C melanoma.

2.5.1. Discussion on clinical safety

Safety data from the pivotal Phase 3 Study CA20976K was submitted to support the use of nivolumab as monotherapy in the adjuvant setting of Stage IIB/C melanoma following complete resection. The safety data from study CA20976K included 524 patients that were treated with nivolumab and 264 patients that were treated with placebo.

Further, the safety results of Study CA20976K were compared with pooled safety data (n=4646 treated patients) of all study conducted in different tumour types with nivolumab monotherapy.

Adult melanoma patients randomized to the nivolumab arm received 480 mg Q4W as a 30 min-infusion.

The planned dosing for adolescents 12 years of age and older weighing ≥40 kg was the same as the adult dose. The planned dose for adolescents (12 years of age and older and weighing < 40 kg) 6 mg/kg Q4W over 60 min. However no adolescents were included in the study.

In line with the current information in the Opdivo SmPC, dose reductions were not permitted with nivolumab or placebo. Dose delays of study drug (proportion of patients with at least 1 dose delay) were reported in 36.3% patients in the nivolumab arm and 33.3% patients in the placebo arm.

The planned treatment duration in the study was 12 months. The median number of nivolumab doses received was 12 (range: 1 – 14) and the median number of placebo doses received was 13 (range: 1-14). The proportion of treated patients who received ≥ 90% of the planned nivolumab dose intensity was 89.7%. The median duration of therapy was 11.04 months in the nivolumab arm and 11.07 months in the placebo arm.

It is noted that 17 patients in the nivolumab arm and 10 patients in placebo arm, had a treatment duration of more than 12 months, as the planned treatment duration in the study was 12 months. These were reported as protocol deviations, and not considered to impact efficacy or safety.

Adverse events

Any-grade AEs (regardless of causality) were reported in 502 (95.8%) patient in the nivolumab arm, and 229 (86.7%) patients in the placebo arm. Drug-related any-grade AEs in 433 (82.6%) patients in the nivolumab, and 142 (53.8%) patients in the placebo arms. The most frequently reported AEs (regardless of causality) were for the patients treated with nivolumab; fatigue (26.1%), diarrhoea (22.5%), and pruritus (20.0%). The most frequently reported AEs in the placebo arm were; fatigue (25.0%), diarrhoea (15.2%), and headache (12.5%).

Grade 3-4 AEs (regardless of causality) were reported in 115 (21.9%) patients in the nivolumab arm, and 32 (12.1%) patients in the placebo arm. The most frequently reported Grade 3-4 AEs (regardless of causality) were for patients treated with nivolumab; blood creatinine phosphokinase increased (1.9%), ALT increased, AST increased, and hypertension (1.5% each), while in the placebo arm the most frequently reported AE was headache (0.8%).

The frequencies of any grade, all-causality, and drug-related AEs were comparable for nivolumab treated subjects in CA20976K with what is reported for the pooled data-set including safety data of other clinical studies with nivolumab monotherapy.

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

Selected Adverse events

Selected AEs included the usual categories along nivolumab clinical development: endocrine, gastrointestinal, hepatic, pulmonary, renal, skin, and hypersensitivity/infusion reactions. Selected AEs were reported more frequently in the nivolumab arm than the placebo arm. Most selected AEs reported were Grade 1-2 and most were considered drug-related by the investigator. The most frequently reported drug-related selected AE categories (any grade) were for patients treated with nivolumab; skin (34.5%), endocrine (20.6%), and gastrointestinal (16.2%). For patients included in the placebo arm, the most frequently reported AE categories (any grade) were skin (17.8%), gastrointestinal (9.5%), and hepatic (6.1%).

Immune-Mediated Adverse Events

Immune-Mediated Adverse Events (IMAEs) were also more frequently reported in the nivolumab arm than in the placebo arm. The most frequently reported IMAEs (any grade) by category in each treatment arm were for the nivolumab arm; hypothyroidism/thyroiditis (12.2%), rash (8.6%), and hyperthyroidism (7.6%) and for the placebo arm; hyperthyroidism (1.5%), rash (1.5%), and adrenal insufficiency (1.1%).

Across IMAE categories, most non-endocrine IMAEs were manageable using established algorithms, with resolution occurring when immune-modulating medication (commonly systemic corticosteroids) was administered. Except for hyperthyroidism, many endocrine IMAEs were not considered resolved at time of DBL due to the continuing need for hormone replacement therapy.

Other Events of Special Interest events

Other Events of Special Interest (OESIs) were reported in 21/524 patients in the nivolumab arm, including pancreatitis, uveitis, myocarditis, and myositis/rhabdomyolysis categories. Frequency of all OESI categories (any grade; any causality) with nivolumab were < 1%, except for myositis/rhabdomyolysis (1.5%) and pancreatitis (1.5%). Most of the OESIs in the nivolumab arm were considered drug-related by the investigator.

Serious Adverse events

Any-grade SAEs (regardless of causality) were reported in 74 (14.1%) patients in the nivolumab arm vs 29 (11.0%) patients in the placebo arm. Grade 3-4 SAEs were reported in 55 (10.5%) patients in the nivolumab arm and 20 (7.6%) patients in the placebo arm. The most frequently reported SAEs (regardless of causality) were for patients treated with nivolumab COVID-19 (0.8%), ALT increased, AST increased, and pulmonary embolism (0.6% each) and for patients in the placebo arm; melanoma recurrent and invasive breast carcinoma (0.8% each).

Deaths

As of the 28-June-2022 data cut-off, 13 (2.5%) treated patients in the nivolumab arm and 8 (3.0%) in the placebo arms had died. One additional death occurred in the nivolumab arm prior to the data cut-off, but was reported after the database lock for a total of 14 (2.7%) deaths. Three patients in the nivolumab arm and 4 patients in the placebo arm died due to progressive disease (melanoma). There was one Grade 5 event in each treatment arm that was not a drug-related SAE; myocardial ischemia was reported in the nivolumab arm and sudden death in the placebo arm. Further most frequent cause of death was "other", which included Covid infection, diverticulitis, circulatory failure, suicide, pulmonary embolism, HSV-1 encephalitis, potential allergic reaction during imaging investigation (PET scan), acute cardiac ischemic event not related to therapy, multi-organ failure and sudden death.

One patient in the nivolumab arm thus died by pulmonary embolism, which is among the most frequently reported SAEs in this treatment arm (3 patients [0.6%] vs none in the placebo arm). These events of pulmonary embolism were not considered drug-related. In the pooled safety data including patients who were treated with nivolumab monotherapy in the different clinical studies, pulmonary embolism was also reported in 1.1% of patients and <0.1% was considered drug related.

Discontinuation due to adverse events

Any-grade AEs leading to discontinuation (regardless of causality) were reported in 91 (17.4%) patients in the nivolumab arm, and 9 (3.4%) patients in the placebo arm. The most common AEs leading to discontinuation for patients treated with nivolumab were arthralgia (1.7%) and diarrhoea, ALT increased, and AST increased (1.1% each) and for patients in the placebo arm ALT increased and AST increased (0.8% each).

Immunogenicity

The observed incidence of nivolumab ADA in Study CA20976K was low (2.6%) and generally consistent with those observed in other tumour types following nivolumab monotherapy. There was no apparent impact on hypersensitivity or infusion-related reactions.

Assessment of paediatric data on clinical safety

No patients younger than 18 of age were included in the pivotal study CA20976K. Therefore, there is a need to extrapolate the safety of nivolumab treatment to part of the applied-for target population.

The safety of nivolumab has been evaluated in adolescent patients (≥ 12 to < 18 years old) in the type II variation for extension of the indication for nivolumab as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older, and for nivolumab as monotherapy for the adjuvant treatment of adults and adolescents 12 years of age and older with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (EMEA/H/C/003985/II/0125/G). For this procedure, safety data for the use of nivolumab monotherapy and in combination with ipilimumab in adolescents have been provided from study CA209070. -T safety data of the paediatric study CA20907, were compared with safety data from the adults studies CA209067 (advanced melanoma), CA209238 (adjuvant setting). Due the limited sample size of the paediatric patients included (n=64 in the nivolumab monotherapy arm) no definitive conclusion could be drawn regarding the safety profile of nivolumab in adolescents, however no significant differences between treatment groups in these studies were observed.

To obtain long-term safety data, the MAH (in procedure EMEA/H/C/003985/II/0125/G) proposed to extend the ongoing post-authorization long-term follow-up safety study CA184557 (NCT04196452) to include paediatric patients treated with nivolumab monotherapy and nivolumab in combination with ipilimumab in the DMTR, as an additional pharmacovigilance activity.

All in all, the extrapolation of the safety of nivolumab treatment to the adolescent part of the applied-for target population is considered acceptable.

2.5.2. Conclusions on clinical safety

Safety data from study CA20976K for the use of nivolumab monotherapy in the adjuvant setting of Stage IIB or IIC melanoma following complete resection was submitted. In general the reported AEs and SAEs were in line with the known safety profile of nivolumab.

No patients younger than 18 of age were included in the pivotal study CA20976K. Therefore, there is a need to extrapolate the safety of nivolumab treatment to part of the applied-for target population.

The safety of nivolumab has been evaluated in adolescent patients (≥ 12 to < 18 years old) in procedure EMEA/H/C/003985/II/0125/G with a positive outcome. Therefore, the extrapolation of the safety of nivolumab treatment to the adolescent part of the applied-for target population is considered acceptable in the current procedure also.

Long-term safety data is unavailable on the use of nivolumab in adolescents 12 years of age and older. Long-term safety data for adolescent patients will be collected in the DMTR study as an additional pharmacovigilance activity (see RMP section).

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 33.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 33.1 with the following content:

Safety concerns

Table 40 **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

Pharmacovigilance plan

Table 41 **Ongoing and Planned Additional Pharmacovigilance Activities**

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
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	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,	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024

Table 41 **Ongoing and Planned Additional Pharmacovigilance Activities**

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
	cancer or melanoma in routine oncology practice	myocarditis, rhabdomyolysis, solid organ transplant rejection, and Vogt-Koyanagi-Harada disease]), and severe infusion reactions		
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

Risk minimisation measures

Table 42 **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:	Additional pharmacovigilance activities:
	Patient Alert Card	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

Table 42 **Summary of Risk Minimisation Measures**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		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
	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

Table 42 **Summary of Risk Minimisation Measures**

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC have being updated. The Annex II and Package Leaflet (PL) are updated accordingly.

2.7.1. User consultation

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

The extension of indication does not result in a relevant impact on the PL that would require performing a full user consultation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This is an extension of indication for Opdivo in the adjuvant treatment of adults and adolescents 12 years of age and older with Stage IIB or IIC melanoma.

3.1.2. Available therapies and unmet medical need

Standard of care for patients with clinical Stage II melanoma of all substages consists of wide surgical excision of the primary melanoma with the option to perform a sentinel lymph node biopsy. Current treatment recommendations for patients with a negative sentinel lymph node biopsy is observation with periodic surveillance to detect disease recurrence. In addition to observation, adjuvant pembrolizumab was recently (June 2022; Keytruda II/111 EPAR) approved for Stage IIB/C resected

melanoma patients and is a recommended treatment option in the NCCN guidelines, but not yet listed in the ESMO guidelines. Patients with stage IIB/IIC have a high risk of recurrence after complete resection and approximately one third of Stage IIB and one half of Stage IIC will have disease recurrence within 5 years. Ten-year melanoma-specific survival is estimated to be 72%-82% and 58%-75% for Stage IIB and Stage IIC patients, respectively. The goal of adjuvant treatment is to cure patients.

Melanoma in adolescents and adults is generally regarded as an analogous disease and is treated similarly using multimodal therapy including surgery, systemic therapy, and in some cases, radiation. As such, current treatment strategies for adolescent patients with melanoma are based on clinical guidelines for adult patients.

3.1.3. Main clinical studies

CA20976K (NCT04099251) is a phase 3, randomized, double-blind study designed to evaluate the use of adjuvant immunotherapy with nivolumab versus placebo after complete resection of Stage IIB/C melanoma in adults and adolescent subjects ≥12 years old. In Part 1 of the study, patients were randomised (2:1) to receive either nivolumab (n=526) 480 mg IV Q4W or placebo (n=264) with a maximum treatment duration of 1 year. Randomisation was stratified by tumour category (T3b vs. T4a vs. T4b). In Part 2 of the study, patients with a recurrence could be treated with nivolumab, regardless of their Part 1 treatment. Only results from Part 1 are presented and discussed. The primary efficacy outcome measure was investigator-assessed recurrence-free survival (RFS). The main secondary outcome measures were OS and distant metastasis-free survival (DMFS, exploratory).

3.2. Favourable effects

At a pre-planned interim analysis (IA; DCO 28-Jun-2022), with a median follow-up of approximately 16 months (minimum ~8 months), the primary endpoint RFS showed a statistically significant improvement in RFS for nivolumab compared to placebo (HR=0.42; 95% CI: 0.30-0.59, p<0.0001). RFS rates were higher in the nivolumab group than in the placebo group at 6 months (95.1% vs 88.1%), and at 12 months (89.0% vs 79.4%). Results were confirmed based on a longer median follow-up of about 24 months (minimum follow-up ~16 months, DCO 21-Feb-2023) with a HR of 0.53 (95% CI: 0.40, 0.71) and 12 month RFS rates of 88.8% and 81.1% in the nivolumab and placebo arm, respectively.

Support was obtained from a numerical improvement in DMFS (HR=0.62; 95% CI: 0.43-0.89) at DCO 21 February 2023.

All subgroup analyses for RFS showed results consistent with the primary analysis, including the results for important subgroups like disease stage (IIB, IIC) and tumour category (T3b, T4a, T4b).

3.3. Uncertainties and limitations about favourable effects

Updated results based on a median follow-up of approximately 24 months are sufficient to conclude on a beneficial effect on RFS of adjuvant nivolumab treatment in the target population, supported by a numerical improvement in DMFS which may be considered a more clinically relevant representative of long-term benefit. Some uncertainty exists on the RFS KM-curves beyond 12 months though, due to the censoring rate. Therefore, further long-term efficacy data should be provided post-approval, including OS data. The MAH will submit updated RFS data with a median follow-up of about 36 months (REC) and OS data from the first interim analysis from study CA20976K (Annex II.D PAES).

3.4. Unfavourable effects

Any-grade AEs (regardless of causality) were reported in 502 (95.8%) patient in the nivolumab arm, and 229 (86.7%) patients in the placebo arm. Drug-related any-grade AEs in 433 (82.6%) patients in the nivolumab, and 142 (53.8%) patients in the placebo arms. The most frequently reported AEs (regardless of causality) were for the patients treated with nivolumab; fatigue (26.1%), diarrhoea (22.5%), and pruritus (20.0%). The most frequently reported AEs in the placebo arm were; fatigue (25.0%), diarrhoea (15.2%), and headache (12.5%).

Grade 3-4 AEs (regardless of causality) were reported in 115 (21.9%) patients in the nivolumab arm, and 32 (12.1%) patients in the placebo arm. The most frequently reported Grade 3-4 AEs (regardless of causality) were for patients treated with nivolumab; blood creatinine phosphokinase increased (1.9%), ALT increased, AST increased, and hypertension (1.5% each), while in the placebo arm the most frequently reported AE was headache (0.8%).

Any-grade SAEs (regardless of causality) were reported in 74 (14.1%) patients in the nivolumab arm vs 29 (11.0%) patients in the placebo arm. Grade 3-4 SAEs were reported in 55 (10.5%) patients in the nivolumab arm and 20 (7.6%) patients in the placebo arm. The most frequently reported SAEs (regardless of causality) were for patients treated with nivolumab COVID-19 (0.8%), ALT increased, AST increased, and pulmonary embolism (0.6% each) and for patients in the placebo arm; melanoma recurrent and invasive breast carcinoma (0.8% each).

As of the 28-June-2022 data cut-off, 13 (2.5%) treated patients in the nivolumab arm and 8 (3.0%) in the placebo arms had died. Three patients in the nivolumab arm and 4 patients in the placebo arm died due to the disease. There was one Grade 5 event in each treatment arm that was not considered a drug related SAE; myocardial ischemia was reported in the nivolumab arm and sudden death in the placebo arm. Further most frequent cause of death was "other", which included Covid infection, diverticulitis, circulatory failure, suicide, pulmonary embolism, HSV-1 encephalitis, potential allergic reaction during TEP scanner, acute cardiac ischemic event not related to therapy, multi-organ failure and sudden death.

3.5. Uncertainties and limitations about unfavourable effects

No patients younger than 18 of age were included in the pivotal study CA20976K. Therefore, the safety of nivolumab treatment in this part of the applied-for target population is based on extrapolation.

3.6. Effects Table

Effects Table for Nivolumab for the adjuvant treatment of melanoma in adult and paediatric (12 years and older) patients with Stage IIB and IIC melanoma following complete resection (CA20976K, data cut-off: 28-JUN-2022, RFS Interim Analysis)

Effect	Short description	Unit	Nivolumab	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
RFS	Time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or	N events (%)	66/526 (12.5)	69/264 (26.1)	Strength: Randomized, placebo-controlled phase 3 study Primary results with a median follow-up of 16 months were confirmed by results with a median follow-up of ~24 months	Table 10 of this report
			HR: 0.42 (95% CI: 0.30-0.59) p<0.0001			

Effect	Short description	Unit	Nivolumab	Placebo	Uncertainties / Strength of evidence	References
	death (due to any cause), whichever occurred first				(DCO 21-Feb-2023) Uncertainties: No long-term efficacy data provided (OS)	
Unfavourable Effects						
Any-grade AEs	Incidence	N events (%)	502/524 (95.8)	229/264 (86.7)	Strength: Randomized, placebo-controlled phase 3 study Uncertainties: No adolescents were included in the clinical study	CRS Table 30
Grade 3-4 AEs	Incidence	N events (%)	115/524 (21.9)	33/264 (12.1)		Table 30
SAEs	Incidence	N events (%)	74/524 (14.1)	29/264 (11.0)		Table 35
AEs leading to discontinuation	Incidence	N events (%)	91/524 (17.4)	9/264 (3.4)		Table 39

Abbreviations: RFS=recurrence free survival, DMSF=Distant metastasis free survival; IA=interim analysis; CSR=clinical study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients with Stage IIB and IIC melanoma are at high risk of recurrence and could therefore be candidates for adjuvant treatment after complete resection of all detectable disease. In the adjuvant setting, the ultimate aim is to increase cure rate. Nevertheless, effects on RFS are considered relevant to the individual patient and it is, therefore, considered an acceptable primary endpoint in registrational studies of adjuvant treatment in melanoma.

The clinical data indicate an improvement in RFS of nivolumab over placebo. The primary endpoint is supported by an effect on distant metastases (DMFS), which is considered a clinically relevant endpoint as melanoma is generally considered to be incurable when distant metastasis is present. The results on RFS and DMFS were confirmed with longer follow-up (median approximately 24 months) and are considered sufficient to conclude on a beneficial effect of adjuvant nivolumab on RFS in the target population. As censoring rates beyond 12 months are still high and a plateau was not yet reached, the RFS results need further confirmation with longer follow-up, though this can be provided post approval. As the use of adjuvant therapy may limit therapeutic options at time of recurrence, OS data should also be reported in due time (post approval). The MAH has committed to submit updated RFS data (REC) as well as interim OS results from study CA20976K (Annex II D).

The toxicity profile of nivolumab treatment as observed in study CA20976K was generally in line with the known safety profile of nivolumab. There were no new safety signals.

No patients younger than 18 of age were included in the pivotal study. The extrapolation approach from adults to adolescents proposed is based on two main principles: 1) the drug behaves similarly and a comparable exposure-response to treatment can be expected between adults and adolescents; and 2) the disease biology can be considered similar between the two populations. This is considered acceptable for efficacy.

Moreover, the exposure and the safety of nivolumab in adolescent patients (≥ 12 to < 18 years old) has been evaluated in another procedure with a positive outcome (EMEA/H/C/003985/II/0125/G). Therefore, the extrapolation of the safety of nivolumab treatment to the adolescent part of the applied indication is considered acceptable.

3.7.2. Balance of benefits and risks

A statistically significant treatment effect on recurrence-free survival of adjuvant nivolumab over placebo was observed in patients with completely resected Stage IIB and IIC melanoma. Results were confirmed with longer follow-up. Therefore, a beneficial effect of nivolumab in the adjuvant treatment of melanoma is considered demonstrated. The toxicity profile of nivolumab treatment as observed in study CA20976K was generally in line with what is known, is considered acceptable, and to outweighed by the beneficial effects in the applied-for target population. The benefit/risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

As censoring rates beyond 12 months are still high and a plateau was not yet reached, the RFS results need further confirmation with longer follow-up. In addition, OS data are needed to better understand whether adjuvant nivolumab increases OS or only delays the progression of disease, these data are considered key to the benefit/risk. The OS analysis from study CA20976K was not available at the time of this submission and is included as an Annex II condition. The MAH will submit updated RFS data with a median follow-up of about 36 months (REC) and OS data from the first interim analysis (Annex II.D) from study CA20976K.

3.8. Conclusions

The overall B/R of Opdivo is positive.

The following measures are considered necessary to address issues related to efficacy, in accordance with the Commission Delegated Regulation (EC) No 357/2014, (a) an initial efficacy assessment that is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions:

Post authorisation efficacy study (PAES): In order to further characterise the efficacy of nivolumab as adjuvant treatment of adults and adolescents aged 12 years and older with stage IIB or stage IIC melanoma, the MAH should submit the OS data from the first interim OS analysis of the Phase III study CA20976K.

4. Recommendations

Outcome

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

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I, II and IIIB

	of a new therapeutic indication or modification of an approved one		

Extension of indication to include OPDIVO for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma who have undergone complete resection, based on results from study CA20976K; This is a phase III, randomized, double-blind study of adjuvant immunotherapy with nivolumab versus placebo after complete resection of stage IIB/C melanoma. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 33.1 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

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

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0130'