23 April 2026
EMADOC-1700519818-3070473
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Opdualag

International non-proprietary name: nivolumab / relatlimab

Procedure No. EMA/VR/0000303785

Note

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

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List of abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best overall response
BRAF	B-Raf proto-oncogene
C1D1, C2D1	Cycle 1 Day 1, Cycle 2 Day 1
CD4, CD8 T cells	cluster of differentiation
CI	confidence interval
CM	central memory
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated protein 4
DBL	database lock
DCO	Data cutoff
dNLR	derived neutrophil-to-lymphocyte ratio
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EU	European Union
FDC	fixed-dose combination
GCP	Good Clinical Practice
HR	hazard ratio
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMM	Immune-modulating medication
IV	intravenous
K-M	Kaplan-Meier
LAG-3	lymphocyte activation gene 3
LDH	lactate dehydrogenase
mPFS	median progression-free survival
M stage	metastasis stage
N.A.	not applicable
NR	not reported
OESI	other event of special interest
ORR	overall response rate
OS	overall survival
PD	progressive disease

PD-L1	programmed death-ligand 1
PIP	Paediatric investigation plan
PFS	progression-free survival
PR	partial response
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of product characteristics
TFS	treatment-free survival
UTD	unable to determine
USA	United States America
vs	versus

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 06 October 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include patients with tumour cell PD-L1 expression ≥ 1% in the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older for OPDUALAG, based on updated descriptive 4-year data from pivotal Study CA224047; this is a randomized, double-blind phase 2/3 study of relatlimab combined with nivolumab versus nivolumab in participants with previously untreated metastatic or unresectable melanoma; As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to remove Annex IV from the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection.

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/0070/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was completed.

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP in the context of this application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Peter Mol

Timetable	Actual dates
Submission date	6 October 2025
Start of procedure:	1 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	22 December 2025
PRAC Rapporteur's preliminary assessment report circulated on:	29 December 2025
Joint Rapporteur's updated assessment report circulated on:	22 January 2026
Request for supplementary information and extension of timetable adopted by the CHMP on:	29 January 2026
MAH's responses submitted to the CHMP on:	20 February 2026
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	30 March 2026
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	16 April 2026
CHMP opinion:	23 April 2026

2. Scientific discussion

2.1. Introduction

At time of the initial marketing authorisation application (MAA) submitted on 10 September 2021, the applicant had applied for the following indication: Opdualag is indicated for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents (12 years and older and weighing at least 40 kg). Following the assessment, the CHMP approved Opdualag for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1% (authorised 15/9/2022, see Opdualag EPAR). Study CA224047 was the pivotal study that met its primary endpoint of PFS per BICR for nivo+rela FDC compared with nivo in all randomized subjects: HR = 0.75 (95% CI: 0.62, 0.92), p = 0.0055 (minimum follow-up of 1.3 months based on the clinical data cutoff 25-Jan-2021 for the CA224047 Primary CSR). Results of the final analysis of OS (secondary endpoint) showed a trend in favour nivo+rela FDC over nivo: HR = 0.80 (95% CI: 0.64, 1.01); p = 0.0593 (minimum follow-up of 8.7 months based on the clinical data cutoff 07-Sep-2021 for CA224047 Addendum 01 clinical study report (CSR)). The indication was restricted to the PD-L1 low subgroup as the use of the combination appears to offer additional PFS benefit in this subgroup while there is no additional benefit observed in subjects with a higher expression on PD-L1 (HR 0.66; 95% CI: 0.54, 0.84 vs HR 0.95; 95% CI: 0.68, 1.33 with a cut-off of 1%). Similar to PFS, the KM curves of OS separate for PD-L1 negative patients (see Opdualag EPAR). KM-curves for OS only start to separate late (30 months) in the PD-L1 positive subgroup where there is still extensive censoring. At the same time, the combination is more toxic and

less well tolerated than nivolumab monotherapy, rendering the B/R balance negative for the subgroup with PD-L1 expression ≥ 1%.

2.1.1. Problem statement

The MAH aims to extend the indication to include patients with tumour cell PD-L1 expression ≥ 1% in the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older, based on updated descriptive 4-year data from the pivotal Study CA224047.

The current first-line treatments for unresectable stage III/IV melanoma in adults and adolescents, besides Opdualag, are PD-1 blockade as monotherapy (nivolumab, pembrolizumab), or combined with cytotoxic T lymphocyte associated protein 4 (CTLA-4) blockade (nivolumab and ipilimumab), independent of PD-L1 expression level. In addition, targeted therapies are available for BRAFV600-mutated melanoma.

2.1.2. About the product

Opdualag is a fixed-dose combination (FDC) of nivolumab, a programmed death-1 inhibitor (anti-PD-1) and relatlimab, a lymphocyte-activation gene-3 inhibitor (anti-LAG-3). Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2 and reduces PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. Relatlimab is a human IgG4 monoclonal antibody that binds to the LAG-3 receptor, blocks its interaction with ligands, including MHC II, and reduces LAG-3 pathway-mediated inhibition of the immune response. Antagonism of this pathway promotes T cell proliferation and cytokine secretion.

Opdualag is currently approved for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%.

The recommended dose for adults and adolescents 12 years of age and older is 480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as an intravenous infusion over 30 minutes.

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

Relevant aspects for the pivotal Study CA224047 were previously presented at the initial MA (see Opdualag EPAR). The current submission is based on updated descriptive 4-year data from the pivotal study. No SA was received in this context.

2.1.4. General comments on compliance with GCP

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

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 and relatlimab are proteins composed of natural amino acids. Proteins are expected to biodegrade in the environment and not be a significant risk for the environment. As a protein, nivolumab and relatlimab are exempt from submitting environmental risk assessment studies in line with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00 Rev. 1- Corr.). Opdualag and the product excipients do not pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Summary of the pivotal trial CA224047 supporting the proposed unresectable or metastatic melanoma indication

Study	Design/ *Primary Objective*	No. Planned Subjects (N)	Population	Dose/Schedule	Treated (N)
Pivotal Phase 3 Study Supporting Efficacy and Safety					
CA224047 RELATIVITY -047 NCT 03470922 Countries: 25 Sites: 114	Phase 2/3 randomised, double-blind study of BMS-986213 vs nivolumab *PFS per BICR*	700	Adults and adolescents (≥ 12 years) with histologically confirmed **unresectable Stage III or metastatic Stage IV MEL with no prior systemic therapy for advanced disease**	Rela+nivo 160/480 mg Q4W **FDC**	355
				Nivolumab 480 mg Q4W	359

2.3.2. Clinical pharmacology

The pharmacokinetic, pharmacodynamic, exposure-response, and immunogenicity information was adequately addressed at the time of the initial MAA (see Opdualag EPAR). Therefore, no Summary of Clinical Pharmacology, PopPK report, exposure-response report, or immunogenicity information are included in this submission. This is considered acceptable by CHMP.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

See Opdualag EPAR

2.4.2. Main study(ies)

Study CA224047, Phase 2/3, randomised, double-blind study of relatlimab + nivolumab vs. nivolumab monotherapy in subjects with previously untreated metastatic or unresectable melanoma.

A brief summary of the study design, methods and endpoints is presented below. A full description can be found in the Opdualag EPAR.

Methods

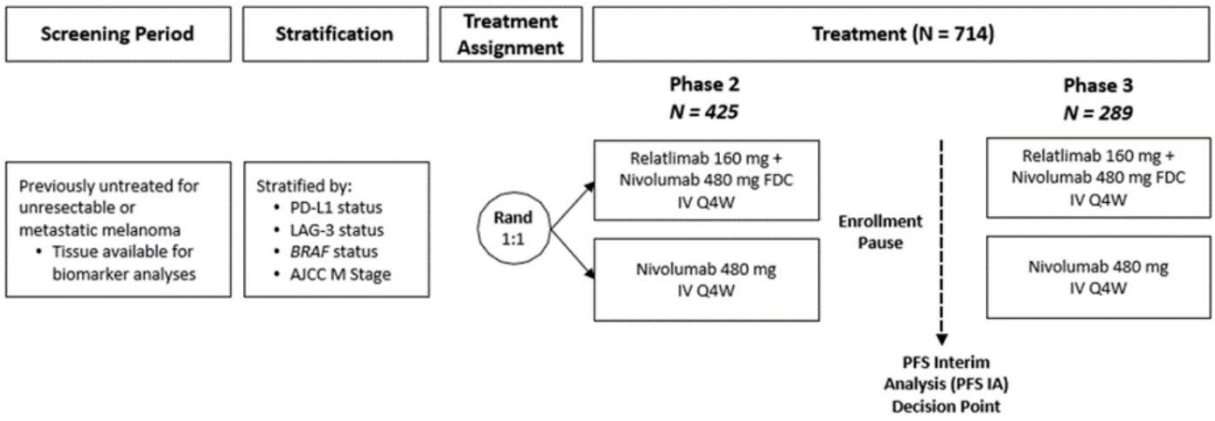
A total of 714 patients were randomised (1:1) to receive either relatlimab plus nivolumab 160/480 mg intravenous (IV) Q4W FDC, or nivolumab monotherapy 480 mg IV Q4W administered as ~60-minute IV infusions. Although adults and adolescents ≥ 12 years of age were allowed to enroll, no adolescents were enrolled in the study.

Randomisation was stratified by PD-L1 expression (≥ 1% vs. < 1%, tumour cells), LAG-3 expression (≥ 1% vs. < 1%, immune cells within the tumour region), B-Raf proto-oncogene (BRAF) mutation (V600 mutation positive vs. V600 wild-type), and American Joint Committee on Cancer (AJCC) M stage (M0/M1 with normal lactate dehydrogenase (LDH) vs. M1 with elevated LDH).

PD-L1 expression was defined as the percent of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells per the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test. The baseline PD-L1 was defined as the last quantifiable test result before, or on the date of randomisation. Subjects with indeterminate or unevaluable PD-L1 status results were not permitted to be randomised to a treatment arm.

LAG-3 expression was determined using an analytically validated immunohistochemistry (IHC) assay. LAG-3 expression was defined as the percentage of positive-staining immune cells with a morphological resemblance to lymphocytes relative to all nucleated cells within the tumour region in samples containing a minimum of 100 viable tumour cells. The baseline LAG-3 was defined as the last quantifiable test result before, or on the date of randomisation. Subjects with indeterminate or unevaluable LAG-3 status results were not permitted to be randomised to a treatment arm.

Figure 1 Schematic study design for Study CA224047



Objectives, endpoints and estimands

Primary endpoint:

PFS time per BICR, using RECIST v1.1. PFS was defined as the time between the date of randomisation and the first date of documented progression, or death due to any cause, whichever occurs first. The primary question of interest/estimand was whether PFS in patients aged 12 years of age or older with first-line advanced (unresectable or metastatic) melanoma was superior in patients who received the combination therapy of rela + nivo compared with monotherapy alone, regardless of treatment discontinuation, but under the assumption that an alternative anticancer therapy was not available to patients prior to progression.

A supplementary analysis for which it was assumed that anticancer therapy could be received prior to progression was also planned.

Key secondary endpoints:

- Overall survival (OS) was defined as the time between the date of randomisation and the date of death due to any cause. Patients were to be followed up regardless of any intercurrent events that occurred after randomisation, including treatment discontinuation and use of new anticancer therapy.
- Objective response rate (ORR) was assessed by a BICR and defined as the number of subjects with a BOR of CR or PR divided by the number of randomised subjects for each treatment group. Confirmation of response is required at least 4 weeks after the initial response. The BOR is defined as the best response designation, recorded between the date of randomisation and the date of objectively documented progression per RECIST v1.1 or the date of subsequent anti-cancer therapy, whichever occurs first.

On-study tumour assessments began 12 weeks from randomization and continued every 8 weeks up to Week 52, and every 12 weeks thereafter until BICR-confirmed disease progression or treatment discontinuation, whichever occurred later. Revised Protocol 04 (dated 05-Jan-2024) allowed the extension of scan frequency from every 12 weeks to every 24 weeks until BICR-confirmed disease progression for subjects without investigator- or BICR-assessed disease progression who had sustained clinical benefit (complete response (CR), partial response (PR), or stable disease (SD)) as assessed per investigator for at least 2 years.

Statistical methods

- PFS per BICR: For inference, the stratified log-rank test was estimated and for estimation of the treatment effect, the Hazard ratio (HR) and the corresponding 2-sided 95% confidence interval (CI) of PFS per BICR were estimated using a stratified Cox proportional hazards model, with treatment group as a single covariate. Stratification factors for these analyses were: LAG-3 expression, BRAF status, and AJCC M-stage. PFS curves, PFS medians with 95% CIs, and PFS rates with 95% CIs were estimated using the Kaplan Meier product limit method.
- OS: For OS, the same approach as for the PFS per BICR was used.
- ORR per BICR: The number and percentage of subjects in each category of ORR and BOR per BICR (CR, PR, SD, progressive disease (PD), or unable to determine (UTD)) were presented by treatment arm. The estimate of response rate, with its exact 2-sided 95% CI based on the Clopper and Pearson method was presented by treatment arm. A 2-sided 95% CI was calculated for the odds ratio of response between the treatment arms adjusted for stratification factors (LAG-3, BRAF and AJCC M-stage) and also for the difference in response rates between treatment arms.
- Exploratory subgroup analyses were provided to evaluate the influence of pre-specified baseline demographics and disease characteristics (including PD-L1 and LAG-3 status) on efficacy.

Newly added post-hoc analyses in support of the extension of indication to the PD-L1 ≥ 1% subgroup

The final PFS analysis (Database lock (DBL): 9 March 2021) and the final OS analysis (DBL: 28 October 2021) have been conducted. As stated in the Opdualag EPAR, the marketing authorisation holder was recommended to provide additional descriptive OS data. Survival follow-up continues for approximately 5 years and was to be submitted when available. In Statistical Analysis Plan (SAP) version 6 (25 May 2022) it was stated that additional locks and descriptive analyses [including for OS] will continue to be conducted on approximately a yearly basis as needed.

Additional sensitivity and exploratory analyses:

- Multivariate analysis of OS (including new covariates, ie, derived neutrophil-to-lymphocyte ratio at baseline (dNLR), baseline lesion count, and baseline sum of reference diameter).
- Receiver operating characteristic analysis (ROC) based on OS (results not provided)
- Subsequent cancer therapy: pre- and post-unblinding, for all progressors
- Baseline disease characteristics for subjects with early PFS events (within the first 3 months)
- KM OS curves: for progressors vs non-progressors, subjects with and without early PFS events (within the first 3 months), for responders (CR/PR) vs non-responders, based on treatment duration (≤1, ≤2, and ≤3 years)
- Competing risk for melanoma specific survival (MSS)

Treatment-free survival (TFS)

TFS was an exploratory analysis in the initial submission. TFS was defined as the time from end of protocol therapy until initiation of subsequent systemic anticancer therapy, with the event being initiation of such therapy. This analysis was restricted to subjects who were off study treatment and remained under follow-up prior to subsequent therapy. Subjects who discontinued both treatment and study without receiving further therapy were excluded, thereby focusing on subjects with known post-treatment follow-up status.

The MAH performed an additional analyse, in which TFS was estimated indirectly as the difference between restricted mean survival times for 2 time-to-event endpoints: (A) time to protocol therapy cessation or death while on treatment and (B) time to subsequent systemic therapy initiation or death. This method included all randomized subjects and accounted for censoring patterns in both endpoints. The area under each KM curve was estimated as restricted mean survival time (RMST), in months, over a maximum follow up of 60 months. Between-treatment arm comparisons were based on the estimated within arm differences in RMSTs, 95% CIs were generated via bootstrapping (10,000 iterations). The primary analyses were conducted in the ITT population, with subgroup analyses by PD-L1 expression (≥ 1% vs < 1%).

Biomarker analyses

The following exploratory post-hoc analyses of biomarker data from the CA224047 study were conducted to investigate the mechanistic rationale for the delayed OS benefit of nivo+rela FDC in the PD-L1 ≥ 1% subgroup:

- Box plots: frequency of baseline exploratory biomarker populations from multiparametric flow analyses. A Wilcox test was used to compare the differences of the mean of the different populations within each treatment arm.
- KM curves of OS:

- Median frequencies of baseline PD-1+ CD8 T cells in blood and median frequencies of baseline LAG-3+ CD8 T cells in blood or in tumour
- Overlay of KM curves by treatment and PD-L1 status and KM curves by PD-L1 cutoffs: 1-25%, 1-49%, and 1-75%

- Forest plots: log odds ratio of CR or PR per BICR and log HR for different immune cell populations by treatment arm and PD-L1 status:
  - log HRs derived from Cox proportional hazard models for OS and PFS analyses, and log OR for BOR derived from generalized linear models.
  - Forest plots based on an interaction model with treatment arm/PD-L1 1% cutoff status
  - Covariates used in the multivariate generalized model and Cox proportional hazards model included: Eastern Cooperative Oncology Group Performance Status (ECOG PS) (≥ 1 vs 0), age group, sex, geographic region (USA vs Rest of World), and BRAF mutation status (positive vs wild-type).
  - A Wald test was used to evaluate the significance of regression coefficients in the models.

Stacked bar plots: median frequency of different CD8 T cell populations at baseline (C1D1) and on-treatment (C2D1), faceted by treatment arm and PD-L1 tumor IHC status: 1) grouped by OS < or > 30 months and 2) grouped by PFS < or > 3 months.

Results

Updated descriptive 4-year efficacy data from pivotal Study CA224047 were submitted. At the time of the clinical DCO of 24-Sep-2024 for the CA224-047 Addendum 03 CSR, median follow-up was 34.9 months (range: 0.3 - 76.3).

Subject disposition

A similar proportion of subjects in each treatment arm (90.1% of subjects overall) had discontinued treatment, mainly due to disease progression (*Table 2*). Of the 714 treated subjects, 38.9% were ongoing in the study.

Table *2 Subject disposition – All treated subjects*

Status (%)	Nivo+rela FDC N = 355	Nivo N = 359	Total N = 714
ONGOING TREATMENT	38 (10.7)	33 (9.2)	71 (9.9)
DISCONTINUED TREATMENT	317 (89.3)	326 (90.8)	643 (90.1)
REASON FOR DISCONTINUATION OF TREATMENT			
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	38 (10.7)	32 (8.9)	70 (9.8)
SUBJECT WITHDREW CONSENT	1 (0.3)	4 (1.1)	5 (0.7)
DEATH	1 (0.3)	4 (1.1)	5 (0.7)
POOR/NON COMPLIANCE	1 (0.3)	0	1 (0.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (0.3)	1 (0.1)
OTHER	12 (3.4)	12 (3.3)	24 (3.4)
DISEASE PROGRESSION	162 (45.6)	201 (56.0)	363 (50.8)
STUDY DRUG TOXICITY	79 (22.3)	47 (13.1)	126 (17.6)
ADVERSE EVENT UNRELATED TO STUDY DRUG	17 (4.8)	21 (5.8)	38 (5.3)
MAXIMUM CLINICAL BENEFIT	6 (1.7)	3 (0.8)	9 (1.3)
DISEASE RECURRENCE	0	1 (0.3)	1 (0.1)
REASON FOR DISCONTINUATION OF TREATMENT DUE TO COVID-19	2 (0.6)	5 (1.4)	7 (1.0)
ONGOING STUDY	155 (43.7)	123 (34.3)	278 (38.9)
DISCONTINUED STUDY	200 (56.3)	236 (65.7)	436 (61.1)
REASON FOR DISCONTINUATION OF STUDY			
DEATH	177 (49.9)	208 (57.9)	385 (53.9)
LOST TO FOLLOW-UP	6 (1.7)	10 (2.8)	16 (2.2)
SUBJECT WITHDREW CONSENT	13 (3.7)	15 (4.2)	28 (3.9)
OTHER	3 (0.8)	2 (0.6)	5 (0.7)
NOT REPORTED	1 (0.3)	1 (0.3)	2 (0.3)
REASON FOR DISCONTINUATION OF STUDY DUE TO COVID-19	2 (0.6)	4 (1.1)	6 (0.8)
DEATH	2 (0.6)	4 (1.1)	6 (0.8)

- **Baseline data**

Baseline characteristics are described in the Opdualag EPAR. Briefly, a total of 714 patients were randomised to receive either nivolumab in combination with relatlimab (n = 355), or nivolumab (n = 359). Baseline characteristics in the ITT population were balanced between the two groups. The median age was 63 years (range: 20-94) with 47% ≥ 65 years of age and 19% ≥ 75 years of age. The majority of patients were white (97%) and male (58%). Baseline ECOG PS was 0 (67%) or 1 (33%). The majority of the patients had AJCC Stage IV disease (92%); 38.9% had M1c, 2.4% had M1d disease, 8.7% had prior systemic therapies, 36% had a baseline LDH level greater than ULN at study entry. Thirty nine percent of patients had BRAF mutation-positive melanoma, 75% had LAG-3 ≥ 1% and 41% of patients had PD-L1 ≥ 1% tumour cell membrane expression. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the two treatment groups. Results for baseline characteristics by baseline PD-L1 expression (< 1%, ≥ 1%) were generally consistent with those for all randomized subjects and balanced between the 2 treatment arms, except for LAG3-expression. For patients with PD-L1 <1%, 62.5% had LAG3 ≥1% and 19.7% had LAG3 ≥5%. On the other hand, for patients with PD-L1 ≥1%, 93.5% had LAG3 ≥ 1% and 58.7% had LAG3 ≥5%.

- **Subsequent anti-cancer therapy**

Overall, about 40% of all randomized subjects received subsequent systemic anti-cancer therapy, mostly PD-1/CTLA4 inhibitors (about 16%-20%) and targeted BRAF/MEK treatment (about 15%). Results for subsequent anti-cancer therapy by baseline PD-L1 expression (< 1%, ≥ 1%) are shown in *Table 3*. In the PD-L1 ≥ 1% subgroup, a smaller proportion of nivo+rela FDC- than nivo-treated subjects received subsequent therapy (42.5% vs 50.3%). This was driven by a lower proportion of nivo+rela FDC than nivo-treated subjects who received subsequent systemic therapy (30.8% vs 37.4%), and especially PD-1/CTLA4 inhibitors (10.3% vs 19.7%). Reasons for not receiving subsequent systemic therapy have not been reported.

Table *3 Subsequent cancer therapy by baseline PD-L1 expression (< 1%, ≥ 1%) – All randomized subjects*

	Number of Subjects (%)	
Subgroup: PD-L1 Expression < 1%	Nivo + Rela FDC N = 209	Nivo N = 212
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	113 (54.1)	108 (50.9)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	36 (17.2)	32 (15.1)
SUBJECTS WHO RECEIVED ALLOWED ON-TREATMENT RADIOTHERAPY (%)	32 (15.3)	27 (12.7)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	19 (9.1)	26 (12.3)
SUBJECTS WHO RECEIVED ALLOWED ON-TREATMENT SURGERY (%)	16 (7.7)	21 (9.9)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	93 (44.5)	89 (42.0)
PD-1/CTLA4 INHIBITORS	42 (20.1)	42 (19.8)
AVELUMAB	0	1 (0.5)
BMS-986218	1 (0.5	1 (0.5)
CEMIPLIMAB	0	1 (0.5)
DURVALUMAB	0	2 (0.9)
IPILIMUMAB	13 (6.2)	13 (6.1)
IPILIMUMAB;NIVOLUMAB	14 (6.7)	19 (9.0)
NIVOLUMAB	14 (6.7)	15 (7.1)
PEMBROLIZUMAB	6 (2.9)	6 (2.8)
PEMBROLIZUMAB;QUAVONLIMAB	1 (0.5)	0
PEMBROLIZUMAB;TALIMOGENE LAHERPAREPVEC	2 (1.0)	1 (0.5)
QUAVONLIMAB	1 (0.5)	0
TARGETED BRAF/MEK MONO AND COMBO	33 (15.8)	36 (17.0)
OTHER	38 (18.2)	45 (21.2)
Subgroup: PD-L1 Expression ≥ 1%	Nivo + Rela FDC N = 146	Nivo N = 147
SUBJECTS WITH ANY SUBSEQUENT THERAPY (%) (1)	62 (42.5)	74 (50.3)
SUBJECTS WHO RECEIVED SUBSEQUENT RADIOTHERAPY (%)	25 (17.1)	24 (16.3)
SUBJECTS WHO RECEIVED ALLOWED ON-TREATMENT RADIOTHERAPY (%)	19 (13.0)	19 (12.9)
SUBJECTS WHO RECEIVED SUBSEQUENT SURGERY (%)	16 (11.0)	18 (12.2)
SUBJECTS WHO RECEIVED ALLOWED ON-TREATMENT SURGERY (%)	14 (9.6)	15 (10.2)
SUBJECTS WHO RECEIVED SUBSEQUENT SYSTEMIC THERAPY (%)	45 (30.8)	55 (37.4)
PD-1/CTLA4 INHIBITORS	15 (10.3)	29 (19.7)
BOTENSILIMAB	1 (0.7)	0
IPILIMUMAB	5 (3.4)	10 (6.8)
IPILIMUMAB;NIVOLUMAB	4 (2.7)	10 (6.8)
NIVOLUMAB	7 (4.8)	13 (8.8)
PEMBROLIZUMAB	1 (0.7)	5 (3.4)
QUAVONLIMAB	1 (0.7)	0
TARGETED BRAF/MEK MONO AND COMBO	20 (13.7)	21 (14.3)
OTHER	18 (12.3)	20 (13.6)

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

A table of subsequent therapies before unblinding of the study was also provided. The majority of patients who received any subsequent therapy did so in the blinded phase of the study (56/62 (90%) in the nivo + rela arm and 64/74 (86%) in the nivo arm) (data not shown).

Outcomes and estimation

Intention-to-treat population

The results at the time of approval as well as the updated 4-year data for PFS and OS are shown in the ITT population (*Table 4* and *Figure 3 Overall Survival – All randomised subjects*) and by PD-L1 subgroup (*Table 5* and *Figure 5*).

For the ITT, median OS has been reached in the nivo+rela arm with the updated results; mOS was 53.3 months vs 33.2 months in the nivo monotherapy arm (HR: 0.77; 95% CI: 0.64, 0.94).

In a new supportive analysis (Competing Risk Time to Event Analysis), nivo+rela FDC lowered the risk of melanoma specific death compared with nivo: HR = 0.74 (95% CI: 0.59, 0.92).

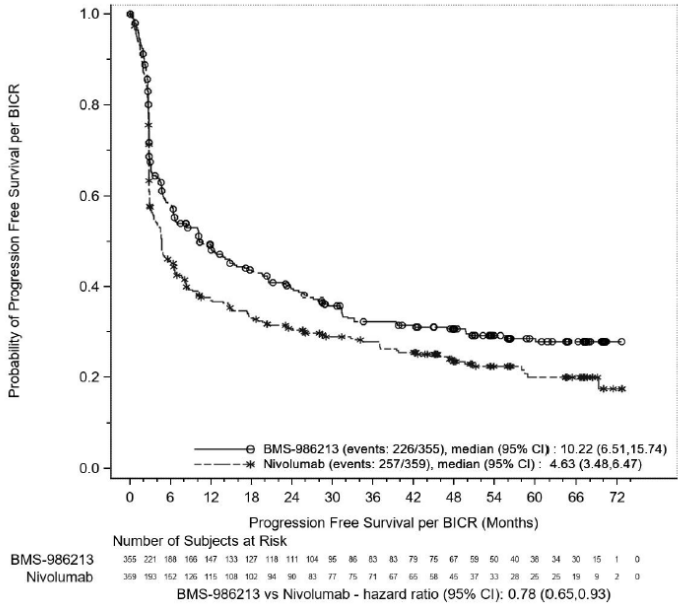
PFS results and ORR in the ITT remained consistent across the two data cuts in favour of nivo+rela FDC.

Table *4 Summary of key efficacy results from study CA224047 – All randomized subjects (ITT)*

	Data from Addendum 01		Updated 4-Year Data	
	Clinical Data Cutoff: 07-Sep-2021 Minimum FU: 8.7 months		Clinical Data Cutoff: 24-Sep-2024 Minimum FU: 45.3 months	
Endpoints	**Nivo+Rela FDC N = 355**	**Nivo N = 359**	**Nivo+Rela FDC N = 355**	**Nivo N = 359**
Overall Survival				
Events, n (%)	137 (38.6)	160 (44.6)	182 (51.3)	218 (60.72)
Median OS (95% CI), mo[a]	NA (34.20, NA)	34.10 (25.23, NA)	53.26 (34.04, NA)	33.18 (25.23, 45.77)
HR (95% CI)[b]	0.80 (0.64, 1.01); p = 0.0593[c]		0.77 (0.64, 0.94)	
OS Rates (95% CI), %[a]				
12-month	77.0 (72.2, 81.1)	71.6 (66.6, 76.0)	76.7 (72.0, 80.8)	71.4 (66.5, 75.8)
24-month	63.7 (58.1, 68.7)	58.3 (52.7, 63.4)	61.9 (56.6, 66.7)	57.9 (52.6, 62.8)
36-month	55.8 (49.8, 61.4)	48.8 (42.7, 54.7)	54.6 (49.3, 59.7)	47.8 (42.5, 52.9)
48-month	--	--	52.0 (46.6, 57.1)	42.8 (37.5, 47.9)
Supportive Analysis, Competing Risk Time to Event Analysis:[d] HR (95% CI)				
Melanoma specific death (n = 317)/ death due to other reason (n = 83)	Not available		0.74 (0.59, 0.92)	
PFS per BICR (Primary Definition)[e]				
Events, n (%)	204 (57.5)	233 (64.9)	226 (63.7)	257 (71.6)
Median PFS (95% CI), mo.[a]	10.22 (6.51, 14.75)	4.63 (3.48, 6.44)	10.22 (6.51, 15.74)	4.63 (3.48, 6.47)
HR (95% CI)[b]	0.78 (0.64, 0.94)		0.78 (0.65, 0.93)	
PFS Rates (95% CI), %[a]				
12-month	48.0 (42.5, 53.4)	36.9 (31.7, 42.1)	48.9 (43.4, 54.2)	36.9 (31.8, 42.1)
24-month	38.5 (32.7, 44.2)	29.0 (23.8, 34.4)	39.6 (34.2, 45.0)	30.7 (25.8, 35.8)
36-month	28.5 (21.9, 35.5)	25.5 (19.7, 31.6)	32.2 (27.0, 37.5)	27.8 (23.0, 32.8)
48-month	--	--	30.6 (25.4, 35.9)	23.6 (18.9, 28.5)
Confirmed ORR per BICR				
N events (responders %)	153 (43.1)	117 (32.6)	156 (43.9)	120 (33.4)
95% CI[f]	37.9, 48.4	27.8, 37.7	38.7, 49.3	28.6, 38.6
ORR Diff. (95% CI), %[g]	10.3 (3.4, 17.3)		10.3 (3.3, 17.3)	
Odds ratio (95% CI) [g]	1.58 (1.16, 2.15)		1.57 (1.15, 2.14)	

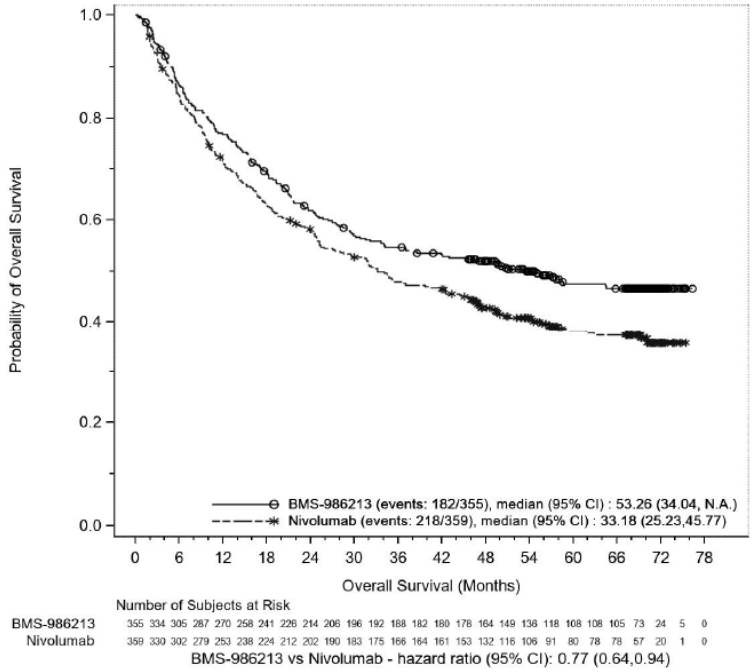
[a] Based on KM estimates; [b] Stratified Cox proportional hazards model. HR is nivo+rela over nivo;
[c] O'Brien Fleming boundary for significance of OS final analysis is p < 0.04302 (2-sided);
[d] HR using the Fine and Gray method which uses a cumulative incidence function to derive sub-distribution hazards;
[e] Censoring at the last evaluable tumor assessment on or prior to the date of subsequent therapy

Figure 2 PFS per BICR, Primary definition – All randomised subjects



Note: Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3 (≥ 1% vs < 1%), BRAF (mutation positive vs mutation wild-type), AJCC M-Stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from the statistical model because it led to subgroups with fewer than 10 subjects.
Symbols represent censored observations. The number of subjects at risk in the KM plot corresponds to every 3-month intervals, regardless of the x-axis tick marks, which are labelled at 6-month intervals for visual clarity.
Clinical Data Cutoff: 24-Sep-2024; Minimum FU: 45.3 months
Source: Figure 7.2-1 in CA224047 Addendum 03

Figure 3 Overall Survival – All randomised subjects



Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3 (≥ 1% vs < 1%), BRAF (mutation positive vs mutation wild-type), AJCC M-stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from the statistical model because it led to subgroups with fewer than 10 subjects.
Symbols represent censored observations.
The number of subjects at risk in the KM plot corresponds to every 3-month intervals, regardless of the x-axis tick marks, which are labelled at 6-month intervals for visual clarity.
Clinical Data Cutoff: 24-Sep-2024; Minimum FU: 45.3 months
Source: Figure 7.3-1 in CA224047 Addendum 03

PD-L1 (< 1%, ≥ 1%) subgroups

PD-L1 ≥ 1% subgroup

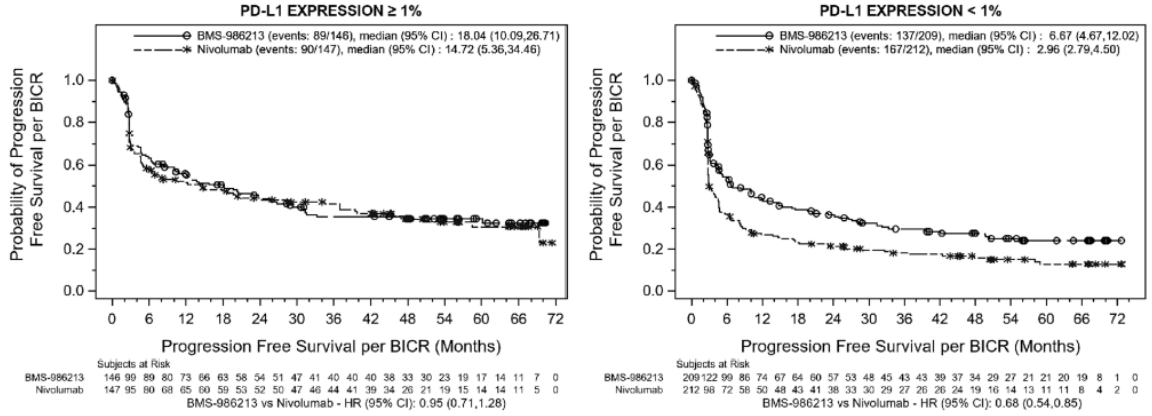
Within the PD-L1 ≥1% subgroup, mOS was not reached in the nivo+rela arm and 42.0 months in the nivo mono arm (HR: 0.76, 95% CI: 0.55, 1.05) based on the 4-year update. The 36-month OS rates were 59.8% with nivo+rela FDC and 52.0% with nivo monotherapy.

Median PFS in the nivo+rela FDC arm increased from 15.7 to 18.0 months and remained consistent in the nivo monotherapy arm (14.7 months) (HR: 0.95; 95% CI: 0.71, 1.28). ORR remained consistent with the primary analysis.

Table 5 Summary of efficacy results by PD-L1 expression (< 1%, ≥ 1%)

	Data from Addendum 01				Updated 4-Year Data			
	Clinical Data Cutoff: 07-Sep-2021 Minimum FU: 8.7 months				Clinical Data Cutoff: 24-Sep-2024 Minimum FU: 45.3 months			
	PD-L1 ≥ 1%		PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 1%	
	Nivo+Rela FDC N = 146	Nivo N = 147	Nivo+Rela FDC N = 209	Nivo N = 212	Nivo+Rela FDC N = 146	Nivo N = 147	Nivo+Rela FDC N = 209	Nivo N = 212
OS								
HR (95% CI)	0.84 (0.57, 1.24)		0.78 (0.59, 1.04)		0.76 (0.55, 1.05)		0.79 (0.62, 1.01)	
Events, n	48	56	89	104	65	82	117	136
Median OS, mo. (95% CI)	NA (NA, NA)	NA (31.97, NA)	NA (27.43, NA)	27.04 (17.12, NA)	NA (41.89, NA)	41.95 (31.70, NA)	38.28 (24.31, 58.64)	25.82 (18.73, 42.41)
OS Rates, (95% CI) %								
12-month	Not Available				81.4 (74.1, 86.9)	77.6 (69.9, 83.5)	73.5 (66.9, 78.9)	67.2 (60.4, 73.1)
24-month	Not Available				68.2 (60.0, 75.1)	64.6 (56.3, 71.7)	57.4 (50.3, 63.8)	53.1 (46.1, 59.6)
36-month	Not Available				59.8 (51.3, 67.3)	52.0 (43.6, 59.8)	51.0 (44.0, 57.6)	44.9 (38.0, 51.5)
48-month	Not Available				56.1 (47.6, 63.8)	45.4 (37.1, 53.3)	49.0 (42.0, 55.6)	40.9 (34.1, 47.5)
Supportive Analysis, Competing Risk Time to Event Analysis (95% CI)								
Melanoma specific death/death due to other reason	Not Available				0.76 (0.53, 1.10)		0.72 (0.55, 0.95)	
PFS per BICR								
HR (95% CI)	0.96 (0.70, 1.31)		0.68 (0.53, 0.86)		0.95 (0.71, 1.28)		0.68 (0.54, 0.85)	
Events, n	80	78	124	155	89	90	137	167
Median PFS, mo. (95% CI)	15.74 (10.12, 28.45)	14.72 (5.36, 22.97)	6.67 (4.67, 11.99)	2.96 (2.79, 4.50)	18.04 (10.09, 26.71)	14.72 (5.36, 34.46)	6.67 (4.67, 12.02)	2.96 (2.79, 4.50)
PFS Rates, (95% CI) %								
12-month	Not Available				56.0 (47.4, 63.8)	51.5 (42.9, 59.5)	43.5 (36.3, 50.5)	26.7 (20.8, 33.1)
24-month	Not Available				44.1 (35.6, 52.3)	44.2 (35.7, 52.4)	36.3 (29.3, 43.2)	21.4 (15.9, 27.4)
36-month	Not Available				35.5 (27.4, 43.8)	41.6 (33.1, 49.8)	29.7 (23.0, 36.6)	18.2 (13.1, 24.1)
48-month	Not Available				34.6 (26.4, 42.8)	34.4 (26.0, 42.9)	27.6 (21.1, 34.5)	16.0 (11.1, 21.8)
ORR per BICR								
CR+PR, n (%)	77 (52.7)	66 (44.9)	76 (36.4)	51 (24.1)	77 (52.7)	66 (44.9)	79 (37.8)	54 (25.5)
95% CI	44.3, 61.1	36.7, 53.3	29.8, 43.3	18.5, 30.4	44.3, 61.1	36.7, 53.3	31.2, 44.7	19.8, 31.9
ORR Diff. (95% CI), %	7.8 (-3.6, 19.0)		12.3 (3.5, 20.8)		7.8 (-3.6, 19.0)		12.3 (3.4, 21.0)	
Odds ratio (95% CI)	1.37 (0.86, 2.17)		1.80 (1.18, 2.75)		1.37 (0.86, 2.17)		1.78 (1.17, 2.70)	

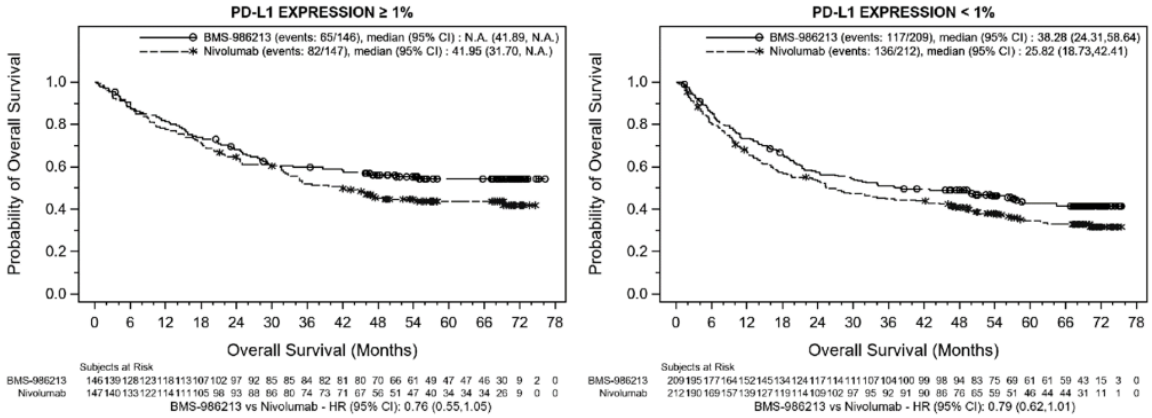
Figure 4 Progression-Free Survival per BICR by baseline PD-L1 (≥ 1%, < 1%) expression



Symbols represent censored observations.

Source: Figure 14.6.3.1 in in CA224047 Addendum 03[4]

Figure 5 Overall survival by baseline PD-L1 (< 1%, ≥ 1%) expression – All randomised subjects



Symbols represent censored observations.
The number of subjects at risk in the KM plot corresponds to every 3-month intervals, regardless of the x-axis tick marks, which are labelled at 6-month intervals
for visual clarity.
Source: Figure 7.5.1-2 in CA224047 Addendum 03

Of note, results for the approved PD-L1 < 1% subgroup were overall consistent with the initial analyses. Median OS has now been reached in the nivo+rela arm; mOS was 38.3 months vs 25.8 months in the nivo mono arm (HR: 0.79, 95% CI: 0.62, 1.01).

Additional efficacy sensitivity analyses to support the PD-L1 ≥ 1% subgroup

- Competing risk for melanoma specific survival

Nivo+rela FDC numerically lowered the risk (sub-distribution HR = 0.76; 95% CI: 0.53, 1.10, same estimates for the 4- and 5-year data) of melanoma specific death compared with nivo. The estimate for the cause-specific hazard ratio based on the 5-year data was consistent with the sub-distribution hazard ratio (HR = 0.75; 95% CI: 0.52, 1.08).

- Sensitivity analyses for OS

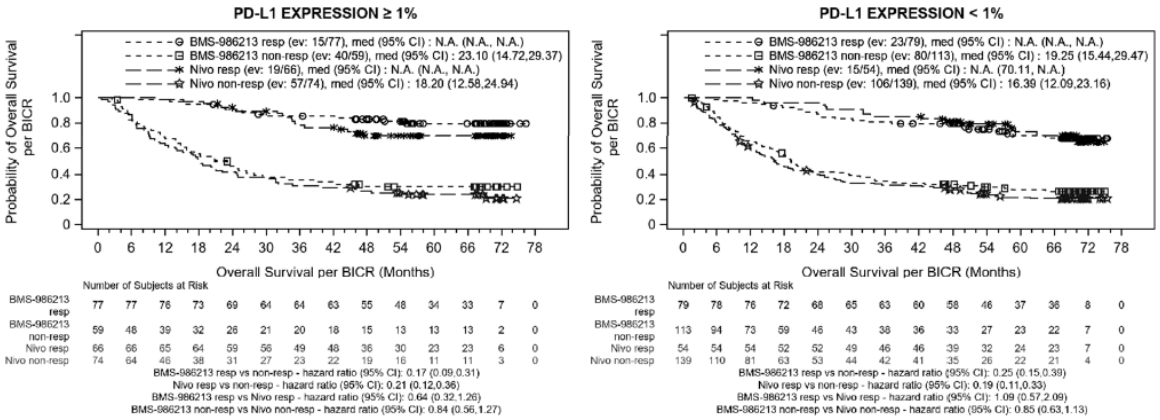
Table 6 Overall Survival Sensitivity Analyses for Nivo+Rela FDC vs Nivo by PD-L1 (≥1%, <1%) Subgroups: All Randomized Subjects

	Results	
Sensitivity Analyses	**PD-L1 ≥ 1% (N = 293)**	**PD-L1 < 1% (N = 421)**
Overall Survival, HR (95% CI)	**0.76 (0.55, 1.05)**	**0.79 (0.62, 1.01)**
Restricted Mean Survival Time (RMST) using a Chi-square test		
RMST with prespecified Tau (60 months: time point up to which the area under the survival curve is calculated to determine RMST)	p = 0.2147 RMST difference = 3.32 (95% CI: -1.92, 8.56)	p = 0.1063 RMST difference = 3.80 (95% CI: -0.81, 8.41)
RMST minimax (74.64 for PD-L1 ≥ 1% and 75.43 for PD-L1 < 1%) based on the minimum of the maximum observed event or censoring time between the 2 treatment arms.	p = 0.1512 RMST difference = 4.97 (95% CI: -1.82, 11.76)	p = 0.0818 RMST difference = 5.21 (95% CI: -0.66, 11.08)
Fleming-Harrington weighted log-rank test to account for delayed effect		
Overall	p = 0.1005	p = 0.0582
Early difference	p = 0.1704	p = 0.0627
Middle difference	p = 0.0564	p = 0.1189
Late difference	p = 0.0402	p = 0.1144
MaxCombo test using a weighted log-rank test	p = 0.0694	p = 0.1025
Piecewise exponential HR using a Cox proportional hazard model, HR (95% CI)		
0 to ≤ 9 months	0.89 (0.50, 1.57)	0.79 (0.53, 1.18)
9 to ≤ 18 months	0.92 (0.46, 1.82)	0.71 (0.43, 1.16)
18 to ≤ 27 months	0.82 (0.39, 1.73)	1.14 (0.59, 2.21)
27 to ≤ 36 months	0.52 (0.21, 1.30)	0.88 (0.37, 2.12)
36 to ≤ 45 months	0.53 (0.13, 2.20)	0.71 (0.19, 2.65)
45 to ≤ 54 months	0.49 (0.12, 2.04)	0.50 (0.16, 1.54)
> 54 months	0.41 (0.04, 4.47)	0.66 (0.24, 1.82)
Multivariate Cox model (unstratified) adjusted for baseline factors, HR (95% CI): LDH (≤ ULN, > ULN), metastasis stage (M1a/M1b/M0, M1/M1c/M1d), ECOG PS (0, 1), BRAF (wild type, positive), melanoma subtype (cutaneous non acral, acral/mucosal/other), dNLR (derived neutrophil-to-lymphocyte ratio at baseline).	0.68 (0.49, 0.96) p = 0.0258 LDH, melanoma subtype, and dNLR were significant prognostic variables.	0.71 (0.55, 0.92) p = 0.0086 ECOG PS, LDH, melanoma subtype, and dNLR were significant prognostic variables.
Multivariate Cox model (unstratified) adjusted for baseline factors, includes factors corresponding to tumor burden, HR (95% CI): LDH (≤ ULN, > ULN), ECOG PS (0, 1), melanoma subtype (cutaneous non acral, acral/mucosal/other), dNLR (derived neutrophil-to-lymphocyte ratio at baseline), count of lesions, sum of reference diameters for target lesions.	0.60 (0.42, 0.85) p = 0.0044 All baseline factors were significant prognostic variables except ECOG PS and sum of reference diameters for target lesions.	0.71 (0.54, 0.94) p = 0.0150 All baseline factors were significant prognostic variables in this model.
Subjects with ≤ X year(s) of treatment, HR (95% CI). HR from unstratified Cox proportional hazard model:		
≤ 1 year	0.84 (0.58, 1.21)	0.70 (0.53, 0.92)
≤ 2 years	0.72 (0.52, 1.01)	0.75 (0.58, 0.97)
≤ 3 years	0.71 (0.51, 0.99)	0.74 (0.58, 0.95)

Clinical Data Cutoff: 24-Sep-2024; Minimum FU: 45.3 months

- Overall Survival in responders and non-responders in in PD-L1 (≥1%, < 1%) Subgroups

Table 7 Overall Survival by Responder (CR+PR)/Non-Responder per BICR All Randomised Subjects by Baseline PD-L1 Expression



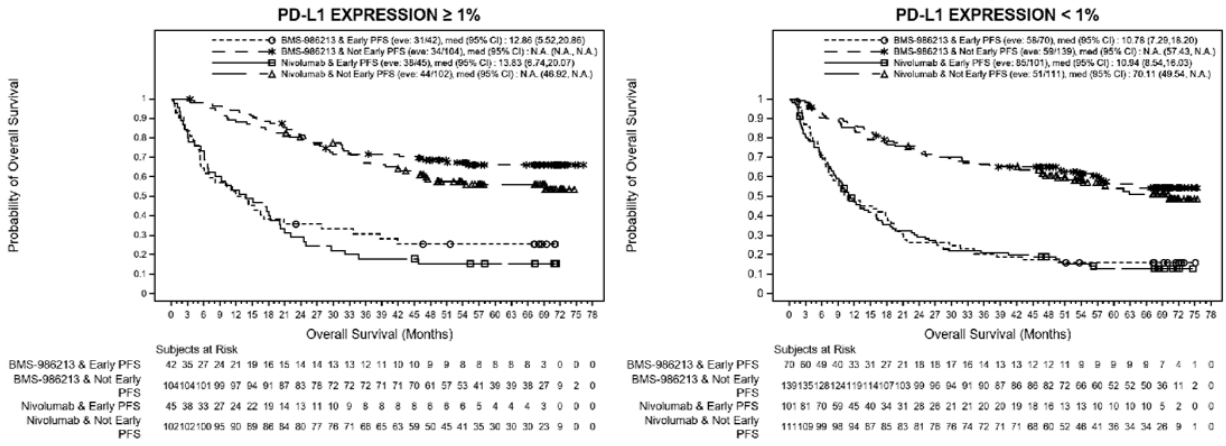
Symbols represent censored observations. HR from unstratified Cox proportional hazard model. Excludes subjects with response of unable to determine.
resp = responders which are CR+PR; non-resp = non-responders which are SD, PD, and non CR/non PD
Source: Figure 14.6.2.2 in Appendix 2

- Overall Survival in Subjects with Early (≤3 months) or Late (> 3 months) PFS Events

Table 8 Subjects with a PFS Events (≤3 or > 3 months) by Baseline PD-L1 (≥ 1%, <1%) Expression: All Randomised Subjects

	PD-L1 ≥ 1%		PD-L1 < 1%	
	Nivo + Rela FDC (N = 146)	Nivo (N = 147)	Nivo + Rela FDC (N = 209)	Nivo (N = 212)
Early PFS Events (≤ 3 months)				
Progression	36 (24.7)	42 (28.6)	65 (31.1)	95 (44.8)
Death without Progression	6 (4.1)	3 (2.0)	5 (2.4)	6 (2.8)
Progression or Death	42 (28.8)	45 (30.6)	70 (33.5)	101 (47.6)
Cumulative PFS Events > 3 months				
Progression	38 (26.0)	35 (23.8)	53 (25.4)	59 (27.8)
Death without Progression	9 (6.2)	10 (6.8)	14 (6.7)	7 (3.3)
Progression or Death	47 (32.2)	45 (30.6)	67 (32.1)	66 (31.1)

Figure 6 Overall Survival for Subjects With and Without an Early PFS Event (⩽ 3 months), per BICR: All Randomized Subjects by Baseline PD-L1(⩾ 1%, < 1%) Expression

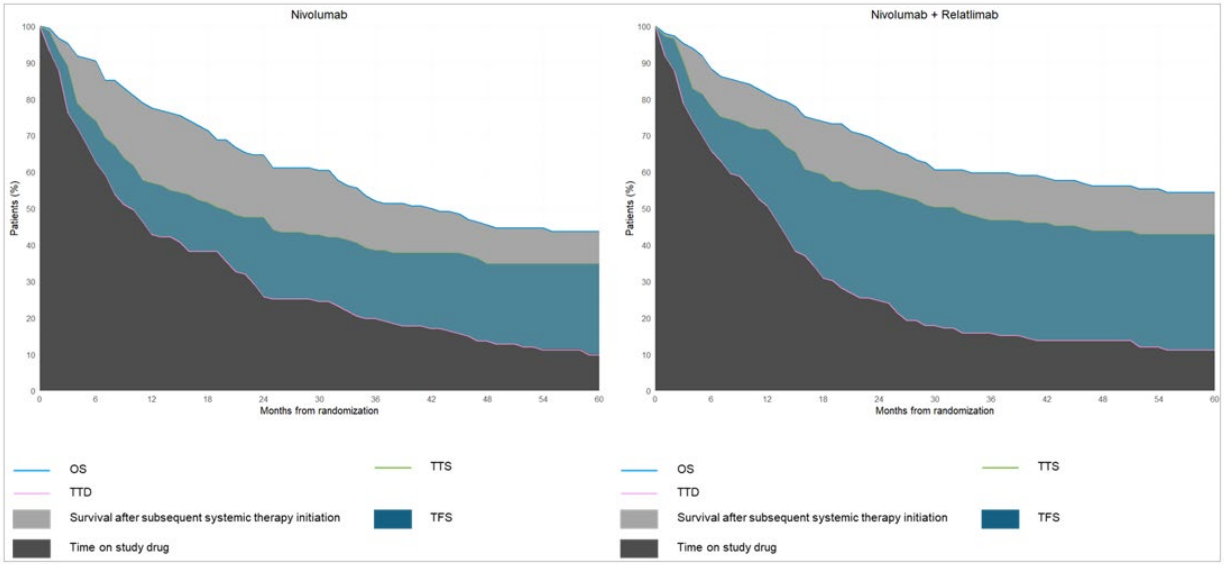


Symbols represent censored observations.
Subjects who had a PFS event, per BICR, defined as progression or death occurring within 3 months of randomization, are considered to have experienced an early PFS event.

Treatment-free survival

Subjects treated with nivo+rela FDC had longer TFS than subjects treated with nivo (*Figure 7*). RMST estimates of TFS over 60 months were 16.07 vs 10.43 months with nivo+rela FDC and nivo, respectively.

Figure 7 Kaplan-Meier Estimates of Treatment-Free Survival (TFS), Time to Protocol Therapy Cessation or Death (TTD), Time to Subsequent Systemic Anticancer Therapy Initiation or Death (TTS) and Overall Survival (OS) in the PD-L1 ⩾ 1% Subgroup



Target lesion reduction

A total of 52.1% (nivo+rela FDC) vs 40.8% (nivo) of subjects had a ≥ 50% reduction in target lesion burden.

Descriptive data from the final 5-year survival follow-up

The MAH presented descriptive OS data from the final 5-year survival follow-up with a median follow-up time of 35.14 (range: 0.3, 88.1) months (DCO: 25 Sep 2025). For the ITT, mOS was 54.8 months in the nivo+rela arm vs 33.2 months in the nivo monotherapy arm (HR: 0.80; 95% CI: 0.67, 0.94).

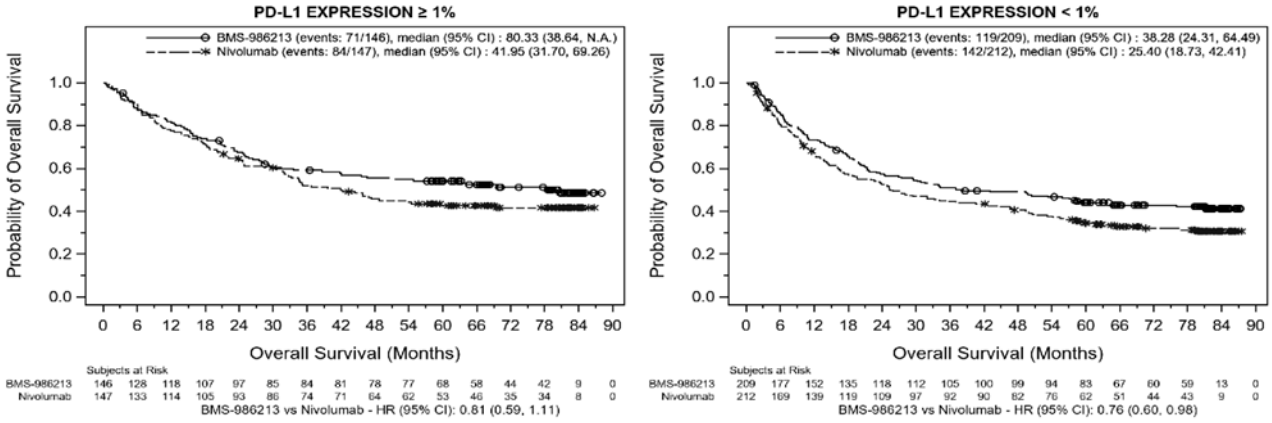
Results for the PD-L1 subgroups are shown below:

Table 9. Summary of OS results by PD-L1 expression at 5-year data cutoff (25-Sep-2025)

Overall Survival	PD-L1 < 1%			PD-L1 ≥ 1%	
		Nivo+rela FDC (n=209)	Nivo (n=212)	Nivo+rela FDC (n=146)	Nivo (n=147)
	HR (95% CI)	0.76 (0.60, 0.98)		0.81 (0.59, 1.11)	
	Events, n	119	142	71	84
	Median OS, Months (95% CI)	38.28 (24.31, 64.49)	25.50 (18.73, 42.41)	80.33 (38.64, N.A.)	41.95 (31.70, 69.26

CI: confidence interval based on the Clopper and Pearson method. PD-L1 vales were evaluated at LabCorp L.A.; N.A.: Not applicable, median or limit of CI not estimable.

Figure 8. Kaplan-Meier plot of OS by baseline PD-L1 biomarker expression – All randomized subjects (DCO: 25-Sep-2025).



Ancillary analyses

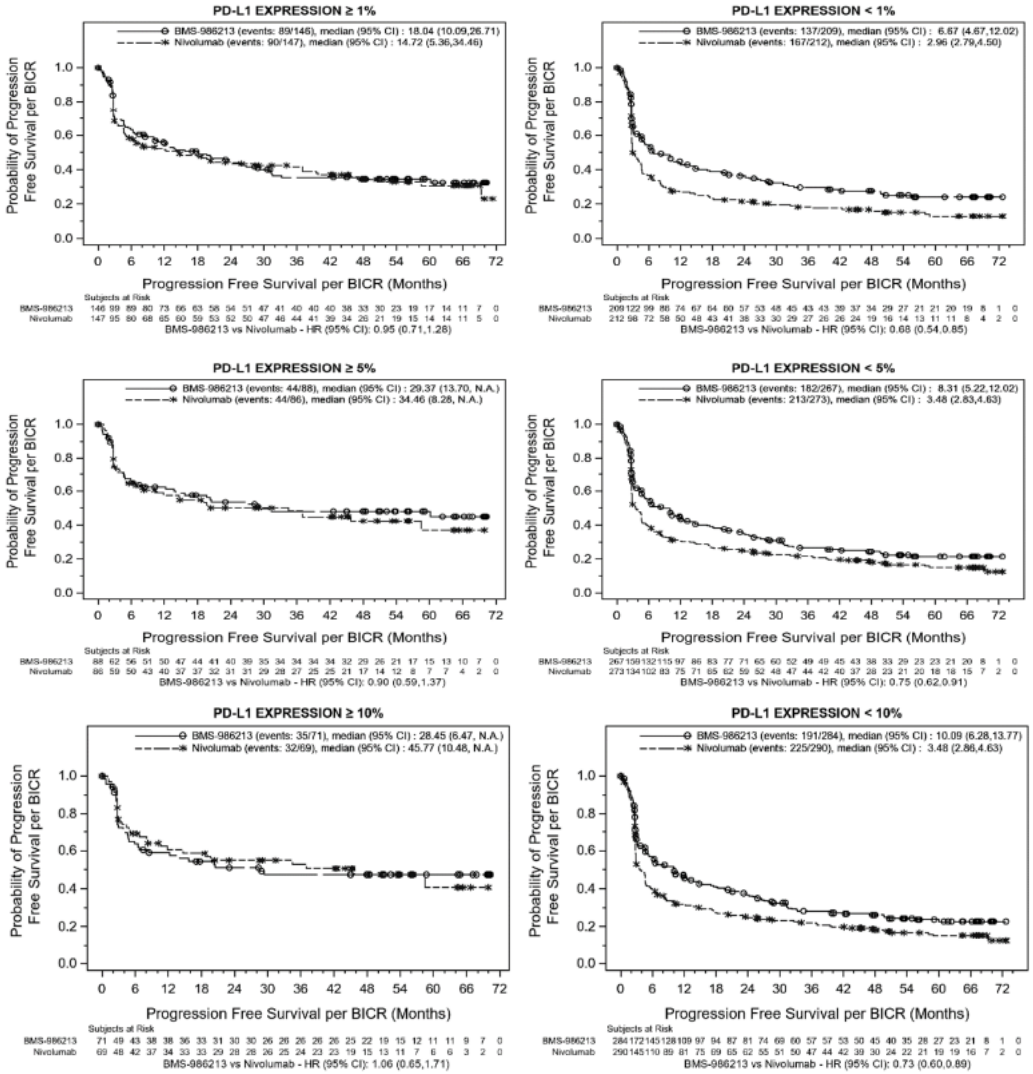
Preplanned biomarker analyses (exploratory endpoints)

- Efficacy results by different PD-L1 cutoffs (1%, 5% and 10%)

Table *10*. Efficacy by Baseline Tumour Cell PD-L1 Expression Levels - All Randomised Subjects

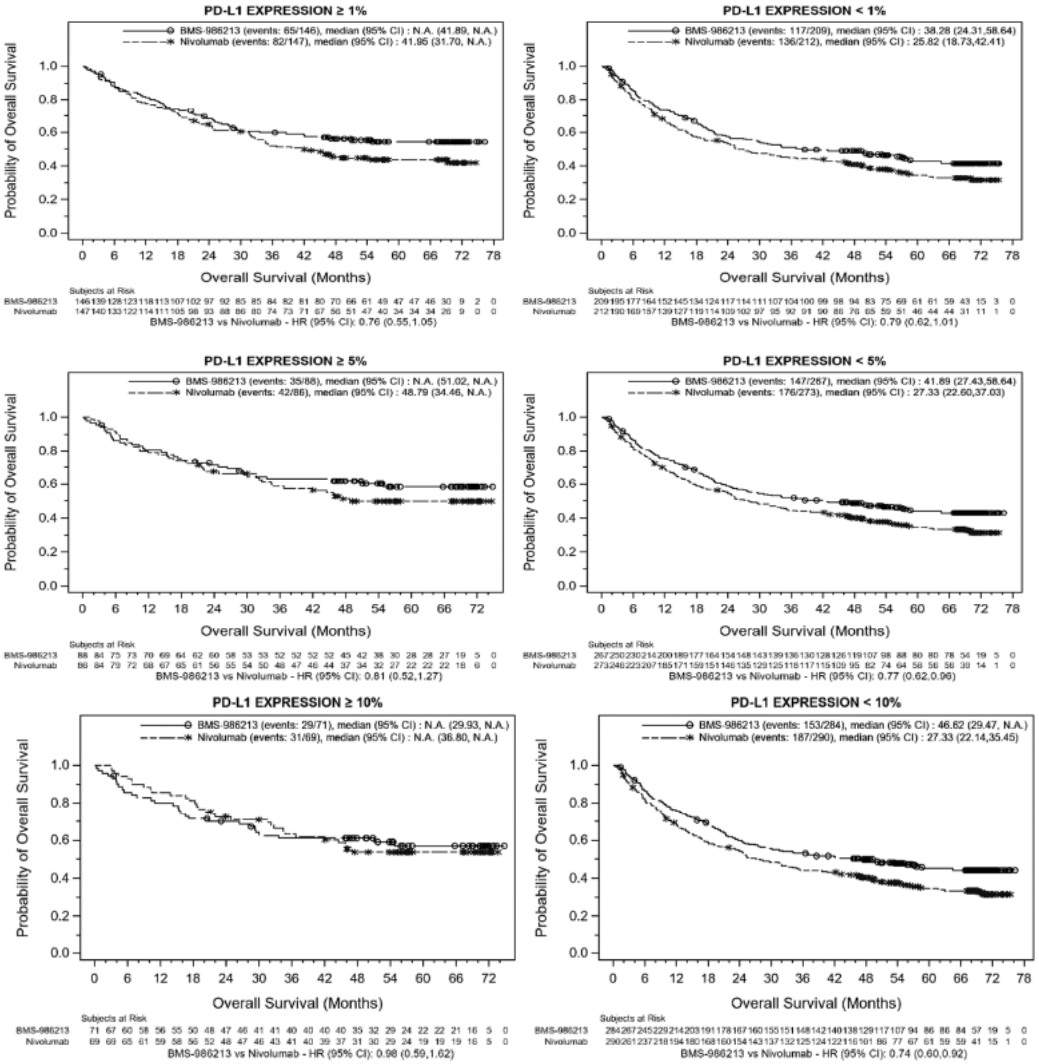
	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	BMS-986213 N = 209	Nivolumab N = 212	BMS-986213 N = 146	Nivolumab N = 147	BMS-986213 N = 267	Nivolumab N = 273	BMS-986213 N = 88	Nivolumab N = 86	BMS-986213 N = 284	Nivolumab N = 290	BMS-986213 N = 71	Nivolumab N = 69
PFS per BICR												
HR (95% CI)	0.68 (0.54, 0.85)		0.95 (0.71, 1.28)		0.75 (0.62, 0.91)		0.90 (0.59, 1.37)		0.73 (0.60, 0.89)		1.06 (0.65, 1.71)	
Events, n	137	167	89	90	182	213	44	44	191	225	35	32
Median PFS, mo. (95% CI)	6.67 (4.67, 12.02)	2.96 (2.79, 4.50)	18.04 (10.09, 26.71)	14.72 (5.36, 34.46)	8.31 (5.22, 12.02)	3.48 (2.83, 4.63)	29.37 (13.70, N.A.)	34.46 (8.28, N.A.)	10.09 (6.28, 13.77)	3.48 (2.86, 4.63)	28.45 (6.47, N.A.)	45.77 (10.48, N.A.)
OS												
HR (95% CI)	0.79 (0.62, 1.01)		0.76 (0.55, 1.05)		0.77 (0.62, 0.96)		0.81 (0.52, 1.27)		0.74 (0.60, 0.92)		0.98 (0.59, 1.62)	
Events, n	117	136	65	82	147	176	35	42	153	187	29	31
Median OS, mo. (95% CI)	38.28 (24.31, 58.64)	25.82 (18.73, 42.41)	N.A. (41.89, N.A.)	41.95 (31.70, N.A.)	41.89 (27.43, 58.64)	27.33 (22.60, 37.03)	N.A. (51.02, N.A.)	48.79 (34.46, N.A.)	46.62 (29.47, N.A.)	27.33 (22.14, 35.45)	N.A. (29.93, N.A.)	N.A. (36.80, N.A.)
ORR per BICR												
CR+PR, n (%)	79 (37.8)	54 (25.5)	77 (52.7)	66 (44.9)	102 (38.2)	79 (28.9)	54 (61.4)	41 (47.7)	114 (40.1)	83 (28.6)	42 (59.2)	37 (53.6)
95% CI	31.2, 44.7	19.8, 31.9	44.3, 61.1	36.7, 53.3	32.3, 44.3	23.6, 34.7	50.4, 71.6	36.8, 58.7	34.4, 46.1	23.5, 34.2	46.8, 70.7	41.2, 65.7

Figure 9. Kaplan-Meier Plot of PFS per BICR by Baseline PD-L1 Expression - All Randomised Subjects



Symbols represent censored observations. PD-L1 values were evaluated using the PD-L1 28-8 IUO IHC assay at LabCorp LA. N.A.: Not Applicable.

Figure *10*. Kaplan-Meier Plot of OS by Baseline PD-L1 Expression - All Randomised Subjects



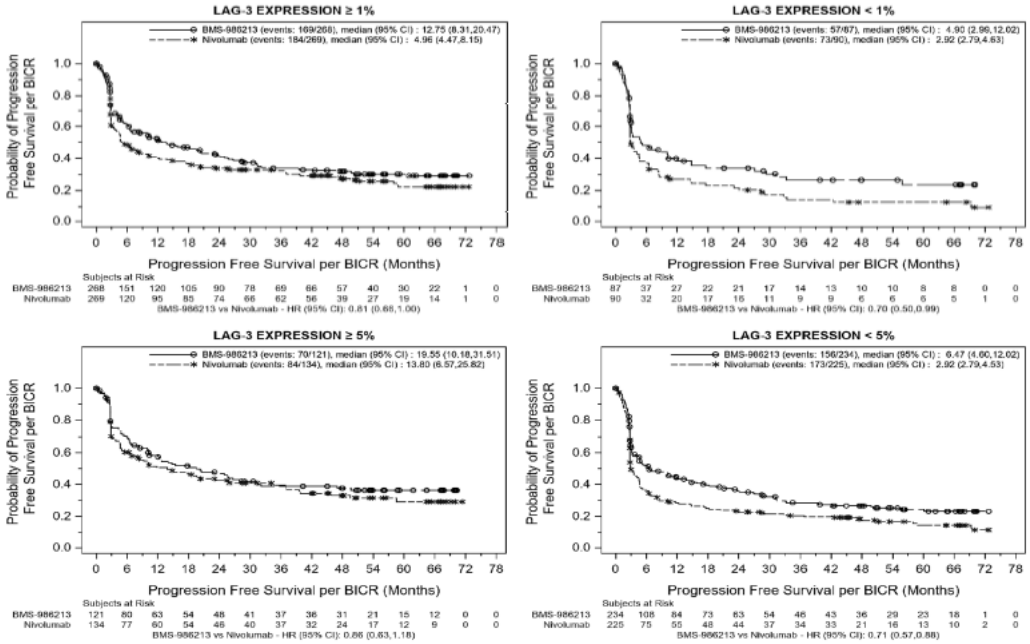
Symbols represent censored observations. PD-L1 values were evaluated using the PD-L1 28-8 IUO IHC assay at LabCorp LA. N.A.: Not Applicable.

- Efficacy by different LAG3-expression cutoffs (1%, 5%)

Table *11*. Efficacy by Baseline LAG-3 Expression Levels - All Randomised Subjects

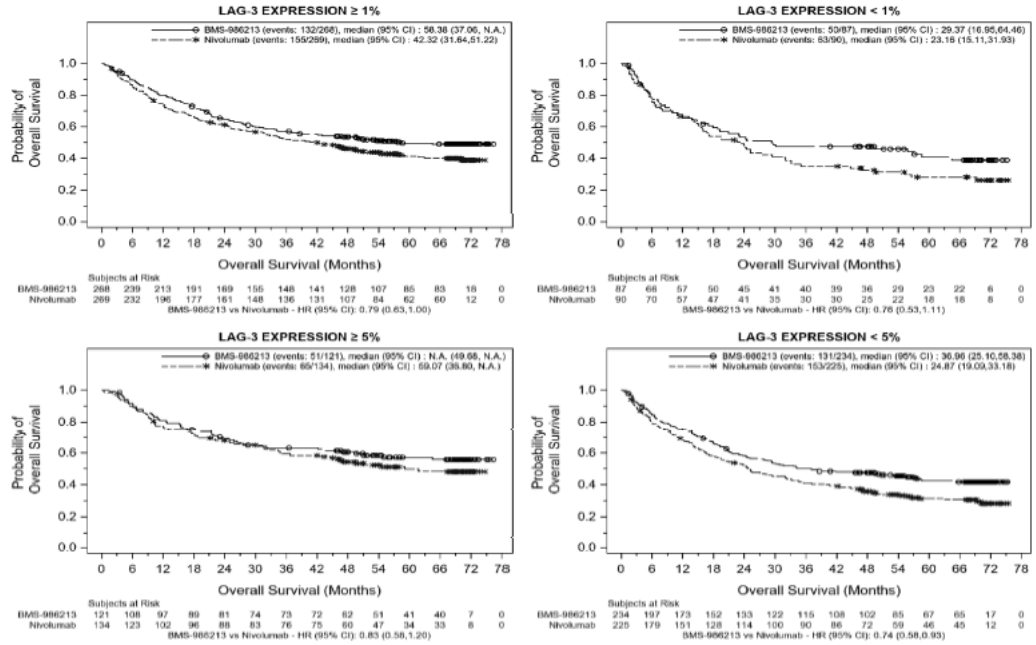
	LAG-3 Expression < 1%		LAG-3 Expression ≥ 1%		LAG-3 Expression < 5%		LAG-3 Expression ≥ 5%	
	BMS-986213 N = 87	Nivolumab N = 90	BMS-986213 N = 268	Nivolumab N = 269	BMS-986213 N = 234	Nivolumab N = 225	BMS-986213 N = 121	Nivolumab N = 134
PFS per BICR								
HR (95% CI)	0.70 (0.50, 0.99)		0.81 (0.66, 1.00)		0.71 (0.57, 0.88)		0.86 (0.63, 1.18)	
Events, n	57	73	169	184	156	173	70	84
Median PFS, mo. (95% CI)	4.90 (2.99, 12.02)	2.92 (2.79, 4.63)	12.75 (8.31, 20.47)	4.96 (4.47, 8.15)	6.47 (4.60, 12.02)	2.92 (2.79, 4.53)	19.55 (10.18, 31.51)	13.80 (6.57, 25.82)
OS								
HR (95% CI)	0.76 (0.53, 1.11)		0.79 (0.63, 1.00)		0.74 (0.58, 0.93)		0.83 (0.58, 1.20)	
Events, n	50	63	132	155	131	153	51	65
Median OS, mo. (95% CI)	29.37 (16.95, 64.46)	23.16 (15.11, 31.93)	58.38 (37.06, N.A.)	42.32 (31.64, 51.22)	36.96 (25.10, 58.38)	24.87 (19.09, 33.18)	N.A. (49.68, N.A.)	59.07 (36.80, N.A.)
ORR per BICR								
CR+PR, n (%)	28 (32.2)	22 (24.4)	128 (47.8)	98 (36.4)	85 (36.3)	59 (26.2)	71 (58.7)	61 (45.5)
95% CI	22.6, 43.1	16.0, 34.6	41.6, 53.9	30.7, 42.5	30.2, 42.8	20.6, 32.5	49.4, 67.6	36.9, 54.3

Figure *11*. Kaplan-Meier Plot of PFS per BICR by Baseline LAG-3 Expression - All Randomised Subjects



Symbols represent censored observations.

Figure *12*. Kaplan-Meier Plot of OS by Baseline LAG-3 Expression - All Randomised Subjects



Symbols represent censored observations.

- Efficacy by PD-L1/LAG-3 expression

Table *12*. Efficacy by Baseline PD-L1/LAG-3 Expression Levels - All Randomised Subjects

	PD-L1 ≥ 1% LAG-3 ≥ 1%		PD-L1 ≥ 1% LAG-3 < 1%		PD-L1 < 1% LAG-3 ≥ 1%		PD-L1 < 1% LAG-3 < 1%	
	BMS-986213 N = 134	Nivolumab N = 140	BMS-986213 N = 12	Nivolumab N = 7	BMS-986213 N = 134	Nivolumab N = 129	BMS-986213 N = 75	Nivolumab N = 83
PFS per BICR								
HR (95% CI)	0.96 (0.71, 1.31)		Not reported		0.67 (0.50, 0.89)		0.70 (0.48, 1.01)	
Events, n	81	83	8	7	88	101	49	66
Median PFS, mo. (95% CI)	18.04 (10.12, 26.71)	14.72 (4.96, 36.93)	17.10 (2.56, N.A.)	Not reported	10.09 (5.16, 20.37)	3.75 (2.83, 4.70)	4.90 (2.83, 10.15)	2.79 (2.79, 4.11)
OS								
HR (95% CI)	0.77 (0.55, 1.08)		Not reported		0.79 (0.58, 1.09)		0.79 (0.53, 1.18)	
Events, n	58	75	7	7	74	80	43	56
Median OS, mo. (95% CI)	N.A. (45.57, N.A.)	45.77 (31.97, N.A.)	26.23 (7.69, N.A.)	Not reported	43.01 (26.94, N.A.)	35.45 (18.73, 51.22)	29.60 (16.95, N.A.)	22.60 (14.26, 32.00)
ORR per BICR								
CR+PR, n (%)	73 (54.5)	62 (44.3)	4 (33.3)[a]	4 (57.1)[a]	55 (41.0)	36 (27.9)	24 (32.0)	18 (21.7)
95% CI	45.7, 63.1	35.9, 52.9	9.9, 65.1	18.4, 90.1	32.6, 49.9	20.4, 36.5	21.7, 43.8	13.4, 32.1

[a] To interpret the percentage with caution as the sample size is small and no conclusions can be made.

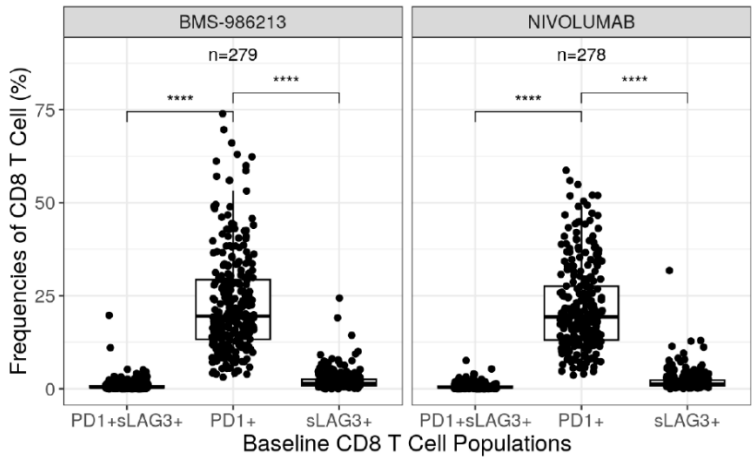
Post-hoc analyses

A. Exploratory biomarker data in support of the mechanism of action for the delayed OS benefit

The following summary of the data was presented in support of the mechanistic rationale for the delayed OS benefit (benefit starting from 30 months onward) with nivo+rela FDC vs nivo in the PD-L1 ≥ 1% subgroup based on exploratory post-hoc analyses of biomarker data from the CA224047 study.

Baseline PD-1+ sLAG3+ CD8 T-cell, PD-1+ CD8 T-cell, and sLAG3+ CD8 T Cell Populations in blood are shown below.

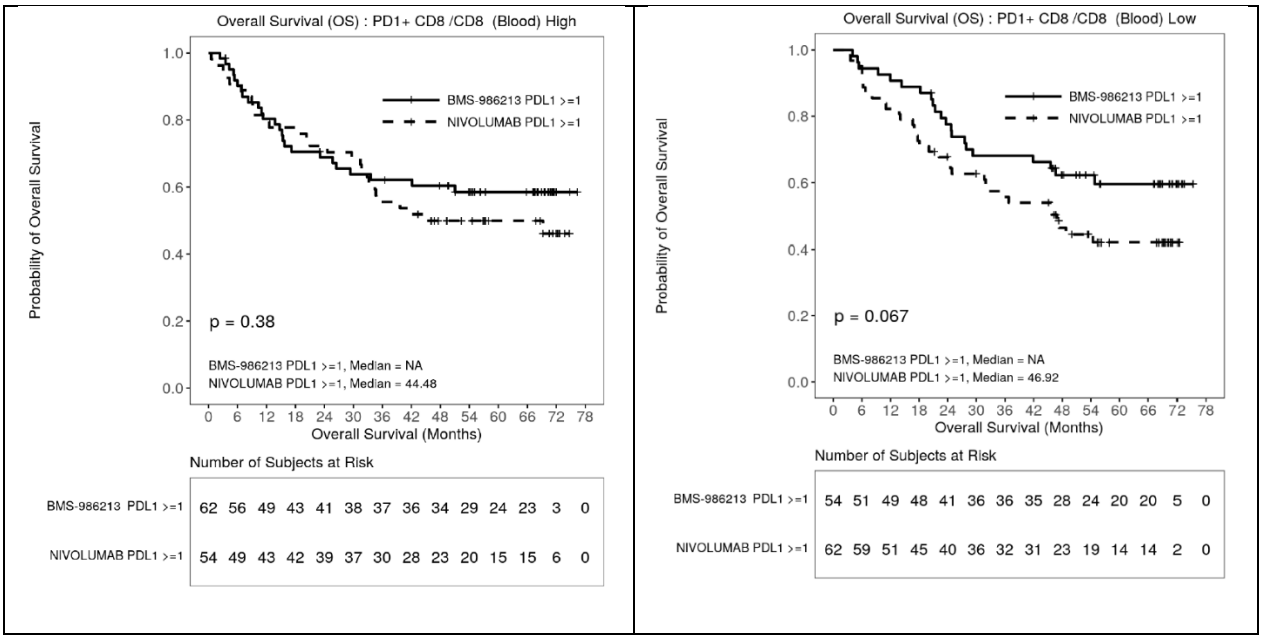
Figure *13*. Frequencies of Baseline PD-1+ sLAG3+ CD8 T-cell, PD-1+ CD8 T-cell, and sLAG3+ CD8 T Cell Populations in Blood in Each Arm



"n=" is the number of Subjects per population per arm.
P-values corresponding to significance levels are denoted as follows: * for p ≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001, and **** for p ≤ 0.0001. Wilcoxon Test is used to compare the non-parametric differences in frequencies of populations within each treatment arm. sLAG3 = surface lymphocytes activation gene 3, PD-1 = Programmed cell death protein 1
Source: Figure 1 in Appendix 3

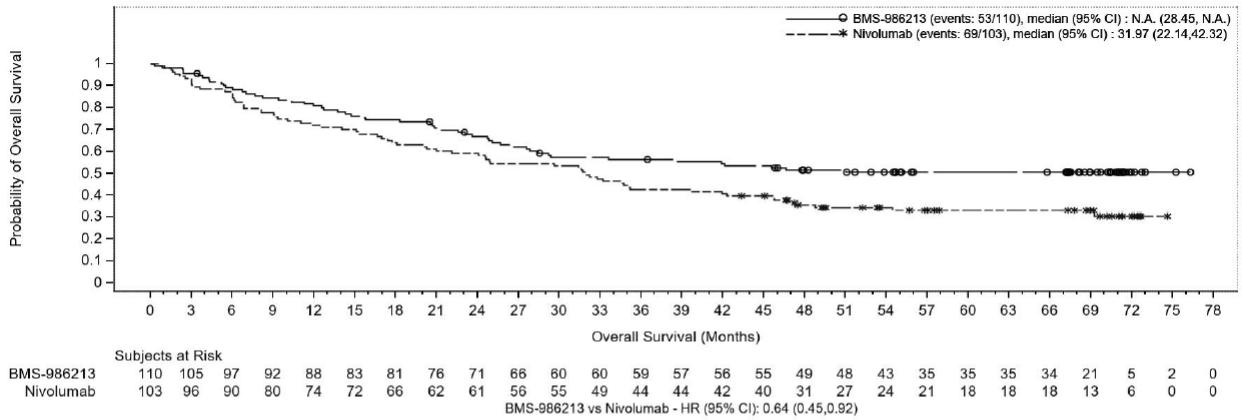
OS survival of nivo+rela FDC vs nivo in the PD-L1 ≥ 1% subgroup was shown separately for subjects with baseline peripheral PD-1+ CD8 T cells above and below the median baseline frequency PD-1+ CD8 T cells.

Figure *14. Overall Survival of Subjects with Tumour PD-L1 ⩾ 1% with Lower than Median Frequencies of PD-1+ CD8 T-Cells/CD8 T-Cells in Blood Separated by Treatment Arm*

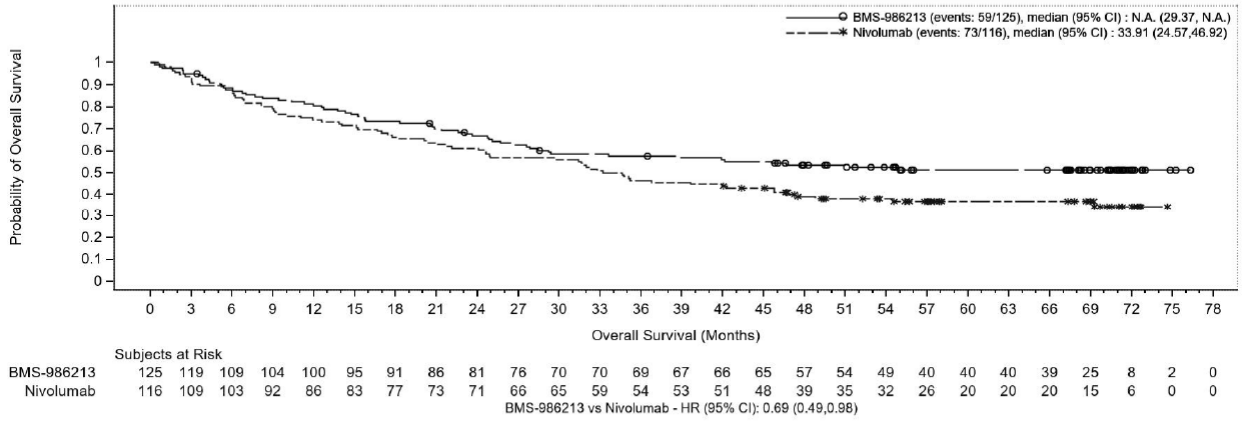


Symbols represent censored observations. Median cutoff is 20.4% PD-1+CD8/CD8. PD-1 = Programmed cell death protein 1

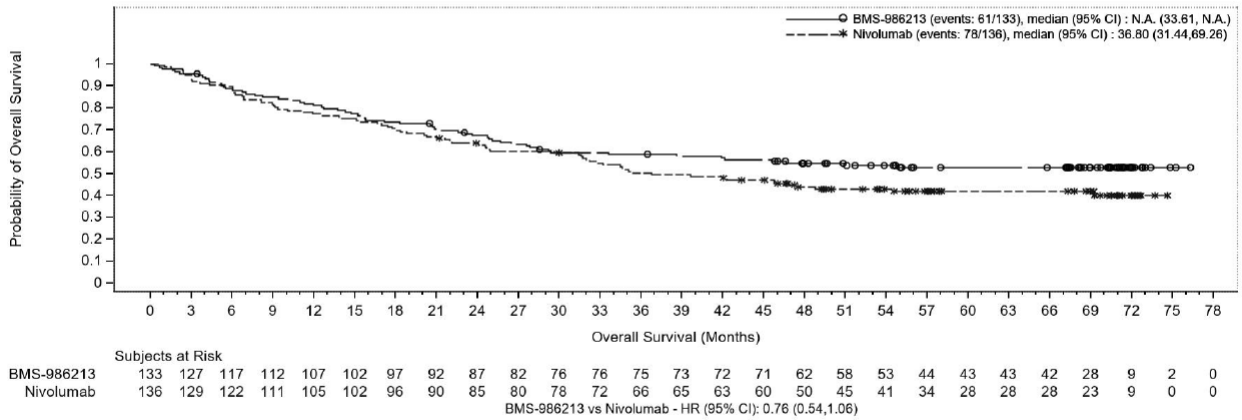
Figure *15*. Overall Survival by baseline tumour PD-L1 expression (1-25%, 1-49%, 1-75%) – All randomised subjects



PD-L1: 1-49%



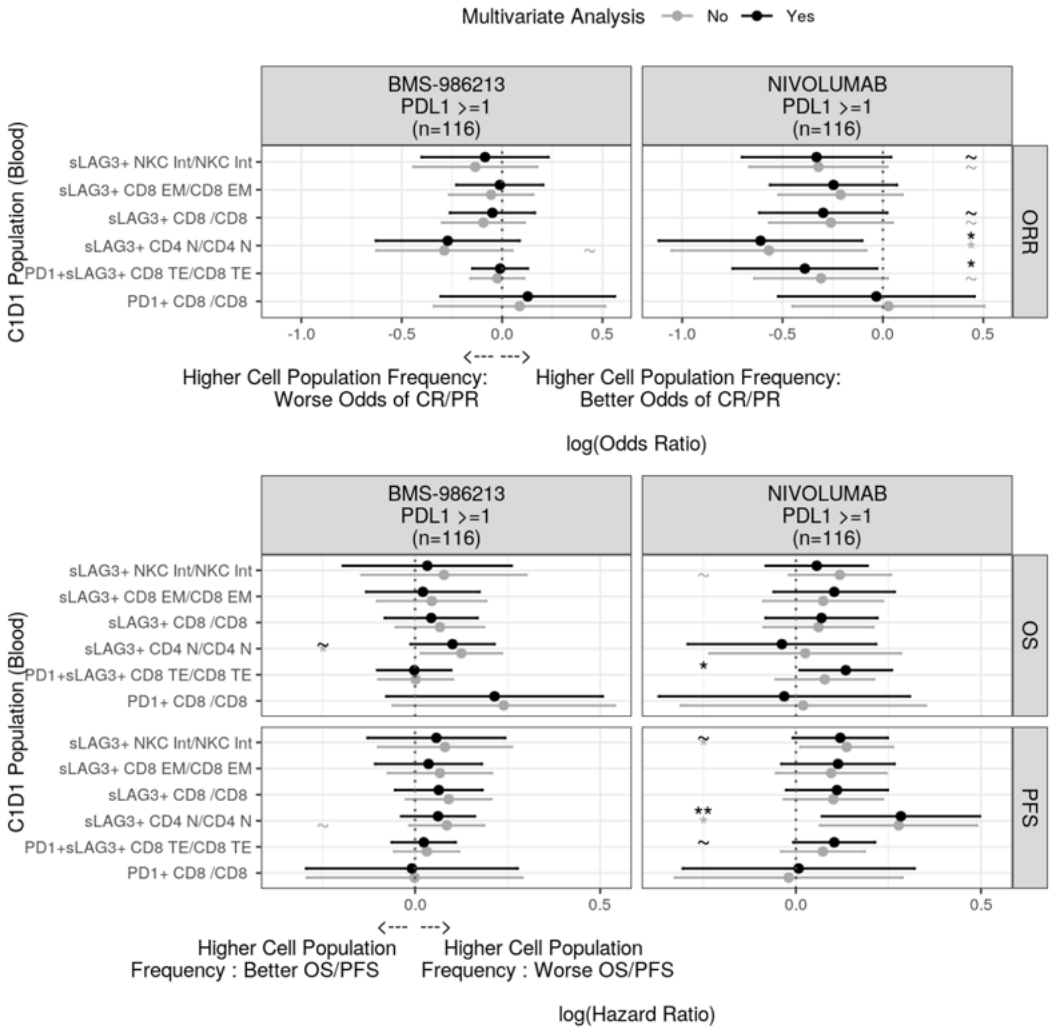
PD-L1: 1-75%



Symbols represent censored observations. HR from unstratified Cox proportional hazard model.
Source: Figure 14.2.7.12.1.1 (1-25%), Figure 14.2.7.12.2.1 (1-49%), Figure 14.2.7.12.3.1 (1-75%) in Appendix 2

Baseline levels of various peripheral immune cells and their association with efficacy endpoints ORR, PFS and OS by treatment arm in patients with PD-L1 ≥1% expression are shown in *Figure 16*.

Figure *16. Log Odds Ratio (OR) of CR/PR and log Hazard Ratio (HR) for Different Baseline (C1D1) Immune Cell Populations in Subjects with Tumor PD-L1 ⩾ 1% by Treatment Arm: Univariate and Multivariate Analysis Faceted by ORR by BICR, OS, and PFS*

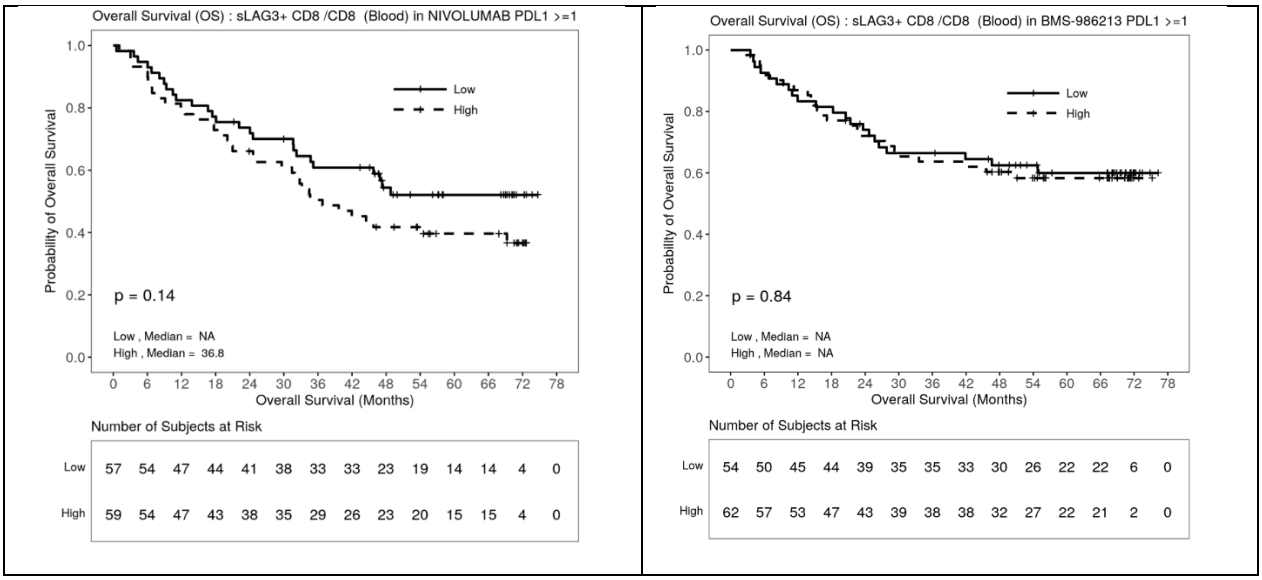


"n=" number of subjects per treatment arm/PD-L1 subgroup. This figure displays log HRs for OS and PFS estimated using Cox proportional hazards models, and log ORs for ORR by blinded investigator review (ORR) estimated using generalized linear models. Each estimate, with associated 95% confidence intervals, represents the relative effect comparing patients with high (75th percentile) versus low (25th percentile) baseline biomarker levels. Log HR and log OR were estimated separately for the combinations of treatment arm and PD-L1 1% cutoff status based on a model with interaction terms. The adjusted estimates from multivariable analysis are shown in black and the unadjusted estimates are shown in gray. The following covariates are included in the multivariable model: ECOG status, age, sex, region, and BRAF mutation status. Wald tests were used to evaluate the statistical significance of each biomarker as associated with the outcomes. For log OR, a value greater than 0 indicates that the biomarker is associated with a better response (CR/PR). For log HR, a value less than 0 indicates that the biomarker is associated with better OS/PFS.

p-values corresponding to significance levels are denoted as follows: ~ for <= 0.1, * for p ⩽ 0.05, ** for p ⩽ 0.01, and *** for p ⩽ 0.001.

Baseline expression of LAG-3+ CD8 T cells in the periphery and in tumour and the impact on OS were evaluated. Within the nivo arm, subjects in the PD-L1 ≥1% subgroup with low peripheral LAG-3+ CD8 expression (below median cutoff 1.4% sLAG3+ CD8/CD8) had improved OS compared to subjects with high peripheral LAG-3+CD8 expression (above median cutoff 1.4% sLAG3+ CD8/CD8). There was no impact of LAG-3+ CD8 expression on OS in the nivo+rela FDC arm (*Figure 17*).

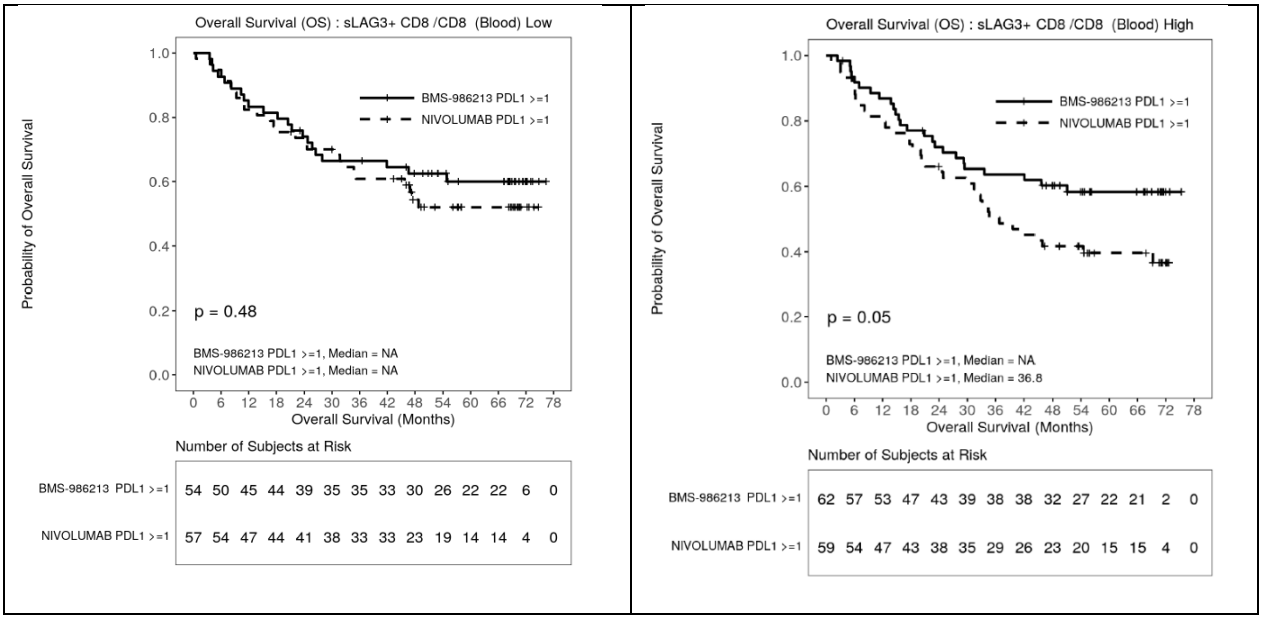
Figure *17. Overall Survival in Tumour PD L1 ⩾ 1% subgroup by median frequencies of baseline sLAG3+ CD8 T Cell/ CD8 in blood for Nivolumab-treated and Nivo+Rela FDC-treated subjects separately*



Symbols represent censored observations. Median cutoff is 1.4% sLAG3+ CD8/CD8. sLAG3 = surface lymphocytes activation gene 3, CD8 = CD8 T cells.

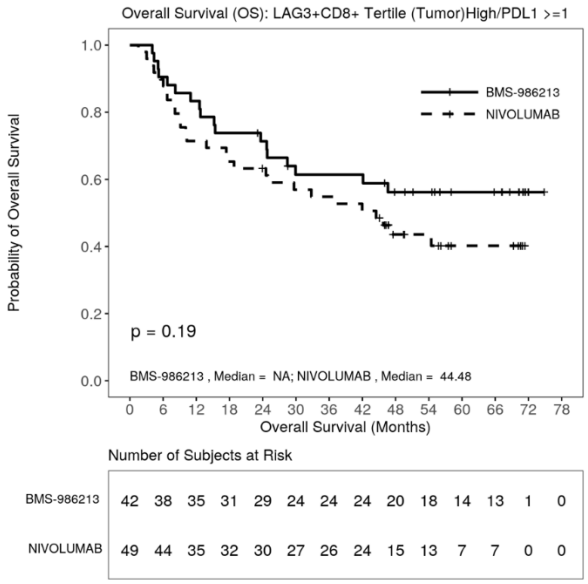
The OS results by low and high peripheral LAG-3+ CD8 expression (median cutoff 1.4% CD8 cells) for combination vs nivo monotherapy are shown in *Figure 18*. The impact of high LAG3 expression on CD8 cells in the tumour (> 0.0443% LAG3+CD8+) is shown in *Figure 19*.

Figure *18. Overall Survival of Subjects with Tumour PD-L1 ≥1% with Higher than Median Frequencies of Baseline Surface LAG3+ CD8 T-Cell/CD8 in Blood Separated by Treatment Arm*



Symbols represent censored observations. Median cutoff is 1.4% sLAG3+ CD8/CD8. sLAG3 = surface lymphocytes activation gene 3, CD8 = CD8 T cells

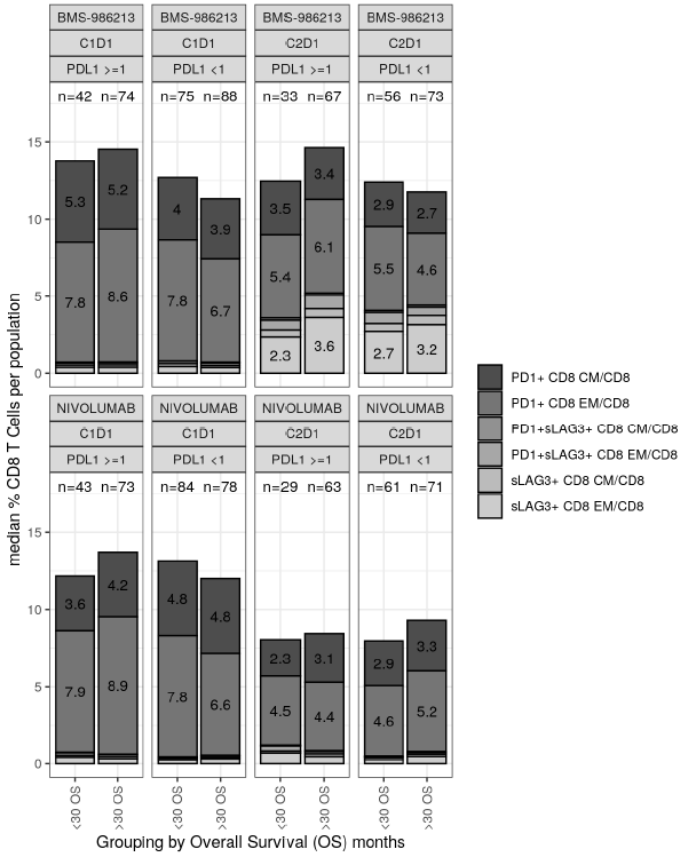
Figure *19. Overall Survival of Subjects with Tumor PD L1 ⩾ 1% with High Tertile Frequencies of Baseline LAG3+ CD8 T Cell/ CD8 in Tumour Separated by Treatment Arm*



Symbols represent censored observations. Tertile cutoff for high is above 0.0443% LAG3+CD8+.
LAG3 = lymphocytes activation gene 3, CD8 = CD8 T cells

Different PD1+ and sLAG3+ cell populations in peripheral blood were also measured at the next cycle of treatment (4 weeks after start, C2D1) grouped by PD-L1 expression status (cutoff 1%) and OS < or ≥30 months, see Figure 20 and *Table 13*.

Figure *20*. Stacked Bar Plots of Median Frequency (%) of Different CD8 T-Cell Popula*tions at Baseline (C1D1) and On-Treatment (C2D1) Faceted by Treatment Arm and PD-L1 Tumour IHC Status, Grouped by Overall Survival Less Than or Greater Than 30 Months*



"n=" is the number of Subjects per treatment/PD-L1 subgroup/timepoint. Stacked bar blots where the median is < 0.4 are not labeled. CM = central memory, EM = effector memory, sLAG3 = surface lymphocytes activation gene 3, PD-1 = programmed cell death protein 1, CD8 = CD8 T cells
Source: Figure 6 in Appendix 3

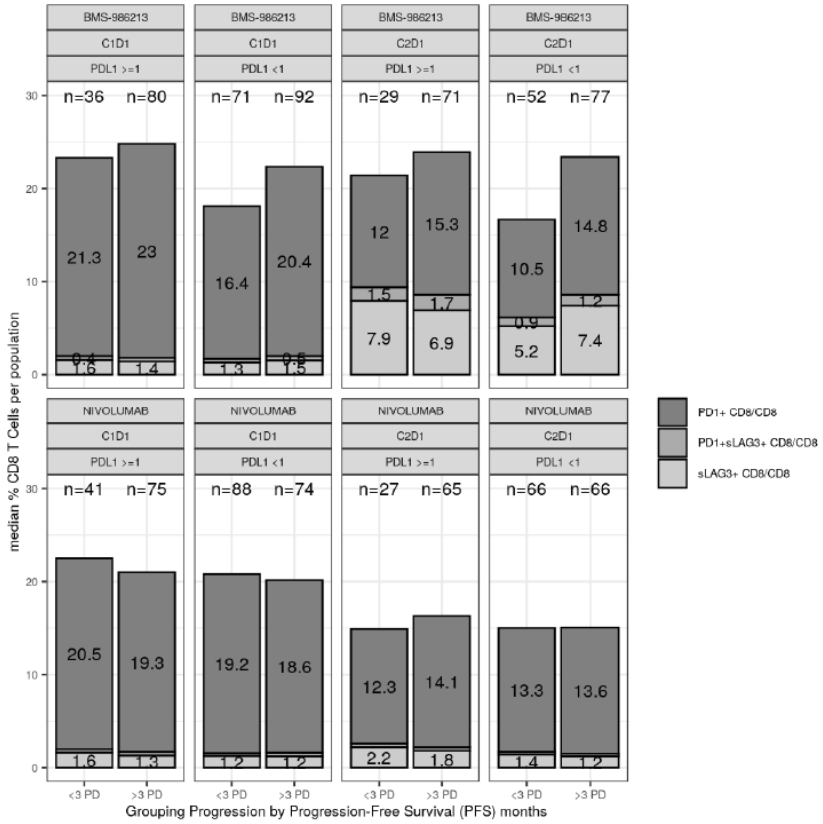
Table *13*. Sums of Memory T-cells from Baseline and On-Treatment by Arm, PD-L1 Status, and OS (< 30 and > 30 months)

	Nivo+Rela FDC (BMS-986213)							
	C1D1				C2D1			
Median Frequency of Populations (%)	PD-L1 ≥ 1% < 30 OS	PD-L1 ≥ 1% > 30 OS	PDL1 < 1% < 30 OS	PDL1 < 1% > 30 OS	PD-L1 ≥ 1% < 30 OS	PD-L1 ≥ 1% > 30 OS	PDL1 < 1% < 30 OS	PDL1 < 1% > 30 OS
PD-1+ CD8 CM/CD8	5.3	5.2	4	3.9	3.5	3.4	2.9	2.7
PD-1+ CD8 EM/CD8	7.8	8.6	7.8	6.7	5.4	6.1	5.5	4.6
PD-1+sLAG3+ CD8 CM/CD8	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1
PD-1+sLAG3+ CD8 EM/CD8	0.1	0.1	0.2	0.2	0.7	0.9	0.7	0.5
sLAG3+ CD8 CM/CD8	0.1	0.2	0.2	0.1	0.4	0.6	0.5	0.6
sLAG3+ CD8 EM/CD8	0.4	0.4	0.4	0.4	2.3	3.6	2.7	3.2
Total LAG3+ Memory Cells	**0.7**	**0.8**	**0.9**	**0.8**	**3.6**	**5.2**	**4**	**4.4**
Total Memory Cells	**13.8**	**14.6**	**12.7**	**11.4**	**12.5**	**14.7**	**12.4**	**11.7**
	Nivolumab							
	C1D1				**C2D1**			
Median Frequency of Populations (%)	**PD-L1 ≥ 1% < 30 OS**	**PD-L1 ≥ 1% > 30 OS**	**PDL1 < 1% < 30 OS**	**PDL1 < 1% > 30 OS**	**PD-L1 ≥ 1% < 30 OS**	**PD-L1 ≥ 1% > 30 OS**	**PDL1 < 1% < 30 OS**	**PDL1 < 1% > 30 OS**
PD-1+ CD8 CM/CD8	3.6	4.2	4.8	4.8	2.3	3.1	2.9	3.3
PD-1+ CD8 EM/CD8	7.9	8.9	7.8	6.6	4.5	4.4	4.6	5.2
PD-1+sLAG3+ CD8 CM/CD8	0	0	0	0	0	0.1	0	0.1

PD-1+sLAG3+ CD8 EM/CD8	0.2	0.1	0.1	0.1	0.3	0.1	0.1	0.1
sLAG3+ CD8 CM/CD8	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.1
sLAG3+ CD8 EM/CD8	0.4	0.3	0.2	0.3	0.7	0.5	0.3	0.5
Total LAG3+ Memory Cells	**0.7**	**0.5**	**0.4**	**0.5**	**1.1**	**0.9**	**0.6**	**0.8**
Total Memory Cells	**12.2**	**13.6**	**13**	**11.9**	**7.9**	**8.4**	**8.1**	**9.3**

A similar analysis was presented for different PD1+ and sLAG3+ cell populations in peripheral blood grouped by PD-L1 expression status (cutoff 1%) and PD < or ⩾3 months, see *Figure 21*.

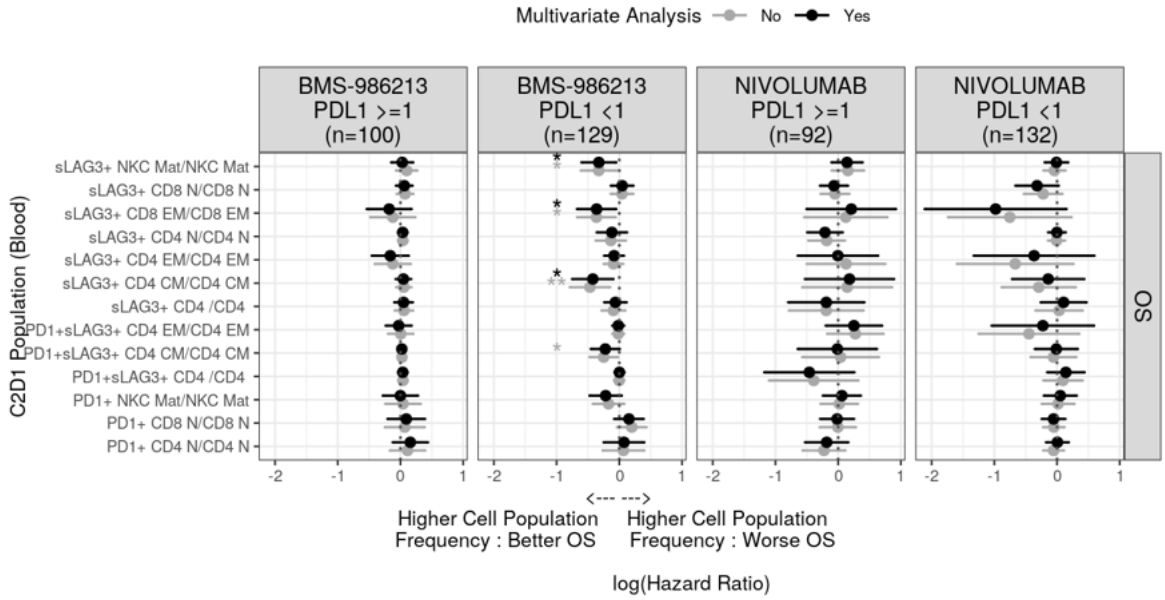
Figure *21*. Stacked Bar Plots of Median Frequency (%) of Different CD8 T-Cell Populations at Baseline (C1D1) and On-Treatment (C2D1) Faceted by Treatment Arm and PD-L1 Tumour *IHC Status Grouped by Progressed Disease (PD) Less Than or Greater Than 3 Months*



"n=" is the number of subjects per arm, timepoint, PD-L1 status, and survival subgroup.
Stacked bar blots where the median is < 0.4 are not labeled.
Source: Figure 7 in Appendix 3

The association of different immune cell populations at Cycle 2 day 1 and OS is shown in *Figure 22* by treatment arm and PD-L1 expression.

Figure *22*. Log Hazard Ratio (HR) for Different On-Treatment Cycle 2 Day 1 (C2D1) Immune Cell Populations by Treatment Arm and PD-L1 Tumour IHC Status Univariate and Multivariate Analysis Faceted by Overall Survival



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

n/a

2.4.3. Discussion on clinical efficacy

Opdualag is currently approved for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1% (EC decision issued on 15/9/2022). An all-comer indication was requested at the time of the initial application based on the results of the pivotal study CA224047 (DCO: 9 March 2021 primary analysis). However, the CHMP concluded that a beneficial effect had only been demonstrated in the PD-L1 low subgroup based on the PFS results with support from OS, whereas the use of the combination did not appear to offer additional PFS benefit in subjects with a PD-L1 expression ≥ 1%. Further, OS curves up till about 40 months largely overlapped (DCO: 7 Sep 2021 for Addendum 01 CSR). Considering the lack of additional benefit observed with rela+nivo FDC in patients with PD-L1 ≥1% and that the proposed combination is more toxic and less well tolerated than nivolumab monotherapy, the indication was restricted to the PD-L1 < 1% subgroup (Opdualag EPAR).

Design and conduct of clinical studies

With the current submission, the MAH aims to extend the indication to patients with tumour cell PD-L1 expression ≥ 1% based on updated descriptive 4-year data from the pivotal Study CA224047. The timing of the current OS analysis was not fully pre-specified and is based on version 6 of the SAP to continue to conduct additional locks and descriptive analyses on approximately a yearly basis as needed.

There were no changes to study design and conduct except for a prolonged scan frequency from 12 to 24 weeks until BICR-confirmed disease progression after two years. The study was fully unblinded for the Sponsor and investigators on 15 March 2022.

Several additional sensitivity analyses were performed by the MAH to support robustness of the OS result in the PD-L1 ≥ 1% subgroup. Additional post-hoc analyses of biomarkers were performed to explore the mechanism of action of the late separation of OS results in support of the mechanism rationale, which are discussed below.

At the time of CHMP approval, median follow-up was 19.3 months and most patients had already discontinued treatment with 25% of patients still on treatment. With the current update, median follow-up was 34.9 months (range: 0.3-76.3); about 10% of patients were still on treatment and about 40% were ongoing in the study. Most patients discontinued treatment due to disease progression (overall 51%). About 40% of all randomized subjects received subsequent systemic anti-cancer therapy, mostly PD-1/CTLA4 inhibitors and targeted BRAF/MEK treatment. It is noted that within the PD-L1 ≥ 1% subgroup, a smaller proportion (~10%) of nivo+rela FDC- than nivo-treated subjects received subsequent systemic therapy, especially PD-1/CTLA4 inhibitors. Reasons for not receiving subsequent therapy were not provided.

Efficacy data and additional analyses

Statistical significance was not reached for OS in the ITT at the time of the pre-specified final OS analysis (DBL: 28 Oct 2021). With longer follow-up, the descriptive analysis confirms the trend for an OS benefit of the combination over nivolumab monotherapy in the ITT. Median OS has now been reached in both treatment arms (mOS: 53.3 months vs 33.2 months for the combi vs nivo). The PFS benefit as well as the difference in ORR (10%) remained stable, as expected. Updated analyses also support the trend for an OS benefit in the PD-L1 < 1% subgroup, with an estimated increase in mOS of approximately 12 months. As for the ITT, the benefit in mPFS (3.7 months) and ORR (12%) remained stable.

Within the PD-L1 ≥ 1% subgroup, the KM-curve shows a trend for a sustained separation of OS from 30 months onwards in favour of the combination treatment. mOS was estimated to be 42 months in the nivo arm and was not reached in the combination arm, although the curves for both treatment arms show a noticeable plateau before this time. The clinical relevance of the observed difference in OS rate of 8% at 36 months is questionable. Censoring rates are high from 42 months onwards and the curves up until around 30 months appear to come back together after a separation. The absolute benefit is therefore uncertain. Although the mPFS of the combination treatment increased with about 2 months during longer follow-up, the KM-curves for PFS overlap showing crossing of curves sometimes in favour of the combination arm or vice versa (e.g. at 36 months PFS rate in favour of the nivo arm). Further, the potential impact of unblinding of the study on the PFS results is unclear. Therefore, the conclusions on the lack of additional PFS benefit in the rela + nivo arm remain. The difference in ORR (8%) in favour of the combination arm remained stable. It was already discussed within the initial submission that it is uncertain whether this translates into clinical benefit for these patients. The MAH now claims that a deeper reduction in target lesion burden (≥50% reduction) with nivo+rela FDC supports the beneficial effect of the combination over nivo monotherapy, however, this is not a validated surrogate endpoint for OS benefit.

The late separation of OS curves in the absence of a PFS benefit is difficult to interpret. It has not been observed before in this setting, nor are there any other data available from a combination with a LAG3-inhibitor in support of a late separation of OS curves. The MAH performed an additional analysis using the propensity score model to adjust for observed imbalances in patient characteristics between studies. The KM-curve for OS for nivo monotherapy based on the current study CA224047 remained below the nivo monotherapy arm observed in study CA20906, however, no conclusions can be drawn based on this indirect comparison (data not shown).

The MAH performed several additional analyses that were aimed to estimate the OS effect including Restricted Mean Survival Time (RMST) based on two specifications of tau, and weighted log-rank and piecewise estimation methods. In line with the results from the cox proportional hazards model, the results from the RMST suggested a numerical benefit in mean OS in favour of the rela + nivo arm. As would be expected with the weighted log-rank and piecewise estimation methods, these became more supportive as the late separation of the curves was taken into account in the analysis. These analyses are calculated on non-randomised comparisons and are not suitable for drawing conclusions on the full subgroup of patients with PD-L1 ≥ 1%. The MAH also performed analyses for which several covariates were included in the model, and an exploratory analysis that estimated the hazard ratio based on the time of treatment discontinuation. These also appeared to support an OS benefit, although given relevant methodological considerations, these are not sufficient to support a conclusion that the treatment effect is robust.

Exploratory analyses of OS by responders and non-responders showed that for the combination treatment, responders displayed the late separation of the OS KM curves in the PD-L1 ≥ 1% subgroup. Further, nivo+rela FDC improved OS compared with nivo in both subjects with and without an early PFS event (≤ 3 months). In this subgroup, the timing of OS events appears to be less connected to the timing of PFS events as observed in the PD-L1 < 1% subgroup. Separation of the OS KM curves favouring nivo+rela FDC over nivo occurred after 30 months for subjects without an early PFS event and after 20 months for subjects with an early PFS event. However, these analyses are based on post-randomisation events of CR and PR, and the randomised comparison between the two treatment arms is lost. Therefore, any inference of OS gain from these data is questionable.

Another post-hoc analysis was performed to compare the groups on melanoma-related survival rather than all-cause mortality. The details of the analyses and full definition of the endpoint were not provided in the SAP. In this analysis, non-melanoma related deaths were treated as a competing risk and both sub-distribution and cause-specific hazards were estimated. The estimated HRs were in line with those for the main analyses that were based on all-cause mortality and have no additional influence on the benefit risk assessment.

The MAH also performed exploratory analyses comparing the duration of treatment free survival (TFS) after discontinuation of the allocated therapy. TFS was estimated based on the area between the curves for TTD (time to protocol therapy cessation or death) and TTS (time to subsequent systemic anticancer therapy initiation or death). These were also compared with or without toxicity. The results showed a slightly longer treatment free survival period in the rela + nivo arm compared with the nivo monotherapy arm. While it is acknowledged that a period without treatment may be beneficial to patients, the reasons for not receiving treatment also need to be taken into account. For example, not receiving subsequent therapy might also be related to the status of the patient and the tumour. Methodologically there are also a range of concerns related to the analysis including the (in)ability to follow up patients for subsequent therapy.

The MAH also presented results from a propensity score–weighted indirect comparison between the nivo arm of CA224047 and the nivo+rela arm of Phase 1/2a CA224020 in order to demonstrate replication of the OS findings of the pivotal study (data not shown). The main limitation of this comparison is the lack of a direct comparison with the nivo arm and these results do not replace the need for an additional trial.

The MAH has submitted the final 5-year survival data (DCO: 25-Sep-2025). These descriptive data are in line with the 4-year data, however, the same uncertainties as described above apply to these data.

The MAH has performed several post-hoc exploratory biomarker analyses to provide a mechanistic rationale for the observed late separation of OS curves in the absence of a PFS benefit, focusing on PD-

1 and LAG3. It is hypothesized that the PD-1/PD-L1 pathway is dominant from the start of study treatment in the PD-L1 ≥ 1% subgroup, while the anti-LAG3 activity becomes more prominent over time as resistance to anti-PD-1 develops. The dominance of the PD-1/PD-L1 pathway was explored by showing OS curves by baseline frequencies of PD-1+ CD8 T-cells/CD8 T-cells in blood (below or above median) and various ranges of baseline tumour PD-L1 expression. These results showed early separation of OS curves in case of lower levels in blood or tumour but not at higher levels, indicating that addition of relatlimab may be less beneficial at high PD-L1 levels. This observation is in line with the original CHMP decision to restrict the use of relatlimab to patients with PD-L1 expression levels of < 1%. Additionally, exploratory analyses showed an earlier and more pronounced separation of OS curves in favour of combination treatment over nivo alone in patients with high LAG3+ expression (above median cutoff 1.4% sLAG3+ CD8/CD8 in blood at baseline), which was not seen in patients with low LAG3+ expression (below median cutoff 1.4% sLAG3+ CD8/CD8 in blood at baseline). Analyses per treatment arm showed that only in the nivo monotherapy arm OS curves were impacted by the LAG3+ expression, but not the combination treatment, suggesting that LAG3-expression may be a mechanism of resistance to PD-L1 inhibition that can be overcome with relatlimab. An additional analysis in patients with baseline LAG3+ CD8 T cell/CD8 in tumour above the tertile cutoff 0.0443% also shows a trend for a more early and pronounced separation of OS curves in favour of the combination treatment.

The effort of the MAH to explore a mechanistic rationale for the late OS separation is acknowledged. Regarding the impact of various cut-offs of PD-L1 expression in the tumour, it was already discussed at the time of the initial submission, that there may be some heterogeneity in results within the subgroup with PD-L1 ≥ 1%. However, as these analyses are based on non-randomised comparisons and not pre-planned in the SAP, the PD-L1 of 1% was considered the most reasonable cut-off point as this was included as a stratification factor for randomization. The exploratory analyses also included inconsistent numbers of patients in the treatment arms and subgroups, which is likely related to the (in)ability to measure the relevant biomarkers.

The presented post-hoc exploratory biomarker analyses are considered hypothesis-generating and the level of evidence supporting the observed late separation of OS KM-curves is low. The reported increase in LAG-3$^+$ memory T cells at week 4 is biologically plausible as it may reflect the establishment of a long-lived memory T-cell population capable of repeated responses to tumor antigens. However, the cut-off values applied for LAG3$^+$ and PD-1$^+$ cells were defined post-hoc and no external confirmatory data are available. Baseline LAG3$^+$ cells were barely detectable and increased to a median of 3%-5% of total memory T cells at week 4. However, information on the underlying distribution is lacking, and it remains unclear whether this represents a true difference within the context of the assay used, particularly as not all patients had evaluable samples at both time points. Furthermore, the biological relevance of the observed difference in LAG3$^+$ memory cells at week 4 (5.2% in patients with OS >30 months vs 3.6% in patients with OS <30 months) is unknown. Longitudinal follow-up data on LAG-3 demonstrating the persistence/trajectory of the signal, are not available and intra-tumoral LAG-3 data are limited restricting the interpretability of the peripheral LAG-3 expression observations.

It also remains unclear why the overcoming of the negative effect of LAG-3–mediated resistance would not translate in any PFS benefit, particularly given the increase in the LAG3+ memory cells was demonstrated as early as week 4. The MAH presented additional post-hoc analyses showing that in PD-L1 ≥ 1% tumors, a PFS trend favoring the combination emerged only in the LAG3$^+$CD8$^+$ high tertile subgroup whereas this was observed independent of LAG3+CD8+ in the subgroup with PD-L1 <1% (data not shown). The LAG-3+CD8+ high segment within the PD-L1 ≥ 1% subgroup may represent subjects that have primary resistance to anti-PD-1, who would progress early, and in whom the PFS

benefit of adding anti-LAG-3 is detectable. Nevertheless, these findings remain exploratory and hypothesis-generating only.

Similar limitations and uncertainties apply to the postulation that the early difference in disease progression (cutoff 3 months) by nivo+rela FDC in the PD-L1 < 1% subgroup may be mediated by elevation of early LAG-3+ effector cells.

It is further noted that pre-planned extrapolatory analyses using other cut-offs for tumour PD-L1 (5% or 10%) or LAG3+ immune cells in the tumour region (5%) suggest that a difference in OS curves is not seen/diminished in patients with high levels of PD-L1 (10%) or LAG3+ immune cells (5%). Results, therefore, appear to be dependent on the chosen cutoff and these results stress the importance of predefined cutoffs for confirmatory data.

In conclusion, the proposed mechanism of action relies on descriptive and exploratory data that have only been observed in the current study. An additional study in patients with PD-L1 ≥ 1% would be required to confirm the OS treatment effect, and ideally to substantiate the hypothesized mechanism through the collection of robust longitudinal biomarker data. Such data are needed in order to confirm the benefit of the rela+nivo combination over nivo monotherapy in patients with PD-L1 ≥ 1%.

The MAH submitted a variation application under category C.I.6 of the variation classification Guideline with the scope to include "Extension of indication to include patients with tumour cell PD-L1 expression ≥ 1% in the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older for OPDUALAG, based on updated descriptive 4-year data from pivotal Study CA224047; this is a randomized, double-blind phase 2/3 study of relatlimab combined with nivolumab versus nivolumab in participants with previously untreated metastatic or unresectable melanoma; As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to remove Annex IV from the PI. As part of the application, the MAH is requesting a 1-year extension of the market protection".

Based on the assessment of the data contained in the application, the CHMP is of the view that the following changes to the MA should be introduced "Update of section 4.8 and 5.1 of the SmPC based on updated descriptive 5-year data from pivotal Study CA224047; this is a randomized, double-blind phase 2/3 study of relatlimab combined with nivolumab versus nivolumab in participants with previously untreated metastatic or unresectable melanoma. The Package Leaflet is updated in accordance". These changes fall under category C.I.4 of the variation classification Guideline.

The MAH updated the electronic Application Form and the product information accordingly.

2.4.4. Conclusions on the clinical efficacy

A beneficial effect of Opdualag over nivolumab monotherapy in patients with PD-L1 ≥ 1% expression is not considered demonstrated. Uncertainties remain on the rationale for the observed separation of OS KM curves after 30 months based on a descriptive OS analysis and no beneficial effect on PFS. Moreover, the initial approval was based on a positive study that utilized the inferential PFS analysis in the ITT population with support from a non-detrimental OS outcome. Then the indication was restricted due to lack of improved PFS and OS in the PD-L1 ≥ 1% subgroup. The final OS analysis in the ITT population was not statistically significant. This updated analysis is exploratory and not considered suitable to support a re-evaluation of the initial decision, despite the apparently similar OS HR in both PD-L1 subgroups.

2.5. Clinical safety

Introduction

The safety of nivolumab in combination with relatlimab has been evaluated in 355 patients with advanced (unresectable or metastatic) melanoma (study CA224047). The all treated population was the primary population for safety analyses. Adverse reactions reported in the dataset for patients treated with nivolumab in combination with relatlimab, with a median follow-up of 19.94 months, are reported in the SmPC. In this procedure, updated safety data were submitted with a DCO of 24-Sep-2024.

Patient exposure

With the safety follow-up, median extent of follow-up was 34.91 months (range: 0.3 – 76.3). Patient exposure is shown in *Table 14* and *Table 15*. About half of the patients had at least one dose delay, dose infusion interruptions occurred in 6-7% of subjects (data not shown).

Table *14*. Cumulative Dose and Relative Dose Intensity - All Treated Subjects

	Nivo+Rela FDC N = 355	Nivo N = 359
NUMBER OF DOSES RECEIVED		
MEAN (SD)	17.6 (20.05)	18.0 (20.98)
MEDIAN (MIN - MAX)	10.0 (1 - 79)	8.0 (1 - 80)
CUMULATIVE DOSE (MG)		
MEAN (SD)	11261.440 (12821.9508)	8654.317 (10070.1211)
MEDIAN (MIN - MAX)	6400.000 (640.00 - 50560.00)	3840.000 (480.00-38400.00)
RELATIVE DOSE INTENSITY (%)		
≥ 110%	0	0
90% to < 110%	309 (87.0)	302 (84.1)
70% to < 90%	41 (11.5)	51 (14.2)
50% to < 70%	5 (1.4)	6 (1.7)
< 50%	0	0
NOT REPORTED	0	0

Table *15*. Duration of study therapy summary – All treated subjects

	Nivo+Rela FDC N = 355	Nivo N = 359
DURATION OF THERAPY (MONTHS)		
MEAN (MIN, MAX)	16.08 (0.03, 72.51)	16.34 (0.03, 72.77)
MEDIAN	8.312	6.472
≥ 3 MONTHS (%)	242 (68.2)	245 (68.2)
≥ 6 MONTHS (%)	195 (54.9)	185 (51.5)
≥ 9 MONTHS (%)	172 (48.5)	157 (43.7)
≥ 12 MONTHS (%)	145 (40.8)	138 (38.4)
≥ 24 MONTHS (%)	80 (22.5)	86 (24.0)
≥ 48 MONTHS (%)	40 (11.3)	38 (10.6)
≥ 72 MONTHS (%)	2 (0.6)	4 (1.1)

Adverse events

Table *16*. Summary of safety – All treated subjects

	CA224047 Addendum 03		CA224047 Addendum 01	
	No. of Subjects (%)			
Safety Parameters	**Nivo+rela FDC (N=355)**	**Nivo (N=359)**	**Nivo+rela FDC (N=355)**	**Nivo (N=359)**
Deaths	182 (51.3)	218 (60.7)	137 (38.6)	160 (44.6)
Primary Reason for Death				
Disease	139 (39.2)	178 (49.6)	106 (29.9)	132 (36.8)
Study Drug Toxicity[a]	4 (1.1)	2 (0.6)	4 (1.1)[c]	2 (0.6)[c]

	CA224047 Addendum 03				CA224047 Addendum 01			
	No. of Subjects (%)							
Safety Parameters	**Nivo+rela FDC (N=355)**		**Nivo (N=359)**		**Nivo+rela FDC (N=355)**		**Nivo (N=359)**	
Unknown	10 (2.8)		15 (4.2)		4 (1.1)		8 (2.2)	
Other[b]	29 (8.2)		23 (6.4)		23 (6.5)		18 (5.0)	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	141 (39.7)	111 (31.3)	124 (34.5)	88 (24.5)	131 (36.9)	101 (28.5)	115 (32.0)	75 (20.9)
Drug-related SAEs	57 (16.1)	40 (11.3)	30 (8.4)	19 (5.3)	55 (15.5)	38 (10.7)	30 (8.4)	19 (5.3)
All-causality AEs Leading to DC	84 (23.7)	47 (13.2)	62 (17.3)	30 (8.4)	74 (20.8)	44 (12.4)	49 (13.6)	27 (7.5)
Drug-Related AEs Leading to DC	63 (17.7)	35 (9.9)	34 (9.5)	14 (3.9)	54 (15.2)	32 (9.0)	26 (7.2)	13 (3.6)
All-causality AEs	352 (99.2)	168 (47.3)	345 (96.1)	142 (39.6)	352 (99.2)	154 (43.4)	344 (95.8)	126 (35.1)
Drug-related AEs	303 (85.4)	79 (22.3)	263 (73.3)	43 (12.0)	297 (83.7)	75 (21.1)	260 (72.4)	40 (11.1)
All-causality Select AEs (by Category)								
Endocrine	111 (31.3)	9 (2.5)	86 (24.0)	3 (0.8)	102 (28.7)	9 (2.5)	83 (23.1)	3 (0.8)
Gastrointestinal	109 (30.7)	11 (3.1)	76 (21.2)	5 (1.4)	94 (26.5)	9 (2.5)	69 (19.2)	5 (1.4)
Hepatic	81 (22.8)	19 (5.4)	69 (19.2)	12 (3.3)	76 (21.4)	18 (5.1)	59 (16.4)	12 (3.3)
Pulmonary	20 (5.6)	4 (1.1)	14 (3.9)	1 (0.3)	19 (5.4)	4 (1.1)	10 (2.8)	1 (0.3)
Renal	40 (11.3)	7 (2.0)	23 (6.4)	1 (0.3)	33 (9.3)	6 (1.7)	22 (6.1)	1 (0.3)
Skin	178 (50.1)	7 (2.0)	153 (42.6)	9 (2.5)	171 (48.2)	6 (1.7)	145 (40.4)	7 (1.9)
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Hypersensitivity/infusion reaction	26 (7.3)	1 (0.3)	17 (4.7)	1 (0.3)	25 (7.0)	0	16 (4.5)	1 (0.3)
Drug-Related Select AEs (by Category)								
Endocrine	103 (29.0)	7 (2.0)	79 (22.0)	3 (0.8)	94 (26.5)	7 (2.0)	75 (20.9)	3 (0.8)
Gastrointestinal	65 (18.3)	8 (2.3)	42 (11.7)	2 (0.6)	56 (15.8)	7 (2.0)	37 (10.3)	2 (0.6)
Hepatic	50 (14.1)	15 (4.2)	38 (10.6)	6 (1.7)	47 (13.2)	14 (3.9)	33 (9.2)	6 (1.7)
Pulmonary	18 (5.1)	3 (0.8)	14 (3.9)	1 (0.3)	18 (5.1)	3 (0.8)	10 (2.8)	1 (0.3)
Renal	20 (5.6)	5 (1.4)	6 (1.7)	1 (0.3)	16 (4.5)	5 (1.4)	6 (1.7)	1 (0.3)
Skin	166 (46.8)	5 (1.4)	138 (38.4)	7 (1.9)	160 (45.1)	5 (1.4)	132 (36.8)	7 (1.9)
Hypersensitivity/infusion reaction	26 (7.3)	1 (0.3)	16 (4.5)	1 (0.3)	24 (6.8)	0	16 (4.5)	1 (0.3)
All-causality Non-endocrine IMAEs Within 100 Days of Last Dose Treated with IMM								
Rash	49 (13.8)	3 (0.8)	34 (9.5)	5 (1.4)	39 (11.0)	3 (0.8)	28 (7.8)	5 (1.4)
Diarrhea/Colitis	29 (8.2)	6 (1.7)	14 (3.9)	5 (1.4)	25 (7.0)	5 (1.4)	12 (3.3)	5 (1.4)
Hepatitis	23 (6.5)	18 (5.1)	13 (3.6)	6 (1.7)	21 (5.9)	15 (4.2)	11 (3.1)	6 (1.7)
Pneumonitis	16 (4.5)	3 (0.8)	10 (2.8)	2 (0.6)	14 (3.9)	2 (0.6)	7 (1.9)	2 (0.6)
Nephritis/Renal Dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	6 (1.7)	1 (0.3)	5 (1.4)	0	5 (1.4)	0	5 (1.4)	0
All-Causality Endocrine IMAEs Within 100 Days of Last Dose with or Without IMM								
Hypothyroidism/Thyroiditis	71 (20.0)	0	55 (15.3)	0	66 (18.6)	0	53 (14.8)	0
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Hypothyroidism	67 (18.9)	0	52 (14.5)	0	62 (17.5)	0	50 (13.9)	0
Adrenal Insufficiency	21 (5.9)	6 (1.7)	4 (1.1)	0	19 (5.4)	6 (1.7)	4 (1.1)	0
Hyperthyroidism	24 (6.8)	0	26 (7.2)	0	23 (6.5)	0	25 (7.0)	0
Hypophysitis	11 (3.1)	2 (0.6)	4 (1.1)	1 (0.3)	10 (2.8)	2 (0.6)	4 (1.1)	1 (0.3)
Thyroiditis	10 (2.8)	0	5 (1.4)	0	10 (2.8)	0	5 (1.4)	0

	CA224047 Addendum 03				CA224047 Addendum 01			
	No. of Subjects (%)							
Safety Parameters	**Nivo+rela FDC (N=355)**		**Nivo (N=359)**		**Nivo+rela FDC (N=355)**		**Nivo (N=359)**	
Diabetes Mellitus	2 (0.6)	2 (0.6)	4 (1.1)	2 (0.6)	2 (0.6)	2 (0.6)	3 (0.8)	2 (0.6)
All-Causality OESIs Within 100 Days of Last Dose with or Without IMM[c]								
Troponin Event	45 (12.7)	2 (0.6)	37 (10.3)	3 (0.8)	43 (12.1)	1 (0.3)	36 (10.0)	2 (0.6)
Uveitis	6 (1.7)	1 (0.3)	5 (1.4)	2 (0.6)	6 (1.7)	1 (0.3)	5 (1.4)	2 (0.6)
Myocarditis	6 (1.7)	2 (0.6)	2 (0.6)	0	6 (1.7)	2 (0.6)	2 (0.6)	0
Pancreatitis	6 (1.7)	1 (0.3)	6 (1.7)	1 (0.3)	5 (1.4)	0	4 (1.1)	1 (0.3)
Encephalitis	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)
Myositis/Rhabdomyolysis	2 (0.6)	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0	0
Guillain-Barre Syndrome	1 (0.3)	0	0	0	1 (0.3)	0	0	0

a Since the DBL of 28-Oct-2021 (the CA224047 CSR Addendum 01 CSR),**Error! Bookmark not defined.** there were no new deaths r eported due to study drug toxicity. Prior to the current DBL of 29-Oct-2024, a total of 6 deaths were attributed to study drug toxicity: 4 deaths in the nivo+rela FDC arm (reported causes: hemophagocytic lymphohistiocytosis; acute oedema of the lung; multi-organ failure; pneumonitis) and 2 deaths in the nivo arm (reported causes: sepsis and myocarditis; worsening pneumonia) [Appendix 16.2.7.1 of the CA224047 CSR Addendum 03].**Error! Bookmark not defined.**

b Since the DBL of 28-Oct-2021 (the CA224047 CSR Addendum 01 CSR), there were 11 additional deaths with a primary reason of 'other' (ie, deaths not due to disease progression, study drug toxicity, or unknown reasons): 6 in the nivo+rela FDC arm (verbatim terms: septic shock and lung infection; sepsis; peritonitis, septic shock post perforated appendix, no malignancy noted; pulmonary embolism; death from age and co-morbidities; aortic dissection), and 5 in the nivo arm (verbatim terms: severe ketoacidosis and diabetes mellitus 2, lower respiratory infection; constant decline due to a stroke per relative; myeloid leukemia type B; pneumonia and hematological cancer) [Appendix 16.2.7.1 of the CA224047 CSR Addendum 03].

c The PTs of Myasthenic Syndrome, Demyelination, Graft Versus Host Disease, and Meningitis had 0 events recorded in either treatment group and are therefore not presented.

MedDRA version 27.0 CTCAE version 5.0 (used for CSR Addendum 03 data); MedDRA version 23.1 CTCAE version 5.0 (used for CSR Addendum 01 data). All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Grade 3-4 AEs

The most frequently reported Grade 3-4 adverse events (AE)s were:

- Nivolumab+relatlimab FDC: malignant neoplasm progression (3.9%); anemia (2.8%); diarrhea (2.3%); fatigue, hypertension, and hyponatremia (1.7% each); arthralgia, back pain, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), weight decreased, dyspnea, hyperglycemia, and adrenal insufficiency (1.4% each); rash, urinary tract infection, and COVID-19 (1.1% each).
- Nivolumab: malignant neoplasm progression (4.5%); anemia (3.1%); hyperglycemia (2.2%); hypertension (1.7%); diarrhea (1.4%); increased ALT (1.1%).

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

- Nivolumab+relatlimab FDC: increased lipase (1.7%); fatigue, diarrhea, increased ALT and increased AST (1.4% each); adrenal insufficiency (1.1%).
- Nivolumab: increased lipase (1.1%); pruritus, rash, rash maculopapular, diarrhea, increased ALT, increased amylase, hyperglycemia, diabetic ketoacidosis, and anemia (0.6% each).

Adverse reactions in section 4.8 of the SmPC

The following methodology was used to generate the adverse reactions with rela+nivo FDC table in Section 4.8 of the SmPC.

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

2. Identify clinically relevant events based on BMS medical review of the drug-related re-mapped AE summary table.
3. Present resulting clinically relevant re-mapped events by SOC and all-causality frequency in the final ADR table.

ADR selection for the SmPC was performed by applying the following criteria for excluding ADRs from Table 2 in Section 4.8 of the SmPC:

- Overly general/non-specific
- No suspected causal relationship to study treatment per BMS medical review
- Single case events with limited data
- Medical concept captured under a different term

For this application based on approximately 4 years of follow-up in study CA224047, the below changes were included in SmPC section 4.8:

In the current OPDUALAG SmPC**Error! Bookmark not defined.**, the most common adverse reactions i ncluded in the "Summary of the safety profile" in Section 4.8 are presented based on a frequency cutoff of ≥ 10%. The common adverse reactions meeting this cutoff were updated in the SmPC based on the 4-year safety data, i.e. "upper respiratory tract infection", "dizziness", and "oedema" terms were added to this section of the SmPC as they met the ≥ 10% frequency cutoff at 4 years of follow-up.

The most common serious adverse reactions included in SmPC section 4.8 are presented based on a 1% frequency cutoff. The PTs of "back pain" and "pneumonia" were not identified as ADRs but were inadvertently included as serious ADRs at the time of the initial MAA. These two PTs do not qualify as ADRs and are deleted.

In the ADR Table 2 of the SmPC, ADRs are presented by SOC and by frequency grouping. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, ADRs are presented in the order of decreasing number of cases. Frequencies provided in the ADR table of Section 4.8 are provided based on all reported ADRs, regardless of the investigator assessment of causality, per EMA guidelines. In this application, although there were no updates to the ADR terms included in Table 2 in Section 4.8 of the SmPC, some ADR frequencies were updated based on the 4-year safety data as presented in the table below.

Table 17. Adverse Events (Any Grade, Grade 3-4, Grade 5) with 30 Days follow-up - All treated subjects

		Any Grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)
Total n of subjects with an event		352 (99.2)	166 (46.8)	6 (1.7)
System Organ Class	Preferred Term			
General disorders and administration site conditions				
	Fatigue	157 (44.2)	8 (2.3)	0
	Pyrexia	46 (13.0)	0	0
	Oedema	37 (10.4)	2 (0.6)	0
Musculoskeletal and connective tissue disorders				
	Musculoskeletal pain	122 (34.4)	9 (2.5)	0
	Arthralgia	102 (28.7)	5 (1.4)	0
Skin and subcutaneous tissue disorders				
	Rash	108 (30.4)	7 (2.0)	0
	Pruritus	100 (28.2)	0	0
	Vitiligo	51 (14.4)	0	0
	Psoriasis	4 (1.1)	0	0

	Urticaria	5 (1.4)	0	0
Gastrointestinal disorders				
	Diarrhoea	106 (29.9)	8 (2.3)	0
	Nausea	75 (21.1)	2 (0.6)	0
	Abdominal pain	55 (15.5)	1 (0.3)	0
	Constipation	46 (13.0)	2 (0.6)	0
	Vomiting	42 (11.8)	2 (0.6)	0
Nervous system disorders				
	Headache	74 (20.8)	1 (0.3)	0
	Dizziness	37 (10.4)	0	0
Respiratory, thoracic and mediastinal disorders				
	Cough	63 (17.7)	1 (0.3)	0
	Dyspnoea	42 (11.8)	5 (1.4)	0
	Pleural effusion	4 (1.1)	1 (0.3)	0
Endocrine disorders				
	Hypothyroidism	63 (17.7)	0	0
	Hypopituitarism	3 (0.8)	0	0
Infections and infestations				
	Folliculitis	5 (1.4)	0	0
	Urinary tract infection	48 (13.5)	4 (1.1)	0
	Upper respiratory tract infection	44 (12.4)	0	0
Metabolism and nutrition disorders				
	hypernatraemia	3 (0.8)	0	0
	Increased bilirubin	4 (1.1)	0	0
	C-reactive protein increased	4 (1.1)	0	0

MedDRA version: 27.0.
AEs reported between first dose and 30 days after last dose of study therapy.
n (%) = number of subjects with at least one event / total number of subjects in the safety population.
Subjects may have more than one event in the same category.
Grade based on CTCAE version applicable at time of study conduct.
Drug-related adverse events as assessed by the investigator.

The derivation of the absolute neutrophil count (ANC) was corrected and the resultant determination of subjects whose ANC values worsened to Grade 3-4 relative to baseline changed from 1 (at the time of the MAA) to 0 and as a result "neutropenia" has been removed from the subsection of *Laboratory Abnormalities* within SmPC Section 4.8.

Serious adverse event/deaths/other significant events

- **Deaths**

Across both treatments arms, 6 deaths were attributed to study drug toxicity (4 in the nivo+rela FDC arm and 2 in the nivo arm), and no new such cases were reported since the DBL for CA224047 CSR Addendum 01.

Table *18*. Death summary – All treated subjects

	Nivo + Rela N = 355	Nivo N = 359	Total N = 714
NUMBER OF SUBJECTS WHO DIED (%)	182 (51.3)	218 (60.7)	400 (56.0)
PRIMARY REASON FOR DEATH (%)			
DISEASE	139 (39.2)	178 (49.6)	317 (44.4)
STUDY DRUG TOXICITY	4 (1.1)	2 (0.6)	6 (0.8)
UNKNOWN	10 (2.8)	15 (4.2)	25 (3.5)
OTHER	29 (8.2)	23 (6.4)	52 (7.3)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	11 (3.1)	20 (5.6)	31 (4.3)
PRIMARY REASON FOR DEATH (%)			
DISEASE	1 (0.3)	9 (2.5)	10 (1.4)
STUDY DRUG TOXICITY	1 (0.3)	1 (0.3)	2 (0.3)
UNKNOWN	1 (0.3)	2 (0.6)	3 (0.4)
OTHER	8 (2.3)	8 (2.2)	16 (2.2)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	56 (15.8)	70 (19.5)	126 (17.6)
PRIMARY REASON FOR DEATH (%)			
DISEASE	35 (9.9)	49 (13.6)	84 (11.8)
STUDY DRUG TOXICITY	3 (0.8)	1 (0.3)	4 (0.6)
UNKNOWN	1 (0.3)	3 (0.8)	4 (0.6)
OTHER	17 (4.8)	17 (4.7)	34 (4.8)

Since the 28-Oct-2021 DBL (of the CA224047 CSR Addendum 01), there were 11 additional deaths reported with a primary reason of 'other' (ie, deaths not due to disease progression, study drug toxicity, or unknown reasons. Six additional deaths occurred in the nivo+rela FDC arm (verbatim terms): septic shock and lung infection; sepsis; peritonitis, septic shock post perforated appendix, no malignancy noted; pulmonary embolism; death from age and co-morbidities; aortic dissection. Five additional deaths occurred in the nivo monotherapy arm (verbatim terms): severe ketoacidosis and diabetes mellitus 2, lower respiratory infection; constant decline due to a stroke per relative; myeloid leukemia type B; pneumonia and hematological cancer. Further, there were 8 additional deaths reported due to 'unknown' reasons: 3 in the Nivolumab+relatlimab FDC arm and 5 in the nivolumab monotherapy arm.

- **Serious adverse events (SAEs)**

Table *19*. SAEs Summary by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) in ≥ 2 Subjects - All Treated Subjects

System Organ Class (%) Preferred Term (%)	Nivo + rela N = 355			Nivo N = 359		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	**141 (39.7)**	**110 (31.0)**	**6 (1.7)**	**124 (34.5)**	**83 (23.1)**	**13 (3.6)**
Infections and infestations	32 (9.0)	28 (7.9)	1 (0.3)	22 (6.1)	20 (5.6)	0
Pneumonia	5 (1.4)	4 (1.1)	1 (0.3)	3 (0.8)	3 (0.8)	0
Urinary tract infection	4 (1.1)	4 (1.1)	0	3 (0.8)	2 (0.6)	0
COVID-19	3 (0.8)	3 (0.8)	0	2 (0.6)	0	0
COVID-19 pneumonia	3 (0.8)	3 (0.8)	0	1 (0.3)	1 (0.3)	0
Diverticulitis	2 (0.6)	2 (0.6)	0	0	0	0
Encephalitis	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Sepsis	2 (0.6)	2 (0.6)	0	2 (0.6)	1 (0.3)	0
Septic shock	2 (0.6)	2 (0.6)	0	0	0	0
Cellulitis	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Erysipelas	1 (0.3)	1 (0.3)	0	2 (0.6)	2 (0.6)	0
Urosepsis	0	0	0	2 (0.6)	2 (0.6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	29 (8.2)	20 (5.6)	1 (0.3)	36 (10.0)	22 (6.1)	6 (1.7)
Malignant neoplasm progression	14 (3.9)	13 (3.7)	1 (0.3)	20 (5.6)	13 (3.6)	6 (1.7)
Basal cell carcinoma	3 (0.8)	1 (0.3)	0	3 (0.8)	3 (0.8)	0
Metastases to central nervous system	3 (0.8)	1 (0.3)	0	3 (0.8)	2 (0.6)	0
Transitional cell carcinoma	2 (0.6)	0	0	1 (0.3)	1 (0.3)	0
Tumour haemorrhage	1 (0.3)	0	0	2 (0.6)	1 (0.3)	0
Squamous cell carcinoma	1 (0.3)	1 (0.3)	0	4 (1.1)	1 (0.3)	0
Gastrointestinal disorders	25 (7.0)	16 (4.5)	0	13 (3.6)	9 (2.5)	0
Diarrhoea	5 (1.4)	3 (0.8)	0	2 (0.6)	2 (0.6)	0
Colitis	4 (1.1)	3 (0.8)	0	1 (0.3)	0	0
Abdominal pain	2 (0.6)	1 (0.3)	0	0	0	0
Constipation	2 (0.6)	2 (0.6)	0	0	0	0
Gastritis	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Vomiting	2 (0.6)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Musculoskeletal and connective tissue disorders	19 (5.4)	13 (3.7)	0	9 (2.5)	4 (1.1)	0
Back pain	4 (1.1)	3 (0.8)	0	2 (0.6)	0	0
Myalgia	3 (0.8)	1 (0.3)	0	0	0	0
Arthralgia	2 (0.6)	2 (0.6)	0	0	0	0
Arthritis	2 (0.6)	2 (0.6)	0	1 (0.3)	0	0
Muscular weakness	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Pain in extremity	0	0	0	2 (0.6)	2 (0.6)	0
Cardiac disorders	15 (4.2)	10 (2.8)	1 (0.3)	13 (3.6)	5 (1.4)	2 (0.6)
Myocarditis	4 (1.1)	2 (0.6)	0	1 (0.3)	0	0
Acute myocardial infarction	3 (0.8)	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.3)
Myocardial infarction	3 (0.8)	3 (0.8)	0	2 (0.6)	0	1 (0.3)
Atrial fibrillation	2 (0.6)	1 (0.3)	0	1 (0.3)	0	0
Respiratory, thoracic and mediastinal disorders	12 (3.4)	7 (2.0)	2 (0.6)	13 (3.6)	8 (2.2)	1 (0.3)
Dyspnoea	3 (0.8)	3 (0.8)	0	1 (0.3)	1 (0.3)	0
Pneumonitis	3 (0.8)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Pulmonary embolism	2 (0.6)	1 (0.3)	0	0	0	0
Respiratory failure	2 (0.6)	0	1 (0.3)	2 (0.6)	1 (0.3)	1 (0.3)
Pneumothorax	0	0	0	2 (0.6)	2 (0.6)	0
Nervous system disorders	11 (3.1)	9 (2.5)	0	7 (1.9)	4 (1.1)	1 (0.3)
Syncope	3 (0.8)	3 (0.8)	0	2 (0.6)	2 (0.6)	0
Endocrine disorders	10 (2.8)	8 (2.3)	0	1 (0.3)	0	0
Adrenal insufficiency	5 (1.4)	5 (1.4)	0	0	0	0
Hypophysitis	2 (0.6)	2 (0.6)	0	0	0	0
General disorders and administration site conditions	9 (2.5)	4 (1.1)	1 (0.3)	15 (4.2)	6 (1.7)	3 (0.8)
Pyrexia	3 (0.8)	0	0	4 (1.1)	1 (0.3)	0
General physical health deterioration	2 (0.6)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Sudden death	0	0	0	2 (0.6)	0	2 (0.6)
Metabolism and nutrition disorders	8 (2.3)	7 (2.0)	0	10 (2.8)	9 (2.5)	0
Dehydration	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Hypokalaemia	2 (0.6)	1 (0.3)	0	0	0	0
Hyponatraemia	1 (0.3)	1 (0.3)	0	2 (0.6)	1 (0.3)	0
Type 2 diabetes mellitus	0	0	0	2 (0.6)	2 (0.6)	0
Diabetic ketoacidosis	0	0	0	2 (0.6)	2 (0.6)	0
Renal and urinary disorders	8 (2.3)	7 (2.0)	0	1 (0.3)	0	0
Acute kidney injury	2 (0.6)	2 (0.6)	0	1 (0.3)	0	0
Renal failure	2 (0.6)	1 (0.3)	0	0	0	0
Blood and lymphatic system disorders	7 (2.0)	5 (1.4)	0	3 (0.8)	3 (0.8)	0
Anaemia	5 (1.4)	3 (0.8)	0	1 (0.3)	1 (0.3)	0
Hepatobiliary disorders	7 (2.0)	5 (1.4)	0	4 (1.1)	4 (1.1)	0
Bile duct stone	2 (0.6)	1 (0.3)	0	0	0	0
Injury, poisoning and procedural	7 (2.0)	6 (1.7)	0	10 (2.8)	7 (1.9)	0

complications						
Wound	2 (0.6)	1 (0.3)	0	0	0	0
Hip fracture	0	0	0	2 (0.6)	2 (0.6)	0
Infusion related reaction	0	0	0	2 (0.6)	1 (0.3)	0
Vascular disorders	6 (1.7)	5 (1.4)	0	2 (0.6)	2 (0.6)	0
Investigations	3 (0.8)	2 (0.6)	0	2 (0.6)	0	0
Psychiatric disorders	3 (0.8)	3 (0.8)	0	0	0	0
Confusional state	2 (0.6)	2 (0.6)	0	0	0	0
Eye disorders	2 (0.6)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Skin and subcutaneous tissue disorders	2 (0.6)	2 (0.6)	0	6 (1.7)	4 (1.1)	0

MedDRA version 27.0, CTC version 5.0

Safety in relation to PD-L1 expression

Table 20. Summary of Safety by Baseline PD-L1 Biomarker Expression - All Treated Subjects

Safety Parameters	No. of Subjects (%)							
	Nivo+Rela FDC				Nivo			
	PD-L1 < 1% N = 209		PD-L1 ≥ 1% N = 146		PD-L1 < 1% N = 212		PD-L1 ≥ 1% N = 147	
Deaths	5 (2.4)		6 (4.1)		12 (5.7)		8 (5.4)	
	Adverse Event Grades							
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	84 (40.2)	64 (30.6)	57 (39.0)	47 (32.2)	75 (35.4)	57 (26.9)	49 (33.3)	31 (21.1)
Drug-related SAEs	32 (15.3)	21 (10.0)	25 (17.1)	19 (13.0)	17 (8.0)	11 (5.2)	13 (8.8)	8 (5.4)
All-causality AEs leading to DC	45 (21.5)	26 (12.4)	39 (26.7)	21 (14.4)	31 (14.6)	14 (6.6)	31 (21.1)	16 (10.9)
Drug-Related AEs leading to DC	32 (15.3)	17 (8.1)	31 (21.2)	18 (12.3)	17 (8.0)	5 (2.4)	17 (11.6)	9 (6.1)
All-causality AEs	207 (99.0)	98 (46.9)	145 (99.3)	70 (47.9)	204 (96.2)	88 (41.5)	141 (95.9)	54 (36.7)
Drug-related AEs	176 (84.2)	39 (18.7)	127 (87.0)	40 (27.4)	148 (69.8)	23 (10.8)	115 (78.2)	20 (13.6)

MedDRA Version 27.0, CTCAE Version 5.0; Includes events reported between first dose and 30 days after last dose of study therapy.

Post marketing experience

Nivo+rela FDC was approved for marketing in the EU on 15 Sep-2022. Based on PV activities conducted by BMS Patient Safety, the post-marketing safety data is consistent with the clinical trial safety data for nivo+rela FDC.

A comprehensive and detailed review of all safety information received during the most recent PBRER for nivo+rela FDC did not reveal a significant safety/efficacy concern that changed the currently known positive benefit-risk balance of nivo+rela FDC for the treatment of unresectable or metastatic melanoma.

2.5.1. Discussion on clinical safety

With the 4-year update and a median follow-up of 34.9 months, the median treatment duration was 8.3 months for nivo+rela FDC treated subjects and 6.5 months for nivolumab monotherapy treated subjects, and nearly 40% subjects have been treated ≥ 12 months. These results were similar to that

of the previous DCO of 7 Sept 2021 with a median follow-up of 19.3 months. With the updated results, about 24% of patients were treated for ≥ 24 months.

No new safety issues were identified with the longer follow-up. The safety profile of the combination is characterized by immune mediated AEs. As seen before, frequencies of AEs leading to discontinuation as well as SAEs were slightly higher in the nivo+rela arm compared to nivo monotherapy. Deaths due to study toxicity were limited and no new deaths due to study drug toxicity were observed.

The safety information in the product information was based on the all-comer population as there were no consistent differences observed in the frequencies of all-causality or drug-related AEs, SAEs, or AEs leading to discontinuation between PD-L1 expression subgroups. This is supported with the current data, showing only slightly higher frequencies in the PD-L1 ≥ 1% subgroup. The safety information in the SmPC is considered to adequately reflect the safety profile of nivo+rela FDC. Frequencies of adverse reactions in section 4.8 of the SmPC were updated based on longer follow-up which is acceptable. The reported frequencies of selected irARs in Section 4.8 of the current SmPC are based on all drug-related selected irARs (ie, drug-related Selected AEs, as reported by investigators) in all treated subjects with nivo+rela FDC. irAR frequencies were updated based on the 4-year safety data.

2.5.2. Conclusions on clinical safety

Based on the 4-year results, the safety profile remains consistent with the known safety profile of nivo+rela FDC and no new safety signals have been raised with longer follow-up.

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. However, as the variation scope was changed during the assessment by the CHMP (see Efficacy discussion/conclusion) and the

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

The PRAC considered that the risk management plan version 3.0 is acceptable.

Safety concerns

Table 21. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)
Important potential risks	Embryofetal toxicity

Summary of safety concerns	
Missing information	Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age

The summary of safety concerns remains unchanged based on the data submitted in this procedure.

Pharmacovigilance plan

Table 22. On-going and planned additional pharmacovigilance activities

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA224122: Long-term follow-up of paediatric patients exposed to nivolumab + relatlimab FDC in the DMTR.	The primary objective is to evaluate Grades 3-4 AEs (which includes irARs) experienced by paediatric patients ≥ 12 to < 18 years of age, along with their management, and outcome. Secondary objectives include evaluating long-term outcomes (with emphasis on growth and development).	Long term safety (including growth and development disorders) in paediatric patients ≥ 12 to < 18 years of age. Use in these patients is part of the proposed on-label indication for Opdualag but there is no data from clinical development in this patient population.	Planned Voluntary PASS	1. Protocol synopsis submission: 13-Sep-2021 2. Full Protocol submission: 2Q 2023 3. Interim reports[a]: 4Q 2026 4Q 2029 4Q 2032 4Q 2035 4. Final report[a]: 4Q 2038

Error! Bookmark not defined. Milestone(s) due dates are based on the approval for the nivolumab + relatlimab FDC in the Netherlands.

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

NO changes to the pharmacovigilance plan were made as part of this procedure.

Risk minimisation measures

Table 23. Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs, myocarditis and other irARs)	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4, and 4.8 Package Leaflet Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: Patient Card	**Additional pharmacovigilance activities:** None
Embryofetal toxicity	**Routine risk minimisation measures:** SmPC Sections 4.6 and 5.3 Package Leaflet Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age	**Routine risk minimisation measures:** SmPC Section 4.2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** PASS CA224122

Safety concern	Routine risk minimisation activities
Immune-related ARs (including immune-related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin ARs,	**Routine risk communication:** The SmPC warns of the risks of irARs in Sections 4.4 and 4.8. In addition, the package leaflet also includes specific warnings and descriptions of the most important irARs in the language suitable for patients. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on monitoring and management, including treatment delay or discontinuation and intervention with corticosteroids or other

myocarditis and other irARs)	immunosuppressive therapy, are provided in SmPC Sections 4.2, 4.4 and 4.8, as appropriate. **Other routine risk minimisation measures beyond the Product Information:** None
Embryofetal toxicity	**Routine risk communication:** SmPC includes embryofetal toxicity in Sections 4.6 and 5.3. In addition, the package leaflet also includes warnings that nivolumab + relatlimab FDC could harm an unborn baby and relevant advice regarding contraception for patients. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Long term safety (including growth and development disorders) in paediatric patients ⩾ 12 years of age	**Routine risk communication:** The SmPC includes information for the paediatric population in Section 4.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None

Additional risk minimisation measures

Table 24. Additional Risk Minimisation Measures

Additional Risk Minimisation:	**Objectives/Rational:**
Educational Material Patient Card	**Objectives:** To further raise awareness of patients on signs and symptoms of important risks of irARs. **Rationale for the additional risk minimisation measure:** This communication tool will provide the opportunity for reinforcing the key messages to ensure early recognition and appropriate management of important identified risks of irARs to maintain favorable benefit/risk of nivolumab + relatlimab FDC in market use. **Target audience and planned distribution path:** Patients via healthcare professionals. **Plans to evaluate the effectiveness of the interventions and criteria for success:** Routine PV activities will provide information on any changes in the occurrence, severity, and outcome of important identified risks as it relates to the established safety profile, and will be reported in future regulatory safety reports (eg, PBRERs/PSURs).

The Additional Risk Minimisation Measures have not been amended as part of this procedure.

2.7. Update of the Product information

As a consequence of this variation, sections 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Opdualag is:

Opdualag is indicated for the first line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.

This concerns an extension of the current indication (tumours with PD-L1 < 1%) to include the PD-L1 ≥ 1% subgroup.

Melanoma is a heterogeneous and complex disease with various clinical factors and molecular defects playing a key role in outcomes. The target population is confined to unresectable stage III (regional metastatic) and stage IV (distinct metastatic) melanoma. The five-year survival is about (10%-)20% when distant metastases are present. Clinical factors associated with poor survival include elevated LDH, visceral metastases (notably liver and brain), multiple metastatic sites, and poor performance status (Luke JJ et al, 2017).

3.1.2. Available therapies and unmet medical need

The current first-line standard of care treatments for unresectable stage III/IV are PD-1 blockade (nivolumab, pembrolizumab), and PD-1 blockade (nivolumab) combined with CTLA-4 blockade (ipilimumab) for the all-comer population. Opdualag is currently indicated for patients with tumour cell PD-L1 expression < 1%.

BRAF inhibition (vemurafenib, dabrafenib, encorafenib) combined with MEK inhibition (cobimetinib, trametinib, binimetinib) is indicated for BRAFV600-mutated melanoma.

Combination treatment of ipilimumab and nivolumab has markedly improved survival with a 5-year OS rate of 52% (Wolchok JD et al, 2021). However, as the toxicity profile of the ipilimumab and nivolumab combination is non-negligible, there is still a need for more safe therapies. Similarly, there remains a need for more effective therapies, as a significant proportion of patients either fail to respond or initially respond but subsequently relapse. There are no standard approaches to treating patients without BRAF mutations once they progress after receiving anti-PD-1 therapy.

3.1.3. Main clinical studies

The pivotal study CA224047 is an adaptive Phase 2/3, randomised, double-blind study of relatlimab + nivolumab vs. nivolumab monotherapy in subjects with previously untreated metastatic or unresectable melanoma. A total of 714 patients were randomised (1:1) to receive either relatlimab plus nivolumab, or nivolumab monotherapy. Randomisation was stratified by PD-L1 expression (≥ 1% vs. < 1%), LAG-3 expression (≥ 1% vs. < 1%), BRAF mutation (V600 mutation positive vs. V600 wild-type), and AJCC M stage (M0/M1 with normal LDH vs. M1 with elevated LDH).

The approved indication is based on the results from 421 patients with PD-L1 < 1% at the primary DCO of 9 March 2021, and updated results from DCO 7 Sep 2021. The MAH has now submitted updated descriptive results based on the DCO of 24 Sep 2024 to support the extension of indication with the PD-L1 ≥ 1% subgroup (n=239). In addition, descriptive OS results from the final 5-year survival follow-up were also submitted (DCO: 25 Sep 2025).

3.2. Favourable effects

PD-L1 ≥ 1% subgroup: With a median follow-up period of 34.9 months, mOS was not reached in the combination arm and 41.2 months in the nivo mono arm (HR: 0.76; 95% CI: 0.55, 1.05). mPFS was 18.0 months and 14.7 months in the combination and nivo mono therapy arm, respectively (HR: 0.95; 95% CI: 0.71, 1.28). ORR data showed an increase in ORR for the combination treatment over monotherapy of 8%.

ITT: mOS was 53.3 months in the combination arm and 33.2 months in the nivo mono arm (HR: 0.77; 95% CI: 0.64, 0.94). mPFS was 10.2 months and 4.6 months in the combination and nivo mono therapy arm, respectively (HR: 0.78; 95% CI: 0.65, 0.93). ORR data showed an increase in ORR for the combination treatment over monotherapy of 10%. Results from the 5-year survival follow-up were comparable to the 4-year update.

Updated results within the PD-L1 < 1% subgroup confirm the beneficial effect on PFS and OS. mOS was now reached in both treatment arms, 38.3 month and 25.8 months in the combination and monotherapy arm, respectively.

3.3. Uncertainties and limitations about favourable effects

PD-L1 ≥ 1% subgroup:

- KM OS curves only start to separate after 30 months of follow-up, and censoring rates are high from 42 months onwards.
- KM-curves of PFS largely overlap.
- Prespecified final OS analysis in the ITT did not reach statistical significance. Results are based on descriptive analyses after study unblinding.
- The hypothesized mechanism of action that the delayed OS benefit (after 30 months) from nivo+rela FDC is driven by rela overcoming developed resistance to anti-PD-1 treatment and promoting memory T-cell increases over time, is based on exploratory data within the study and lacks confirmatory results including longitudinal biomarker data.

3.4. Unfavourable effects

The safety profile of nivo+rela FDC is characterised by immune-mediated AEs (IMAEs). The safety profile remained consistent with the known safety profile of nivo+rela FDC and no new safety signals have been raised with longer follow-up. Frequencies were largely comparable to the previous DCO of 7 Sep 2021.

Grade 3-4 AEs were reported in 47.3% in the combination arm and 39.6% in the nivo arm. Drug-related grade 3-4 AEs occurred in 22.3% and 12.0%, respectively. Grade 3-4 SAEs were reported in 31.3% in the combination arm versus 24.5% in the nivo arm. A comparable proportion of subjects in the rela+nivo FDC (1.1%; 4 subjects) and nivolumab (0.6%; 2 subjects) arms died due to study drug toxicity during the study.

AEs leading to discontinuation were reported in 23.7% in the nivo+rela arm and 17.3% in the nivo arm. Drug-related AEs leading to discontinuation were reported in 17.7% and 9.5% in the combination and monotherapy arm, respectively.

3.5. Uncertainties and limitations about unfavourable effects

n/a

3.6. Effects Table

Table 25. Effects Table for Opdualag for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents ⩾12 yrs with tumour cell PD-L1 ≥ 1% expression (Study CA224047, data cut-off 24 Sep 2024)

Effect	Short description	Unit	Rela+nivo FDC (n=146)	Nivolumab (n=147)	Uncertainties / Strength of evidence	References
Favourable Effects						
PD-L1 ≥ 1%						
OS	Overall survival	Median (Months)	N.A. (95% CI: 41.89, N.A.)	41.95 (95% CI: 31.70, N.A.)	8% increased OS rate at 36 months with combination HR: 0.76 (95% CI: 0.55, 1.05), exploratory analyses Separation KM-curves only after 30 months. Final 5-year OS update in line with 4-year data	
PFS	Patients alive and free of progression (all randomised patients)	Median (Months)	18.04 (95% CI: 10.09, 26.71)	14.72 (95% CI: 5.36, 34.46)	HR: 0.95 (95% CI: 0.71, 1.28), exploratory analyses Overlapping KM-curves	
ORR	Overall response rate	%	52.7 (95% CI: 44.3, 61.1)	44.9 (95% CI: 36.7, 53.3)		
Unfavourable Effects*						
AEs gr. 3-4	All causality Drug-related	%	47.3 22.3	39.6 12.0		
AEs leading to discontinuation	All causality Drug-related	%	23.7 17.7	17.3 9.5		
SAEs grade 3-4	Serious AEs	%	31.3	24.5		
Deaths due to study toxicity		%	1.1	0.6		

Abbreviations: CI: confidence interval; HR: Hazard rate; ORR: overall response rate; OS: overall survival; PFS: progression free survival; DCO: clinical data cutoff; SAE: serious adverse event, N.A.: not available.
* Unfavourable effects are based on the all-treated population

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The initial approval was based on a positive study that utilized the inferential PFS analysis in the ITT population with support from a non-detrimental OS outcome. The indication was restricted due to lack of improved PFS and OS in the PD-L1 ≥ 1% subgroup. A formal effect on OS was not demonstrated at the time of the final OS analysis (DBL: 28 Oct 2021). With the 4-year updated descriptive OS results

from study CA224047, the KM-curve shows a trend for a sustained separation of OS from 30 months onwards in favour of the combination treatment. The clinical relevance of an increase in OS rate of 8% at 36 months is questionable. The curves up until around 30 months appear to come back together after a separation. Though KM-curves remain separated up till 72 months of follow-up, extensive censoring is seen from 42 months onwards, limiting the conclusion that can be drawn with longer follow-up. Few additional events were observed at the final 5-year survival follow-up. The potential OS benefit observed in this descriptive OS analysis is not supported by a PFS benefit, as already observed at the time of submission, which makes it difficult to interpret. Further, no external data replicating this finding are available. Overall, the updated OS analysis is exploratory and not considered suitable to support a re-evaluation of the initial decision for an approval in PD-L1 <1%.

The presented post-hoc exploratory biomarker analyses have many limitations and are considered hypothesis-generating. These cannot be used to support the late separation of KM-curves for OS.

A replication of these results, with support from longitudinal biomarker data to support the hypothesized mechanism would be required to confirm the benefit of the rela+nivo combination over nivo monotherapy in patients with PD-L1 ≥ 1%.

Overall, given the identified limitations, a beneficial effect of the combination over nivo monotherapy is not considered demonstrated for the PD-L1 ≥ 1% subgroup.

Based on the 4 years follow-up, the safety profile remained consistent with the known safety profile of nivo+rela FDC and no new safety signals have been raised. Frequencies were largely comparable to the previous DCO of 7 Sep 2021.

3.7.2. Balance of benefits and risks

A beneficial effect of relatlimab+nivolumab FDC in the PD-L1 ≥ 1% subgroup is not considered demonstrated based on the descriptive OS results. As the proposed combination is more toxic and less well tolerated than nivolumab monotherapy, the B/R remains negative for the PD-L1 ≥ 1% subgroup.

3.7.3. Additional considerations on the benefit-risk balance

n/a

3.8. Conclusions

The overall B/R of Opdualag for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents with tumour cell expression PD-L1 < 1% is positive. The B/R remains negative for the PD-L1 ≥ 1% subgroup. The MAH requested a change in scope to C.I.4 during the procedure.

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.4	Change(s) in the Summary of Product Character istics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	II	I and IIIB

Update of section 4.8 and 5.1 of the SmPC based on updated descriptive 4-year data from pivotal Study CA224047; this is a randomized, double-blind phase 2/3 study of relatlimab combined with nivolumab versus nivolumab in participants with previously untreated metastatic or unresectable melanoma. The Package Leaflet is updated in accordance.

The variation leads to amendments to annexes I and IIIB.

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

The Patient Card shall contain the following key messages:

- That Opdualag treatment may increase the risk of:
    - Immune-related pneumonitis
    - Immune-related colitis
    - Immune-related hepatitis
    - Immune-related endocrinopathies
    - Immune-related nephritis and renal dysfunction
    - Immune-related skin ARs
    - Immune-related myocarditis
    - Other immune-related ARs
- Signs or symptoms of the safety concern and when to seek attention from a HCP

- Contact details of the Opdualag prescriber

The MAH shall agree about the format and content of the above educational material with the National Competent Authority prior to launch of Opdualag in each Member State.

Additional market protection

Considering the change in scope, the request for a one year of market protection for a new indication is not applicable and was withdrawn.