21 July 2022
EMA/720884/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Opdualag

International non-proprietary name: nivolumab / relatlimab

Procedure No. EMEA/H/C/005481/0000

Note

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

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List of abbreviations

1L	first-line
ADA	anti-drug antibodies
ADCC/P	antibody-dependent cytotoxicity/phagocytosis
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AJCC	American Joint Committee on Cancer
APCs	antigen-presenting cells
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BICR	blinded independent central review
BOR	best overall response
BRAF	B-Raf proto-oncogene
Cavg	average concentration
Cavg1	average concentration after the first dose
Cavgd28	average concentration over the first 28 days
Cavgss	average concentration at steady-state
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
Cmax	maximum concentration
Cmax1	maximum concentration after the first dose
Cmax	maximum concentration at steady-state
Cminss	minimum concentration
Cmin1	minimum concentration after the first dose
Cmind28	minimum concentration over the first 28 days
Cminss	minimum concentration at steady-state
CMC	chemistry, manufacturing, controls
CMP	commercial manufacturing process

CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse event
CTLA-4	cytotoxic T lymphocyte associated protein 4
CV	coefficient of variation
CYP P450	cytochrome P450
DBL	database lock
DCO	data cut-off
DCR	disease control rate
DDI	drug-drug interaction
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	durability of response
DP	drug product
DRAE	drug-related adverse event
DS	drug substance
EC	ethics committee
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
E-R	exposure-response
EU	European Union
FA	final analysis
FACT-M	functional assessment of cancer therapy - melanoma
FACIT GP	FACT Item General population 5
FDA	Food and Drug Administration
FDC	fixed dose combination
FFPE	formalin-Fixed Paraffin-Embedded
Gr2+	grade 2 or greater
Gr3+	grade 3 or greater
HR	hazard ratio
IA	Interim analysis

ICH	International Conference on Harmonization
Ig	immunoglobulin
IgG4	immunoglobulin G4
IL	interleukin
IL-2	interleukin-2
IFN	interferon
IHC	immunohistochemistry
IMAE	immune-mediated adverse event
IMM	immune-modulating medication
IND	investigational New Drug
IO	immuno-oncology
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	intravenous
K-M	Kaplan-Meier
LAG-3	lymphocyte-activation gene 3
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MEL	melanoma
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not applicable
NAb	neutralising antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
Nivo	nivolumab
NK	natural killer
NSCLC	non-small cell lung cancer

OESI	other event of special interest
OR	objective response
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PD-1	programmed death-1
PD-L1	programmed death–ligand 1
PD-L2	programmed death–ligand 2
PFS	progression-free survival
PFS2	progression-free survival after the next line of subsequent therapy
PIP	paediatric investigation plan
PK	pharmacokinetics
PMA	phorbol-12 myristate-13 acetate
PPK	population pharmacokinetic
PR	partial response
Prior IO	subjects who progressed while on prior IO therapy
PRO	patient reported outcome
PSUR	periodic safety update report
PT	preferred term
Q2W	every 2 weeks
Q4W	every 4 weeks
QTc	corrected QT
RECIST	response criteria evaluation in solid tumours
Rela	relatlimab
RCC	renal cell carcinoma
RO	receptor occupancy
ROss	receptor occupancy at steady state
SAE	serious adverse event
SAP	statistical analysis plan
SAV	single agent vial
SCE	summary of clinical efficacy
SCP	summary of clinical pharmacology
SCS	summary of clinical safety

SD	stable disease
sLAG-3	soluble LAG-3
SMQ	standardized MedDRA queries
t1/2	effective half-life
TCR	T cell receptor
TFI	treatment-free interval
TFS	treatment-free survival
TNF	tumour necrosis factor
Tregs	T regulatory cells
TTR	time to response
ULN	upper limit of normal
US	United States
UTD	unable to determine
Vc	central volume of distribution
WPAI:GH	work productivity and activity impairment: General health

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 10 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Opdualag, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant 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).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/00070/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/00070/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/00070/2021.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance relatlimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
30 January 2020	EMEA/H/SA/4345/1/2019/II	Pierre Demolis and Dieter Deforce
28 May 2020	EMEA/H/SA/4345/1/FU/1/2020/II	Olli Tenhunen and Paolo Foggi

The Scientific advice pertained to the following clinical aspects:

- The overall rationale for studying relatlimab in combination with nivolumab in the proposed indication
- The overall design of a randomised, double-blind Phase 2/3, study CA224047 to support a B/R assessment in the proposed indication, and specifically:
    - The proposed study population, primary endpoint and secondary endpoints, the rationale for the fixed dosing, and the proposed biomarker analyses and methodologies.
    - The statistical analyses including a proposed interim analysis of the primary endpoint to support a B/R assessment, and hierarchical testing strategy for the secondary endpoints

1.7. Steps taken for the assessment of the product

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

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Blanca Garcia-Ochoa

The application was received by the EMA on	10 September 2021
The procedure started on	30 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 December 2021
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	5 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 January 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 March 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 May 2022

The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation to be sent to the applicant on	19 May 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 June 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	6 July 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Opdualag on	21 July 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on	21 July 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applied indication for Opdualag was 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).

2.1.2. Epidemiology

Melanoma, a form of skin cancer, is the 6th most common cause of cancer in Europe with an estimated 144,209 new cases, and more than 25,000 deaths, annually. The European annual incidence of malignant melanoma varies from 3–5/100.000 in Mediterranean countries to 12–35/100.000 in Nordic countries, whereas it can reach over 50/100.000 in Australia or New Zealand. The incidence of melanoma has been rising steadily over the last 40 years, with a trend towards stabilisation of mortality, except in elderly males[1]. Melanoma incidence peaks at 65 years, though any age can be affected[2]. While rare in the adolescent population, the incidence of melanoma rises sharply to over 10 per million in the second decade, and 15–19-year-old account for between 70% and 80% of all melanoma cases diagnosed in individuals < 20 years of age[3,4].

2.1.3. Biologic features, aetiology and pathogenesis

Most melanomas arise as superficial, indolent tumours that are confined to the epidermis, where they remain for several years. At some point, probably in response to the stepwise accumulation of genetic abnormalities, the melanoma is transformed into an expansile nodule that extends beyond the biologic boundary of the basement membrane and invades the dermis. Frequently observed mutations in order of decreasing frequency are BRAF, RAS and NF1[5]. Melanoma is a heterogeneous and complex disease with various clinical factors and molecular defects playing a key role in outcomes. Cutaneous melanoma is by far the most common melanoma subtype, accounting for in excess of 90% of cases of melanoma[6]. Approximately 50% of cutaneous melanomas bear an oncogenic driver mutation in the BRAF gene which is associated with a worse prognosis. Mutation testing for actionable mutations is mandatory in patients with resectable or unresectable stage III or stage IV. In addition to the mutational status, programmed death-ligand 1 (PD-L1) expression, reported as the percentage of positive tumour cells, can be useful to assess and record for all resectable or unresectable stage III and IV

[1] Hollestein LM, van den Akker SAW, Nijsten T et al. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann Oncol 2012; 23(2): 524–530.
[2] National Cancer Registration and Analysis Service, Public Health England, https://www.cancerresearchuk.org (15 October 2019, date last accessed).
[3] Jen M, Murphy M, Grant-Kels JM. Childhood melanoma. Clin Dermatol 2009;27:529–36.
[4] Brecht IB, De Paoli A, Bisogno G et al, Pediatric patients with cutaneous melanoma: A European study. Pediatr Blood Cancer. 2018 Jun;65(6):e26974.
[5] Shain AH, Yeh I, Kovalyshyn I, et al. The Genetic Evolution of Melanoma from Precursor Lesions. N Engl J Med 2015; 373:1926
[6] Ali Z., Yousaf N, and Larkin J. Melanoma epidemiology, biology and prognosis, EJC Suppl. 2013 Sep; 11(2): 81–91.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Metastatic melanoma can spread to bone, lung, central nervous system (CNS), liver and skin. It can lead to pain, neurologic sequelae including chord compression and nerve impingement, haemorrhage, and laboratory abnormalities. Generalised effects of metastatic disease also include cachexia, thrombotic and embolic events, and infections. Clinical factors associated with poor survival include elevated LDH, visceral metastases (notably liver and brain), multiple metastatic sites, and poor performance status[7]. These are negative prognostic and predictive markers for both targeted and immunotherapies.

The eighth version of the American Joint Committee on Cancer (AJCC) staging and classification system, which includes sentinel node staging, is the preferred classification system[8]. The target population is confined to unresectable stage III (regional metastatic) and stage IV (distinct metastatic) melanoma.

The prognosis of metastatic melanoma was extremely poor (5-year survival rate of 25% between 2009-2015) until the advent of targeted and immuno-therapies which have dramatically changed the treatment paradigm.

Both strategies have shown markedly improved survival compared with the use of chemotherapy regimens. The initial approval of ipilimumab (Yervoy) in 2011, increased the median OS for patients from 6 - 9 months to 19.9 months. Since then, 2 checkpoint inhibitors (nivolumab, pembrolizumab) targeting the PD-1 pathway further extended the median OS to > 30 months and incurring a lower frequency and severity of side effects. Further benefit was realised with the addition of ipilimumab to nivolumab, with the combination demonstrating an unprecedented 5-year OS rate of 52% and more recently, a 6.5 year OS rate of 49% for patients with advanced melanoma, though toxicity was higher with the combination[9,10].

In addition to immunotherapy, treatment options for patients with BRAF mutated melanoma include targeted BRAF/MEK combination therapies. While these agents are effective in a high proportion of patients with BRAF mutated disease, most patients acquire resistance over time.

Despite progress in its current treatment and management, there is still a considerable proportion of patients who fail to respond to these therapies or respond but then later relapse. There are no standard approaches to treating patients once progresses after receiving anti-PD-1 therapy. An analysis of real-world Flatiron Health data (2014 - 2019) revealed that over 40% of BRAF mutant and 60% of BRAF wild-type patients did not initiate a new treatment after disease progression on anti-PD-1, highlighting an unmet need to identify effective and tolerable therapies in this setting[11].

2.1.5. Management

EU approved immune-oncology (IO) and targeted therapies for first-line advanced melanoma and efficacy outcomes are shown in the Table below (ESMO guideline) (Table 1).

[7] Manola J. et al. Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncolgy Group trials. J Clin Oncol 2000; 18: 3782-93.
[8] Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging:evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67(6):472–492.
[9] Robert C, Ribas A, Schachter J, et al. Supplementary Appendix to: Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): Post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;1-13.
[10] Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. J Clin Oncol 2021;39:9506.
[11] Hernandez-Aya LF, Burke M, Collins JM, et al. Real-world treatment patterns and clinical outcomes of advanced melanoma patients following disease progression on anti-PD-1-based therapy. J Clin Oncol 2020;38, no. 15_suppl.e22036

The current first-line standard of care treatments for unresectable stage III/IV are PD-1 blockade (nivolumab, pembrolizumab), PD-1 blockade (nivolumab) combined with cytotoxic T lymphocyte associated protein 4 (CTLA-4) blockade (ipilimumab) and, in addition for BRAFV600-mutated melanoma, B-Raf proto-oncogene (BRAF) inhibition (vemurafenib, dabrafenib, encorafenib) combined with mitogen-activated protein kinase (MEK) inhibition (cobimetinib, trametinib, binimetinib). First-line decision between targeted therapies or immuno-therapies is currently being studied in prospective trials (SECOMBIT, NCT02631447) to define the best sequencing combination treatment in terms of OS, the primary efficacy variable. No direct randomised comparison exists between the two approaches, but meta-analyses suggest that, despite better out-come within the first 12 months for targeted therapies, immuno-therapy patients may have a better survival after 1 year. Patients for whom immunotherapy can be delivered safely for the first few months, i.e. patients with tumours not progressing very quickly and not immediately threatening an important organ or function, should be considered for immunotherapy first, preserving targeted therapies for the subsequent lines.

Table 1 EU-approved IO and targeted therapies for first-line systemic treatment of advanced, unresectable melanoma in routine clinical use (ESMO guidelines)

		Nivolumab (CM66)	Nivolumab + Ipilimumab (CM67)	Nivolumab (CM67)	Pembrolizumab (KN006)	Dabrafenib + Trametinib (COMBI-d)	Dabrafenib + Trametinib (COMBI-v)	Vemurafenib + Cobimetinib (coBRIM)	Encorafenib + Binimetinib (COLUMBUS)
Study design	Primary Endpoint	OS	PFS, OS	PFS, OS	PFS, OS	PFS	OS[b]	PFS	PFS
	BRAF status	WILD TYPE	AC	AC	AC	MUTANT	MUTANT	MUTANT	MUTANT
	Study Arms	**Nivo** (n=210) vs **Dacarbazine** (n=208)	**Nivo+Ipi** (n=314) vs **Ipi** (n=315)	**Nivo** (n=316) vs **Ipi** (n=315)	**P** (n=279 Q2W, n=277 Q3W) vs **I** (n=278)	**D+T** (n=211) vs **Dabrafenib** (n=212)	**D+T** (n=352) vs **Vemurafenib** (n=352)	**V+C** (n=247) vs **Vemurafenib** (n=248)	**E+B** (n=192) vs **Vemurafenib** (n=191)
Efficacy	mPFS (mos) (HR)	**mFU 6.8m: Investigator** 5.1 vs 2.2 (HR 0.43)	**mFU 12.2m: Investigator** 11.5 vs 2.9 (HR 0.42)	**mFU 12.2m: Investigator** 6.9 vs 2.9 (HR 0.57)	**mFU 7.9m: BICR** 5.5m/4.1m vs 2.8m (HR 0.58)	**mFU 9m: Investigator** 9.3 vs 8.8 (HR 0.75)	**mFU 11m: Investigator** 11.4 vs 7.3 (HR 0.56)	**mFU 7.3m: Investigator** 9.9 vs 6.2 (HR 0.51)	**mFU 16.6m: BICR** 14.9 vs 7.3 (HR 0.54)
	mOS (mos) (HR)	**Min FU 60m:** 37.3 vs 11.2 (HR 0.5)	**Min FU 60m:** NR vs 19.9 (HR 0.52)	**Min FU 60m:** 36.9 vs 19.9 (HR 0.63)	**mFU 66.7m:** 32.7 vs 15.9 (HR 0.74)	**mFU 22m (pooled):** 25.9m[a]	**mFU 22m (pooled):** 25.9m	**mFU 21.2m:** 22.5 vs 17.4	**mFU 60.6m:** 33.6 vs 16.9 (HR 0.62)
Safety	D/C due to any grade AE/Rs	**mFU 6.8m:** 6.8% vs 11.7% (AEs)	**mFU 12.2m:** 36.4% vs 14.8% (ARs)	**mFU 12.2m:** 7.7% vs 14.8% (ARs)	**mFU 7.9m:** 4%/6.9% vs 9.4% (ARs)	**mFU 20m:** 11% vs 7% (AEs)	**mFU 11m:** 13% vs 12% (AEs)	**mFU 14.2m:** 11% vs 7% (ARs)	**mFU 16.6m:** 6% vs 14% (ARs)

Abbreviations: mFU = median follow-up; minFU = minimum follow-up.

[a] This was the pooled combination experimental arm.

[b] The combi-V OS primary data was: mFU 11m, NR vs 17.2 (HR 0.69)

2.2. About the product

Opdualag is a fixed dose combination (FDC) of relatlimab, an anti- lymphocyte-activation gene 3 (LAG-3) human Immunoglobulin G4 (IgG4) monoclonal antibody, and nivolumab, an anti-PD-1 human IgG4 monoclonal antibody.

Relatlimab binds selectively to LAG-3 with high affinity and potently blocks ligand binding thereby stimulating enhanced in vitro antigen-specific T-cell responses and cytokine signalling and promoting anti-tumour immunity. Nivolumab binds selectively and with high affinity to PD-1 and potently blocks binding to PD-L1 and PD-L2, thereby inhibiting PD-1 pathway-mediated suppression of anti-tumour immunity.

The dual blockade of LAG-3 and PD-L1 is supported by co-expression on immune cells and both inhibitory receptors playing a role in immune-escape by tumours. Dual inhibition of LAG-3 and PD-1 in the preclinical setting elicited enhanced anti-tumour immune response and demonstrated synergistic anti-tumour activity through blocking two distinct immune checkpoint pathways.

Pharmacological classification:

Opdualag belongs to the pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XY03.

Claimed indication and recommendation for use:

The initially claimed indication was:

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).

The final approved indication 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 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. This dose is established for adolescent patients weighing at least 30 kg (see section 5.2).

Treatment with Opdualag should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

2.3. Type of application and aspects on development

The clinical development programme in support of the proposed indication concerns two ongoing clinical studies; 1 phase 1/2a study (CA224020, RELATIVITY-020) in subjects with a broad spectrum of advanced solid tumours and one phase 2/3 RCT (CA224047, RELATIVITY-047) in the proposed indication.

The study considered to be key to the proposed indication is study CA224047 is a phase 2/3 randomised, double-blind study comparing relatlimab in combination with nivolumab to nivolumab alone. Supportive evidence is derived from study CA224020, which is a Phase 1/2a open-label study of relatlimab alone and in combination with nivolumab.

Specific CHMP guidelines relevant for the current application:

- Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95 Rev.5, 22 September 2017.
- Guideline on clinical development of fixed combination medicinal products. EMA/CHMP/158268/2017. 23 March 2017

Scientific Advice

CHMP scientific advice (SA) on the clinical development was given on 30 January 2020 (EMA/H/SA/4345/1/2019/II) and a follow-up advice on 28 May 2020 (EMEA/H/SA/4345/1/FU/1/2020/II).

Brief summary EMA/H/SA/4345/1/2019/II:

The applicant Bristol-Myers Squibb International Corporation requested scientific advice for their product Relatlimab, Nivolumab from the CHMP on 30 January 2020. The Scientific Advice was aimed to get agreement on the following clinical aspects:

- the rationale for studying relatlimab in combination with nivolumab in patients with previously untreated, unresectable or advanced metastatic melanoma; on the general design of the study CA224047, the targeted study population address the unmet medical need.
- the proposed primary endpoint of PFS determined by a Blinded Independent Committee Review (BICR) and OS and objective response rate (ORR), be tested as secondary endpoints are appropriate for the assessment of untreated, unresectable or advanced metastatic melanoma.
- the dosing rationale for the FDC relatlimab/Nivolumab and Nivolumab in study CA224047.
- the proposed biomarker plan in Study CA224047.
- the clinically meaningful efficacy, with an acceptable safety profile, in a well-defined population in study CA224047 would be sufficient to allow for a benefit/risk assessment of relatlimab plus nivolumab for the treatment of untreated, unresectable or advanced metastatic melanoma.

The CHMP agreed that there is a need for new drugs and combination strategies in the target population and supported the investigation in the first line setting. The overall study design was supported, including the interim PFS efficacy analysis and the proposed study population. PFS was considered an acceptable primary endpoint, provided mature OS data excluding a negative effect were available and the effect was homogenous across sub-populations. It was recommended that analyses were delayed to allow reaching at least 50% maturity in all subgroups. The dose for relatlimab/nivolumab was considered acceptable and the nivolumab monotherapy comparator arm (480 mg Q4W) was agreed. A follow-up advice was strongly suggested once more information on the biomarker plan was available.

Brief summary EMA/H/SA/4345/1/FU/1/2020/II:

The applicant received follow-up SA on the development of Nivolumab, Relatlimab for treatment of advanced melanoma from the CHMP on 28 May 2020 (EMEA/H/SA/4345/1/FU/1/2020/II*)*. The SA pertained to the following clinical aspects:

1. Introduction of an additional interim analysis (IA2) of PFS for study CA224047
2. Proposed to move OS to the first secondary endpoint in the statistical hierarchy

The CHMP discouraged to perform the proposed PFS IA2 (minimum 80% planned PFS events), planned to occur 3 months before the final PFS. The benefits of introducing this unplanned interim analysis, resulting in few weeks of anticipation of the readings of the PFS results, did not seem to outweigh the risks of hampering a proper assessment of the outcome in the various subgroup of interest, whose importance was clearly stated in the previous CHMP advice. The proposal to move OS to the first of the secondary endpoints was acceptable. It was agreed that it better reflects the role of OS as a more robust measurement of benefit to patients over ORR, which is often used more as a surrogate measure of benefit.

Paediatric Investigation Plan

The indication targeted by the PIP: Treatment of adolescents from 12 to less than 18 years of age with unresectable or metastatic melanoma. A waiver was given for the paediatric population from birth to less than 12 years of age.

The PIP includes two extrapolations, modelling and simulation studies:

Study 1

Modelling and simulation study to determine the dose of relatlimab/nivolumab fixed dose combination to be used in paediatric patients from 12 years of age to less than 18 years of age with unresectable or metastatic melanoma.

Study 2

Extrapolation study to evaluate the use of relatlimab/nivolumab fixed dose combination in adolescents from 12 to less than 18 years of age with unresectable or metastatic melanoma.

2.4. Quality aspects

2.4.1. Introduction

Nivolumab and relatlimab, the two active substances contained in Opdualag are human immunoglobulin G4 (IgG4) monoclonal antibodies (MAbs) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. Nivolumab is the active substance in the authorised medicinal product Opdivo (EMEA/H/C/3985).

Opdualag is presented as a concentrate for solution for infusion in a single use Type I glass vial. One vial of 20 mL contains 240 mg of nivolumab (12 mg/mL) and 80 mg of relatlimab (4 mg/mL).

Nivolumab and relatlimab are formulated with histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid (diethylenetriaminepentaacetic acid), polysorbate 80 and water for injections.

2.4.2. Active substance - Relatlimab

2.4.2.1. General information

Relatlimab is a fully human IgG4 MAb consisting of four polypeptide chains: two identical heavy chains of 446 amino acids and two identical kappa light chains of 214 amino acids, which are linked through inter-chain disulfide bonds. Relatlimab is directed against LAG-3 receptor, a negative T-cell regulator associated with T-cell exhaustion. The mechanism of action of relatlimab is to bind to LAG-3 on T-cells and block the interaction between LAG-3 and major histocompatibility complex (MHC) Class II, the peptide antigen presentation molecule recognised by CD4+ T-cells. By blocking the normal down regulatory pathway, relatlimab reverses LAG-3-mediated inhibition of T-cell activation. The mechanism of action does not involve effector function, such as activation of complement dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC).

Relatlimab has a theoretical mass of 148.2 kDa for the intact antibody and one consensus site for N-linked glycosylation (Asn297 of the heavy chain).

2.4.2.2. Manufacture, characterisation and process controls

Manufacturing process and process controls

Active substance manufacturing takes place at a single-use facility (SUF) at Bristol-Myers Squibb Company, Devens, MA, USA (BMS-Devens).

Relatlimab is produced as a secreted protein in a manufacturing-scale cell culture using a CHO cell line that was transfected with an expression vector containing the coding sequences for the heavy and light chains of the relatlimab IgG.

A pre-harvest sample from the bioreactor is tested for bioburden, endotoxin, mycoplasma, minute virus of mice (MVM) and *in vitro* adventitious agents. Subsequent filtering through depth filter and membrane filters produces a clarified bulk which is further processed.

The downstream process is designed to reduce impurities and potential adventitious viral agents and to formulate the active substance. The relatlimab protein is processed across a series of chromatography, viral inactivation, viral filtration, and ultrafiltration/diafiltration steps. The active substance in bioprocess containers is transferred to the cryogenics facility at BMS-Devens where it is frozen. The active substance may be stored refrigerated with protection from light prior to transfer at the manufacturing facility and prior to freezing.

The relatlimab active substance manufacturing process does not include any reprocessing steps.

Control of materials

Raw materials used in the manufacture of relatlimab active substance are either of compendial grade or controlled to ensure the quality and safety of the active substance and to maintain the consistency of the manufacturing process. Information provided on raw materials of biological origin do not give rise to safety concerns with regard to potential viral contamination or TSE.

A master cell bank was prepared from the RCB in 2012 and one working cell bank, was generated from the MCB in 2014. The MCB and WCB are stored frozen and are re-evaluated. Results from the initial re-evaluations raise no issues. Cell bank testing is performed in line with ICH Q5A and Q5D guidelines. Future WCBs are qualified based on provided analytical test procedures, the performance in the bioreactor and release results of one active substance lot. The stability of the cell line after normal production and after extended passaging was demonstrated by characterisation of the end-of-production cell banks (EPCBs). The limit of *in vitro* cell age (LIVCA) was determined through extended cell age development followed by evaluation of the stability of the production cell line in scale-down model bioreactors.

Control of critical steps and intermediates

The in-process control (IPC) strategy for the manufacture of relatlimab active substance is described as a tiered set of in-process ranges to ensure consistent monitoring and control of the manufacturing process. IPC ranges for individual inputs (process parameters or PPs) and outputs (performance attributes or PAs) are classified as critical (CPPs and CPAs) when a potential impact of the parameter on the manufacturing process or an active substance critical quality attribute (CQA) was recognised during manufacturing process development. Excursions outside the ranges for PPs and PAs are investigated according to a established procedure. Excursions from the ranges for CPPs and CPAs are investigated for product quality impact and could lead to lot rejection. A confirmed excursion outside any CQA range or distribution results in rejection of the lot. This IPC strategy and the defined set of (C)PPs and (C)PAs are considered adequate for control of the manufacturing process.

Process validation

The process validation strategy encompasses three stages: design, process verification (also referred to as PPQ) and ongoing process verification. The PPQ protocols included prospectively defined acceptance criteria consisting of numerical limits for release testing results, CPAs, CPPs, PAs, and PPs, as defined in the IPC strategy presented. Acceptance criteria for the upstream and downstream manufacturing process were met, demonstrating that the manufacturing process is effective and consistent for the production of relatlimab active substance. All PPQ lots met the proposed commercial

active substance release specification. Supporting qualification studies included shipping validation, chromatography resin lifetime studies, impurity clearance studies, extended testing of intermediates, viral clearance studies, microbial control strategy studies, single-use systems studies, and in-process hold biochemical stability studies. After PPQ was completed, the IPC ranges and classifications were reviewed and changed when appropriate. Overall, process validation is considered satisfactory.

Manufacturing process development

The relatlimab active substance manufacturing process development is divided in Process A, Process B, Process B.1, and the Commercial Manufacturing Process (CMP).

Process A material was used to support toxicology studies. Material from the CMP process was used in early-phase studies as well as in pivotal clinical studies as a component of the fixed-dose combination (FDC) product, and no changes were introduced during or after the pivotal study. Therefore, no concerns are raised regarding differences between the commercial and clinically tested material. Nevertheless, comprehensive data is provided on analytical comparability for each manufacturing process development step and as well as a comparison of all processes. Analytical comparability between Process A and Process B, Process B and Process B.1, and Process B.1 and CMP is considered sufficiently demonstrated.

Potential CQAs were identified for product-related variants, process-related impurities and formulation related quality attributes. The available knowledge for each attribute, both specific to relatlimab and from relevant supporting class knowledge was compiled and then each attribute was assigned as critical or non-critical.

The development of individual manufacturing steps is studied through comprehensive process characterisation studies and were used to establish the IPC strategy. This includes the definition of parameter ranges and the identification of (C)PPs and (C)PAs. Process parameter risk assessments were performed evaluating the potential impact on CQAs and (C)PAs. Parameters were ranked based on their overall risk score which determined whether or not further evaluation through Design of Experiments (DoE) was performed. Appropriate ranges were determined to evaluate in modelling DoEs, and results evaluated using statistical software. For each parameter it was determined if there was a statistically significant and/or a practical significant impact on a process output to determine the classification of parameters for the IPC strategy implementation. Scale-down models were qualified by demonstrating equivalence between the manufacture-scale and scale-down model. Overall, the studies demonstrate adequate control and understanding of the manufacturing process and support the ranges for (C)PPs and (C)PAs as proposed in the IPC strategy.

Overall, information on manufacturing process development is considered satisfactory.

Characterisation

Characterisation of relatlimab was performed to provide a comprehensive understanding of the chemical structure and the biochemical, biophysical, and biological properties of the protein allowing a precise description of its quality attributes. Several state-of-the-art methods were used to evaluate the properties of nivolumab that relate to its primary, secondary, tertiary and quaternary protein structure. In addition, post-translational modifications related to N- and C-terminal heterogeneity, glycosylation, disulfide bonding, Met and Trp oxidation, deamidation, and charge variant characterisation were included in the evaluation. The biological activity of relatlimab was also characterised.

2.4.2.3. Specification

Specification

Relatlimab quality control testing for batch release includes appearance, quantity, pH, purity, identity, potency, process-related impurities and endotoxins/bioburden.

Analytical procedures

Method descriptions for all non-compendial analytical procedures are provided and validations are performed according to ICH Q2(R1).

Batch analyses

Batch (lot) information for relatlimab active substance (31) including the process designation, site of manufacture, date of manufacture, batch size and designated use for each active substance batch is presented for all Process A, B, B1 and CMP lots. All batch analysis data were in line with the acceptance criteria that applied at the time of testing.

Reference standards

The primary reference standard and working reference standard are prepared using the CMP and have both supported pivotal clinical trials. The PRS and WRS were initially qualified using release methods and additional testing followed by qualification of release tests relative to a previous research reference standard (RRS) or the PRS, respectively, to demonstrate suitability for their intended use. The PRS and WRS are requalified. Future WRSs are qualified using the PRS lot.

Container closure system

Relatlimab active substance is filled into single-use bioprocess containers. Extractables studies were performed. The quantification of volatile extractables in the test solutions show very low levels (ppb) and no metals were detected for any test solution. Leachable studies were performed by exposing the active substance or the final formulation buffer. The leachables that increased above baseline values during the hold period were assessed for their potential impact on patient safety. The toxicological review concluded that no leachable compounds are anticipated to pose a safety risk when relatlimab is administered as directed.

Bioprocess container integrity testing confirmed the integrity of the container closure system.

2.4.2.4. Stability

A shelf life of 36 months is claimed for the active substance when stored at -60°C ± 10°C.

Stability studies were conducted on four CMP batches of relatlimab active substance in accordance with ICH stability guidelines and demonstrate that the active substance is stable for up to 36 months when stored at -60°C ± 10°C and protected from light. The long-term stability is continued for up to 60 months to support optional shelf-life extension post-authorisation.

2.4.3. Active substance - Nivolumab

2.4.3.1. General information

Nivolumab is a fully human IgG4 MAb with 440 amino acid heavy chains and 214 amino acid kappa light chains linked through inter-chain disulfide bonds. Nivolumab is a highly specific programmed death 1 (PD-1) immune checkpoint inhibitor. The co-inhibitory receptor PD 1 has important T-cell

regulatory functions. It mediates tumour-specific inhibition of T-cell responses in tumours, but does not mediate ADCC of activated human T-cells. Engagement of PD-1 by its ligands PD-L1 and PD-L2 is a key interaction that allows tumours to evade immune-mediated destruction by inhibition of T-cell proliferation, survival and cytokine secretion. Nivolumab blocks PD 1, thereby inhibiting multiple PD-1 ligand interactions and restoring T-cell responsiveness and the ability to mount a direct T cell immune attack against tumour cells.

Nivolumab-histidine has a theoretical mass of 146.2 kDa for the intact antibody and one consensus site for N-linked glycosylation (Asn290 of the heavy chain). The heavy chain includes S221P mutation which is known to impart increased stability to IgG4 antibodies.

The active substance is identical to nivolumab in Opdivo (referred to as nivolumab-citrate). The manufacturing process of nivolumab-histidine (Process C-histidine) is also highly similar to the approved commercial manufacturing process for nivolumab-citrate (Process C) with respect to the expression system, upstream and downstream manufacturing process, process controls and control strategy, and the active substance dossiers have been aligned when appropriate. Therefore, the assessment of the dossier focussed on the differences between the two dossiers.

2.4.3.2. Manufacture, characterisation and process controls

Manufacturing process and process controls

Active substance manufacturing also takes place at Bristol-Myers Squibb Company in Devens, MA, USA (BMS-Devens). It is manufactured following Process C-Histidine to produce nivolumab active substance formulated in a histidine-based buffer (referred to as nivolumab-histidine). Process C-Histidine was developed based on Process C, which is the commercially approved manufacturing process to produce nivolumab active substance formulated in citrate-based buffer (nivolumab citrate, BMS 936558).

One vial of the working cell bank (WCB) is thawed and expanded in several steps to inoculate the production bioreactor, which leads to one formulated active substance lot. Active substance lots are not combined at the active substance stage.

Nivolumab-histidine is produced as a secreted protein in a manufacturing-scale cell culture using the same Chinese hamster ovary (CHO) cell line that is used to produce nivolumab-citrate. A conventional two-tiered cell banking system is employed, consisting of a MCB from which the WCBs are derived.

The upstream manufacturing process is a conventional fermentation process and is identical to that for nivolumab-citrate with the exception of minor facility related changes and a change to the primary recovery step which was altered to align with manufacturing facility capabilities.

The downstream manufacturing steps for the production of nivolumab-histidine up to the ultrafiltration and diafiltration (UF/DF) step are the same as for the production of nivolumab-citrate, except for minor facility related changes. The UF/DF step, formulation, filtration and fill steps, and active substance handling and cryogenics steps were changed to accommodate the increase in protein concentration, the change in formulation buffer, the change in container closure and the frozen storage of the active substance. Hold conditions for in-process intermediates were re-established when appropriate. The active substance in bioprocess containers is transferred to the cryogenics facility at BMS-Devens where it is frozen. The active substance may be stored refrigerated with protection from light prior to transfer at the manufacturing facility and prior to freezing.

The nivolumab-histidine active substance manufacturing process does not include any reprocessing steps.

Control of materials

All raw materials, media, buffers, filters and solutions used in the Process C-histidine are the same as those used in the commercially approved Process C, with the exception of formulation specific materials and the addition of primary recovery filters. Information provided on raw materials of biological origin do not give rise to safety concerns with regard to potential viral contamination or TSE.

Cell bank testing is performed in line with ICH Q5A and Q5D guidelines. The MCB and WCB are stored frozen facilities. The MCB is re-evaluated, a WCB is re-evaluated. The stability of the WCB after production of nivolumab-histidine was demonstrated by characterisation of the end-of-production cell bank (EPCB).

Control of critical steps and intermediates

The in-process control (IPC) strategy for Process C-Histidine is based on the IPC strategy for Process C and aligns with the commercially approved ranges when appropriate. All ranges for Process C that were considered alert ranges are action ranges for Process C-Histidine. The IPC strategy for altered steps was developed based on data from process development, process characterisation, and active substance commercial manufacturing experience.

Process validation

The process validation strategy encompasses three stages: design, process qualification, and continued process verification. The PPQ protocols included prospectively defined acceptance criteria consisting of numerical limits for release testing results, CPAs, CPPs, PAs, and PPs, as defined in the IPC strategy presented. Acceptance criteria for the upstream and downstream manufacturing process were met, demonstrating that the manufacturing process is effective and consistent for the production of relatlimab active substance. All PPQ lots met the proposed commercial active substance release specification. Supporting qualifications include studies performed for the validation of Process C when appropriate. After PPQ was completed, the IPC ranges and classifications were reviewed and changed when appropriate.

Manufacturing process development

Process C-histidine for the manufacture of nivolumab-histidine is based on Process C and was initially implemented for early clinical manufacturing at BMS-Bothell before transfer to BMS-Devens. Detailed development information reflecting the changes from Process C to Process C-histidine for each step in the manufacturing process are provided. Overall, the studies demonstrate adequate control and understanding of the manufacturing process and support the ranges for (C)PPs and (C)PAs as proposed in the IPC strategy.

Analytical comparability between Process C and Process C-histidine is performed in accordance with ICH Q5E. Based on results from release testing, extended characterisation studies, and comparability assessment of stability, Process C-histidine and nivolumab-histidine active substance are considered comparable to Process C and nivolumab-citrate active substance.

Critical quality attributes for nivolumab-histidine DS are aligned with those for nivolumab-citrate DS with the exception of formulation related attributes and changes to the criticality of some attributes as justified.

Characterisation

The nivolumab molecule and its process- and product-related impurities are identical between the nivolumab-histidine and nivolumab-citrate active substances, therefore this information is unchanged. Tests that were used for the comparability assay are indicated.

2.4.3.3. Specification

Specifications

Nivolumab quality control testing for batch release includes appearance, quantity, pH, purity, identity, potency, process-related impurities and endotoxins/bioburden.

The nivolumab-histidine active substance specification is aligned with the approved nivolumab-citrate active substance specification when appropriate. Changes to the appearance and protein concentration reflect the differences in formulation. As no meaningful trends are observed under the recommended storage condition of -50°C to -70°C, the acceptance criteria for release and stability are the same and aligned with the nivolumab-citrate shelf-life specifications when appropriate.

Analytical procedures

Method descriptions for all non-compendial analytical procedures are provided and validations are performed according to ICH Q2(R1). When validations performed on nivolumab-citrate were applicable to nivolumab-histidine active substance and they were not repeated, additional experiments were performed, as applicable, to demonstrate the suitability of the methods for nivolumab-histidine active substance.

Reference standards or materials

The reference standards for nivolumab-histidine active substance are the same for nivolumab-citrate active substance. For the two-tiered reference standard programme, the PRS and two WRS have been used. The stability of PRS and WRS will be monitored through annual testing. New lots of WRS will also be identified from released nivolumab-citrate active substance lots according to the previously approved qualification protocol.

Batch analyses

Batch analysis data from all 20 nivolumab-histidine active substance batches currently produced are used to support the proposed specification. The information provided does not call for comment.

Container closure system

Nivolumab-histidine active substance is filled into the same single-use, pre-sterilised bioprocess containers as relatlimab active substance. The extractables and leachables studies are identical to those in the relatlimab active substance dossier. For the leachable study, the relatlimab active substance and the relatlimab final formulation buffer test solutions are considered worst-case for nivolumab histidine active substance as the relatlimab final formulation is more acidic compared to the nivolumab histidine final formulation. This is acceptable.

2.4.3.4. Stability

A shelf life of 36 months is claimed for the active substance when stored at -60°C ± 10°C.

Stability studies are being conducted on four Process C-histidine batches of nivolumab-histidine active substance in accordance with ICH stability guidelines and demonstrate that the active substance is stable for up to 36 months when stored at -60°C ± 10°C and protected from light. The long-term stability is continued for up to 60 months to support optional shelf-life extension post-authorisation.

2.4.4. Finished Medicinal Product

2.4.4.1. Description of the product and pharmaceutical development

Description of the product

Opdualag is a sterile, non-pyrogenic, single-use, preservative-free, isotonic, aqueous solution for intravenous infusion. It contains relatlimab and nivolumab-histidine as active substances at a protein-mass ratio of 1:3, co-formulated as a FDC medicinal product in a single glass vial.

The vial presentation of Opdualag, containing 80 mg of relatlimab and 240 mg of nivolumab within the label volume of 20-mL, is packaged in a 25R Type I glass vial, closed with a 20-mm FluroTec film-laminated rubber stopper and yellow flip-off seal.

Nivolumab and relatlimab are formulated with commonly used excipients: histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid (diethylenetriaminepentaacetic acid), polysorbate 80 and water for injections (Table 4).

Opdualag may be infused undiluted or diluted with either 9 mg/mL (0.9%) sodium chloride injection (normal saline) or 50 mg/mL (5%) (5%) glucose solution for injection to the required concentration prior to administration.

Pharmaceutical development

The applicant has developed a FDC finished product containing relatlimab and nivolumab co-formulated within a single glass vial at a protein-mass ratio of 1:3. The relatlimab and nivolumab active substances that are used to manufacture Opdualag are both formulated in a histidine-based buffer system. The finished product is prepared by diluting the thawed and pooled active substances with buffer solution for dilution. The buffer solution for dilution contains all the excipients that are used in each active substance and, additionally, the metal-ion chelator pentetic acid.

To evaluate the feasibility of co-formulating relatlimab and nivolumab, the stability profile of the FDC was compared against the stability profiles of the separate components. The results of the study show no difference in the stability profile of the FDC and the samples containing only relatlimab or nivolumab-histidine No new degradation products were observed in the FDC solution in comparison to the individual antibodies in the FDC formulation buffer. In addition, various state-of-the-art techniques were applied to exclude protein-protein interaction.

The excipients added during the manufacture of the finished product formulation meet compendial requirements. No excipients of human or animal origin are used.

A use-time compatibility study was performed to demonstrate the compatibility of the finished product with infusion fluids, IV infusion containers, IV sets, syringes and in-line filters. A high (undiluted at 16 mg/mL) and low (0.8 mg/mL) concentration was used to bracket all intermediate concentrations and all anticipated clinical doses. IV bags made of Polyolefin (PO), Ethylene Vinyl Acetate (EVA), and Polyvinyl chloride (PVC), administration sets made of PVC, Polyurethane (PUR), and Di-2-ethylhexyl phthalate (DEHP)-free PVC, and in line filter types were 0.2-1.2 µm and made of PES (Polyethersulfone), Nylon and PVDF (polyvinylidene fluoride) were included in the study.

The applicant performed studies to support storage of the prepared finished product infusion solutions (either undiluted at 16 mg/mL or diluted to a concentration as low as 0.8 mg/mL in NS or D5W) under refrigeration conditions (2ºC to 8ºC) for up to 24 hours, with a maximum of 8 hours of the total 24 hours at room temperature (15 °C to 25 °C), room light.

Manufacturing process development

No changes were made to the finished product manufacturing process during clinical studies. Process development studies included material compatibility studies, extractable and leachable studies, mixing studies, a filter adsorption study, filling studies, and process hold time studies.

Materials used during the manufacturing process were found to be compatible with the finished product. The identified extractables and leachables identified for the bag/carboy were detected at levels that are not expected by the applicant to pose a hazard or safety risk when patients are treated once every 28 days at the therapeutic dose.

Mixing studies were performed for the manufacture of the polysorbate 80/pentetic acid solution, for the manufacture of the buffer solution for dilution, and for finished product formulation. Process parameter ranges were defined in accordance with the mixing studies. As an alternative supplier of pentetic acid with larger particle size was introduced, a longer mixing time was introduced during PPQ for the polysorbate 80/pentetic acid solution.

Process hold time evaluation was performed during the manufacture of a registrational stability batch. As part of the process hold-time studies, additional in-process samples were tested above those that are collected and tested during routine manufacture. Hold times were evaluate for active substance thaw, buffer solution for dilution, formulated finished product, bulk finished product, total time out of refrigeration (TOR), and room temperature/light exposure.

2.4.4.2. Manufacture of the product and process controls

All sites involved in the manufacture and control of the finished product are EU GMP compliant.

Manufacturing process and process controls

The finished product manufacturing process consists of thawing, mixing, filtration and aseptic filling process. Mixing conditions (speed and duration), hold times, and in process controls have been defined.

Process validation

Three PPQ batches covering minimum and maximum batch sizes were manufactured. Two batches were manufactured using holding times in excess of the proposed commercial hold times. All specifications and pre-defined acceptance criteria for the manufacture of the PPQ batches were met.

In addition to the PPQ and process development studies, the applicant performed validation of aseptic processing via media fills, validation of sterile filtration and a shipping qualification study.

2.4.4.3. Product specification

Specifications

The finished product specifications include control of identity, purity, potency and other general tests.

Analytical methods

Method descriptions and summaries of the method validations are provided. In-house reference standards for relatlimab and nivolumab are used in release and stability testing (see active substance section).

Characterisation of impurities

Process-related impurities are described in the active substance section.

The applicant conducted a risk assessment for elemental impurities in accordance with ICH Q3D guideline showing that there are no concerns. It is concluded that the risk is low and it is not necessary to include any elemental impurity controls in the finished product specification. This is acceptable.

A risk assessment regarding the potential presence of N-nitrosamines impurities in the active substance and finished product was provided. This assessment concludes the risk is low and as a consequence there is no need for testing either active substance or finished product for the presence of N-nitrosamines. This conclusion is endorsed.

Reference standard

Reference standards are the same as used to test the active substance.

Batch analysis

Batch analysis data are provided, including information on batch numbers, manufacturing site, batch size, Active substance batch numbers and manufacturing process, finished product use, and, if applicable, clinical study number. A total of 10 finished product batches have been manufactured to date, of which nine used active substances manufactured according to the commercial process. The data do not call for comment.

Container closure

The finished product is supplied in 25 mL vials (Type I glass), with a stopper (coated butyl rubber) and a yellow flip-off aluminium seal. The glass vials are sterilised with ethylene oxide (ETO) according to *ISO 11135-1, Sterilization of Health Care Products – Ethylene oxide – Part 1: Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices*. In addition, the glass vial material does not contain materials of animal origin or natural rubber latex.

The stoppers are steam sterilised. The stopper material does not contain materials of animal origin, natural rubber latex, 2-mercaptobenzothiazole, or any related substance or nitrosamines.

The flip-off seal is gamma-irradiated.

The vials are (secondary) packaged in a paperboard folding carton.

2.4.4.4. Stability of the product

A shelf-life of 36 months is proposed for Opdualag stored at the recommended storage condition of 2°C to 8°C, protected from light.

Stability studies were conducted on four registrational batches and three PPQ batches according to ICH guidelines. Long-term, accelerated and stress stability data, time out of refrigeration (TOR) stability data, stress-and-store stability data, and photostability data are provided.

Long-term stability data are available for 36 months for all batches at the long-term storage conditions. All acceptance criteria were met and no significant trends were observed in any of the parameters tested. Based on the stability data provided the claimed shelf-life of 36 months for Opdualag (unopened vial) when stored at the recommended storage condition of 2°C to 8°C is considered acceptable.

Results from the TOR and stress-and-store studies showed no impact on product quality of short durations of exposure to room temperature/room light (up to one month) and of short-term exposure to temperatures ranging from -20°C to 40°C followed by long-term storage.

Photostability data demonstrated that the finished product is sensitive to light exposure and therefore, it is recommended to store the finished product vials in the original package (a folded paperboard carton) to protect from light. An appropriate warning has been included in section 6.4 of the proposed SmPC.

In use physical-chemical stability is claimed for:

1) 30 days at 2-8°C for the undiluted product, and product diluted with 0.9% sodium chloride (9 mg/mL), and

2) 7 days for product diluted with 5% glucose solution (50 mg/mL).

In both cases, stability for 24 hours storage at room temperature (≤ 25°C) and room light is claimed (of total of 30 days and 7 days storage, respectively). This is acceptable.

Microbiological in-use stability is claimed for 24 hours at 2-8°C, which is considered acceptable. The applicant was requested to amend SmPC section 6.3 with the following standard statement: "From a microbiological point of view, the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless preparation has taken place in controlled and validated aseptic conditions".

2.4.4.5. Adventitious agents

Relatlimab and nivolumab are produced using CHO host cell lines. No human- or animal-derived raw materials are used in the manufacture. The raw materials of biological origins used in the relatlimab and nivolumab manufacturing processes are listed in the dossier and this does not call for comments. Foetal calf serum / foetal bovine serum was used during development of both MCBs. The applicant provided the certificates of suitability.

The manufacturing process of the antibodies have been evaluated for their capacity to remove or inactivate viruses.

The model viruses chosen are commonly used model viruses in viral clearance studies and cover relevant physico-chemical characteristics (RNA, DNA, enveloped, non-enveloped, size range 18-200 nm). This is in line with ICH Q5A (R1) and can be accepted. The results of the virus validation study demonstrate effective reduction of all model viruses by the manufacturing process of relatlimab and nivolumab.

The data provided do not give rise to safety concerns as regards to potential viral contamination or TSE.

2.4.5. Discussion on chemical, pharmaceutical and biological aspects

Active substance (relatlimab)

The active substance manufacturing process is generally described in sufficient detail. Materials used during the manufacturing process are listed and tested when appropriate. Critical steps and intermediates are controlled by an IPC strategy that is essentially approvable. Issues regarding the classification of process parameters have been addressed and intermediate hold conditions are

supported by stability studies. Process validation demonstrates that the manufacturing process is effective and consistent for the production of relatlimab active substance. Missing information on the qualification of buffers and solutions has been provided. The list of CQAs of the active substance is considered approvable. The manufacturing process development is described in sufficient detail. Analytical comparability between all successive manufacturing processes has been demonstrated. Material from the commercial manufacturing process (CMP) was used in early and pivotal clinical studies. A comprehensive list of quality attributes (QAs) is provided and divided in active substance attributes, process-related impurity attributes, and formulation-related attributes. The individual manufacturing steps are studied in comprehensive process characterisation studies. The robustness of the manufacturing process is demonstrated using scale-down worst-case studies.

Relatlimab physicochemical, biological and immunological properties, and heterogeneity of the active substance are sufficiently addressed in the characterisation section of the dossier.

The proposed relatlimab active substance specification is provided with acceptance criteria for release and stability. The panel of tests for active substance release and during manufacturing is according to the test programme for the active substance of monoclonal antibodies for human use stated in the Ph. Eur. <2031>. As no trends are observed during frozen storage of the active substance, the acceptance criteria for stability are identical to those for release with the exception of tests that are not regarded stability-indicating. Analytical procedures are adequately described and validated. Batch analyses demonstrate a high level of batch-to-batch consistency. The proposed specification for relatlimab active substance is acceptable.

Adequate information has been provided for the relatlimab reference standards. Future WRSs are relative to the PRS and should comply with acceptance criteria for qualification.

Drawings and materials of the bioprocess containers in which relatlimab active substance is filled, frozen, stored and transported are provided. Additional information regarding BSE/TSE compliance, cytotoxicity, extractables and leachables has been provided. The container closure system is considered qualified as appropriate for use in the storage of active substance with regard to integrity from microbial contamination.

The data presented support the proposed relatlimab active substance shelf-life of 36 months stored at -60°C ± 10°C and protected from light.

Active substance (Nivolumab-histidine)

The nivolumab-histidine active substance is identical to the approved nivolumab-citrate active substance of Opdivo with the exception of protein concentration and formulation. Consequently, this section of dossier is highly similar to the active substance section of the approved Opdivo dossier.

Nivolumab-histidine is an IgG4 human monoclonal antibody selectively binding to the programmed death-1 (PD-1) receptor on the surface of target T-cells and structurally identical to nivolumab-citrate.

The nivolumab-histidine active substance manufacturing process, Process C-histidine, is based on Process C for the manufacture of nivolumab-citrate active substance and is generally described in sufficient detail. Materials used during the manufacturing process are listed and tested when appropriate. The MCB for the production of nivolumab-histidine and nivolumab-citrate are identical. Critical steps and intermediates are controlled by an IPC strategy that is essentially approvable. An issue regarding intermediate hold conditions was adequately addressed. Process validation demonstrates that the manufacturing process is effective and consistent for the production of nivolumab-histidine active substance. The list of CQAs of the active substance is considered approvable.

Nivolumab-histidine is identical to nivolumab-citrate with regard to physicochemical, biological and immunological properties and heterogeneity of the active substance and new studies are considered unnecessary. The active substances are also shown to be similar with regard to impurities.

The proposed relatlimab active substance specification is provided with acceptance criteria for release and stability. The panel of tests for active substance release and during manufacturing is according to the test programme for the active substance of monoclonal antibodies for human use stated in the Ph. Eur. (2031). As no trends are observed during frozen storage of the active substance, the acceptance criteria for stability are identical to those for release with the exception of tests that are not regarded stability-indicating. Analytical procedures are adequately described and validated. Batch analyses demonstrate a high level of batch-to-batch consistency. The proposed specification is considered acceptable.

Adequate information has been provided for the nivolumab-histidine active substance reference standards, which are the same as those for nivolumab-citrate active substance.

The container closure system is identical to that for relatlimab active substance. Drawings and materials of the bioprocess containers in which relatlimab active substance is filled, frozen, stored and transported are provided. Extractables and leachables were studied. The container closure system is considered qualified as appropriate for use in the storage of active substance with regard to integrity from microbial contamination.

The data presented support the proposed nivolumab-histidine active substance shelf-life of 36 months stored at -60°C ± 10°C and protected from light.

Finished product

The pharmaceutical development of the finished product is sufficiently described. Prior to the development of the FDC, the administration of relatlimab-nivolumab combination therapy was performed by using two separate finished products. However, all clinical trials were performed with the FDC.

The selection of excipients is sufficiently justified. For pentetic acid (USP-grade), additional detail was provided on its quality control. The other excipients are Ph. Eur. Grade. No novel excipients are used. The studies to evaluate potential interaction between relatlimab and nivolumab give no reason for concern and support feasibility of coformulation. Ruggedness of the finished product formulation is demonstrated, but showed that pH can impact charge variants during storage. Batch analysis data suggest that the proposed specification for pH is unnecessary wide, but the acceptance criterium has been aligned with active substance and is thus considered acceptable.

No changes were made to the finished product manufacturing process during clinical studies. Process development studies, which included material compatibility studies, extractable and leachable studies, mixing studies, a filter adsorption study, filling studies, and process hold time studies, give no reason for concern. Further information on the evaluation of extractables/leachables is provided and does not give rise to any concerns. Operational ranges for the finished product manufacturing process are in general supported by the mixing studies. A comprehensive description of the finished product control strategy and information on the approach used for criticality assignment of the process parameters has been provided.

Sufficient information on the sites involved in finished product manufacturing is provided. The manufacturing process is, in general, described in sufficient detail. Information on the filling procedure is provided. In addition, some of the critical equipment has been further specified and was laid down in P.3.3. No intermediates are defined in the finished product manufacturing process. Hold times for the different manufacturing stages are provided and supported by the PPQ, media-fill, and hold-time

studies. IPCs for the manufacture of the buffer solution and finished product are listed and have been supplemented with concise information on the actions taken in case a limit is not met. The acceptance criterion for bioburden of the dilution buffer prior to sterile filtration has been sufficiently justified and is in line with EMA/CHMP/CVMP/QWP/850374/2015.

The PPQ study is in line with expectations. All acceptance criteria were met and results demonstrate that the process is capable to consistently produce finished product batches that comply with the specifications. Additional validation studies that were performed, include validation of aseptic processing via media fills, validation of sterile filtration and a shipping qualification study. Based on these studies, aseptic processing and sterile filtration are considered sufficiently validated. For the shipping qualification a summary is provided. Temperature excursions outside of the approved range were sufficiently explained.

The applicant has provided justification for the acceptance criteria for the finished product release test and for the omission of a number of test methods that are part of the specifications of the single-protein products. In general, the proposed finished product test panel and acceptance criteria are considered sufficiently justified. The provided method descriptions are in general considered sufficient, and details were laid down in the dossier. Methods have been validated in accordance with ICH Q2(R1) and all acceptance criteria were met.

The container closure system, consisting of a Type I glass vial, stoppered with a 20-mm FluroTec film-laminated chlorobutyl rubber stopper, and 20-mm aluminium ferrule with yellow polypropylene flip-off seal, is sufficiently detailed. Information on the ethylene oxide sterilisation of the empty vials and proof of ISO certification were provided.

The available long term stability data support the proposed shelf life of 36 months at 5°C. Photostability data demonstrated that the finished product is sensitive to light exposure and therefore, it is recommended to store finished product vials in the original package (a folded paperboard carton) to protect from light. This package provides sufficient protection.

The proposed physical chemical in-use stability claim is sufficiently supported by data. The proposed microbiological in-use stability claim was not agreed, and the applicant was requested to be aligned with the Guideline CPM/QWP/159/96 on maximum shelf-life for sterile products for human use after first opening or following reconstitution.

Adventitious agents

Adventitious agents' safety including TSE have been sufficiently assured.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Opdualag is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the marketing authorisation application for Opdualag is considered approvable from the quality point of view.

2.4.7. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

In Opdualag, treatment with relatlimab is combined with nivolumab.

Nivolumab has already market authorisation under the name Opdivo for several cancer indications. There is no new information presented on single administration of nivolumab. The non-clinical information on nivolumab is available in the EPAR and the SmPC for Opdivo (see Opdivo EPAR). The non-clinical information presented below involves either the studies with relatlimab alone or the combination of relatlimab and nivolumab, which are the two monoclonal antibodies present in the Opdualag formulation. As the therapeutic is a biological product developed for a cancer indication, it falls within in the scope of ICH S6 and ICH S9.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro binding assays

Binding of relatlimab to its target human LAG-3 (EC50 0.49 nM) or to the LAG-3 loop insertion peptide (EC50 0.44 nM) was assessed by means of ELISA in study BDX-1408-242. Via SPR (study BDX-1408-241) the binding of relatlimab to human recombinant LAG-3 (EC50 0.12 nM) was determined. The binding of relatlimab to LAG-3 expressed on the membrane of an activated human CD4+ T-cell was assessed by means of Scatchard (KD 0.51 nM) (BDX-1408-243). With FACS, binding of relatlimab to human (EC50 0.11 nM) and cynomolgus (EC50 29.11 nM) activated CD4+T cells, hLAG-3 (EC50 2.33 nM) and cynLAG-3 (EC50 28.73 nM) expressing CHO cells and muLAG-s expressing 3A9 cells (not measurable) was assessed in study BDX-1408-243. Relatlimab has highest affinity for human LAG-3, followed by cynomolgus LAG-3, albeit 265x lower. Affinity for LAG-3 protein compared to affinity to LAG-3 expressed on CD4+ T-cells is comparable upon different analysis methods and EC50 appears slightly lower than nanomolar range for human LAG-3 and is 10-100-fold higher for cynomolgus LAG-3). The affinity for murine LAG-3 appears not detectable.

Besides expression on (exhausted) CD-4 T-cells, LAG-3 is also expressed on the membrane of plasmacytoid DCs.

Using MHC class II positive Daudi (B-Lymphoma) cells, the ability of relatlimab to block binding huLAG-3-mFc (fixed concentration, pre-incubated with antibody) compared to isotype control was assessed and resulted in an IC50 of 0.67 nM, which is in the range comparable to EC50 values for binding of relatlimab to its target, LAG-3, as assessed in *in vitro* binding studies (study BDX-1408-244).

In ELISA and Octet binding assays (study IO00330), LAG-3 binding to FGL1 was confirmed, and BMS-986016 was able to potently block recombinant LAG-3/FGL1 binding with an estimated IC50 of 0.02 nM by ELISA. This binding was also observed in an *in vitro* co-culture assay. Parental LK35.2 cells (murine B-cell line), expressing MHC II, were engineered to co-express membrane-anchored human FGL1 on their surface (LK35-FGL1TM), together with endogenous MHC Class II. Co-culture with 3A9-huLAG-3 cells (producing soluble LAG-3) resulted in enhanced repression of IL-2 production by the T cells. This was used as a read-out to measure the effect of the LAG-3 blocking antibody relatlimab. In a dose-dependent manner, relatlimab enhanced T-cell IL-2 production to a similar Y_{max} in co-culture with either parental (expressing only MHC II) or LK35-FGL1TM (expressing both MHC II and FGL1) cell lines, with a similar estimated IC50 (1.39 nM and 0.95 nM, respectively). The IC_{50} values were at the

low end of the nanomolar range and apparently both the blockade of the interaction LAG3/MHC II and the LAG3/FGL1 contribute to the effect. It has to be mentioned that IL-2 repression is further decreased when expressing FGL-1 in the parent cell line.

In vitro functional assays

In study BDX-1408-245 it was shown that an antigen-specific mouse T-cell hybridoma transfected with the human LAG-3 gene (3A9-huLAG-3 cells) was able to functionally interact with APCs that express mouse MHC Class II. This led to an inhibitory signal into the mouse T-cell line which resulted in attenuated responsiveness to a cognate peptide. This *in vitro* assay was used in two ways; 1) titrating the peptide in excess of antibody (relatlimab or IgG4 isotype) and 2) titrating the antibody in presence of intermediate peptide concentration. In the first option, the EC_{50} for peptide-responsiveness in the presence of relatlimab was 0.26 nM compared to 0.95 nM in the presence of isotype control antibody. Via the second more sensitive option; EC_{50} for peptide responsiveness by the T-cells in the presence of relatlimab was 1.05 nM compared to an absence of peptide responsiveness of the cell line exposed to isotype control antibody. The blockade of the LAG-3-mediated inhibition of T-cells and thus the responsiveness to the peptide can be measured by means of IL-2 secretion.

In study BDX-1408-246, the capacity of nivolumab, ipilimumab, relatlimab or a combination of these to enhance the activation of human PBMC upon stimulation with superantigen SEB (staphylococcus enterotoxin B) was evaluated. Relatlimab alone was not able to enhance IL-2 secretion upon stimulation with increasing levels of SEB, whereas nivolumab and ipilimumab were able to enhance IL-2 secretion upon increasing levels of SEB. A combination of nivolumab or ipilimumab with relatlimab is able to increase the enhancement of IL-2 secretion, with the combination of ipilimumab with relatlimab seemingly more effective than the combination of nivolumab with relatlimab.

In study BDX-1408-247 it was demonstrated that relatlimab lacked measurable induction of ADCC or CDC on LAG-3+ activated human T-cells. Exposure of activated T-cells to either relatlimab or isotype control did not result in measurable ADCC or CDC whereas exposure to the positive controls, anti-CD30 antibody (ADCC) or anti-MHC Class I (CDC) resulted in dose-dependent cytotoxicity. ADCC and CDC were assessed at concentrations up to 10 ug/ml and 50 ug/ml respectively, which are lower than those clinically relevant (Cmax in patients=61.5 ug/ml). However, depletion of T cells was not observed in *in vivo* non-clinical studies.

In report IO00197 allogeneic mixed lymphocyte reactions (MLR) containing HLA-mismatched mature dendritic cells and CD4 T-responding cells showed that mAb blockade of PD-1 exhibited consistent and marked enhancement (2.1- to 11.4-fold) of IL-2 and IFN-γ production. PD-1 antagonism also resulted in consistently enhanced cytokine levels (3.1- to 53.1-fold) in the allogeneic MLR suppressed with Treg cells. Subsequent monoclonal antibody blockade of LAG-3 yielded more modest enhancement (0.5- to 3.4-fold) of cytokine production in the MLR and Treg MLR assays. However, in experiments that surveyed both IL-2 and IFN-γ, different donor cell pairs, different levels of PD-1 mAb combinations, and at different Treg:CD4 T-cell ratios, statistically significant enhancement of CD4 T cell activity was observed. Almost universally, significant IL-2 and IFN-γ enhancement due to LAG-3 antagonism required the combination with PD-1 receptor antagonism. Thus LAG 3 blockage showed more significant effects in combination when low concentrations of PD1 blocker were added. These results together with *in vivo* pharmacology studies suggest a reasonable expectation that LAG-3 antagonism could enhance anti-tumour immunity in patients treated with PD-1 antagonists, either with or without high levels of suppression by Treg cells.

In vivo animal studies with tumour models

Several *in vivo* animal studies have been conducted with murine tumour models. In these models, the mouse surrogates for relatlimab (19C7 and C9B7W) were used.

In an immunogenic Sa1N fibrosarcoma tumour model (study BDX-1408-251, dosing at D7, 10 and 14), the anti-tumour effect of 1, 3.3, 10 and 30 mg/kg anti-LAG-3 antibody (19C7) was 30%, 60%, 40% and 60%, respectively.

In two other studies Study (MDX-1106-059 & Study BDX-1408-224), the effect of the combination of 10 mg/kg anti-LAG3 antibody (C9B7W) and 10 mg/kg anti-PD-1 antibody (4H2) was evaluated. In study MDX-1106-059 (dosing at D7, 10 and 14), the combination showed an 80% antitumour response compared to 40% with anti-LAG-3 alone and no anti-tumour effect with anti-PD-1 alone. In Study BDX-1408-224 (dosing at D9, 14 and 17), the combination of anti-PD-1 and anti-LAG-3 showed a 90% antitumour response compared to 20% with anti-LAG-3 alone and no antitumour effect with anti-PD-1 alone. Apparently the combination of anti-PD-1 antibody with anti-LAG3 antibody is more effective in raising an antitumour response compared to anti-LAG3 alone in a Sa1N fibrosarcoma tumour model. It should be noted that in study BDX-1408-251, the 19C7 antibody and in study MDX-1106-059 & Study BDX-1408-224 the C9B7W antibody was used as the anti-LAG3 antibody. Both seem to be effective in the syngeneic mouse model.

In study BDX-1408-253, the antitumour activity of 10 mg/kg anti-LAG-3 antibody (19C7) and 10 mg/kg anti-PD-1 antibody (4H2) as single agents and in combination (0.34, 1, 3.4 and 10 mg/kg anti-LAG-3 antibody (19C7) and 10 mg/kg anti-PD-1 antibody (4H2) were evaluated in the colon carcinoma MC38 model, in which tumour free mice (day 0) were IP dosed with antibodies on D7, 10 and 14). Anti-LAG-3 antibody (19C7) showed modest tumour growth inhibition at the 10 mg/kg dose and did not yield any tumour-free mice while anti-PD-1 antibody led to 40% of mice being rendered tumour free. The combination of anti-LAG-3 and anti-PD-1 antibody led to enhanced antitumour activity (58%-67%-83% tumour-free mice for 1, 3.4 and 10 mg/kg anti-LAG3 respectively) compared to anti-PD-1 antibody alone (40%).

In study MDX-1408-206-R and study BDX-1408-207 anti-tumour effect of anti-LAG-3 antibody (C9B7W) as a single agent and in combination with anti-PD-1 antibody (4H2) or anti-CTLA-4 antibody (9D9) was evaluated in 2 independent studies in the MC38 colon carcinoma model. In study MDX-1408-206-R (dosing at D7, 10 and 12) anti-PD-1 antibody treatment alone resulted in 40% anti-tumour activity and in 70% anti-tumour activity when combined with anti-LAG-3. Anti-LAG-3 was not effective in this tumour model. In study BDX-1408-207 (dosing at D8, 11 and 14) only monotherapy with anti-PD-1 resulted in anti-tumour activity. Combination of anti-LAG3 with anti-CTLA4 or anti-PD-1 resulted in 30% and 70% antitumour activity respectively. A combination of anti-LAG3 with anti-PD-1 results in a higher anti-tumour activity in the MC38 colon carcinoma model as compared to the combination with an anti-CTLA-4 antibody and compared to an anti-PD-1 antibody alone. However, the data for the combination of anti-LAG3 and anti-CTLA-4 are not relevant for the current application.

In study IO00232 the antitumour activity of anti-LAG-3 antibody (19C7) as a single agent and in combination with anti-CTLA-4 antibody (9D9) was evaluated in the CT26 Murine Carcinoma model. As compared to the isotype control antibody, 10 mg/kg single-agent anti-LAG-3 antibody resulted in 13% median tumour growth inhibition and 1 out of 10 tumour-free mice whereas 10 mg/kg single-agent anti-CTLA-4 antibody resulted in 78% median tumour growth inhibition and 1 out of 10 tumour-free mice. The combination of 10 mg/kg each of anti-LAG-3 and anti-CTLA-4 antibodies resulted in synergistic antitumour activity with 100% median tumour growth inhibition and 10 out of 10 tumour-free mice. Apparently an anti-CTLA4 antibody, in particular in combination with an anti-LAG-3 antibody, is effective in raising an anti-tumour response against this murine carcinoma model.

In addition to solid tumour models, the antitumour activity of anti-LAG-3 antibody (19C7) as a single agent and in combination with anti-PD-1 antibody (4H2) or anti-CTLA-4 antibody (9D9) were also evaluated in the disseminated murine A20 model of B-cell lymphoma (study BDX-1408-263). Anti-LAG-3 (10% TF) and anti-PD-1 (20% TF) antibodies were only marginally efficacious as single agents while anti-CTLA-4 provided modest survival benefit on its own (30% TF). While the combination of anti-LAG-3 with anti-CTLA-4 (20% TF) showed no enhancement of survival compared to either antibody alone, the co-administration of anti-LAG-3 and anti-PD-1 resulted in 60% of mice surviving until the end of the study, without evidence of tumours upon necropsy. Apparently, a combination of an anti-LAG3 antibody with an anti-PD-1 antibody is more effective against a A20 B-cell lymphoma model in mice compared to the combination of anti-LAG3 with anti-CTLA4 or monotherapy with one of the three antibodies tested.

2.5.2.2. Secondary pharmacodynamic studies

There were no studies addressing a secondary pharmacologic mechanism of action of relatlimab as its target and mechanism of action are selective.

2.5.2.3. Safety pharmacology programme

Since relatlimab is an IgG4 monoclonal antibody with a selective mechanism and does not belong to a drug or chemical class expected to cause cardiovascular effects, specific safety pharmacology studies, including cardiovascular telemetry safety pharmacology studies, were not conducted. Safety pharmacology assessments, including clinical evaluations of cardiovascular, respiratory, and neurologic function, were included in repeat-dose general toxicology studies, which is agreed. There were no effects on safety pharmacology parameters when relatlimab was administered as a single agent or in combination with nivolumab in the 4 week and the 3-month GLP repeated dose toxicity studies.

2.5.2.4. Pharmacodynamic drug interactions

The pharmacodynamic activity of relatlimab and nivolumab administered in combination was evaluated in a 1-month toxicity study in cynomolgus monkeys (toxicology study BMS-986016 and BMS-936558). This study was not intended to investigate effects of a specific ratio of relatlimab plus nivolumab. Relatlimab or nivolumab alone (30 and 100 mg/kg relatlimab or 50 mg/kg nivolumab) and in combination (100 mg/kg relatlimab and 50 mg/kg nivolumab) were administered weekly, and the following parameters were assessed: *in vivo* antibody responses and ex vivo recall responses to keyhole limpet hemocyanin (KLH) antigen and hepatitis B surface antigen (HBsAg), and immunophenotypic analyses of peripheral blood and splenic T-lymphocyte subsets. When dosed in combination, relatlimab and nivolumab did not alter each other's systemic exposures indicating no toxicokinetic drug-drug interactions. There were no relatlimab/nivolumab-related changes in T cell-dependent antibody responses to KLH and HBsAg or ex-vivo recall responses to KLH in CD8+CD4- T cells or HBsAg in CD4+CD8+ or CD4-CD8+ T cells. Test article-related changes in ex vivo recall responses to KLH included reversible increases in mean percent: (1) CD69+, TNF-α+, and CD69+TNF-α+ CD4+CD8- T cells in females at all dose groups and in males at 100 mg/kg relatlimab alone and in the combination therapy group without meaningful differences in degree between relatlimab alone or in combination with nivolumab; and (2) IFN-γ+, CD69+IFN-γ+, and CD69+TNF-α+IFN-γ+ CD4+CD8- T cells in both sexes at 100 mg/kg relatlimab and 50 mg/kg nivolumab when administered individually, with further non-additive increases in the combination group.

Changes in lymphocyte phenotypes at 100 mg/kg relatlimab alone were limited to increases in mean percent CD25+FoxP3+ CD8+ T cells. In the combination group, there were modest increases in mean

percent of peripheral blood CD4+ regulatory T cells in male monkeys on and after Day 15 that were not reversible; similar changes were observed at 50 mg/kg nivolumab but were reversible. Additionally, in the combination group, decreases in mean percent naive CD4+ T cells and concomitant increases in central memory CD4+ T cells were noted during the recovery period. Changes that were not considered different between groups dosed in combination or with 50 mg/kg nivolumab alone: (1) statistically significant non-reversible increases in mean percent splenic CD4+ regulatory T cells; (2) non-reversible increases in mean percent splenic CD25+FoxP3+CD8+ T cells; and (3) decreases in mean percent splenic naive CD8+ T cells and concomitant increases in central memory CD8+ T cells during the recovery period. Increases in the mean percent of CD4+ regulatory T cells and CD25+FoxP3+ CD8+ T cells may correlate with the high expression of the targets (i.e., LAG-3 and PD-1) on regulatory T cells54 in the presence of relatlimab and nivolumab.

The changes above are consistent with the pharmacological mechanisms of action of relatlimab and nivolumab and highlight the potential for enhanced effects when the two are administered in combination.

Pharmacodynamic activity was also explored in the 1-month exploratory combination study in which LAG3.1-G4P was administered weekly as a single agent (50 mg/kg) or in combination (10 or 50 mg/kg) with 50 mg/kg nivolumab to cynomolgus monkeys (study MDX-1408 AND BMS-936558). In this study, pharmacodynamic endpoints included evaluation of T-cell-dependent antibody responses to Hep A/Hep B, KLH and SKMEL-3 cells, phenotyping of peripheral blood and splenic lymphocytes, and immunostaining of splenic tissue. No T-cell-dependent antibody responses were observed.

LAG3.1-G4P- and nivolumab-related changes consisted of modest increases in the CD4+ lymphocytes expressing CD25 (activated CD4+ T lymphocytes) in the peripheral blood in all dose groups as compared to vehicle control with no appreciable differences between dose groups. An increase in splenic CD4+ lymphocytes expressing CD25 was also noted with 50 mg/kg LAG3.1-G4P alone with further increases upon combination treatment with nivolumab (50 mg/kg) in a LAG3.1-G4P dose-dependent manner as compared to vehicle control. Additional changes in spleen consisted of moderate increases in CD4+ lymphocytes expressing CD28hi and CD95 (CD4+ central memory T lymphocytes) with concomitant decreases in CD4+ lymphocytes expressing low CD28 and no CD95 (CD4+ naive T lymphocytes) in all dose groups, and an elevation in the CD3+ lymphocytes expressing HLA-DR in the LAG3.1-G4P and nivolumab high-dose combination (50 mg/kg and 50 mg/kg) group.

Immunostaining and microscopic analysis of frozen splenic tissue revealed increases in CD3+ lymphocytes expressing CD4 and CD25 (activated CD4+ T lymphocytes) relative to vehicle control upon combination treatment with LAG3.1-G4P and nivolumab in an LAG3.1-G4P dose-dependent manner, which were more pronounced in females than in males. Splenic activated CD4+ T lymphocyte cell counts upon LAG3.1-G4P (50 mg/kg) treatment alone, however, were elevated only in females, but not in males. Overall, the microscopic findings in the spleen correlated well with the parallel findings of increases in activated CD4+ T lymphocytes in the spleen and peripheral blood via flow cytometry and reflect an anticipated pharmacologic response to LAG3.1-G4P and/or nivolumab treatment.

2.5.3. Pharmacokinetics

Relatlimab pharmacokinetic profile was characterised in *in vivo* pharmacokinetic (PK) experiments in cynomolgus monkeys with relatlimab administered alone or in combination with nivolumab. In addition, since relatlimab does not bind to mouse LAG-3, *in vivo* efficacy studies in mouse tumour models were conducted with a surrogate antibody, clone 19C7, that recognises mouse LAG-3, and 19C7 serum exposure data was obtained. In addition, multiple dose toxicokinetics (TK) profiles were

characterised in Cynomolgus monkey following once weekly (QW) intravenous (IV) dosing, which is the intended clinical route, for a total duration of up to 4 weeks and 3 months.

Nivolumab has been previously well-characterised in the nonclinical setting as part of BLA 125,554 and a brief summary of the nonclinical data is also presented here.

2.5.3.1. Methods of analysis

Assays were developed for the evaluation of PK and immunogenicity in the nonclinical studies. For the GLP studies in Cynomolgus monkey and mouse (embryo-foetal development study), assays were developed and validated according to guidelines and, while not validated under GLP, sample analysis was conducted in compliance with GLP. Relatlimab was quantified using a sandwich enzyme-linked immunosorbent assays (ELISA) with a capture antibody against relatlimab and a detecting antibody against IgG4 (LLOQ 75 ng/ml, ULOQ 8000 ng/ml) or relatlimab (LLOQ 50 ng/ml, ULOQ 3200 ng/ml). The provided validation reports, which included (amongst others) the evaluation of precision and accuracy (both intra- and inter-assay), specificity, selectivity, and sample stability (long-term at -70ºC, freeze-thaw), demonstrate that both assays were suitable for quantification of relatlimab in cynomolgus monkey serum. ISR was shown to be acceptable for relatlimab in monkey serum analysis.

The ELISA method for quantification of anti-LAG-3 C9B7W surrogate antibody in mouse serum utilises a recombinant dimeric mouse LAG-3(D1-4) huFcG1 as capture and a commercial goat anti-rat IgG (H+L) detecting antibody and was considered fit for purpose for use in the mouse embryo-foetal development study (LLOQ 10 ng/ml, ULOQ 1000 ng/ml). Although long-term stability (-70ºC) was not established, this is not considered an issue for IgG storage.

For the measurement of nivolumab in monkey serum a fit for purpose ELISA (DS10061) and a validated ECL (DN12123) method was used.

For the detection of anti-drug antibodies (ADAs) against relatlimab or nivolumab in monkey serum, bridging immunoassays with Meso Scale Discovery ECL-based detection were developed. The ADA assays were validated and the sensitivity was found to be 0.23 - 0.68 and 50 ng/mL for the anti-relatlimab and anti-nivolumab assay, respectively. Drug tolerance was 3.33 - 10 µg/mL of relatlimab in the presence of 25 ng/mL ADA in cynomolgus monkey serum.

2.5.3.2. Absorption

Upon a single-dose IV bolus of 3, 16.5 or 30 mg/kg (n=1, non-GLP) to male cynomolgus monkeys, a multicompartmental decline in relatlimab serum exposure was seen with a terminal elimination half-life (t½) of about 11 days and a serum clearance of 0.16 ml/h/kg. Exposure (AUC0-inf) was found to be proportional to dose.

Repeat-dose toxicokinetics (TK) were performed in the 4-week and 3-month toxicology studies (GLP), where male and female cynomolgus monkeys (n=5-6/sex) received once weekly (QW) IV doses of relatlimab (30 or 100 mg/kg). In general, relatlimab showed a biphasic decline, with an initial distribution phase, followed by a very slow elimination phase. Relatlimab systemic exposure in the dosing period ($AUC_{0\text{-}168}$) increased dose-proportionally for the 30 and 100 mg/kg dose in both the 4-week and 3-month study as shown by the comparable dose normalised AUCs. No clear or consistent sex difference was observed on serum exposure. After 4-week IV multiple (QW) dosing, the volume of distribution, as estimated by population PK analysis, was low (i.e. 0.072 L/kg), about 2–fold the plasma volume in monkey, and in line with human (~0.095 L/kg). Clearance in monkey was very low (i.e. 0.12 ml/h/kg) and is about 1.5-fold higher than in humans (~0.078 ml/h/kg). Terminal elimination half-life ($T_{1/2}$) in monkeys was about 20 days in the 4-week study and about 20 – 30 days

in the 3-month toxicology study and was ~25.7 days in human. Exposure accumulation ratios upon multiple dosing were ~2.2-fold (Day 22) in the 4-week study and 4.4-fold (D85) in the 3-month study indicating that steady state was not yet reached in the 4-week study, which is in line with the dosing period and the long elimination half-life. Steady state exposures were generally achieved by Day 50. In the 4-week study, relatlimab (100 mg/kg) treatment was also combined with nivolumab (50 mg/kg), and this did not impact the exposure or accumulation ratio of relatlimab.

In support of pharmacology mouse xenograft studies, the systemic exposure of the anti-LAG-3 murine surrogate antibody (19C7) was determined in serum from the Sa1N and the MC38 mouse xenograft models upon intraperitoneal (IP) administration at 7, 10 and 14 days after implantation. In both mouse models an increase in 19C7 serum exposure was found over a 9-10-day period upon multiple injections and with increasing dose but the PK data are insufficient to conclude on the respective PK parameter values. In mouse embryo-foetal development (EFD) study, serum concentrations of C9B7W, the murine surrogate anti LAG-3 antibody, were determined on GD10 after intraperitoneal treatment (25 or 51.5 mg/kg, Q2D) from GD6 to 14. Considering the different route of administration and time points of analysis in relation to the dosing periods, no further conclusions can be made on PK parameter values for C9B7W.

2.5.3.3. Immunogenicity

ADA formation against relatlimab was found in about 70% to 80% of the treated monkeys in both the 4-week and the 3-month QW repeat-dose toxicology study. The serum levels of relatlimab were generally unaffected, with the exception of 1 monkey at the low dose in the 3-month study.

2.5.3.4. Distribution

Formal tissue distribution and protein binding studies were not conducted with relatlimab. Consistent with the known biodistribution of monoclonal antibodies, relatlimab and nivolumab have a low volume of distribution (62-79 and 46-71 ml/kg, respectively), suggesting limited extravascular distribution as it is lower than twice that of the plasma volume (45 mL/kg).

Foetal exposure to relatlimab (or C9B7W as surrogate anti-mouse LAG-3 antibody) was not investigated in the embryo-foetal development study in mice. However, both relatlimab and nivolumab are IgG4 antibodies, and are likely to be transported through placenta by the neonatal FcR (FcRn) receptor, especially during the latter half of gestation.

Relatlimab transfer to maternal milk was not examined. However, as an IgG, relatlimab would be expected to be present in the first milk.

2.5.3.5. Metabolism

In accordance with ICH S6(R1), no metabolism studies with relatlimab were conducted in animals.

2.5.3.6. Excretion

In accordance with ICH S6(R1), no specific studies to measure excretion of relatlimab were conducted. As relatlimab is a monoclonal antibody, no renal excretion is anticipated due to its molecular size.

2.5.3.7. Pharmacokinetic drug interactions

Drug-drug interaction at the PK level is highly unlikely for this type of product since biotechnology-derived substances do not metabolise via CYP P450 enzymes. As the mechanism of action may have an effect on CYP450 activities via cytokine release, this was further explored in the clinical pharmacology (section 2.6.2).

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No dedicated IV single-dose toxicity studies were performed with relatlimab. Potential acute effects were monitored in the repeat-dose toxicity studies. One subcutaneous single-dose toxicity study was conducted to evaluate local tolerance (see Section 2.5.4.7).

2.5.4.2. Repeat dose toxicity

Three repeat-dose toxicity studies in cynomolgus monkeys were conducted to evaluate the toxicity of LAG3.1-G4P (a predecessor non-clinical molecule differing from relatlimab by 2 amino acids) or relatlimab when administered either as a single agent or in combination with nivolumab. In an exploratory non-GLP study, mature male and female monkeys were administered 10 or 50 mg/kg LAG-3.1-G4P with or without 50 mg/kg nivolumab once a week for 4 weeks. In one definitive GLP combination study, mature male and female monkeys were administered 30 or 100 mg/kg relatlimab with or without 50 mg/kg nivolumab once a week for 4 weeks, with a subsequent recovery period of 6 weeks. In a second definitive GLP study, male and female monkeys were administered 30 or 100 mg/kg relatlimab - without nivolumab - once a week for 3 months, followed by a recovery period of 10 weeks. Although significant exposure margins were obtained in the repeat-dose toxicology studies for both antibodies, for interpretation of safety data and extrapolation of findings to humans it should be considered that relatlimab showed a 265-fold higher affinity for the human epitope than for the monkey epitope in activated T cells (29.11 nM vs. at 0.11 nM) and a different dosing ratio between nivolumab and relatlimab was used in these studies compared to humans.

Relatlimab was well tolerated in monkeys when administered IV QW as a single agent at ≤ 100 mg/kg (margin-of-exposure based on AUC (MoE): 223) for up to 3 months with no relatlimab-related findings. In the pivotal 1-month combination study, one male dosed IV QW at 100 mg/kg relatlimab (MoE: 97), in combination with 50 mg/kg nivolumab (MoE: 13), was prematurely sacrificed due to moribund conditions and histopathology revealed signs of central nervous system (CNS) vasculitis (lymphoplasmacytic inflammation of the choroid plexus; lymphohistiocytic inflammation of the vasculature of the brain parenchyma, meninges, and spinal cord) and epididymitis. Additional findings in this antibody combination group were irreversible lymphoplasmacytic inflammation of the choroid plexus in the brain in both sexes and lymphohistiocytic inflammation of the vasculature of the brain parenchyma in one male monkey. Irreversible lymphoplasmacytic inflammation of choroid plexus in the brain was also observed in multiple animals dosed with 50 mg/kg nivolumab alone, but not in animals dosed with relatlimab alone. None of the animals displayed abnormal neurological clinical findings.

Anti-drug-antibodies (ADAs) against nivolumab were detected in 2/8 animals dosed with 50 mg/kg nivolumab in the exploratory non-GLP study, with no apparent impact on nivolumab serum levels or exposures. In the definitive combination study, ADAs against nivolumab were detected in one monkey at 50 mg/kg nivolumab and one monkey in the combination group, and resulted in slightly lower serum

nivolumab levels. ADAs against LAG3.1-G4P were not detected in the exploratory study. In the definitive combination study, ADAs against relatlimab were detected in 24/40 monkeys administered either relatlimab alone or in combination with nivolumab. The presence of relatlimab-specific antibodies had no impact on relatlimab toxicokinetics. In the second definitive GLP study, ADAs against relatlimab were detected in 20/24 monkeys. In general, the presence of treatment-emergent ADAs had no substantial impact on systemic exposures, although substantially high levels of ADAs may have led to decreased serum relatlimab concentrations in one low-dose monkey. This animal exhibited decreased activity, hunched posture, emesis and tremors. These findings are not considered treatment-related, but rather secondary to treatment-emergent ADAs with subsequent compliment activation. Since relatlimab and nivolumab are human antibodies, these treatment-emergent ADAs in monkeys can be expected and are likely not relevant for humans.

2.5.4.3. Genotoxicity

According to the ICH Guideline S6(R1), no genotoxicity studies were performed for relatlimab.

2.5.4.4. Carcinogenicity

According to the ICH Guideline S1A, S6(R1) and S9, no carcinogenicity studies were performed for relatlimab.

2.5.4.5. Reproductive and developmental toxicity

According to the ICH Guideline S9, no studies of fertility and early embryonic development were performed with relatlimab and nivolumab.

During the pivotal 1-month and 3-month repeat-dose toxicity studies in cynomolgus monkeys (Section 2.5.4.2), no relatlimab-related findings in the reproductive organs were observed. However, one male dosed IV QW 100 mg/kg relatlimab (MoE: 97), in combination with 50 mg/kg nivolumab (MoE: 13) showed histopathological signs of epididymitis (i.e. mixed-cell inflammation of the epididymis, seminal vesicles, and testes).

One exploratory pregnancy study and one definitive GLP-compliant embryo-foetal development study were conducted in mice. These studies were designed using syngeneic and allogeneic breeding models. Based on the lack of cross-reactivity in rodents, surrogate anti-LAG-3 antibodies (mLAG3.4 mIgG1-D265A or C9B7W) were used. In the exploratory pregnancy study, ADAs were detected in all treated groups, but the effect on serum mLAG3.4 mIgG1-D265A levels was not determined. However, there were no ADA-mediated toxicities. In the definitive embryo-foetal development study, ADAs were detected in 8/41 allogeneic animals and 6/22 syngeneic animals, with no substantial effect on anti-LAG-3 C9B7W serum levels.

Anti-LAG-3 antibodies were well-tolerated by dams at the highest dose tested and no maternal or developmental toxicities were detected, with resulting maternal and developmental NOAELs of 50 mg/kg (mLAG3.4 mIgG1-D265A) and 51.5 mg/kg (C9B7W). It was noted that syngeneic and allogeneic breedings resulted in comparable outcomes, despite the expected risk of higher foetal loss with allogeneic breedings. Considering that the setup of the studies was acceptable and that nivolumab use during pregnancy is not recommended (see below), additional non-clinical reproductive toxicity data were not warranted.

Results from the *in vitro* MLR (study IO00197, Section 2.5.2.1) showed that the combination of relatlimab and nivolumab may increase effector T cell activation compared to regulatory T-cell activation.

According to the ICH Guideline S9, no studies of pre- and postnatal toxicology were performed with relatlimab and nivolumab. No juvenile toxicity studies were performed with relatlimab and nivolumab.

2.5.4.6. Toxicokinetic data

Toxicokinetic data was collected in the three repeat-dose toxicity (IV) studies and local tolerance (SC) study in cynomolgus monkeys, and in the definitive IP embryo-foetal development study in mice. Sufficient exposure levels were achieved for both relatlimab and nivolumab in cynomolgus monkeys. In general, systemic relatlimab exposure increased dose-proportionally between 30 and 100 mg/kg, with no substantial sex differences. Relatlimab exposure margins based on the AUC reached 85-100 fold after 1 month and 183-260 fold after 3 months, at the highest tested dose of 100 mg/kg/week. However, for interpretation of safety data and extrapolation of findings to humans, it should be considered that relatlimab showed significant (256-fold) lower affinity for the monkey epitope than for the human epitope in activated T cells. Nivolumab exposure margins reached 10-14 folds after 1 month, at the highest tested dose of 50 mg/kg/week. No clear gender effect was observed in monkeys. In mice, C9B7W exposure margins reached 13-fold, at the highest tested dose of 51.5 mg/kg.

2.5.4.7. Local tolerance

In a subcutaneous single-dose toxicity study, relatlimab was not considered a local irritant. This is in line with results from IV administration of relatlimab in monkeys (Section 2.5.4.2).

2.5.4.8. Other toxicity studies

The potential induction of ADAs has been described in the pivotal repeat-dose toxicity studies (Section 2.5.4.2). No additional antigenicity studies were warranted.

No dedicated immunotoxicity studies with relatlimab were conducted. Instead, evaluation and discussion on immunotoxicity was incorporated into the repeat-dose toxicity studies (Section 2.5.4.2) in accordance with the ICH S8 and ICH S6(R1) guidelines.

In line with ICH M3 (R2), no studies to evaluate the potential for relatlimab dependence were conducted.

No studies to evaluate relatlimab metabolites were warranted.

No non-clinical studies were conducted to assess relatlimab-related impurities.

Relatlimab alone or in combination with nivolumab does not possess agonistic potential to induce cytokine release syndrome when presented to *in vitro* human PBMCs. In line with this observation, there was no significant T-cell, B-cell or NK-cell activation.

The applicant performed a tissue cross-reactivity study of relatlimab with a panel of human and cynomolgus monkey tissues. Staining was observed in tissues containing LAG-3 expressing immune cells in the plasma membrane, as expected. LAG-3-specific staining was also observed in the adenohypophysis of the human pituitary in a pilot tissue cross reactivity study. In the pivotal cross-reactivity study, relatlimab-FITC staining of endocrine cell epithelial cytoplasm and cytoplasmic granules in the adenohypophysis of the pituitary was also observed. LAG-3 mRNA is known to be expressed in the human pituitary.

2.5.5. Ecotoxicity/environmental risk assessment

In accordance with the current Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), relatlimab and nivolumab are monoclonal antibodies that only consist of naturally occurring substances (amino acids) and are therefore exempt from the ERA requirements.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The applicant submitted information with regard to binding of relatlimab to LAG-3, the inhibition of the binding to its ligands and the functional consequences (T-cell inhibition), demonstrating the proof of principle.

In syngeneic tumour mouse models, the proof of concept was shown from which became clear that combination therapy with nivolumab is more effective.

Although the applicant has submitted data to support the disruption of the LAG-3/FGL-1 binding, FGL-1 is not included as a LAG-3 ligand in 5.1 of the SmPC. LAG-3 binds to its ligands, such as major histocompatibility complex Class II. It is noted that the role of the interaction between FGL-1 and LAG-3 is not yet fully clear. FGL-1 is considered implicitly referred to in the word ligands. SmPC 5.1 refers only explicitly to the functionality of the interaction (and abrogation thereof) with LAG-3 and MHC-II, because this interaction and its implications has been the most studied.

Besides expression on (exhausted) CD-4 T-cells, LAG-3 is also expressed on the membrane of plasmacytoid DCs. According to the applicant the presence of pDCs has been described in the tumour microenvironment (TME) across many human cancers and is generally associated with poor clinical outcome. Tumour-infiltrating pDCs exhibit a dysfunctional state as characterised by an inability to produce type 1 IFN. Plasmacytoid pDCs have been identified in the TME of primary melanoma and in melanoma metastases, but the role for LAG-3 in regulating pDC biology remains poorly understood, including within the TME. Plasmacytoid DCs isolated from tumour-invaded draining lymph node and cutaneous melanoma lesions were enriched (42-55%) for cell surface LAG-3-expression (LAG-3+) and these LAG3+ pDC preferentially localise near and interact directly with major histocompatibility class II-expressing (MHC class II+) melanoma cells and to display a partially activated phenotype, characterised by high levels of TLR-independent IL-6 production, and limited type 1 IFN. IL-6 is a pleiotropic immunomodulatory cytokine. Chronically elevated levels of IL-6 can promote tumour cell survival, drive recruitment of myeloid-derived suppressor cells, and induce angiogenesis and tumour vascularisation, and is a poor prognostic factor in many tumours, including melanoma. MHC class II is frequently expressed by melanoma cells, and thereby may contribute to immune suppression within the TME via engagement of LAG-3 on pDCs. Therefore relatlimab, which blocks LAG-3 from binding to MHC class II, may function to reduce pDC-mediated immunosuppression within the TME and promote anti-tumour efficacy. In addition, related to pDC biology and the safety of Opdualag, pDC hyperactivation has been described in autoimmune diseases. The impact of Opdualag administration to melanoma patients with underlying autoimmune disease remains uncertain, and a reason for excluding patients with known/ suspected autoimmune disease from the study. Therefore, section 4.4 of the SmPC includes the precaution that the administration of a combination of relatlimab with nivolumab (Opdualag) should be undertaken with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

The data from study BDX-1408-245 demonstrate the ability of relatlimab to block, in a dose-dependent manner, LAG-3-mediated inhibition of T-cells.

Several syngeneic tumour models have been tested in the *in vivo* studies in mice. According to the applicant the syngeneic tumour models used in testing the immune checkpoint inhibitors commonly share features of the human TME. These include a varying number of mutation-derived neo-epitopes, a broad range of immune cell infiltration profiles (e.g., 'hot' v. 'cold' tumours), and a broad range of infiltrating immunosuppressive cell types (e.g., dysfunctional tumour-reactive T cells and regulatory T cells). The chosen syngeneic tumour models thus represent different aspects of human TME across and within tumour types, including melanoma and that thereby the preclinical studies are relevant to study the mechanism of action of Opdualag in melanoma patients and establish proof of concept for the therapeutic efficacy of the combination in this indication. Together, the four models in which a combination of anti-PD-1 and anti-LAG-3 were effective, aim to support the rationale for treatment of melanoma. Not because of expression of (one of) the target, but because of the reflection of different features of the TME. This approach can be followed, and the provided explanation is regarded sufficient.

The omission of studies addressing a secondary pharmacologic mechanism of action of relatlimab can be endorsed as its target and mechanism of action are selective.

While some effect was observed with relatlimab alone, the results from the combination studies highlight the potential for enhancing the immunologic effects when relatlimab is administered in combination with nivolumab. Furthermore, these results are consistent with in vitro studies demonstrating the potentiation by relatlimab of nivolumab-mediated T-cell responses, and in vivo study data demonstrating enhanced antitumour activity from the combined administration of LAG-3 and PD-1 blocking antibodies. The effect seems synergistic, suggesting that T-cell inhibition occurs via more pathways and that these two antibodies do not affect each other in a negative way.

Pharmacokinetics

The pharmacokinetic profile of relatlimab was only characterised in cynomolgus monkeys with relatlimab administered alone (30 and 100 mg/kg, IV) or in combination with nivolumab. In addition, since relatlimab does not bind to mouse LAG-3, *in vivo* efficacy tumour models and safety EFD studies in mouse were conducted with a surrogate antibody, 19C7 or C9B7W.

Upon IV administration to monkey, relatlimab showed a biphasic decline, with an initial distribution phase, followed by a very slow elimination phase. Relatlimab systemic exposure in the weekly dosing period ($AUC_{0\text{-}168}$) increased dose-proportionally in both the 4-week and 3-month study. No clear or consistent sex difference was observed on serum exposure. After 4-week IV multiple (QW) dosing, the volume of distribution, as estimated by population PK analysis, was low (i.e 0.072 L/kg), about 2–fold the plasma volume in monkey, and in line with human. Serum clearance in monkey was very low (i.e. 0.12 ml/h/kg) and is about 1.5-fold lower in humans. Terminal elimination half-life ($T_{1/2}$) in monkeys was about 20 – 30 days and was ~25.7 days in human. Exposure (AUC) accumulation ratios upon multiple dosing were ~2.2-fold (Day 22) in the 4-week study and 4.4-fold (D85) in the 3-month study indicating that steady state was not yet reached in the 4-week study, which is in line with the dosing period and the long elimination half-life. Steady state exposures were generally achieved by Day 50. In the 4-week study, relatlimab (100 mg/kg) treatment was also combined with nivolumab (50 mg/kg), and this did not impact the exposure or accumulation ratio of relatlimab. Anti-drug antibody (ADA) formation against relatlimab was found in about 70% to 80% of the treated monkeys in both the 4-week and the 3-month QW repeat-dose toxicology study. The high incidence of ADAs is not considered relevant for the clinical situation. Relatlimab transfer to the foetus or to maternal milk was not examined. However, as relatlimab is an IgG, this is expected to occur.

Toxicology

In the pivotal 1-month combination study, 1 male dosed IV QW at 100 mg/kg relatlimab (MoE: 97) in combination with 50 mg/kg nivolumab (MoE: 13), was prematurely sacrificed due to moribund conditions and histopathology revealed signs of central nervous system (CNS) vasculitis (lymphoplasmacytic inflammation of the choroid plexus; lymphohistiocytic inflammation of the vasculature of the brain parenchyma, meninges, and spinal cord) and epididymitis. Additional findings in the combination group were irreversible lymphoplasmacytic inflammation of the choroid plexus in the brain in both sexes and lymphohistiocytic inflammation of the vasculature of the brain parenchyma in 1 male monkey. Irreversible lymphoplasmacytic inflammation of choroid plexus in the brain was also observed in multiple animals dosed with 50 mg/kg nivolumab only, but not in animals dosed with relatlimab only. None of the animals displayed abnormal neurological clinical findings. The applicant indicated that the target organ profile in different species is not fully understood, but that the combined immunostimulatory effects of nivolumab and relatlimab are not unexpected. Variable immune-mediated adverse effects are also observed after treatment with other checkpoint inhibitors, which are not always predictive for specific target organ toxicities in humans.

Although LAG-3 inhibition in mice did not result in maternal or developmental toxicity, the risk for adverse human pregnancy outcome associated with relatlimab + nivolumab FDC administration is considered to be of concern. The relevant argumentation is: (1) LAG-3 is likely to have a role in maintaining maternal tolerance to the developing foetus; (2) nivolumab has been shown to increase third trimester pregnancy loss in cynomolgus monkeys; (3) both relatlimab and nivolumab are IgG4 antibodies, and are likely to be transported through the placenta. The use of relatlimab + nivolumab FDC in pregnancy is not recommended. Human IgG4 is also excreted in milk and thus nursing may result in relatlimab and nivolumab exposure to the infant through FcRn-mediated antibody internalisation. Women are therefore advised not to breastfeed while receiving relatlimab + nivolumab FDC in the period of anticipated IgG4 excretion in milk (SmPC section 4.6).

In conclusion, while relatlimab alone is well tolerated, the combination with nivolumab (and to a certain extent nivolumab alone) resulted in adverse immune-mediated toxicity. The applicant further indicated that clinical monitoring of all patients for neurologic signs and symptoms has been emphasised and should continue and managed using BMS neurological adverse event management algorithms. This is considered adequate. The enhanced immunostimulatory effects of nivolumab and relatlimab are adequately reflected in SmPC Section 5.3.

Although the effect on fertility is not known, the potential relevance of epididymitis for the clinic was mentioned as a significant non-clinical safety finding in the RMP.

In the pivotal cross- reactivity study, relatlimab-FITC staining of endocrine cell epithelial cytoplasm and cytoplasmic granules in the adenohypophysis of the pituitary was also observed. LAG-3 mRNA is known to be expressed in the human pituitary. However, since relatlimab is not expected to have access to the cytoplasmic compartment *in vivo,* this finding is not anticipated to have clinical significance.

Environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, relatlimab is not expected to pose a risk to the environment, also not in the combination with nivolumab (also a natural substance) in the Opdualag formulation.

2.5.7. Conclusion on the non-clinical aspects

No animal studies were conducted with nivolumab in combination with relatlimab to evaluate potential carcinogenicity, genotoxicity or reproductive and developmental toxicity. This is considered acceptable and in line with relevant guidelines. In a 1-month study in monkeys dosed with nivolumab and relatlimab, inflammation within the central nervous system (choroid plexus, vasculature, meninges, spinal cord) and the reproductive tract (epididymis, seminal vesicles and testes) was observed. Although safety margins were not established for these effects with the combination, they occurred at doses that suppose exposure levels significantly higher (13 folds for nivolumab and 97 folds for relatlimab) than those reached in patients. In an embryo foetal toxicity study in mice using murine anti LAG 3 antibodies, no maternal or developmental effects were observed. The effects of relatlimab on prenatal and postnatal development have not been evaluated, however, based on the mechanism of action, blockade of LAG 3 with relatlimab can have a similar negative effect as nivolumab on pregnancy.

In conclusion it can be considered that all non-clinical aspects were sufficiently addressed, and relevant information has been adequately reflected in the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant 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**

Clinical studies in support of the proposed indication are shown in *Table 2*.

Table 2. Applicant-sponsored studies 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
Supportive Phase 1/2 Study Supporting PK, Safety, and Efficacy					
CA224020	Phase 1/2a open-label study of	A: 12-36	Solid tumours, IO naïve	Rela 20 mg to 800 mg Q2W[a]	17

Study	Design/ *Primary Objective*	No. Planned Subjects (N)	Population	Dose/Schedule	Treated (N)
RELATIVITY -020 NCT 01968109 Countries: 14 Site: 53	relatlimab alone and in combination with nivolumab *PK, PD, safety, tolerability, preliminary efficacy*	A1: 12-24	NSCLC/RCC, prior anti-PD-(L)1 allowed	Rela 800 mg Q2W	8
		B: 24-72	Solid tumours	Rela+nivo 20/80 mg to 240/240 mg Q2W[b]	40
				Rela+nivo 160/480 mg to 1440/480 mg Q4W[b]	67
		C: 560	**MEL, prior anti-PD-1**	Rela+nivo 80/240 mg Q2W (**sequential**)	151
			First-line MEL		66
			Other tumours[c]		329
			Bladder cancer, IO naïve	Rela+nivo 160/480 mg Q4W	37
		D1: 300	**MEL, prior anti-PD-1**; focused eligibility[d]	Rela+nivo 80/240 mg Q2W **coadmin**	189
				Rela+nivo160/480 mg Q4W **coadmin**	83
				Rela+nivo 160/480 mg Q4W **FDC**	82
		D2: 250	**MEL, prior anti-PD-1**; expanded eligibility[e]	Rela+nivo 160/480 mg Q4W **coadmin**[f]	164
		E: 225[g]	**MEL, prior anti-PD-1**	Rela+nivo 480/480 mg Q4W **coadmin**	95
			First-line MEL	Rela+nivo 160/480 mg Q4W **coadmin**	38 enrolling
				Rela+nivo 480/480 mg Q4W **coadmin**	38 enrolling

[a] Rela monotherapy dose escalation: 20 mg, 80 mg, 240 mg, and 800 mg Q2W
[b] Rela+nivo dose escalation: 20/80, 20/240, 80/240, 160/240, and 240/240 mg Q2W; 160/480, 240/480, 320/480, 480/480, 960/480, and 1440/480 mg Q4W. Note, per protocol doses could go up to 1600/480 mg Q4W, no subjects were included.
[c] Includes IO naïve RCC, SCCHN, NSCLC, GC/GEJ, and HCC and prior anti-PD-1 treated NSCLC
[d] Focused eligibility: allowed prior therapies (anti-PD-1; nivolumab or pembrolizumab only), only 1 line of a prior anti-PD-1 regimen, and only Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1.
[e] Broader eligibility criteria: allowed prior therapies (any anti-PD-(L)1), multiple prior lines of anti-PD-1 regimens, and ECOG PS 0-2.
[f] Per protocol, there was a 240/480 mg Q4W cohort; however, no subjects were enrolled at this dose.
[g] First line melanoma (1L MEL) cohorts in Part E are currently enrolling

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The PK of relatlimab was characterised by non-compartmental PK analyses of individual subject concentration-time profile data from Phase 1/2a Study CA224020 and by popPK analysis using pooled concentration data from Study CA224020 and Phase 2/3 Study CA224047 in subjects with solid tumours who received relatlimab doses of 20 to 800 mg Q2W and 160 to 1440 mg Q4W either as monotherapy or in combination with nivolumab doses of 80 or 240 mg Q2W or 480 mg Q4W.

Analytical methods

Serum levels of relatlimab in studies CA224020 and CA224047 were quantitated with a chemiluminescence ELISA method (MTD021). The ELISA assay measures relatlimab in human serum using capture antibody (coating onto a plate) and a biotin-labeled detection antibody. The assay range in undiluted human serum is from 50 to 3200 ng/ml. QCs were included at concentrations of 150, 500 and 2400 ng/ml.

During validation, dilutions from the 500,000 ng/ml QC were designed to obtain samples falling within the calibration curve range (1,953, 488, 122 ng/ml). A hook effect was not observed at analyte concentration up to 500,000 ng/ml.

The presence of nivolumab at 300 µg/ml or a ratio of 2000:1 (300:0.15 µg/ml) of nivolumab:relatlimab in serum did not interfere with relatlimab quantitation. In the samples tested for relatlimab concentrations in study CA224020 and CA224047, the highest observed concentration of nivolumab did not exceed 300 µg/ml or a ratio of 2000:1, thus, there was no risk of nivolumab interference with relatlimab detection.

This method was used to analyze all human serum samples in the Phase 1/2a CA224020 and Phase 2/3 CA224047 studies that had PK sample collection for relatlimab. The method performed well in studies CA224020 and CA224047 and met the acceptance criteria with an ISR passing rate of 91.1% and 97.8%, respectively.

Serum levels of nivolumab in studies CA224020 and CA224047 were quantitated with an electrochemiluminescence (ECL) ligand-binding assay (LBA) method using an electrochemiluminescence platform (ICD 416 and MTD035). Both methods (ICD 416 and MTD035) were cross-validated to verify and confirm acceptable accuracy and precision across methods and laboratories. These ECL assays measure nivolumab in human serum using biotin-labeled capture antibody and a ruthenium-labeled detection antibody. The assay range is from 0.2 µg/ml to 6.5 µg/ml in undiluted human serum. In both methods, QCs were included at concentrations of 0.6, 1.5 and 4.8 µg/ml.

Further, during validation, dilutions from a 100 µg/ml QC were designed to generate samples with nivolumab concentrations (amongst others) that fall above and within the calibration curve range (5.00, 1.00, 0.500 and 0.250 µg/ml). A hook effect was not observed at analyte concentration up to 100 µg/ml.

The presence of relatlimab at 200 µg/ml or a ratio of 333:1 (200:0.6 µg/ml) of relatlimab: nivolumab in serum did not interfere with nivolumab quantitation when tested at nivolumab concentrations equivalent to the low quality control (0.6 µg/ml) and high quality control (4.8 µg/ml). In the samples tested for nivolumab concentrations in studies CA224020 and CA224047, the highest observed concentration of relatlimab did not exceed 200 µg/ml or a ratio of 333:1. Thus, there was no risk of relatlimab interference with nivolumab measurements.

Method ICD 416 was used to analyze all human serum samples in the CA224020 study that had pharmacokinetic sample collection for nivolumab, and method MTD035 was used to analyze all human serum samples in the CA224047 study that had pharmacokinetic sample collection for nivolumab.

PopPK models

The PK of relatlimab, alone and in combination with nivolumab, was characterised by a 2-compartment, zero-order IV infusion PK model with parallel nonlinear and time-varying CL. A trend of decreasing contribution of relatlimab nonlinear CL to the total CL with dose was observed. At the recommended dose (relatlimab 160 mg Q4W in combination with nivolumab), nonlinear CL represents ~31% of total CL of relatlimab. The relatlimab popPK model is sufficiently validated, provides a sufficient description of the relatlimab exposure data with reasonable shrinkage for CL and Vc 29.0 and 20.2%, and is considered suitable for investigation towards the consequences of various covariates on relatlimab exposure.

The PK of nivolumab, alone and in combination with relatlimab, was characterised by a 2-compartment, zero-order IV infusion PK model with time-varying CL. Nivolumab CL decreases over time with maximal reduction of 18% in adult 1L MEL subjects. Nivolumab baseline CL in subjects

receiving nivolumab monotherapy or relatlimab SAV + nivolumab (Opdivo) was similar (≤ 5% difference) compared with subjects receiving relatlimab + nivolumab FDC. The popPK model is sufficiently validated, provides a sufficient description of the nivolumab exposure data with reasonable shrinkage of 11.2% and 22.7% for CL and Vc, respectively, and is considered suitable for investigation towards the consequences of various covariates on nivolumab exposure.

In the nivolumab popPK model, paediatric PK data were included. It is apparent that adolescent (≥ 12 to 17 years) and paediatric (< 12 years) subjects showed 36% and 62% lower baseline CL, respectively, than adult 1L MEL subjects. In addition, the adolescent (≥ 12 to 17 years) and paediatric subjects (< 12 years) had 16% and 32% lower Vc, respectively, than adult subjects.

Absorption

Relatlimab and nivolumab plasma exposures obtained from a single agent vial (co-administered) or given as FDC were comparable (Table 3). Therefore, no effect of drug product (single agent vial vs FDC) on the PK of relatlimab and nivolumab is present.

Table 3. Relatlimab and nivolumab PK parameter comparison between SAV coadministration and FDC cohorts for relatlimab + nivolumab 160/480 mg Q4W (Study CA224020 part D1)

Parameter (Unit)	Co-Admin (N)	FDC (N)	Cycle/Day	Estimated Geometric Mean Ratio	95% CI
Relatlimab					
Cmax (ug/mL)	23	23	Cycle 1 Day 1	1.078	(0.947, 1.227)
AUC(TAU) (h*ug/mL)	16	14	Cycle 1 Day 1	0.929	(0.732, 1.180)
Nivolumab					
Ceoi (ug/mL)	21	65	Cycle 1 Day 1	1.097	(0.934, 1.288)
	21	33	Cycle 3 Day 1	1.021	(0.867, 1.201)
Ctrough (ug/mL)	66	63	Cycle 1 Day 29	1.106	0.916, 1.335)
	26	36	Cycle 3 Day 1	1.154	(0.852, 1.563)

Distribution

The geometric mean value for volume of distribution at steady state is 6.65 L both for relatlimab and nivolumab. The nivolumab volume of distribution at steady state in adolescents is 5.16 L. These values are consistent with the expected distribution of mAbs limited to the vascular space.

Elimination

Relatlimab and nivolumab are mAbs that are expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. No active metabolites are therefore expected.

Based on non-compartmental PK analysis in patients with solid tumours, the relatlimab $t_{1/2}$ at doses between 320-1440 mg was approximately 14 to 27 days. Based on popPK analysis, for subjects who received relatlimab/nivolumab 160/480 mg Q4W, the relatlimab effective half-life both was 25.7 days and for nivolumab 26.4 days. The $t_{1/2}$ predicted for nivolumab when given in combination with relatlimab is in line with the $t_{1/2}$ reported for nivolumab when given as monotherapy of 25 days (Opdivo EPAR). Both for relatlimab and nivolumab, the $t_{1/2}$ is in line with the plasma half-life of circulating endogenous human IgG of approximately 21 days.

Based on popPK analyses, single dose clearance is 6.1 ml/h for relatlimab and 9.6 ml/h for nivolumab. Both for relatlimab and nivolumab, clearance decreased at steady state (to 5.5 ml/h, 9.7% lower for relatlimab, and to 7.6 ml/h, 21% lower for nivolumab). Nivolumab clearance under steady state, when given in combination with relatlimab, is comparable to that reported for nivolumab as single agent (7.9 ml/h, EPAR nivolumab).

Based on popPK analyses, adolescent (≥ 12 to < 18 years) and paediatric (< 12 years) subjects showed 36% (95% CI: 22.1-47.5) and 62% (95% CI: 51.9-71.3) lower baseline CL of nivolumab, respectively, than adult unresectable or metastatic melanoma subjects.

Dose proportionality and time dependencies

Relatlimab exposure increased approximately dose proportionally when given as monotherapy (20-800 mg) or in combination with nivolumab across the studied dose ranges (160-1440 mg). Based on information from the Opdivo SmPC, the pharmacokinetics of nivolumab is linear in the dose range of 0.1 to 10 mg/kg (i.e. 7.5 to 750 mg for a 75 kg patient). Applying the 160/480 mg Q4W posology, relatlimab exposure reaches steady-state after approximately 16 weeks (Table 4). The observed relatlimab accumulation ratio of in the range of 1.3 to 1.7 is in line with the $t_{1/2}$ of approximately 25 days and the once every 4 weeks administration schedule.

Table 4. Geometric mean (CV%) of relatlimab and nivolumab steady-state exposures following 160 mg relatlimab and 480 mg nivolumab fixed-dose combination every 4 weeks

	C_{max} (µg/mL)	**C_{min} (µg/mL)**
relatlimab	60.4 (35)	15.0 (53)
nivolumab	176 (34)	59.7 (37)

Special populations

Renal impairment. Considering the fact that both relatlimab and nivolumab are mAbs, an effect of renal impairment on clearance is not expected. Indeed, based on popPK analysis, renal impairment (normal vs mild and moderate) resulted in a 20% decreased CL of relatlimab or nivolumab, which is considered not clinically relevant. The impact of severe renal impairment on the PK of relatlimab or nivolumab is unclear given the limited number of subjects were enrolled with severe impairment.

Hepatic impairment. Considering the fact that both relatlimab and nivolumab are mAbs, an effect of hepatic impairment on clearance is not expected. Indeed, based on popPK analysis, hepatic impairment (normal vs mild and moderate) resulted in a 10% decreased CL of relatlimab or nivolumab, which is considered not clinically relevant. The impact of severe hepatic impairment on the PK of relatlimab or nivolumab is unclear given the limited number of subjects were enrolled with severe impairment.

Gender. Based on popPK analyses, exposure to relatlimab and nivolumab was not affected to a clinically relevant extent by gender.

Race. Based on popPK analyses, exposure to relatlimab and nivolumab was not affected to a clinically relevant extent by race.

Weight. Patient weight, as indicated in the popPK report, ranged from 51.9 to 111 kg. Due to the flat dosing, both for relatlimab and nivolumab, C_{avg} decreases with an increase in body weight and increases with a decrease in body weight. Within this weight range, the relatlimab C_{avgss} were 26% higher in subjects with lower body weight (at 5th percentile, i.e. 50-55 kg) and were ~ 31% lower in subjects with higher body weight (at 95th percentile, i.e. 106-117 kg) relative to the exposure in typical subjects at a body weight of 75 kg. For nivolumab, these differences were <20%.

Elderly.

A summary of the number of elderly patients included in the provided clinical trials and providing dense or sparse PK data for relatlimab and nivolumab was provided (Table 5 and Table 6). The majority of elderly patients included in Studies CA224020 and CA224047 (505 and 591 for relatlimab and nivolumab, respectively) were aged ≥ 65 to < 75 years. Although at lower numbers, also patients aged ≥ 75 to < 85 (approximately 203 and 148, respectively) and patients aged ≥ 85 (approximately 29 and 36, respectively) were included.

Table 5. Summary of elderly subjects in the relatlimab popPK analysis dataset by study

		Number of Subjects (% of all subjects in the analysis)			
Study	**No. of subjects**	**≥ 65 and < 75 years**	**≥ 75 and < 85 years**	**≥ 85 years**	**≥ 65 years**
CA224020	1381	412 (29.8)	146 (10.6)	24 (1.7)	582 (42.1)
CA224047	332	93 (28)	57 (17.2)	5 (1.5)	155 (46.7)

Table 6. Summary of elderly subjects in the nivolumab PopPK analysis dataset by study

		Number of Subjects (% of all subjects in the analysis)			
Study	**No. of subjects**	**≥ 65 and < 75 years**	**≥ 75 and < 85 years**	**≥ 85 years**	**≥ 65 years**
CA224020	1341	405 (30.2)	142 (10.6)	24 (1.8)	571 (42.6)
CA224047	658	186 (28.3)	106 (16.1)	12 (1.8)	304 (46.2)

Adolescents. With respect to nivolumab, PK data in children and adolescents were available for patients with solid tumours. These paediatric PK data were included in the nivolumab popPK model. Comparison of the exposure data in the nivolumab popPK model indicate that adolescent subjects had 24% lower CL0, 28% lower CLss, and 28% lower VC than corresponding parameters of adult subjects. Further simulations indicated that the 6 mg/kg up to 480 mg Q4W posology in adolescents provided nivolumab exposures that were comparable with median adult exposures, with median exposures of adolescent subjects at each body weight group contained within the adult median exposure range of high body weight (≥ 100 kg) and low body weight (40-50 kg) adults (Table 7).

Table 7. Predicted nivolumab exposures for adolescent subjects at doses of 6 mg/kg up to 480 mg FDC Q4W and adult subjects with 1L MEL at 480 mg FDC Q4W (nivolumab popPK model)

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	Adult N	Adult Geo. Mean (%CV)	Adult High - Low Body Weight Geo. Mean[a]
Cavgss	30-40	38	90.5 (40.0)	NA	NA	77.5 - 136
	40-50	118	98.4 (42.9)	6	136 (52.5)	
	50-60	217	115 (52.5)	61	128 (49.6)	
	60-70	163	115 (53.5)	77	104 (56.7)	
	70-80	103	126 (46.6)	122	98.1 (57.4)	
	80-90	67	126 (53.0)	105	91.2 (44.2)	
	90-100	47	121 (53.5)	62	87.9 (47.0)	
	≥ 100	45	90.2 (40.9)	67	77.5 (55.5)	
Cminss	30-40	38	62.6 (50.7)	NA	NA	47.5 - 87.8
	40-50	118	65.3 (56.0)	6	87.8 (65.9)	
	50-60	217	79.5 (66.8)	61	82.0 (65.2)	
	60-70	163	76.7 (69.0)	77	65.6 (75.4)	
	70-80	103	87.0 (59.5)	122	60.4 (76.7)	
	80-90	67	86.9 (66.2)	105	57.4 (57.9)	
	90-100	47	82.8 (69.7)	62	55.7 (61.9)	
	≥ 100	45	59.6 (53.5)	67	47.5 (70.8)	
Cmaxss	30-40	38	170 (28.5)	NA	NA	154 - 261
	40-50	118	189 (30.2)	6	261 (44.4)	
	50-60	217	214 (36.8)	61	247 (34.9)	
	60-70	163	224 (35.6)	77	210 (37.6)	
	70-80	103	235 (35.1)	122	197 (38.7)	
	80-90	67	233 (39.3)	105	177 (31.4)	
	90-100	47	228 (36.4)	62	173 (31.7)	
	≥ 100	45	175 (29.2)	67	154 (37.6)	

[a] The range of geometric mean exposure of high-body-weight adult (≥ 100 kg) and low-body-weight adult (40-50 kg).

With respect to relatlimab, no adolescent PK data were available. Therefore, these simulations were performed with a revised version of the relatlimab popPK model, which incorporated the paediatric effects on CL and VC determined in the nivolumab popPK analysis (i.e., adolescent subjects had 24% lower CL0, 28% lower CLss, and 28% lower VC than corresponding parameters of adult subjects). The applicant 's arguments for accepting this strategy are that both nivolumab and relatlimab are IgG4 mAbs with similar mechanisms of distribution and non-specific elimination. Assuming a comparable effect of age/weight on nivolumab and relatlimab PK, relatlimab simulations indicated that the 2 mg/kg up to 160 mg Q4W posology in adolescents provided relatlimab exposures that were comparable with median adult exposures, with median exposures of adolescent subjects at each body weight group >50 kg contained within the adult median exposure range of high body weight (≥ 100 kg) and low body weight (40-50 kg) adults (Table 8).

Table 8. Predicted relatlimab exposures for adolescent subjects at doses of 2 mg/kg up to 160 mg FDC Q4W and adult subjects with 1L MEL at 160 mg FDC Q4W (relatlimab popPK model)

Exposure (µg/mL)	Body Weight (kg)	Adolescent N	Adolescent Geo. Mean (%CV)	Adult N	Adult Geo. Mean (%CV)	Adult High - Low Body Weight Geo. Mean[a]
Cavgss	30-40	38	12.8 (71.4)	NA	NA	17.5 - 38.7
	40-50	118	18.3 (52.9)	6	38.7 (57.9)	
	50-60	217	22 (61.5)	61	33.3 (53)	
	60-70	163	24.9 (64.6)	77	24.1 (65.9)	
	70-80	103	27.2 (54.2)	122	23.6 (64.3)	
	80-90	67	28.2 (62)	105	21.2 (54.7)	
	90-100	47	26.8 (54.2)	62	19.7 (56.3)	
	≥ 100	45	20 (51.7)	67	17.5 (63.4)	
Cminss	30-40	38	2.88 (130)	NA	NA	7.14 - 21.9
	40-50	118	5.74 (83.8)	6	21.9 (76.4)	
	50-60	217	8.13 (93.4)	61	17.8 (76.8)	
	60-70	163	10.1 (97.6)	77	9.61 (102)	
	70-80	103	12 (80.4)	122	9.91 (99)	
	80-90	67	13.5 (88.2)	105	8.91 (86.7)	
	90-100	47	13.2 (82.5)	62	8.33 (89.9)	
	≥ 100	45	8.7 (84.7)	67	7.14 (94.1)	
Cmaxss	30-40	38	35.7 (32.3)	NA	NA	44.9 - 76.5
	40-50	118	45.2 (30.9)	6	76.5 (45.5)	
	50-60	217	53.1 (34.5)	61	69.9 (33.9)	
	60-70	163	59.8 (36.3)	77	57.8 (38.3)	
	70-80	103	63.4 (34.7)	122	55.8 (37.4)	
	80-90	67	65.1 (38.9)	105	50.3 (31.9)	
	90-100	47	63.3 (33.8)	62	49.3 (31.7)	
	≥ 100	45	51.4 (30.2)	67	44.9 (36)	

[a] The range of geometric mean exposure of high-body-weight adult (≥ 100 kg) and low-body-weight adult (40-50 kg).

60- vs 30-minute infusion. During clinical development, relatlimab and nivolumab were administered via a 60-min infusion. For registration, the applicant aims for a 30 min infusion period. Based on the provided simulations, no relevant difference in exposure to relatlimab and nivolumab is expected using either of the two infusion periods. From a PK perspective, relatlimab and nivolumab C_{min} and C_{avg} data obtained by using a 60-minute administration period are considered relevant for the 30 minutes administration period as well.

Pharmacokinetic interaction studies

Antibodies have a low potential for pharmacokinetic drug interactions as they are not metabolised by liver cytochrome P450 (CYP) or other drug metabolizing enzymes. Therefore, it is unlikely that they have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction. As such, no formal DDI study was conducted.

The across-study assessment of PK interaction between relatlimab and nivolumab were conducted through popPK analyses using pooled data from CA224020 and CA224047. There was no clinically relevant PK interaction between relatlimab and nivolumab when administered in combination. Relatlimab baseline CL in subjects receiving relatlimab monotherapy and relatlimab SAV + nivolumab (sequential or co-administered) was similar to subjects receiving rela+nivo FDC (≤ 5% and ≤ 18%

difference, respectively). Similarly, nivolumab baseline CL in subjects receiving nivolumab monotherapy or relatlimab SAV + nivolumab was similar (≤ 5% difference) compared with subjects receiving rela+nivo FDC. There was no clinically relevant PK interaction between relatlimab and nivolumab when administered in combination.

Therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome P450 enzyme. The extent of cytokine modulation by rela+nivo was explored with the available data of cytokines that have been reported to indirectly affect expression or stability of cytochrome P450 enzyme18 in Studies CA224020 and CA224047. No trend of treatment-associated changes was observed for IL-6, IL-10, IL-1β or TNF-α (data not shown).

2.6.2.2. Pharmacodynamics

Mechanism of action

Binding of relatlimab to the LAG-3 receptor releases the LAG-3 mediated inhibition of immune response by blocking its interaction with ligands. Binding of nivolumab to the PD-1 receptor blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.

In preclinical studies, combined relatlimab (anti-LAG3) and nivolumab (anti-PD-1) mediated inhibition enabled T-cell activation, increased interferon gamma (IFNγ) production, and restored effector function of exhausted T cells, more than the effects of either antibody alone. LAG-3 blockade potentiated the anti-tumour activity of PD-1 blockade in murine syngeneic tumour models, inhibiting tumour growth and promoting tumour regression. Hereby, the mode of action is to some extent demonstrated.

Primary and Secondary pharmacology

In Study CA224020, a relatlimab dose-dependent increase in LAG-3 receptor occupancy (RO) on CD8+ memory T cells was demonstrated. Additionally, exposure-response analysis of peripheral RO predicts > 80% ROavgss with the recommended rela + nivo dose of 160/480 mg Q4W (see exposure response relationships below).

No consistent treatment-induced changes were observed for IFNγ or IFNγ-induced soluble factors and chemokines in subjects treated with relatlimab monotherapy, except for a modest increase of CXCL9. Further, no apparent treatment-induced change of T cell subsets was observed for any subject treated with relatlimab monotherapy, at doses up to 800 mg Q2W. In subjects treated with rela+nivo, IFNγ and IFNγ-induced chemokines and soluble factors (CXCL9, CXCL10, CXCL11, and IL-2Rα) increased consistently with across all dosing regimens evaluated, although no dose-dependency was observed. A consistent trend of increase in proliferating and activated CD4+ and CD8+ central and effector memory T cell subset was observed on Day 8 after the first dose of combination therapy ranging from rela+nivo 20/80 mg to 160/480, no clear dose-dependent changes were observed (limited number of samples at each dose combination).

In Study CA224047, a consistent decrease of free sLAG3 was observed after the administration of rela+nivo FDC, which was not shown in subjects treated with nivolumab monotherapy. The median increase of IFNγ was approximately doubled after the administration of rela+nivo FDC compared to nivolumab alone. Similar treatment-induced increases were also observed for IFNγ-inducible chemokines and soluble factors, including MIG, IP10, and IL-2Rα, but the difference in levels of increase was less significant between subjects treated with rela+nivo FDC or nivolumab monotherapy.

Effect on corrected QT interval (QTc)

The effect of relatlimab and relatlimab in combination with nivolumab on ventricular repolarisation was studied in the phase 1/2a study CA224020, based on the dose escalation parts A and B using rela SAV + nivolumab product. Relatilimab monotherapy had no effect on the QTc interval duration; however, there was limited QTc data (N=7) and therefore the monotherapy data was combined with data from rela+nivo (N = 65) in the concentration-QTc analysis. Overall, QT prolongation was not observed for relatlimab up to 800 mg Q2W as monotherapy and up to 1440 mg Q4W in combination with 480 mg nivolumab. There were no trends of change from baseline in QTcF, PR, and QRS intervals among all evaluable subjects, and no subject assessed had a ΔQTcF > 60 ms. No electrocardiogram (ECG)-assessed patient had an adverse event (AE) associated with abnormal ECG findings potentially related to proarrhythmia. The upper limit of the 90% CI for mean ΔQTcF was <10 ms over the range of observed relatlimab concentrations.

Relationship between plasma concentration and effect

Receptor-binding. With respect to the *exposure-peripheral receptor occupancy*, the predicted peripheral LAG-3 RO was similar between relatlimab/nivolumab 80/240 mg Q2W regimen and the requested relatlimab/nivolumab 160/480 mg Q4W dose regimen. LAG-3 RO was higher following a dose of relatlimab/nivolumab 480/480 mg Q4W as compared to 160/480 mg Q4W (Table 9).

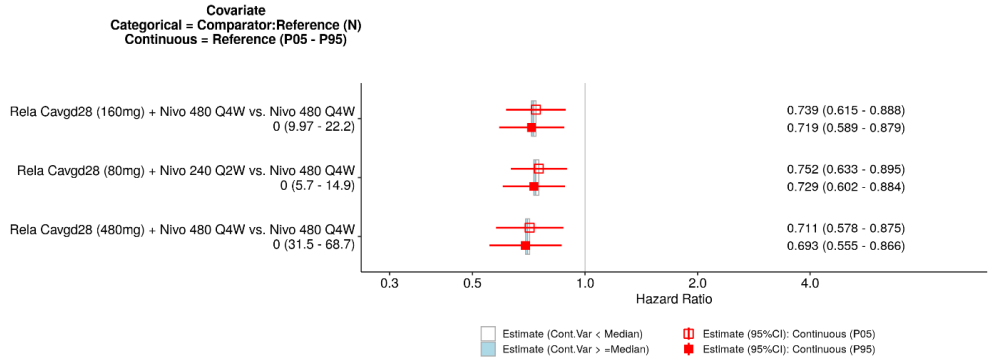
Table 9. Predicted relatlimab peripheral receptor occupancy relative to reference (rela 160 mg + nivo 480 mg Q4W) in melanoma subjects

Peripheral Receptor Occupancy or Exposure (µg/mL)	**Rela 80 mg + nivo 240 mg Q2W Geo. Mean (%CV)** **(A)**	**Rela 160 mg + nivo 480 mg Q4W Geo. Mean (%CV)** **(B)**	**Rela 480 mg + nivo 480 mg Q4W Geo. Mean (%CV)** **(C)**	**% Diff GM[a] (A vs B)**	**% Diff GM[b] (C vs B)**
$RO_{trough1}$ (%)	61.7 (18.6)	61.9 (24.2)	86.4 (6.86)	-0.323	39.6
RO_{avg1} (%)	74.0 (8.78)	78.3 (9.32)	89.5 (5.07)	-5.49	14.3
$RO_{troughss}$ (%)	81.2 (12.6)	74.1 (20.1)	90.4 (5.66)	9.58	22
RO_{avgss} (%)	85.2 (7.84)	84.3 (8.76)	91.7 (4.85)	1.07	8.78

[a] Percent difference calculated for rela 80 mg + nivo 240 mg Q2W relative to the reference %RO and exposure for rela 160 mg + nivo 480 mg Q4W.
[b] Percent difference calculated for rela 480 mg + nivo 480 mg Q4W relative to the reference %RO and exposure for rela 160 mg + nivo 480 mg Q4W

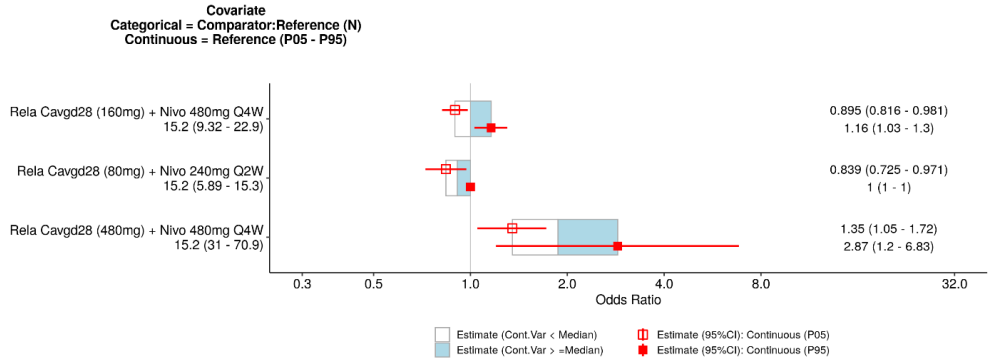
Efficacy. With respect to the *exposure-progression free survival,* PFS was associated with exposure to relatlimab, resulting in a longer PFS in relatlimab + nivolumab combination treatment compared to nivolumab monotherapy. Predicted HRs of PFS were similar across the range of exposures produced by relatlimab/nivolumab 80/240 mg Q2W, 160/480mg Q4W, and 480/480 mg Q4W, suggesting a flat relatlimab E-R relationship with respect to PFS (Figure 1).

Figure 1. Model predicted hazard ratio of PFS in relatlimab + nivolumab combination dose regimens relative to median Cavgd28 of nivolumab 480 mg Q4W regimen



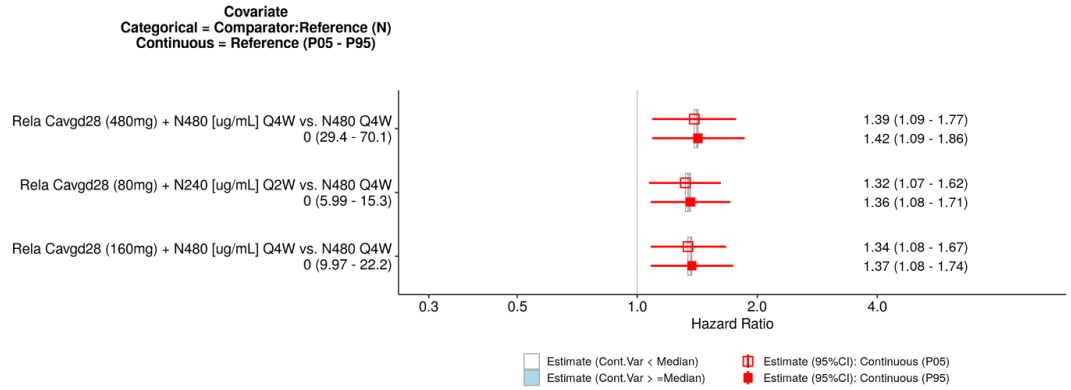
With respect to the *exposure-objective response,* OR was associated with relatlimab exposure, resulting in a higher probability of OR with increase in relatlimab exposure (Figure 2).

Figure 2. Model predicted odds ratio of OR in relatlimab + nivolumab combination dose regimens relative to median Cavgd28 of relatlimab 160 mg + nivolumab 480 mg Q4W regimen



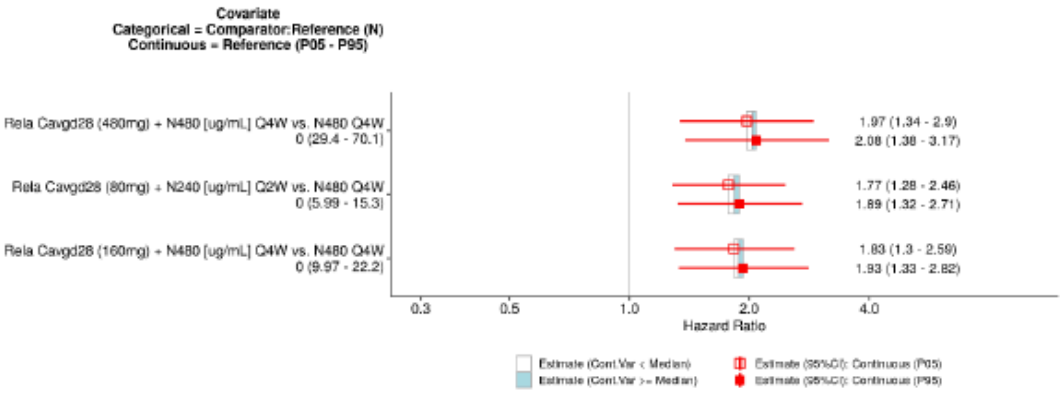
Safety. With respect to the *exposure-Grade 2+ immune-mediated adverse events,* as well as the *exposure Grade 3+ drug-related adverse events*, the risk of these Gr2 and Gr3 AEs was significantly associated with relatlimab and nivolumab exposure, resulting in a higher risk in relatlimab + nivolumab combination compared with nivolumab monotherapy. Nivolumab exposure was not significantly associated with the risk of Gr3+ Drug-related adverse events. The risk for these Gr2 and Gr3 AEs was similar across the range of relatlimab exposures produced by the studied combination dosing regimen in Studies CA224020 and CA224047, supporting a flat relatlimab E-R relationship over this exposure range (Figure 3, Figure 4).

Figure 3. Model predicted hazard ratio of Gr2+ IMAEs in relatlimab + nivolumab combination dose regimens relative to median Cavgd28 of nivolumab 480 mg Q4W regimen



Note: N480: nivolumab 480 mg

Figure 4. Model predicted hazard ratio of Gr3+ DRAEs in relatlimab +nivolumab combination dose regimens relative to median Cavgd28 of nivolumab 480 mg Q4W regimen



2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Analytical methods. The analytical methods for relatlimab and nivolumab appear sufficiently validated and yielded acceptable accuracy and precision. The presence of nivolumab at relevant concentrations did not interfere with relatlimab quantitation and vice versa. A hook effect was excluded. For both analytical assays, the distribution of the QCs is not completely in line with requirements, with a QC at 500 (16% of ULQ) and 2400 ng/ml (75% of ULQ) within the calibration range of 150 to 3200 ng/ml. No QC around 50% is present. Likewise, for the nivolumab assay, QCs were present at 1.5 (23% of ULQ) and 4.8 µg/ml (74% of ULQ) within the calibration range of 0.2 to 6.5 µg/ml. However, during validation of the relatlimab assay, a QC diluted to 1953 ng/ml (61%) was tested as well, yielding acceptable results. Therefore, the absence of a QC around 50% of the ULQ is considered not a critical issue, and the outcome of the bioanalytical assays is considered sufficiently reliable for its intended purpose.

PK variability. Interindividual variability was from moderate to high (34-53%) both for relatlimab and nivolumab.

Excretion. The non-compartmental analysis showed that relatlimab t1/2 had an inverse relationship with dose, since 1440 mg Q4W of relatlimab in combination with nivolumab showed a t1/2 of 14 days, whereas 320 mg Q4W in combination with nivolumab showed a t1/2 of 27 days. The shorter t1/2 as dose increases is unexpected, because the opposite effect would be expected in drugs that show a target-mediated elimination. It is agreed that the number of patients (2) is quite limited to obtain definitive conclusions but this result is confirmed in the population PK analysis, where with the proposed dose (160 mg Q4W in combination with nivolumab) the estimated half-life is 25 days.

Dose proportionality. A dose-proportionality effect was observed on relatlimab exposure when administered as monotherapy and in combination with nivolumab (Q2W and Q4W). The overall impact of dose-dependent target mediated CL on relatlimab exposure at the proposed dosing regimen 160 mg Q4W has also been evaluated, which represents around 31% of the overall clearance.

Pharmacokinetics in the target population.

Relatlimab population PK model

A base, full and final (or refined) population PK model allowed to characterise first the structural and inter-individual and residual random effects, then the covariate analysis and ultimately a model refinement including only the significant covariate relationships. According to the parameter estimates, relative standard errors, shrinkage and condition number, the final popPK model of relatlimab confirmed the adequacy and parsimony of the popPK proposed. Moreover, based on the pcVPC the model is able to describe the observed data, despite the unbalanced distribution of experimental evidence across the different dose levels.

Nivolumab population PK model

The population PK model development of nivolumab includes the re-use of a base population PK model previously established in other cancer indications and the application of the full population PK model with all the significant covariates previously identified. The popPK model for nivolumab consists of a two-compartment model with zero-order IV infusion and linear and time-varying elimination pathway. Moderate (<50%) inter-individual variability has been characterised on several PK parameters. The full popPK model includes 22 covariate effects. However, several covariates are non-significant based on the 95%CI, which includes the null value (and those covariate effects were unreliable estimated based on the high RSE values (>50%)). However, a model comparison was conducted with a reduced version of the population PK model and no differences on final parameter estimates was detected.

The popPK model of nivolumab for paediatric patients <18 years of age demonstrated a reasonably good performance based on the pc-VPC. However, a clinically relevant effect on CL for paediatric patients <12 and 12-18 years of age and Vc for paediatric patients <12 years of age was predicted. It is acknowledged that no indication has been claimed for paediatric patients <12 years of age.

Special populations

Renal impairment. The impact of severe renal impairment on the PK of relatlimab or nivolumab is unclear given the limited number of subjects enrolled with severe impairment. In light of the scarcity of data in the severe renal impairment population, combined with the observed trend up to 17% and 15% difference on exposure metrics of nivolumab and relatlimab in patients with mild/moderate renal impairment, respectively, it is accepted that the information in the SmPC section 4.2 indicates that no dose adjustment is required in patients with mild or moderate renal impairment, and that no conclusions can be drawn for the severe renally impaired population, in line with the SmPC for Opdivo.

Hepatic impairment. The impact of severe hepatic impairment on the PK of relatlimab or nivolumab is unclear given the limited number of subjects were enrolled with severe impairment. In light of the

scarcity of data in the severe hepatic impairment population, it is accepted that the information in the SmPC section 4.2 indicates that no dose adjustment is required in patients with mild or moderate hepatic impairment, and that no conclusions can be drawn for the severe hepatically impaired population, in line with the SmPC for Opdivo.

Gender. Exposure to relatlimab and nivolumab was not affected to a clinically relevant extent by gender. For transparency reasons, the number of males/females (1056/657) included in the development programme for Opdualag is indicated in the SmPC section 5.2. The clinical relevance of gender for relatlimab showed a 19% lower CL in females compared to males, but no impact is expected in terms of response due to the flat exposure-response relationship.

Race. Exposure to relatlimab and nivolumab was not affected to a clinically relevant extent by race. For transparency reasons, the number of the various ethnic subpopulations (1655 White, 41 Asian, 167 African American) included in the development programme for Opdualag is indicated in the SmPC section 5.2.

Weight. Patient weight, as indicated in the popPK report, ranged from 51.9 to 111 kg. Due to the flat dosing, both for relatlimab and nivolumab, C_{avg} decreases with an increase in body weight and increases with a decrease in body weight. The model estimated the relatlimab Cavgd28 was ~ 49% higher in extremely low body weight (~40 kg) and ~ 41% lower in extremely high body weight subjects (100 kg). For nivolumab, the model estimated Cavgd28 is ~ 43% higher in extremely low body weight and ~ 31% lower in extremely high body weight subjects. However, the E-R analysis for PFS and OS is relatively flat. Further, the safety profile of the combination of nivolumab and relatlimab in subjects with low body weight (< 50 kg) was generally similar to the safety profile in subjects with a body weight ≥ 50 - < 106 kg, and no consistent trend was observed for higher frequency or severity of AEs with lower body weight. Therefore, no dose-modifications or special caution appears necessary in the low and high weight patient population (see also Discussion on clinical safety).

Age. Both for relatlimab and nivolumab, age was not considered a significant covariate in the popPK model.

Adolescents. With respect to relatlimab, no adolescent PK data were available. Therefore, the popPK simulations were performed with a revised version of the relatlimab popPK model, which incorporated the paediatric effects on CL and VC determined in the nivolumab popPK analysis (i.e., adolescent subjects had 24% lower CL0, 28% lower CLss, and 28% lower VC than corresponding parameters of adult subjects). Additional consideration in support of this strategy were that both nivolumab and relatlimab are IgG4 mAbs with similar mechanisms of distribution and non-specific elimination was provided based on other oncology MAbs displaying a comparable effect of age on CL and VC, i.e., ipilimumab, atezolizumab, and pembrolizumab. Ipilimumab and atezolizumab are not IgG4, but IgG1 antibodies, pembrolizumab is an IgG4 antibody. However, ipilimumab has a considerable shorter half-life than nivolumab. Further, atezolizumab binds to the tumour while ipilimumab, pembrolizumab, nivolumab and relatlimab bind to the T-cells. Therefore, although some examples have been provided, not all were considered relevant and the evidence for a generally decreased CL of oncology IgG4 MAbs in adolescent patients needed further consideration. A discussion was provided on the comparability of the covariate effects for body weight, albumin and disease for nivolumab and relatlimab. The effect of body weight at the 95th percentile on CL was 34% and on VC was 15% for relatlimab, and for nivolumab the effect was 23% on CL and 25%, respectively. Further, the effect of albumin (with increased CL at lower albumin) was 21% and 28%, for nivolumab and relatlimab respectively. In both cases, CL was higher in patients with ECOG PS >0, although not clinically relevant (<20%). Although these data indicate reasonable comparability of the covariate effects, it was considered that, e.g. due to the different degree of target mediated clearance for nivolumab and relatlimab, uncertainties still remained on the exact comparability of the effect on CL for nivolumab and relatlimab in adolescents.

With respect to the reason for the reduced clearance in adolescent patients, the applicant argued that the reduced clearance of nivolumab and other IgG1 and IgG4 oncology MAbs may be linked to the disease state in adolescent solid tumour subjects. Higher protein turnover rate due to cachexia and hypermetabolic state in cancer patients are expected, dependent on the severity of disease. This effect has been described in literature. The applicant clarified that the actual age of the patient included in Study CA224020 assumed to be 17 years of age was in fact 18. The reason for this deviation was that according to EU regulations, only the year of birth was available in the eCRF. This explanation is acceptable. PcVPC of this particular subject with the reported relatlimab and nivolumab PK model were provided where the applicant treated this subject as 17-year-old in the nivolumab PK model, which was interpreted as applying the reduced CL and Vc for the adolescent population. This was compared to the actual exposure, based on the adult dose. It was noted that in a number of timepoints, the actual exposure was below the predicted nivolumab exposure, while this was less so the case for the predicted relatlimab exposure. This lower actual exposure was explained for a great deal by the fact that the applied CL and Vc in the popPK model for a patient aged 17 years were assumed to be lower than in adults. A new pcVPC for this patient was further provided using the adult covariates (i.e. simulate the patient as 18 year old subject), indicating a higher predicted exposure, more closely in line with the actual exposure. Overall, no new actual nivolumab and relatlimab PK data for adolescent patients was provided, since the identified patient was actually 18 years old. Due to the rarity of melanoma in adolescents and the availability of alternative treatment options for such patients, it is unlikely that confirming PK data in adolescent melanoma patients can be obtained.

Possible scenarios for fixed or weight-based dosing in adolescents were compared, both under the condition that nivolumab or relatlimab clearance and apparent volume of distribution in adolescents is decreased or comparable to that in adults.

As a starting point, in situations of comparable pathophysiology in adolescent and adult patients, as is the case for melanoma, efficacy and safety data can be translated based on comparable exposure.

In this respect, two situations with flat dosing are possible:

In case of flat dosing and assuming a paediatric effect on clearance is present, somewhat increased Cavg1 and Cmax1 for relatlimab and nivolumab (<25%) and increased Cmin1 (~25-50%) is predicted in adolescents as compared to adults.

In case of flat dosing and assuming **no** paediatric effect on clearance is present, Cavg1 and Cmax1 are predicted to be similar in adolescents and adults both for relatlimab and nivolumab (<10%) and somewhat increased and similar Cmin1 (<27% and <15% for relatlimab and nivolumab, respectively).

In case of flat dosing and assuming no paediatric effect on clearance, in general, exposure parameters for relatlimab and nivolumab are therefore predicted to be close to those in adults, and therefore efficacy and safety can be assumed to be comparable based on comparable exposure. In case a paediatric effect is present, exposure parameters increase in adolescents as compared to adults. The effect of this increased exposure is considered most relevant for safety.

Likewise, two situations with weight-based dosing are possible:

In case of weight-based dosing and assuming a paediatric effect on clearance is present, geometric mean of relatlimab and nivolumab Cavg1, Cmin1 and Cmax1 in adolescents with weight-based dosing in body weight groups <70-80 kg were all lower than the same body weight group in adults with flat dosing, with differences increasing down to lower weight patients (with 47-84% (relatlimab) and 38-46% (nivolumab) lower exposure in adolescents in the 30-40 kg weight group).

In case of weight-based dosing and assuming **no** paediatric effect on clearance, geometric mean of relatlimab and nivolumab Cavg1, Cmin1 and Cmax1 in adolescents with weight-based in body weight

groups <70-80 kg were all lower than the same body weight group in adults with flat dosing, with differences increasing down to lower weight patients (with 55-90% (relatlimab) and 52-54% (nivolumab) lower exposure in adolescents in the 30-40 kg weight group). The effect of this decreased exposure a lower body ranges is considered most relevant for efficacy.

Since the pathophysiology of the adolescent and adult melanoma population is considered comparable, and comparable exposure between adolescents and adults has been sufficiently demonstrated for relatlimab and nivolumab applying the same flat 160/480 mg dose, this is considered sufficient to grant extension of the indication to include the adolescent population. In further support of this conclusion, the applicant discussed the exposure-efficacy and exposure-safety relationships in adolescents.

Potential consequences of differences in relatlimab and nivolumab exposure

Though both in case of flat dose and weight-based dosing, overall adolescent exposure was within the range of adult flat-dose exposures, in case of weight-based dosing a risk of underdosing and reduced efficacy in lower weight patients is likely to occur. This possibility is predicted by the outcome of the exposure-PFS and exposure-OR analyses developed in adults, indicating more comparable PFS and OR in adolescents and adults by flat dosing than following weight-based dosing, both in case of a paediatric effect on clearance or not. In this sense, flat dosing, yielding more comparable exposures between adolescents and adults, is preferred.

Moreover, based on the exposure-safety relationship, the increased exposure in case of flat dosing is predicted to yield a limited increase in safety issues (HR ~1.01 and ~1.10 in case of no paediatric effect or presence of a paediatric effect on clearance).

The disease in adolescents and adults is similar and the expected outcome of the treatment is also similar. Therefore, the exposure-efficacy and exposure-safety relationships in adults are considered valid for adolescents as well.

Of note, for nivolumab, PK data in adolescents is available, and therefore for nivolumab comparable exposure can be claimed based on actual data. In case of relatlimab, uncertainties exist whether the same effect on clearance and volume of distribution in adolescents as observed for nivolumab is also present. However, overall, based on the simulations provided, it is expected that differences in exposure that may arise due to the presence of absence of the paediatric effect on clearance and volume of distribution, are limited. The assumption that the increased exposure with the currently proposed dose in case of reduced clearance and volume of distribution in adolescents for a flat dose is not expected to bear clinical relevance, is further supported by limited safety findings in the 480/480 mg Q4W dose applied in part E of Study CA224020, in any case (long term) safety in adolescents will be followed post approval (see RMP).

By applying a flat dose, in case no paediatric effect on clearance and volume of distribution is present, exposure in adults and adolescents will be highly comparable, which indeed can be concluded from the simulation data provided. In the situation of comparable pathophysiology in adolescents and adults as is the case here, this would mean that efficacy and safety in adolescents and adults are expected to be comparable as well. Only in case for relatlimab and nivolumab indeed a 30% reduced clearance and volume of distribution in adolescents occurs, exposure in adolescents with the proposed flat dose will be somewhat higher than that in adults. However, based on exposure-safety analyses, the consequences for safety are expected to be limited.
In contrast, by applying a weight-based dose, adolescent patients with a lower weight are expected to have a lower exposure than adults to such degree (>40%), that an effect on efficacy may be consequential. Therefore, the proposal to apply the same flat dose for adolescents and adults is supported.

Overall, based on the provided simulated exposure in adolescent and adult patients, applying either a flat dose in adolescents and adults or a weight-based dose in adolescents and a flat dose in adults, taking into account either the presence or the absence of a reduced clearance and volume of distribution in adolescents, reasonably comparable predicted exposure to relatlimab and nivolumab is considered acceptable. Considering the comparable pathophysiology of adolescent and adult melanoma patients, this comparable predicted exposure is expected to translate into comparable efficacy and safety in both populations. Therefore, the proposal for a flat dose for relatlimab and nivolumab, being the same in adolescents and adults weighing 30 kg and higher, is supported. The posology in section 4.2 of the SmPC was modified to indicate a flat 160 mg/480 mg Q4W dose in adolescents and adults. This is considered acceptable, although it should be added that this dose was established for patients weighing at least 30 kg with a cross reference to section 5.2 (see SmPC comment section 4.2).

The applicant indicates that it will pursue efforts to include adolescent patients in ongoing melanoma studies with relatlimab/nivolumab. Although it is uncertain, due to the low prevalence of melanoma in adolescent patients, that indeed adolescent patients will be included, the efforts are acknowledged, and the applicant is invited to consider such adolescent patients in the evaluation of the current 160/480 mg Q4W dose advice for relatlimab/nivolumab in adolescent and adult melanoma patients (see RMP).

60 vs 30 minute infusion. From a PK perspective, relatlimab and nivolumab C_{min} and C_{avg} data obtained by using a 60 minutes administration period are considered relevant for the 30 minutes administration period as well. The proposed reduction of the infusion duration is in principle acceptable as a clinically relevant increase of immunogenicity and adverse events is considered unlikely given the limited differences in exposure based on popPK simulations. In addition, both nivolumab and relatlimab have a low immunogenic potential and a limited number of patients experienced hypersensitivity/infusion-related reactions (11/412 pooled data) at the recommended dose. There were no apparent associations between dose (maximum rela + nivo SAV dose up to 1440/480 mg Q4W) and infusion or hypersensitivity reactions in study CA224020. The predicted Cmax after 30 or 60 min infusion is comparable, which is explained by the slow distribution half-life from the systemic circulation, i.e., 42.5 and 32.7 h for relatlimab and nivolumab, respectively. Due to this slow distribution half-life, only a small portion of the administered dose will be cleared from the circulation between 30 and 60 minutes, explaining the comparable Cmax following 30 or 60 minutes infusion.

Exposure relevant for safety evaluation. The relatlimab and nivolumab exposure figures in section 5.2 of the SmPC were obtained from the popPK analysis. Due to their popPK nature, small differences are present between these data and the actual data in Study CA224047. The reported PK data are considered acceptable.

The lack of dedicated in vitro and in vivo DDI studies is acceptable.

Pharmacodynamics

The proof of concept for efficacy of the combination of relatlimab and nivolumab was shown through non-clinical *in vitro* and *in vivo* experiments. Relatlimab administration resulted in dose-dependent changes of peripheral LAG-3 receptor occupancy and sLAG-3 which supports target engagement. Treatment associated increases of IFNγ and IFNγ-inducible chemokines, as well as a trend of increase in proliferating and activated CD4+ and CD8+ central and effector memory T cell subset in peripheral blood on Day 8 after the first dose, support enhanced T-cell activation upon combination treatment. Enhanced T-cell activation was not shown with relatlimab monotherapy, and differences appeared increased compared to nivolumab monotherapy although these data were not available for all parameters.

Relatlimab monotherapy (up to 800 mg Q2W) and relatlimab/nivolumab up to 1440/480mg Q4W did not result in a clinically relevant QTc prolongation in patients with a wide variety of solid tumours. Overall numbers were small, however, relatlimab and nivolumab are highly specific mAbs and not expected to directly inhibit the function of hERG or other ion channels responsible for cardiac repolarisation.

Relationship between plasma concentration and effect.

Receptor-binding. With respect to the *exposure-peripheral receptor occupancy* (RO), LAG-3 RO was higher following a dose of relatlimab/nivolumab 480/480 mg Q4W as compared to 160/480 mg Q4W. The clinical relevance of this increased RO at higher dose is not completely clear, considering the flat exposure-PFS analysis, but at the same time the dose-dependent exposure-OR relationship. No difference in binding RO was apparent comparing the situation of simultaneous administration as FDC or as SAV sequentially.

Efficacy.

With respect to the *exposure-efficacy,* PFS, OS, and OR were significantly associated with relatlimab exposure, resulting in a longer PFS or OS and higher OR compared to nivolumab monotherapy. The efficacy for all the PFS and OS endpoints was similar across the range of relatlimab exposures (Cavgd28) produced by nivolumab/relatlimab 240/80 mg Q2W, 480/160 mg Q4W, and 480/480 mg Q4W suggesting a flat E-R for efficacy. This flat E-R was shown to be applicable both for 1L and prior-IO melanoma patients. Some uncertainty on the E-R comes from the exposure-OR analyses, where OR is predicted to be higher with higher doses of relatlimab (480 mg vs. 160 mg and 80 mg Q4W). The landmark analysis of OS from month 6 by response status in the previously assessed ipilimumab + nivolumab registrational study (CA209067) suggested a survival benefit for those patients who achieve a response (CR or PR), potentially indicating importance of the OR, which appears to increase at higher relatlimab dose. However, some uncertainty remains on the relationship between ORR and OS (see discussion on clinical efficacy). Preliminary data from Part E of the dose-finding study indicate that applying a 480/480 mg relatlimab/nivolumab posology numerically increased ORR but was also less tolerable compared to 160/480 mg relatlimab/nivolumab (see clinical efficacy), supporting the currently recommended dose.

No significant relationship was observed between relatlimab exposure and HR of PFS, OS and OR, since no differences were observed across the different dosing regimens. Initially, only Cavgd28 was used in these analyses. However, based on the high correlation between relatlimab Cavgd28 and Cmind28 (0.97) and between relatlimab Cavgd28 and Cmax1 (0.95), the E-R relationship with Cavgd28 is expected to be similar with alternative exposures such as Cmind28 or Cmax1. Indeed, based on the provided E-R analyses using the alternative exposure measures Cmind28, the results of E-R relationship of the efficacy end points (OS, PFS, and OR) were similar to those for Cavgd28 exposure, i.e., relatively flat. This was true both in the 1L and prior IO melanoma patient population. The provided additional E-R analyses do not point at a different E-R relationship between exposure and response than previously determined for Cavgd28. Further, the E-R relationship for PFS and OS is considered relatively flat both in the 1L and prior IO melanoma patient population.

Safety.

A higher incidence of Gr2 and Gr3 AEs was observed in patients receiving relatlimab+nivolumab treatment vs. nivolumab alone. However, no dose dependency effect was detected across the different schedules, suggesting that the higher incidence of AEs is basically related to the presence of relatlimab.

2.6.4. Conclusions on clinical pharmacology

Overall, PK and PD for relatlimab and nivolumab when given in combination has been investigated to a reasonable extent. Based on the provided simulated exposure to relatlimab and nivolumab in adolescent and adult patients, applying a flat dose and taking into account either the presence or the absence of a reduced clearance in adolescents, sufficiently comparable exposure between adolescent and adults with body weight ≥30 kg is demonstrated. Considering the comparable pathophysiology of melanoma in adolescents and adults, the proposal for a flat dose for relatlimab and nivolumab, being the same in adolescents and adults, is therefore supported. SmPC section 4.2 clarifies that the dose was established for patients weighing at least 30 kg with a cross reference to section 5.2.

2.6.5. Clinical efficacy

The study considered to be key to the proposed indication is study CA224047, a phase 2/3 randomised, double-blind study comparing relatlimab in combination with nivolumab to nivolumab alone. Supportive evidence is derived from study CA224020, which is a Phase 1/2a open-label study of relatlimab alone and in combination with nivolumab. Study details are summarised in Table *2*.

2.6.5.1. Dose response study

Study CA224020 is a large, ongoing Phase 1/2a, open-label study to assess the safety, tolerability, and efficacy of multiple dosing regimens of relatlimab monotherapy, relatlimab SAV (BMS-986016) + OPDIVO (BMS-936558; nivolumab) (hereafter referred to as rela SAV + nivo), and rela+nivo FDC (BMS-986213) in subjects with selected advanced or recurrent malignancies, including melanoma. As of the 25-Feb-2021 database lock (DBL), 1404 subjects have been treated with either relatlimab monotherapy (n = 25) or in combination with nivolumab (n = 1379) across all study parts. Except for select cohorts in Part E, enrolment to the remaining parts has been completed.

CA224020 consists of 5 parts (Figure 5). Supportive efficacy data includes results from CA224020 Part A, melanoma cohorts in Part C, and Part D. Part E is still enrolling patients and data are not present. Sparse PK of relatlimab and nivolumab from part E along with clinical efficacy (PFS and ORR) were used for exposure-response for efficacy analysis reported in the clinical pharmacology part of this report. Eligible patients were treated with either relatlimab monotherapy (Parts A and A1) or in combination with nivolumab (Part B, Part C, Part D, and Part E). In each cycle, treatment was administered on Days 1, 15, 29, and 43. In Parts B, C and D, Q4W dosing, relatlimab and nivolumab were administered on Days 1 and 29 of each treatment cycle. Subjects in Part B and C received sequential infusion of nivolumab and relatlimab.

The study population included males and females ≥ 18 years. For Part C (melanoma only), Part D, and Part E, males and females ≥ 12 to 17 years were also included if local regulations and/or institutional policies allowed for participants < 18 years of age. All subjects must have had histologic or cytologic confirmation of advanced, nonresectable, or metastatic solid tumours and measurable disease as defined by response criteria evaluation in solid tumours (RECIST) v1.1. Unless otherwise stated, patients must have ECOG PS 0 or 1. Part D1 melanoma subjects with prior IO were more strictly defined than those in part C, whereas Part D2 used expanded eligibility criteria; e.g. multiple prior lines of anti-PD-1 containing regimens allowed, and ECOG PS 0-2. The main objectives of Part D1 were to assess ORR by LAG-3 expression and to provide support for the tolerability of the FDC. Data from the expansion cohorts Part C 1L melanoma patients and Part D1 IO-pretreated melanoma patients are considered of most relevance for the current application.

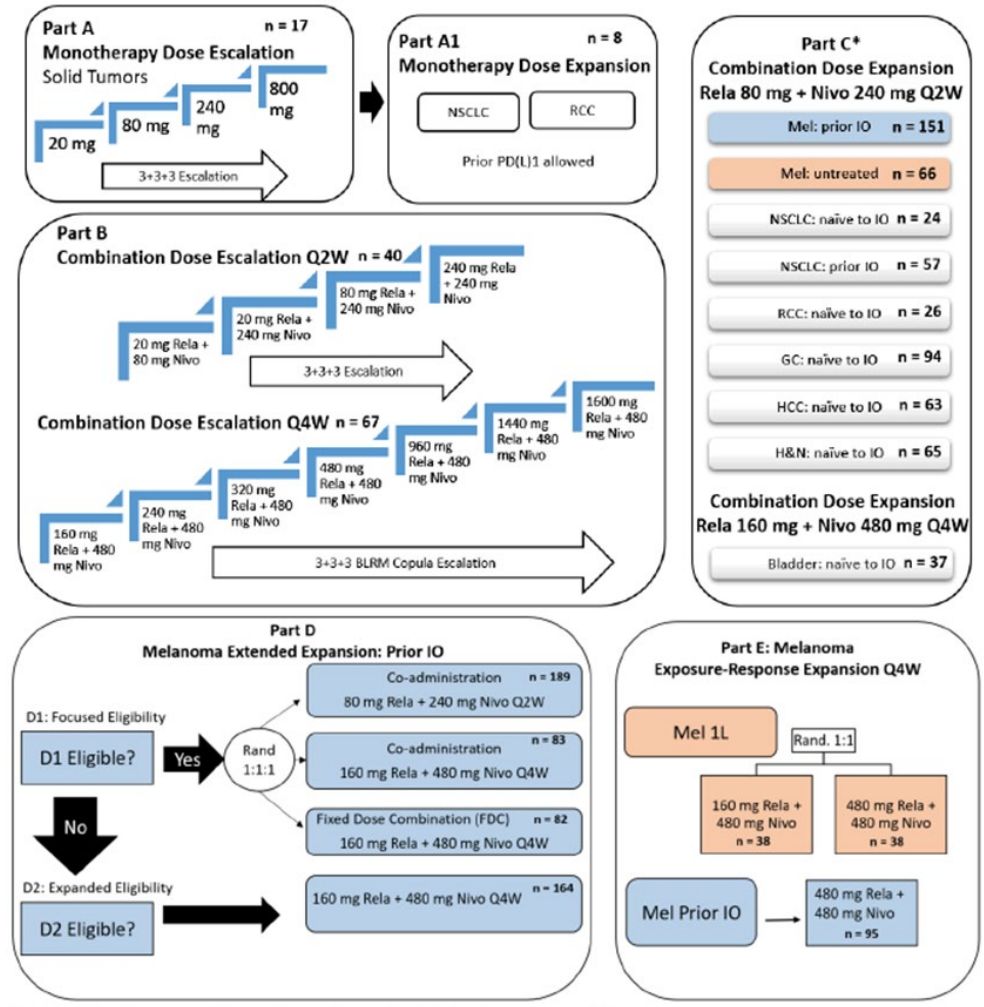
Efficacy assessments were based on tumour assessments using computed tomography (CT) and/or magnetic resonance imaging (MRI), as appropriate, performed at baseline and every 8 weeks during the treatment period. Tumour response was evaluated locally per RECIST v1.1. Subjects continued study therapy until the first occurrence of progressive disease, clinical deterioration, and/or meeting other criteria for discontinuation. Safety assessment included physical examinations, vital sign measurements, 12-lead ECG, and clinical laboratory evaluations. Samples were collected for PK, immunogenicity, PD, and biomarker analyses.

Results

Part A – Relatlimab monotherapy: Forty percent of subjects received prior IO-therapy. No clinically relevant antitumour activity (CR or PR) of relatlimab monotherapy was observed across a dose range of 20 to 800 mg administered Q2W. One out of 8 subjects treated with relatlimab 800 mg Q2W in the expansion cohort Part A1 achieved an investigator-assessed best overall response (BOR) of PR, which was maintained for 2.1 months.

Part B – Rela+nivo dose escalation: About 64% of subjects received prior IO-therapy. Partial responses were variable across dose groups and varied from 0%-25%, no consistent pattern was observed. No CR was observed.

Figure 5. Schematic study design for study CA224020



*Relatlimab administered in combination with nivolumab as sequential infusions.
Note: Part E data are immature and will not be presented in this SCE.

Part C – 1L melanoma: A total of 66 subjects with previously untreated unresectable or metastatic melanoma were treated with sequential administrations of rela SAV 80 mg + nivo 240 mg Q2W in the 1L-Melanoma Expansion Cohort. The median duration of rela+nivo therapy was 34.5 weeks (range: 2-109). The median age was 64.5 (range: 24-87 years). At study entry, 61 (92.4%) subjects had Stage IV disease. Baseline lactate dehydrogenase (LDH) levels were > upper limit of normal (ULN) in 24 (36.4%) subjects and 18 (27.3%) subjects were BRAF mutation positive. With a minimum follow-up time of 31.9 months, BICR confirmed ORR was 47.0% (95% confidence interval (CI): 34.6, 59.7) with CRs reported in 11 (16.7%) subjects and PRs in 20 (30.3%) subjects. The confirmed disease control rate (DCR: CR+PR+stable disease (SD) ≥ 12w) was 59.1%. Median durability of response (DOR) was not reached. Median PFS per BIR was 12.7 months (95% CI: 3.71, 18.17) and median OS was 34.6 months (95% CI: 18.6, NR).

Fifty-five subjects had a quantifiable LAG-3 immunohistochemistry (IHC) result in the 1L melanoma cohort. ORR per BICR was 38.5% (95% CI: 20.2, 59.4) and 58.6% (95% CI: 38.9, 76.5) for subjects with LAG-3 < 1% (n=26) and subjects with LAG-3 ≥1% (n=29), respectively.

Part D1 – prior IO melanoma: Subjects in Part D1 were randomised 1:1:1 to treatment with rela SAV 80 mg + nivo 240 mg Q2W coadministration, rela SAV 160 mg + nivo 480 mg Q4W coadministration, and rela+nivo FDC 160/480 mg Q4W. At study entry, median age was 63-65 years and 89.2%-96.3%

had stage IV disease. Baseline LDH levels were > ULN in 45.5%-53.0% of subjects and 14.6%-27.7% were BRAF mutation positive. Minimum follow-up was 28.0, 19.7 and 19.4 months for Part D1 Arms 1, 2, and 3, respectively. ORR per BICR was 11.8% (95% CI: 7.6, 17.4), 6.0% (95% CI: 2.0, 13.5), and 18.3% (95% CI: 10.6 28.4), for 80/240 mg Q2W, 160/480mg Q4W, and 160/480mg Q4w FDC, respectively. About 3.6%-4.9% of subjects had a CR. DCR was 37.1% (95% CI: 30.1, 44.5), 32.5% (95% CI: 226, 43.7), and 48.8% (95% CI: 37.6, 60.1), respectively. Median DOR was not reached except for the 160/480mg Q4W FDC and was 18.4 months. Median PFS per BIR was between 2-3.6 months and median OS was between 13.1-16.7 months across treatment arms.

Tumour response in the subgroup of LAG-3 expressing (≥ 1%) subjects (n = 109) was consistent with that of the entire cohort; ORR was 11.9% (95% CI: 6.5, 19.5). For subjects with LAG-3 <1%, ORR was 8.9% (95% CI: 2.5, 21.1; n=45).

Part E – 1L melanoma: Subjects in Part E were randomised 1:1 to rela+nivo 160 mg/480 mg Q4W or rela+nivo 480 mg/480 mg Q4W. A total of 77 patients were enrolled in each treatment arm and baseline characteristics were generally balanced between arms. The most common reason for drug discontinuation was disease progression in both treatment arms (35.1% vs 26.0%); the rate of discontinuation due to study drug toxicity was numerically lower in the 480/160 Q4W arm versus the 480/480 Q4W arm (13.0% and 20.8%). As of DBL, minimum follow-up was 4.4 months and efficacy data are not fully mature, yet. The median (range) follow-up was 10.1 (2.9, 28.7) months in the rela+nivo 160/480 mg Q4W arm and 10.0 (1.2, 27.5) months in the 480/480 mg Q4W arm. BICR-assessed ORR was 44.2% (95% CI: 32.8, 55.9) and 58.4% (95% CI: 46.6, 69.6) in the 480/160 mg Q4W and 480/480 mg Q4W arms, respectively. The median DOR was not reached in either arm (range: 1.6+, 26.0+ and 1.3+, 24.0+). Median PFS per BICR was not reached in the 480/160 mg Q4W arm (95% CI: 5.59, NA) and 17.8 months in the 480/480 mg Q4W arm (95% CI: 11.10, NA).

Safety

No maximum tolerated dose (MTD) was identified for relatlimab monotherapy (20-800 mg) or relatlimab + nivolumab (20/80 mg Q2W to 1440/480 mg Q4W).

To support the FDC compared to co-administration, the safety profile of the different treatment arms in Part D1 were compared overall and by the incidence of AEs in the Broad Scope Medical Dictionary for Regulatory Activities (MedDRA) Anaphylactic Reaction Standardized MedDRA queries (SMQ) occurring within 2 days after dosing. Any grade AEs were reported in the majority of subjects (*Table 10*). Grade 3-4 events and serious AEs (SAEs) rates were similar between the rela+nivo 80/240 mg Q2W and 160/480 mg Q4W coadministration. SAE rates were slightly lower in the FDC compared to the SAV coadministration arm for rela+nivo 160/480 mg Q4W. The incidence rates of drug-related AEs were higher in the FDC arm as compared to the rela+nivo coadministration, mostly attributable to low grade (Grade1-2) AEs and in the category of endocrine disorders (hypothyroidism). Endocrine drug-related select AEs were observed in 13.4%, 3.6%, and 5.8% of subjects for the 160/480mg Q4W FDC, 160/480mg Q4W coadministration, and 80/240mg Q2W, respectively. The incidence of AEs in the anaphylactic reaction MedDRA SMQ Broad Scope (all causality) were comparable between the rela+nivo 80/240 mg Q2W coadministration (18.5%) and the rela+nivo 160/480 mg Q4W FDC (17.1%), but numerically higher compared to rela+nivo 160/480 mg Q4W coadministration (10.8%).

Table 10. Summary of safety – rela+nivo subjects treated with melanoma that progressed on anti-PD-1 therapy in study CA224020 Part D1

	No. of Subjects (%)					
	80/240 mg Q2W Coadmin N = 189		160/480 mg Q4W Coadmin N = 83		160/480 mg Q4W FDC N = 82	
Deaths	133 (70.4)		54 (65.1)		52 (63.4)	
Primary Reason for Death						
Disease	124 (65.6)		51 (61.4)		52 (63.4)	
Status indicated death	1 (0.5)[a]		0		0	
Unknown	5 (2.6)		1 (1.2)		1 (1.2)	
Other[b]	3 (1.6)		2 (2.4)		2 (2.4)	
	Adverse Event Grade					
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality AEs	183 (96.8)	82 (43.4)	80 (96.4)	35 (42.2)	80 (97.6)	29 (35.4)
Drug-related AEs	125 (66.1)	29 (15.3)	55 (66.3)	13 (15.7)	59 (72.0)	11 (13.4)
All-causality SAEs	76 (40.2)	50 (26.5)	33 (39.8)	25 (30.1)	22 (26.8)	18 (22.0)
Drug-related SAEs	16 (8.5)	10 (5.3)	7 (8.4)	7 (8.4)	4 (4.9)	4 (4.9)
All-causality AEs leading to DC	19 (10.1)	12 (6.3)	13 (15.7)	10 (12.0)	9 (11.0)	7 (8.5)
Drug-related AEs leading to DC	7 (3.7)	4 (2.1)	7 (8.4)	4 (4.8)	4 (4.9)	3 (3.7)

[a] A subject experienced progressive disease following second dose of study treatment. At the time of this DBL, Karnofsky Performance Status during screening was reported as 0 (dead). No death CRF was completed, resulting in participant disposition categorized as "Status Indicated Death".

[b] The verbatim terms reported for the 'other' reasons for death were:

- **Rela+Nivo 80/240 mg Q2W Coadmin:** massive hemoptysis (COVID test negative), septic shock, and intracerebral hematoma
- **Rela+Nivo 160/480 mg Q4W Coadmin:** multiple cerebral infarctions and intraparenchymal intracranial hemorrhage
- **Rela+Nivo 160/480 mg Q4W FDC:** respiratory failure, and COVID-19 infection

MedDRA version 23.1; CTC version 4.0. All events are within 30 days of the last dose of study drug.

Part E – 1L melanoma: The number of deaths was similar in both treatment arms (18-19%), with the majority due to disease progression (about 15%). One death in the 480/480 arm was considered related to study drug by the investigator (Grade 5 pneumopathy). All causality AEs (93-100%) and SAEs (52-54%) were reported in similar proportions of patients across the 2 arms, but all causality AEs of any grade leading to study drug discontinuation were more frequent in the 480/480 arm (32.5% of patients) vs the 480/160 arm (15.6%). There were numerically higher frequencies of Grade 3-4 drug-related AEs (29.9% vs. 26.0%), drug-related Grade 3-4 SAEs (19.5% vs. 15.6%), and drug-related AEs leading to discontinuation (18.2% vs 13.0%) in the 480/480 arm relative to the 160/480 arm.

2.6.5.2. Main study

Study CA224047: A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with Nivolumab versus Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma.

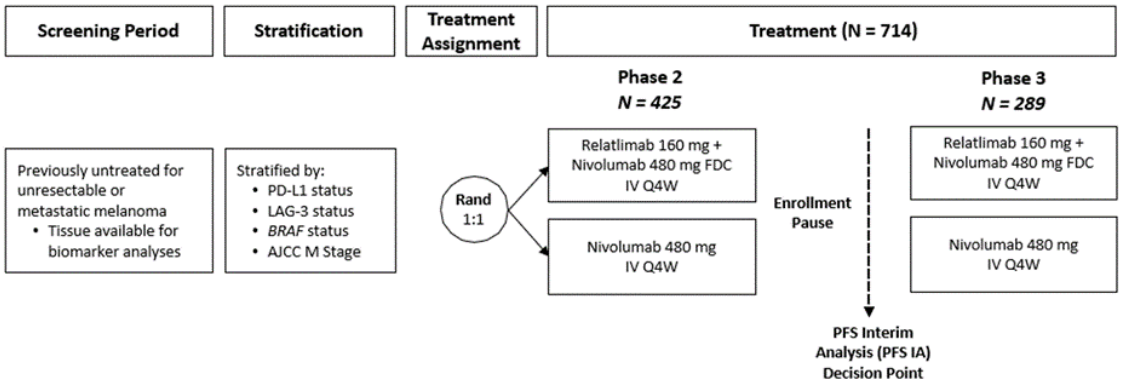
Methods

CA224047 is a seamless Phase 2/3, randomised, double-blind study of relatlimab + nivolumab (FDC at a 1:3 ratio; BMS-986213) vs nivolumab monotherapy in subjects with previously untreated metastatic or unresectable melanoma.

The study design is shown in Figure 6. Adults and adolescents ≥ 12 years of age were eligible for enrolment in Study CA224047. Subjects were randomised 1:1 to treatment with relatlimab + nivolumab 160/480 mg IV Q4W FDC (BMS-986213) or nivolumab 480 mg IV Q4W and study treatment was continued until disease progression, treatment discontinuation, withdrawal of consent, or end of study. Randomisation was stratified by tumour PD-L1 expression (≥ 1% vs < 1%), LAG-3 expression (≥ 1% vs < 1%), BRAF mutation (V600 mutation positive vs V600 wild-type), and AJCCv8 M stage M0/M1any[0] vs M1any[1]). On-study tumour assessments began 12 weeks from randomisation 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. Treatment beyond initial investigator-assessed RECIST v1.1 defined progression was permitted if the subject had investigator-assessed clinical benefit and was tolerating study treatment.

Figure 6 Schematic study design for study CA224047



- **Study Participants**

Key inclusion criteria

- Age ≥ 12 years at the time of informed consent.
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1/Lansky Performance Score ≥ 80% for minors (ages 12-17) only.
- Histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the AJCC staging system (8th edition).
- No prior systemic anticancer therapy for unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant melanoma therapies were permitted if all related adverse events have either returned to baseline or stabilised: Anti-PD-1 or anti-CTLA-4 therapy with at least 6 months between the last dose and date of recurrence; Interferon therapy with the last dose at least 6 weeks prior to randomisation; BRAF- or MEK-inhibitor-containing regimens with at least 6 months between the last dose and date of recurrence.
- Participants must have measurable disease by CT or MRI per RECIST v1.1 criteria.
- Tumour tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomised, a participant must be classified as PD-L1 positive or PD-L1 negative, as well as LAG-3 positive or LAG-3 negative. Participants with indeterminate or unevaluable PD-L1 or LAG-3 status results will not be permitted to randomize to a treatment arm. If an insufficient amount of tumour tissue from an unresectable or metastatic site is available prior to the start of the screening phase, participants must consent to allow the acquisition of additional tumour tissue during the screening period for performance of biomarker analyses.
- Participants must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the screening period.
- Prior radiotherapy must have completed at least 2 weeks prior to study treatment administration.

Key exclusion criteria

- Active brain metastases or leptomeningeal metastases. Participants with brain metastases were eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study treatment administration.
- Ocular melanoma.

- Subjects with active, known, or suspected autoimmune disease. Subjects with type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, conditions not expected to recur in the absence of an external trigger were permitted to enrol.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent were permitted in the absence of active autoimmune disease.
- Prior treatment with an anti-PD-1 (except adjuvant or neoadjuvant therapy for melanoma), anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody (except adjuvant or neoadjuvant therapy for melanoma), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
- Subjects with a history of myocarditis.
- Troponin T (TnT) or I (TnI) > 2x institutional ULN. Subjects with TnT or TnI levels between > 1 to 2x ULN were permitted if repeat levels within 24 hours are ≤ 1x ULN. If TnT or TnI levels are > 1 to 2x ULN within 24 hours, the subject may undergo a cardiac evaluation and be considered for treatment. If TnT or TnI repeat levels beyond 24 hours are < 2x ULN, the subject may undergo a cardiac evaluation and be considered for treatment.
- Inadequate bone marrow function, defined as white blood cells <2000/ml, absolute neutrophil count <1500/mL, platelet count <100 × 10^3/mL, haemoglobin level <9.0 g/dL.
- Inadequate renal function (serum creatinine >1.5xULN or creatinine clearance <40 mL/min using the Cockcroft-Gault equation).
- Inadequate hepatic function, defined as the following:
    - Total bilirubin > 1.5x ULN (except participants with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN)
    - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 3.0x ULN

- **Treatments**

Subjects either received relatlimab + nivolumab 160/480 mg IV Q4W FDC (BMS-986213) or nivolumab 480 mg IV Q4W administered as ~60-minute IV infusions. For adolescent subjects < 40 kg, dosing was planned to be weight-based. However, no adolescents were enrolled. No dose reductions or dose escalations were permitted for both treatment arms. Dose delay criteria were defined and applied for all drug-related AEs according to protocol. Besides the medications already mentioned in the in- and exclusion criteria, any concurrent anti-neoplastic was prohibited. Also, any live / attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days after last dose were prohibited, inactivated vaccines were permitted. Immunosuppressive agents and immunosuppressive doses of systemic corticosteroids were allowed to treat a drug-related AE.

- **Objectives**

Primary objective

- To compare PFS of rela+nivo FDC (BMS 986213) to nivolumab monotherapy in subjects with previously untreated, unresectable, or metastatic melanoma.

Secondary objectives

- To compare OS of rela+nivo FDC (BMS 986213) to nivolumab monotherapy in participants with previously untreated, unresectable or metastatic melanoma.
- To compare ORR of rela+nivo FDC (BMS 986213) to nivolumab monotherapy in participants with unresectable or metastatic melanoma.

Tertiary/exploratory objectives

- To evaluate duration of and time to objective response (DOR and TTR).
- To evaluate PFS, ORR, DOR, and OS of rela+nivo FDC (BMS 986213) to nivolumab in subgroups based on combinations of LAG-3 expression (≥1% vs < 1%) and PD-L1 status (≥1% vs < 1%).
- To evaluate PFS, PFS2, ORR, and DOR of rela+nivo FDC (BMS 986213) and nivolumab per investigator
- To evaluate treatment-free interval (TFI) and treatment-free survival (TFS)

Other exploratory objectives included pharmacokinetics, immunogenicity, potential association between biomarkers (e.g., PD-L1 and LAG-3 and peripheral biomarkers) expression and efficacy endpoints, exposure-response relationships, change in health status (EuroQoL EQ-5D), change in cancer-related symptoms and quality of life (Functional assessment of cancer therapy - melanoma (FACT-M) score), impact of symptomatic AEs (FACIT GP5 item), and impact on work/activity (Work Productivity and Activity Impairment: General Health (WPAI:GH)).

Safety:

- To assess the overall safety and tolerability of rela+nivo FDC (BMS 986213) and of nivolumab monotherapy.

- **Outcomes/endpoints**

Primary endpoint

- PFS time was assessed by 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.

Secondary endpoints

- OS was defined as the time between the date of randomisation and the date of death due to any cause.
- 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.

PD-L1 results

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. For stratification during randomisation, subjects were classified as PD-L1 positive ≥ 1% versus PD-L1 negative <1%. 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 results

LAG-3 expression was determined using an analytically validated 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. For stratification during randomisation, subjects were classified LAG-3 negative: <1% LAG-3 positive cells, or LAG-3 Positive: ≥1% LAG-3 positive 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.

- **Sample size**

The sample size for the study was based on a primary endpoint of PFS using BICR for either a Phase 2 or a Phase 3 study. The overall alpha for the Phase 3 study was 0.05 (two-sided). As the PFS IA met the pre-specified HR of ≤ 0.8, the study transitioned seamlessly to Phase 3 and therefore the sample size justification for Phase 3 is outlined here.

The sample size was calculated in order to compare PFS among subjects randomised to receive rela+nivo FDC (BMS-986213) vs nivolumab monotherapy. The number of events required was simulated based on results from Study CA209067 with a median PFS of 6.9 months for the nivolumab monotherapy arm and 11.8 months for the rela+nivo FDC (BMS-986213) arm. The cure rates were assumed to be 30% in the nivolumab monotherapy arm and 40% in the rela+nivo FDC (BMS-986213) arm. It was estimated that the study required at least 365 PFS events to ensure approximately 85% power to detect a HR of 0.73 with an overall type I error of 0.05. Approximately 700 subjects were to be randomised to the two treatment arms in a 1:1 ratio. The final PFS analysis was planned to occur when 365 participants have had a PFS event.

The sample size was also calculated in order to compare OS among participants randomised to receive BMS-986213 versus nivolumab. The number of OS events (deaths) required was based on results from study CA209067, with a median OS of 36.9 months for nivolumab monotherapy and 49.2 months for nivolumab with relatlimab, resulting in an effective hazard ratio of approximately 0.75. With 300 deaths the power will be approximately 69% with a type I error rate of 0.05.

- **Randomisation and Blinding (masking)**

All participants were centrally randomised using interactive response technology (IRT). Subjects were randomised in a 1:1 fashion into two parallel treatment groups: rela+niv FDC (BMS-986213) IV Q4W and nivolumab IV Q4W. Stratification factors at randomisation were tumour PD-L1 expression (≥ 1% vs < 1%), tumour LAG 3 expression (≥ 1% vs < 1%), BRAF mutation (V600 mutation positive vs V600 wild-type), and AJCCv8 M stage (M0/M1any[0] vs M1any[1]). M1any is defined as all M1 with elevated LDH only. The randomisation procedures were carried out via permuted blocks within each stratum, defined by combination of LAG-3 status (positive or negative), PD-L1 status (positive or negative), BRAF V600 mutational status (positive or wild type), and M Stage (M0/M1any[0] or M1any[1]).

BMS, subjects, investigators, and site staff were blinded (study remained double blinded) to the study therapy administered and randomisation through the DBL. Only the independent data monitoring committee (DMC) reviewed the PFS IA and OS IA1 results, an independent third-party prepared the analyses for the DMC.

- **Statistical methods**

The intention to treat (ITT) population, comprising of all randomised patients was to be used for the primary analysis and the secondary endpoints.

A two-sided log-rank test stratified by LAG-3 expression (≥ 1% vs < 1%), (PD-L1 status (≥ 1% vs < 1%), BRAF status, and AJCC (8th edition) M Stage in randomised participants to compare the PFS of relatlimab + nivolumab arm (BMS-986213) and the nivolumab alone arm. In the event of small strata, it was pre-planned that PD-L1 would be removed from the analysis as a stratification factor. This was the case for the PFS analysis. Hazard ratios (HRs) and corresponding 2-sided 95% CI were to be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

Two definitions were pre-specified for the analysis of PFS. These differed by how subsequent therapy before progression was accounted for in the analysis. Table 11 presents the censoring scheme for the

primary definition. For the secondary definition, patients were followed-up for progression regardless of whether they received subsequent therapy before progression or not.

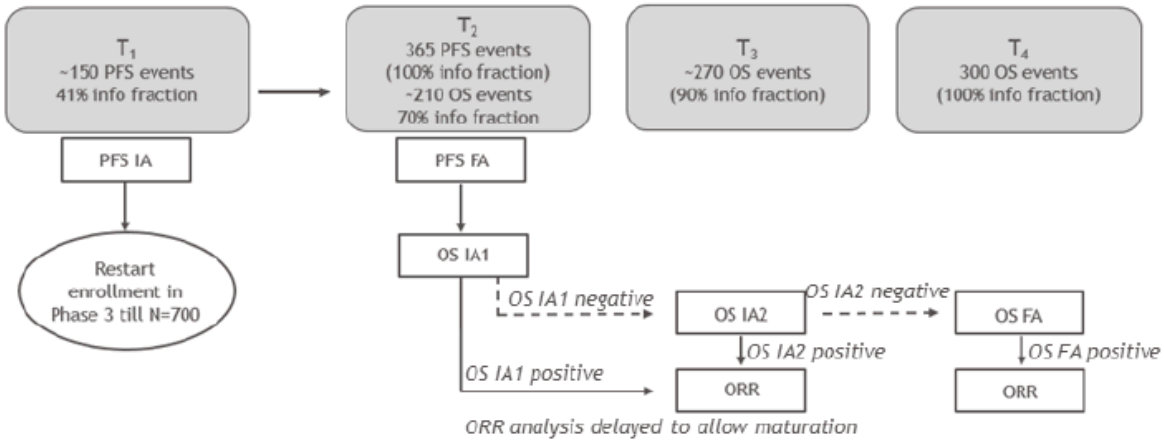
Table 11. Censoring scheme used in primary definition for PFS

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

* Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered. Note: subjects with measurable disease per Investigator but no measureable disease per BICR will be included in the analysis.

The overall alpha for the Phase 3 study is 0.05 (two-sided). Following the seamless phase 2/3 design, an interim PFS futility analysis was performed when approximately 150 PFS events had been observed in the Phase 2 cohort. If the pre-specified HR of ≤ 0.8 was met, then the study would continue to recruit into the Phase 3 stage (T2 onwards). The two secondary endpoints, OS and ORR were to be tested hierarchically following the scheme provided in Figure 7.

Figure 7. Phase 3 hierarchical procedure with group sequential testing in all randomised subjects Study CA224047



Results

- **Participant flow**

At the time of the clinical study report (CSR) data cut-off (DCO) (9 March 2021), 1281 patients were screened, and 714 subjects were randomised in the study; 355 subjects to rela+nivo FDC (BMS-986213) and 359 subjects to nivolumab. Study disposition is shown in Table 12. Reasons for no longer meeting study criteria did not show any single predominant reason and included unevaluable PD-L1, LAG-3, and/or BRAF status, worsening of ECOG performance status (PS), and presence of exclusionary brain metastases.

Overall, the most common reasons for study treatment discontinuation were progressive disease (36.3% vs 46.0% for BMS-986213 and nivolumab, respectively) and AEs (17.7% and 8.9% for rela+nivo FDC and nivolumab, respectively). At the time of DCO, 464 (65.0%) of subjects were ongoing on study treatment.

Table 12 Subject disposition – All enrolled, randomised and treated subjects Study CA224047

Status (%)	BMS-986213	Nivolumab	Total
ENROLLED			1281 (100.0)
RANDOMIZED			714 (55.7)
NOT RANDOMIZED			567 (44.3)
REASON FOR NOT RANDOMIZED			
ADVERSE EVENT			6 (0.5)
SUBJECT WITHDREW CONSENT			41 (3.2)
DEATH			12 (0.9)
LOST TO FOLLOW-UP			0
POOR/NON-COMPLIANCE			2 (0.2)
PREGNANCY			0
SUBJECT NO LONGER MEETS STUDY CRITERIA			465 (36.3)
ADMINISTRATIVE REASONS BY SPONSOR			6 (0.5)
OTHER			35 (2.7)
NOT REPORTED			0
TREATED	355 (100.0)	359 (100.0)	714 (100.0)
ONGOING TREATMENT	117 (33.0)	126 (35.1)	243 (34.0)
COMPLETED TREATMENT	1 (0.3)	0	1 (0.1)
DISCONTINUED TREATMENT	237 (66.8)	233 (64.9)	470 (65.8)
REASON FOR DISCONTINUATION OF TREATMENT			
DISEASE PROGRESSION	129 (36.3)	165 (46.0)	294 (41.2)
STUDY DRUG TOXICITY	63 (17.7)	32 (8.9)	95 (13.3)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	19 (5.4)	12 (3.3)	31 (4.3)
ADVERSE EVENT UNRELATED TO STUDY DRUG	12 (3.4)	14 (3.9)	26 (3.6)
OTHER	7 (2.0)	4 (1.1)	11 (1.5)
DEATH	2 (0.6)	3 (0.8)	5 (0.7)
MAXIMUM CLINICAL BENEFIT	2 (0.6)	1 (0.3)	3 (0.4)
SUBJECT WITHDREW CONSENT	1 (0.3)	2 (0.6)	3 (0.4)
LACK OF EFFICACY	1 (0.3)	0	1 (0.1)
POOR/NON COMPLIANCE	1 (0.3)	0	1 (0.1)
ADMINISTRATIVE REASONS BY SPONSOR	0	0	0
ADVERSE EVENT	0	0	0
COMPLETED TREATMENT AS PER PROTOCOL	0	0	0
DISEASE RECURRENCE	0	0	0
LOST TO FOLLOW-UP	0	0	0
NOT COMPLETED	0	0	0
PREGNANCY	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	0
ONGOING STUDY	237 (66.8)	227 (63.2)	464 (65.0)
DISCONTINUED STUDY	118 (33.2)	132 (36.8)	250 (35.0)
REASON FOR DISCONTINUATION OF STUDY			
DEATH	107 (30.1)	118 (32.9)	225 (31.5)
LOST TO FOLLOW-UP	5 (1.4)	5 (1.4)	10 (1.4)
SUBJECT WITHDREW CONSENT	4 (1.1)	9 (2.5)	13 (1.8)
OTHER	1 (0.3)	0	1 (0.1)
NOT REPORTED	1 (0.3)	0	1 (0.1)

Note: "Other" reasons for discontinuation of treatment include complete metabolic response (1), risks outweighed benefits (2), investigator and subject wishes (1), subject had more than 10 weeks without TX (1), subject was under immunosuppressing treatment (2), AE of jaundice with drug withdrawal (1), physician decision due to multiple AEs and CR (1), subject agreed to follow up by phone calls (1), and maximum clinical benefit (1).

- **Recruitment**

The first subject was enrolled in April 2018 and the first subject was randomised in May 2018. The last subject was randomised in Dec 2020. No subjects were enrolled between Feb 2019 and Aug 2019. Enrolment was paused to allow for sufficient follow-up (minimum 12 weeks) to perform the interim analysis of PFS (PFS IA). On 26-Aug-2019, the study proceeded to Phase 3 based on the DMC

recommendation after the PFS IA, concluding that the pre-specified PFS HR threshold of ≤ 0.8 was met, and enrolment started again in September 2019. A total of 425 subjects were initially randomised within the Phase 2 portion of the study and then additional 289 patients were randomised in the phase 3 portion: up to a total of 714.

Overall, the median duration of follow-up (defined as randomisation to last known alive date) was 13.21 months (range: 0-33.1). The median duration of therapy was 5.55 months (range: 0.0, 31.5) and 4.86 months (range: 0.0, 32.2), respectively.

- **Conduct of the study**

The original protocol for this study was dated 18-Dec-2017. As of the 09-Mar-2021 DBL, there were a total of 3 global revisions, 3 country-specific amendments (UK, Norway and France), and 6 administrative letters. Key study level changes to Study CA224047 after the original protocol are provided below (Table 13).

Table 13. Summary of key global changes to protocol CA224047

Document Date	Summary of Key Changes	Number of Subjects Randomized at Time of Protocol Revision
Revised Protocol 01 15-Aug-2018	Changed Phase 2 primary objective from ORR to PFS; updated interim analysis to include all subjects from Phase 2; clarified procedures for interim analysis and results; updated timing of procedures throughout for clarity; updated PK analyses for current preferred methods; updated IO algorithms for current methods; added myocarditis IO algorithm.	36
Revised Protocol 02 22-Feb-2019	Added PFS2 as an exploratory objective; revised the order of the Phase 3 secondary endpoints hierarchical testing strategy (1. ORR, 2. OS).; moved safety and tolerability objective from exploratory to a separate "Safety" objective for both Phase 2 and Phase 3; updated CTCAE version from 4 to 5; instructed sites that Grade 1 myocarditis is no longer an event term and all troponin elevations should be coded as troponin elevation regardless of myocardial inflammation; re-added pregnancy testing during follow-up visits; made additional minor changes to clarify timing of procedures and improve overall clarity of protocol.	421
	On 26-Aug-2019, the DMC recommended to continue to Phase 3 of this study.	
Revised Protocol 03 23-Nov-2020	Revised the order of the Phase 3 secondary endpoints hierarchical testing strategy (1. OS, 2. ORR). Added two interim analyses of OS. Revised dose delay, criteria to resume treatment, and discontinuation criteria to align with CTCAE V5. Contraceptive guidance for subjects was updated (guidance removed for males). Other minor changes were made to improve clarity.	710

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

The SAP was amended to incorporate a pre-specified sensitivity analysis for the primary endpoint if ≥ 10% of PFS events were attributable to COVID-19.

Changes to planned analyses

The following analyses were performed differently than specified in the SAP or were added post-hoc:

- In the SAP, AEs by subgroups were specified. Region was inadvertently not updated to include the final region categories. The analysis for AEs by region were performed with the same regions that are displayed at baseline and for efficacy.

- Post-hoc: AEs by biomarker subgroups of baseline LAG-3 (≥ 1% vs < 1%) and PD-L1 (≥ 1% vs < 1%/non-quantifiable, and ≥ 10% vs < 10%) were analysed and are presented in this CSR.
- Post-hoc: additional analyses of myocarditis and elevated troponin were performed. These included time to onset/resolution, duration, events leading to discontinuation, events requiring immune-modulating medication (IMMs), and events leading to dose delay.

Protocol deviations

Important protocol deviations (IPDs), previously known as significant protocol deviations, are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. BMS has modified the terminology, reporting process, and categorisation of protocol deviations. IPDs that had the potential to impact PFS were captured as relevant protocol deviations (RPDs) and are summarised in Table 14.

Table 14. Summary of relevant protocol deviations – All randomised subjects Study CA224047

	Number of Subjects (%)		
	BMS-986213 N = 355	Nivolumab N = 359	Total N = 714
SUBJECTS WITH AT LEAST ONE DEVIATION	8 (2.3)	6 (1.7)	14 (2.0)
AT ENTRANCE	8 (2.3)	6 (1.7)	14 (2.0)
HISTOLOGICALLY UNCONFIRMED DIAGNOSIS	0	1 (0.3)	1 (0.1)
INADEQUATE ECOG (ADULTS) OR LANSKY PERFORMANCE (ADOLESCENTS)	0	0	0
PRIOR SYSTEMIC ANTICANCER/PROHIBITED THERAPY	5 (1.4)	3 (0.8)	8 (1.1)
PRE-RANDOMIZATION STATUS OF LAG-3, PD-L1, OR BRAF MUTATION UNAVAILABLE	0	0	0
BASELINE IMAGE PERFORMED OUTSIDE REQUIRED WINDOW	3 (0.8)	2 (0.6)	5 (0.7)
ON-TREATMENT DEVIATIONS	0	0	0
SUBJECT RECEIVED ANTI-CANCER THERAPY	0	0	0
SUBJECT TREATED DIFFERENTLY AS RANDOMIZED	0	0	0

Using the original IRT values for PD-L1, and not the rescore.
Source: Table S.2.4

Overall, 88% and 75% of subjects reported any important protocol deviation in the rela+nivo FDC and nivolumab monotherapy arm, respectively. These were predominantly in the categories Trial Procedures (mostly timing tumour assessment not performed according to protocol), Safety Reporting (mostly related to ECG performance and timely reporting SAEs), and Study Intervention (mostly incorrect stratification factor). More IPDs were seen in the nivo+rela FDC for the Inclusion/Exclusion criteria (39 vs 28), Trial Procedures (96 vs 81), and Informed Consent and/or Independent Ethics Committee and Institutional Review Board (IEC/IRB) (41 vs 27) categories. Percentage of protocol deviations that could potential impact PFS were low; 2.3% and 1.7% in the rela+nivo FDC and nivolumab monotherapy arm, respectively. One site in Mexico was closed, GCP inspections by competent authorities do not question GCP compliance.

During the study, PD-L1 testing was switched to a different laboratory site as PD-L1 ≥ 1% cases were lower than expected, due to under-scoring. PD-L1 re-scoring was performed and these results were used for the primary efficacy analyses. A sensitivity analysis of the PFS primary endpoint was performed using the originally scored PD-L1 to assess the impact of the discrepancies.

Specification of M-stage classification was added, as it was observed that sites were not reliably including LDH lab values into the staging classification needed for randomisation, likely due to confusion with the updated AJCC staging criteria (v8, 2018). Further, it was decided that the AJCC v8 M stage for statistical analysis would be programmed by extracting the actual lab LDH values and the metastasis stage data directly from RAVE clinical database. This was pre-specified in statistical analysis plan (SAP) V2.0 (approval date: 23-Nov-2020). A sensitivity analysis of the PFS primary endpoint was performed based on IRT and RAVE clinical database.

- **Baseline data**

Baseline demographic and disease characteristics are presented in Table 15 and Table 16.

At trial entry, the majority of subjects (91.7%) were AJCC Stage IV and 34.3% of subjects had tumours characterised as M1Any [1] (see *Table 16*). Both the PD-L1 and M-stage factors were balanced between treatment arms, whether using the original values that determined subject stratification at the time of randomisation, or the values used as stratification factors for the statistical efficacy models (data not shown).

Table 15. Key baseline demographic characteristics – All randomised subjects Study CA224047

Parameter	Rela+nivo FDC N = 355	Nivolumab N = 359	Total N = 714
Age (years)			
Mean	61.2	61.2	61.2
Median (range)	63.0 (20-94)	62.0 (21-90)	63.0 (20-94)
Age Categorisation (%)			
≥ 12 and < 18	0	0	0
≥ 18 and < 65	187 (52.7)	196 (54.6)	383 (53.6)
≥ 65 and < 75	102 (28.7)	103 (28.7)	205 (28.7)
≥ 75 and < 85	60 (16.9)	53 (14.8)	113 (15.8)
≥ 85	6 (1.7)	7 (1.9)	13 (1.8)
Sex, n (%)			
Male	210 (59.2)	206 (57.4)	416 (58.3)
Female	145 (40.8)	153 (42.6)	298 (41.7)
Race, n (%)			
White	342 (96.3)	348 (96.9)	690 (96.6)
Black or African American	0	5 (1.4)	5 (0.7)
Asian	0	0	0
American Indian or Alaska Native	0	1 (0.3)	1 (0.1)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	7 (2.0)	4 (1.1)	11 (1.5)
Not Reported	6 (1.7)	1 (0.3)	7 (1.0)
Geographic Region (%)			
US/Canada	45 (12.7)	34 (9.5)	79 (11.1)
Europe	174 (49.0)	190 (52.9)	364 (51.0)
Latin America (Central/South America)	104 (29.3)	106 (29.5)	210 (29.4)
Australia/New Zealand	32 (9.0)	29 (8.1)	61 (8.5)

Table 16. Key baseline disease characteristics – All randomised patients Study CA224047

Parameter	Rela+nivo FDC N = 355	Nivolumab N = 359	Total N = 714
AJCC v8 Stage at Study Entry			
Unresectable Stage III	35 (9.9)	23 (6.4)	58 (8.1)
Metastatic Stage IV	320 (90.1)	335 (93.3)	655 (91.7)
Unknown or Not Reported	0	1 (0.3)	1 (0.1)
AJCC M Stage (%) (From Rave and Lab Values)			
M0/M1Any [0]	232 (65.4)	237 (66.0)	469 (65.7)
M1Any [1]	123 (34.6)	122 (34.0)	245 (34.3)
Baseline Metastasis Stage			
M0	35 (9.9)	23 (6.4)	58 (8.1)
M1	1 (0.3)	3 (0.8)	4 (0.6)

Parameter	Rela+nivo FDC N = 355	Nivolumab N = 359	Total N = 714
M1A	77 (21.7)	107 (29.8)	184 (25.8)
M1B	85 (23.9)	88 (24.5)	173 (24.2)
M1C	151 (42.5)	127 (35.4)	278 (38.9)
M1D	6 (1.7)	11 (3.1)	17 (2.4)
Melanoma Subtype Classification			
Cutaneous Acral	41 (11.5)	41 (11.4)	82 (11.5)
Cutaneous Non Acral	249 (70.1)	254 (70.8)	503 (70.4)
Mucosal	23 (6.5)	28 (7.8)	51 (7.1)
Other	42 (11.8)	36 (10.0)	78 (10.9)
Time from melanoma diagnosis (yrs)			
Median (min, max)	1.21 (0.1, 42.9)	1.31 (0.0, 34.1)	1.26 (0.0, 42.9)
History of Brain Metastasis			
Yes	6 (1.7)	13 (3.6)	19 (2.7)
No	349 (98.3)	346 (96.4)	695 (97.3)
Smoking Status (%)			
Never	213 (60.0)	212 (59.1)	425 (59.5)
Current/Former	127 (35.8)	138 (38.4)	265 (37.1)
Unknown	14 (3.9)	9 (2.5)	23 (3.2)
Not Reported	1 (0.3)	0	1 (0.1)
Performance Status (ECOG) (%)			
0	236 (66.5)	242 (67.4)	478 (66.9)
1	119 (33.5)	117 (32.6)	236 (33.1)
Baseline Biomarker			
PD-L1 < 1%/Non-Quantifiable	209 (58.9)	212 (59.1)	421 (59.0)
PD-L1 ≥ 1%	146 (41.1)	147 (40.9)	293 (41.0)
PD-L1 < 5%/Non-Quantifiable	267 (75.2)	273 (76.0)	540 (75.6)
PD-L1 ≥ 5%/	88 (24.8)	86 (24.0)	174 (24.4)
PD-L1 < 10%/Non-Quantifiable	284 (80.0)	290 (80.8)	574 (80.4)
PD-L1 ≥ 10%	71 (20.0)	69 (19.2)	140 (19.6)
LAG-3 < 1% Expression	87 (24.5)	90 (25.1)	177 (24.8)
LAG-3 ≥ 1% Expression	268 (75.5)	269 (74.9)	537 (75.2)
LAG-3 < 5% Expression	234 (65.9)	225 (62.7)	459 (64.3)
LAG-3 ≥ 5% Expression	121 (34.1)	134 (37.3)	255 (35.7)
BRAF status (%)			
Mutation positive	136 (38.3)	139 (38.7)	275 (38.5)
Mutation wild-type	219 (61.7)	220 (61.3)	439 (61.5)
Baseline LDH Level (%)			
≤ ULN	224 (63.1)	231 (64.3)	455 (63.7)
> ULN	130 (36.6)	128 (35.7)	258 (36.1)
Not Reported	1 (0.3)	0	1 (0.1)
≤ 2 x ULN	322 (90.7)	328 (91.4)	650 (91.0)
> 2 x ULN	32 (9.0)	31 (8.6)	63 (8.8)
Not Reported	1 (0.3)	0	1 (0.1)

Note: PD-L1 values were evaluated at LabCorp LA.

Overall, 8.7% of subjects received prior systemic therapy, mostly interferon (6.3%).

Baseline demographic and disease characteristics were in general comparable between the phase 2 and phase 3 part of the study (data not shown). The main differences between part 2 and part 3 relate to region (20.5% vs 42.6% from Latin America), ECOG 1 (26.4% vs 42.9%), LDH>ULN (33.4% vs 40.1%), and M1C (34.3% vs 42.1%, more pronounced in the nivolumab monotherapy arm). There were no substantial differences in prior systemic cancer therapy.

A total of 87.0% of subjects treated in the rela+nivo FDC (BMS-986213) arm received ≥90% of the planned dose intensity, comparable to the nivolumab monotherapy arm (84.7%). The median duration of therapy was 5.55 months in the rela+nivo FDC (BMS-986213) arm and 4.86 months in the nivolumab monotherapy arm. A total of 29.3% and 28.1% received ≥ 12 months of study drug, respectively.

- **Numbers analysed**

The number of patients in each analysis set are shown in Table 17. The primary and secondary efficacy analyses were based on the randomised population ("intention to treat"). The safety population was based on the treated population, which is similar to the randomised population.

Table 17. Analysis populations Study CA224047

Population	BMS-986213	Nivolumab	Total
Enrolled: All subjects who sign informed consent and were registered into IRT			1281
Randomized: All subjects who are randomized to any treatment group.	355	359	714
Treated: All subjects who received at least one dose of double-blind study medication.	355	359	714
PK: All randomized subjects with available serum-time concentration data			
Relatlimab	335	N/A	335
Nivolumab	335	329	664
PD: All treated subjects with cytokine data			
sLAG-3 evaluable	324	322	646
MIG evaluable	332	327	659
IFNγ evaluable	332	327	659
Immunogenicity: All randomized subjects with available ADA data.			
Relatlimab ADA evaluable	286	N/A	286
Nivolumab ADA evaluable	288	272	560
Biomarker: All randomized subjects with available biomarker data.			
LAG-3 quantifiable	355	359	714
PD-L1 quantifiable	333	347	680
PD-L1 non-quantifiable	22	12	34

- **Outcomes and estimation**

Primary endpoint PFS by BIRC

Median PFS was 10.12 (95% CI: 6.37, 15.74) months in the rela+nivo FDC (BSM-986213) arm and 4.63 (95% CI: 3.38, 5.62) months in the nivolumab arm and the primary endpoint of PFS per BICR was statistically significant (HR: 0.75; 95% CI: 0.62, 0.92) (

Table *18*).

Table 18. Summary of key efficacy results from study CA224047 – All randomised subjects Study Ca224047

	Rela+nivo FDC (BMS-986213) N = 355		Nivolumab N = 359
PRIMARY ENDPOINT			
PFS per BICR (Primary Definition)			
Events, n (%)	180 (50.7%)		211 (58.8%)
Median PFS (95% CI), mo.[a]	10.12 (6.37, 15.74)		4.63 (3.38, 5.62)
HR (95.0% CI)[b]		0.75 (0.62, 0.92)	
Stratified log-rank p-value		0.0055[*]	
6-month PFS Rates (95% CI), %[a]	57.2 (51.5, 62.5)		44.1 (38.5, 49.5)
12-month PFS Rates (95% CI), %[a]	47.7 (41.8, 53.2)		36.0 (30.5, 41.6)
PFS per BICR (Secondary Definition)			
Events, n (%)	194 (54.6)		224 (62.4)
Median PFS (95% CI), mo.[a]	10.05 (6.28, 14.03)		4.60 (3.12, 5.36)
HR (95% CI)[b]		0.76 (0.63, 0.93)	
6-month PFS Rates (95% CI), %[a]	56.8 (51.2, 62.0)		43.8 (38.4, 49.2)
12-month PFS Rates (95% CI), %[a]	46.2 (40.6, 51.7)		35.3 (30.0, 40.7)

The primary definition of PFS accounted for subsequent therapy by censoring at the last evaluable tumour assessment on or prior to the date of subsequent therapy. The secondary definition of PFS was irrespective of, and did not account for subsequent therapy.
[*] Statistically significant at alpha = 0.049. [a] Based on Kaplan-Meier estimates.
[b] Stratified Cox proportional hazards model. HR is rela/nivo 160/480 mg Q4W over nivolumab 480 mg Q4W.

As of the 09-Mar-2021 DBL, a total of 49.3% and 41.2% of randomised subjects in the rela+nivo FDC (BMS-986213) and nivolumab monotherapy arms, respectively, were censored for PFS (per the primary definition), see Table 19.

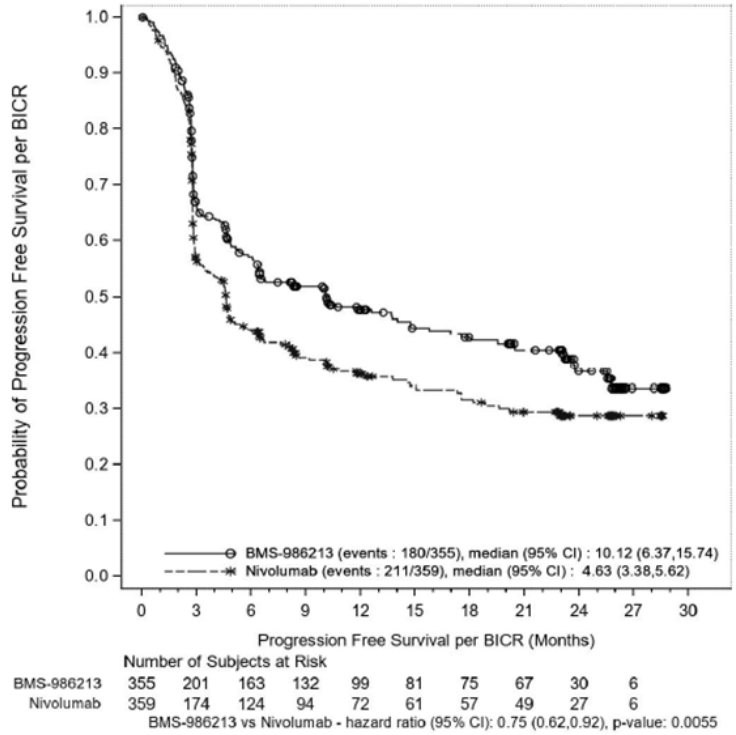
Table 19. Reason for censoring, PFS per BICR – All randomised subjects Study CA224047

	BMS-986213 N = 355	Nivolumab N = 359
NUMBER OF EVENTS (%)	180 (50.7)	211 (58.8)
TYPE OF EVENTS (%)		
PROGRESSION (1)	156 (43.9)	194 (54.0)
DEATH	24 (6.8)	17 (4.7)
NUMBER OF SUBJECTS CENSORED (%)	175 (49.3)	148 (41.2)
CENSORED ON DATE OF RANDOMIZATION	15 (4.2)	20 (5.6)
NO BASELINE TUMOR ASSESSMENT	0	0
NEVER TREATED	0	0
OTHER	0	0
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	15 (4.2)	20 (5.6)
NEVER TREATED	0	0
OTHER	14 (3.9)	15 (4.2)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY	1 (0.3)	5 (1.4)
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY	160 (45.1)	128 (35.7)
RECEIVED SUBSEQUENT ANTI CANCER THERAPY (3)	35 (9.9)	25 (7.0)
RECEIVED SUBSEQUENT SYSTEMIC THERAPY	16 (4.5)	12 (3.3)
RECEIVED SUBSEQUENT RADIOTHERAPY	13 (3.7)	8 (2.2)
RECEIVED SUBSEQUENT SURGERY	6 (1.7)	5 (1.4)
STILL ON TREATMENT	82 (23.1)	82 (22.8)
IN FOLLOW-UP	40 (11.3)	20 (5.6)
OFF STUDY	3 (0.8)	1 (0.3)
LOST TO FOLLOW-UP	1 (0.3)	0
WITHDREW CONSENT	1 (0.3)	1 (0.3)
OTHER	1 (0.3)	0

(1) RECIST 1.1 criteria.
(2) Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered.
(3) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy without a prior reported PFS event. Those subjects were censored at the last evaluable tumor assessment prior to/on start date of subsequent anti-cancer therapy.

Separation of the Kaplan-Meier (K-M) curves favouring rela+nivo FDC (BSM-986213) over nivolumab monotherapy occurred at approximately 3 months, at the time of the first on-study assessment, and this treatment effect was sustained through the period of follow-up (Figure *8*).

Figure 8. Kaplan-Meier Plot of PFS per BICR (primary definition) – All randomised subjects Study CA224047



Note: statistical model for HR and p-value: stratified Cox proportional hazard model and stratified log-rank test. 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 stratification because it led to subgroups with fewer than 10 subjects. Symbols represent censored observations.

Sensitivity analyses for PFS by BIRC

A sensitivity analysis censoring for subsequent therapy was performed and results were comparable to the primary analysis (see

Table *18*). Other prespecified sensitivity analyses were performed for the following assumptions: 1) constant hazards assumption, 2) crossover of treatment effect across strata, 3) adjustment for potentially important covariates, 4) censoring for two missing images in a row, 5) any differences between stratification values in IRT vs. RAVE, and 6) an unstratified analysis. These analyses were all consistent with the primary analysis (data not shown).

Investigator assessment

The exploratory analyses of PFS per investigator were supportive of the primary endpoint results. Rela+nivo FDC (BSM-986213) demonstrated a higher PFS (primary definition) compared with nivolumab monotherapy: HR = 0.85 (95% CI: 0.69, 1.03), with a longer median PFS (primary definition): 10.15 months (95% CI: 8.21, 14.75) vs 6.51 months (95% CI: 4.63, 10.09), respectively. Concordance between BICR and investigator PFS assessments was 83.7% and 85.5% for the primary PFS definition in the rela+nivo FDC (BSM-986213) and nivolumab arm, respectively.

Additional sensitivity analyses were performed post-hoc to justify the assumption of non-informative censoring, including subsequent anticancer therapy as PFS event, combining investigator assessment and BICR for PFS events, counting non-administrative censored times as events, as well as further information after treatment discontinuation. These analyses were reassuring that any potentially informative censoring did not have an influence on the results and related conclusions of efficacy in the ITT population (both for the 09-Mar-2021 DBL and 28-Oct-2021 DBL, see below).

Updated PFS analyses time final OS analysis 28-Oct-2021 DBL:

As of the 28-Oct-2021 DBL, with a median extent of follow-up of 19.27 months, the median duration of therapy was 8.3 months in the nivo+rela FDC arm and 6.5 months in the nivolumab monotherapy arm. The updated PFS analysis including an additional 46 PFS events (primary definition) across both arms supported the primary analysis, see Table 20 and Figure 9. The median PFS in the nivo+rela FDC arm (10.22 months (95% CI: 6.51, 14.75)) was 5.6 months longer compared with the nivolumab monotherapy arm (4.63 months (95% CI: 3.48, 6.44)). About 42% and 35% in the nivo+rela FDC and nivolumab monotherapy arms, respectively, were censored for PFS, the majority of subjects were censored at the time of the last on-study tumour assessment.

Table 20. Summary of updated PFS results – All randomised subjects (28-Oct-2021 DBL)

	Nivo+rela FDC N = 355		Nivolumab N = 359
PFS per BICR (Primary Definition)			
Events, n (%)	204 (57.5)		233 (64.9)
Median PFS (95% CI), mo.[a]	10.22 (6.51, 14.75)		4.63 (3.48, 6.44)
HR (95% CI)[b]		0.78 (0.64, 0.94)	
12-month PFS Rates (95% CI), %[a]	48.0 (42.5, 53.4)		36.9 (31.7, 42.1)
24-month PFS Rates (95% CI), %[a]	38.5 (32.7, 44.2)		29.0 (23.8, 34.4)
PFS per BICR (Secondary Definition)			
Events, n (%)	224 (63.1)		249 (69.4)
Median PFS (95% CI), mo.[a]	10.15 (6.47, 13.70)		4.63 (3.48, 6.44)
HR (95% CI)[b]		0.79 (0.66, 0.95)	
12-month PFS Rates (95% CI), %[a]	47.1 (41.7, 52.3)		36.7 (31.6, 41.7)
24-month PFS Rates (95% CI), %[a]	36.3 (30.9, 41.8)		28.5 (23.5, 33.7)

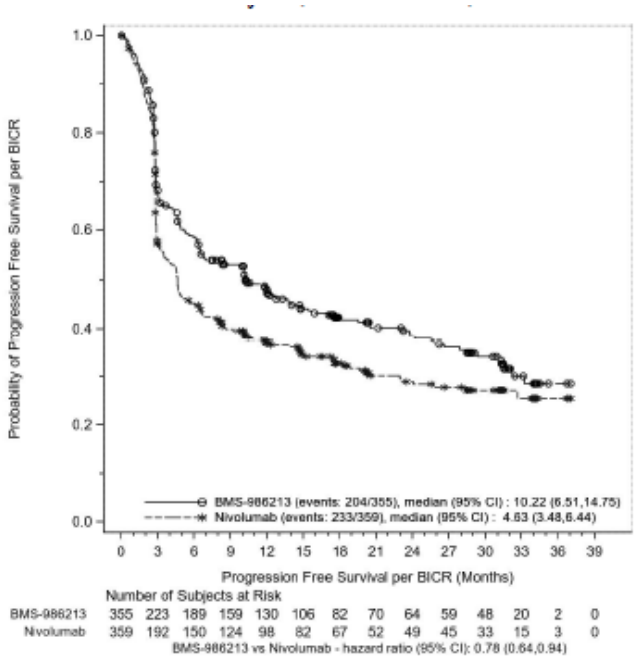
Source: Table 7.1-1, Table S.5.22B.1, and Table S.5.23B.1 in the CA224047 CSR addendum 01.[1]

The primary definition of PFS accounted for subsequent therapy by censoring at the last evaluable tumor assessment on or prior to the date of subsequent therapy. The secondary definition of PFS was irrespective of, and did not account for subsequent therapy.

[a] Based on Kaplan-Meir estimates

[b] Stratified Cox proportional hazards model. HR is nivo+rela FDC over nivolumab.

Figure 9. Kaplan-Meier plot of PFS per BICR (primary definition) – All randomised subjects (28-Oct-2021 DBL)



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 stratification because it led to subgroups with fewer than 10 subjects. Symbols represent censored observations.

Source: Figure S.5.30.1 in the CA224047 CSR addendum 01.[1]

The PFS per BICR analysis using the secondary definition (without censoring for subsequent therapy) also continued to favor nivo+rela FDC compared with nivolumab monotherapy: HR = 0.79 (95% CI: 0.66, 0.95) (Table 20). Further, updated PFS (primary definition) sensitivity analyses were performed and supported the primary analyses (data not shown).

Key secondary endpoints

Overall Survival

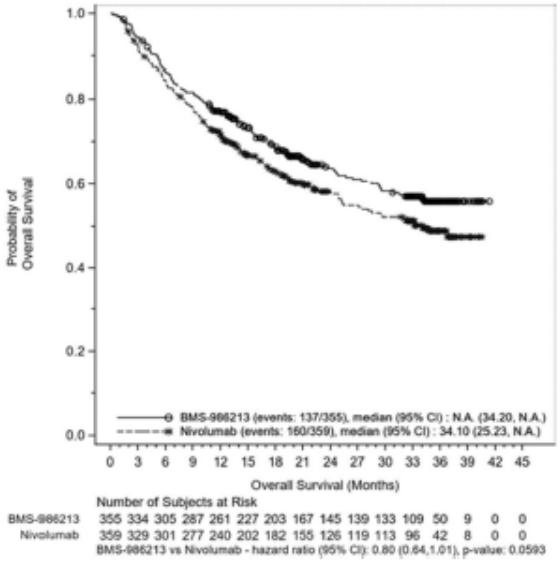
The secondary endpoint of OS, with a cumulative design power of approximately 69%, was analysed based on 297 deaths (nearly 100% of the planned events) for the 28-Oct-2021 DBL. This analysis was considered the final OS analysis. There were 137 (38.6%) deaths in the rela+nivo FDC arm and 160 (44.6%) deaths in the nivolumab monotherapy arm, and 61.4% and 55.4% of subjects were censored for OS, respectively (Table 21). The most common reason for OS censoring was subjects in follow-up, with < 3% censored for being off study in both treatment arms. While OS favoured rela+nivo FDC over nivolumab monotherapy, the improvement was not statistically significant (HR = 0.80 (95% CI: 0.64, 1.01); p value = 0.0593; 2-sided O'Brien Fleming boundary for statistical significance p-value < 0.04302)) (Figure 10). The estimated OS rates at 12, 24 and 36 months were more than 5% higher for rela+nivo FDC with respect to the nivolumab monotherapy arm.

Table 21. status of censored subjects, Overall Survival, All Randomised subjects (28-Oct-212 DBL)

	Number of Subjects (%)	
	BMS-986213 N = 355	Nivolumab N = 359
NUMBER OF DEATHS (%)	137 (38.6)	160 (44.6)
NUMBER OF SUBJECTS CENSORED (%)	218 (61.4)	199 (55.4)
STATUS OF CENSORED SUBJECTS (%)		
STILL ON TREATMENT	86 (24.2)	92 (25.6)
NOT PROGRESSED	65 (18.3)	75 (20.9)
PROGRESSED (1)	21 (5.9)	17 (4.7)
IN FOLLOW-UP	124 (34.9)	99 (27.6)
OFF STUDY	8 (2.3)	8 (2.2)
LOST TO FOLLOW-UP	2 (0.6)	2 (0.6)
SUBJECT WITHDREW CONSENT	6 (1.7)	6 (1.7)

(1) Radiographic or Clinical findings
Source: Table S.5.37 in the CA224047 CSR Addendum 01.[2]

Figure 10 Kaplan-Meier plot of Overall Survival – All randomised subjects



Statistical model for HR and p-value: Stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG3 (≥ 1% vs < 1%), BRAF (Mutation Positive vs Mutation Wild-type), AJCC M Stage (M0/M1any[0] vs M1any[1]).
PD-L1 was removed from stratification because it led to subgroups with fewer than 10 subjects.
Symbols represent censored observations.
Boundary for statistical significance p-value < 0.04302 (2-sided)
Source: Figure S.5.30.3 in the CA224047 CSR Addendum 01.[2]

Objective Response Rate

Due to the position of ORR in the statistical testing hierarchy, ORR per BICR was not formally tested for statistical significance, however rela+nivo FDC demonstrated an improvement in ORR compared with nivolumab in all randomised subjects; ORR = 43.1% (95% CI: 37.9, 48.4) vs 32.6% (95% CI: 27.8, 37.7) respectively (Table 22). ORR rates at 12 weeks were 30.1% vs 21.7% and ORR matured until 28 weeks. A BOR of CR was achieved in 16.3% of patients in the rela+nivo FDC arm and 14.2% of patients in the nivolumab arm.

Table 22. Summary of objective response rate – All randomised subjects (28-Oct-2021 DBL)

	Nivo+rela FDC N = 355		Nivolumab N = 359
Confirmed ORR per BICR			
N events/N responders (%)	153/355 (43.1)		117/359 (32.6)
95% CI[a]	37.9, 48.4		27.8, 37.7
Difference of ORR (95% CI), %[b]		10.3 (3.4, 17.3)	
Odds ratio (95% CI)[c]		1.58 (1.16, 2.15)	
Confirmed BOR per BICR, n (%)			
Complete Response (CR)	58 (16.3)		51 (14.2)
Partial Response (PR)	95 (26.8)		66 (18.4)
Stable Disease (SD)	61 (17.2)		59 (16.4)
Non-CR/non-PD	9 (2.5)		6 (1.7)
Progressive Disease (PD)	105 (29.6)		149 (41.5)
Unable to Determine (UTD)	27 (7.6)		28 (7.8)
Disease Control Rate (CR+PR+SD) per BICR			
N responders (%)	223 (62.8)		182 (50.7)
95% CI	57.6, 67.9		45.4, 56.0
TTR per BICR			
Median (min, max), mo.	2.79 (1.2, 12.2)		2.79 (1.7, 20.1)
DoR per BICR			
N events/N responders (%)	42/153 (27.5)		28/117 (23.9)
Median (95% CI), mo[d]	NA (29.57, NA)		NA (29.93, NA)
Min, Max, mo.[e]	1.9+, 34.3+		1.9+, 34.0+

[a] Based on Kaplan-Meir estimates

[b] CR+PR, CI based on the Clopper and Pearson method.

[c] Strata adjusted difference in odds ratio (nivo+rela FDC over nivolumab) based on Cochran-Mantel-Haenszel method of weighting. Stratified by LAG-3 (≥ 1% vs < 1%), BRAF (Mutation Positive vs Mutation Wild-type), AJCC M Stage (M0/M1any[0] vs M1any[1]).

[d] Strata adjusted difference in ORR (nivo+rela FDC over nivolumab) based on Cochran-Mantel-Haenszel method of weighting. Stratified by LAG-3 (≥ 1% vs < 1%), BRAF (Mutation Positive vs Mutation Wild-type), AJCC M Stage (M0/M1any[0] vs M1any[1]).

[e] Symbol + indicates a censored value.

Source: Table 7.1-1 in the CA224047 CSR Addendum 01.[2]

Concordance between BICR and investigator-assessed ORR was high and similar between treatment arms in all randomised subjects, with a concordance rate of 86.5% and 88.3% for rela+nivo FDC and nivolumab arms, respectively

Disease control rate per BICR was also higher in the BMS-986213 arm relative to the nivolumab monotherapy arm (62.8% vs 50.7%, respectively). The median TTR per BICR was the same in both treatment arms (2.79 months) and the median DOR was not reached in either arm.

Exploratory endpoints

Efficacy by baseline LAG-3 and PD-L1 expression

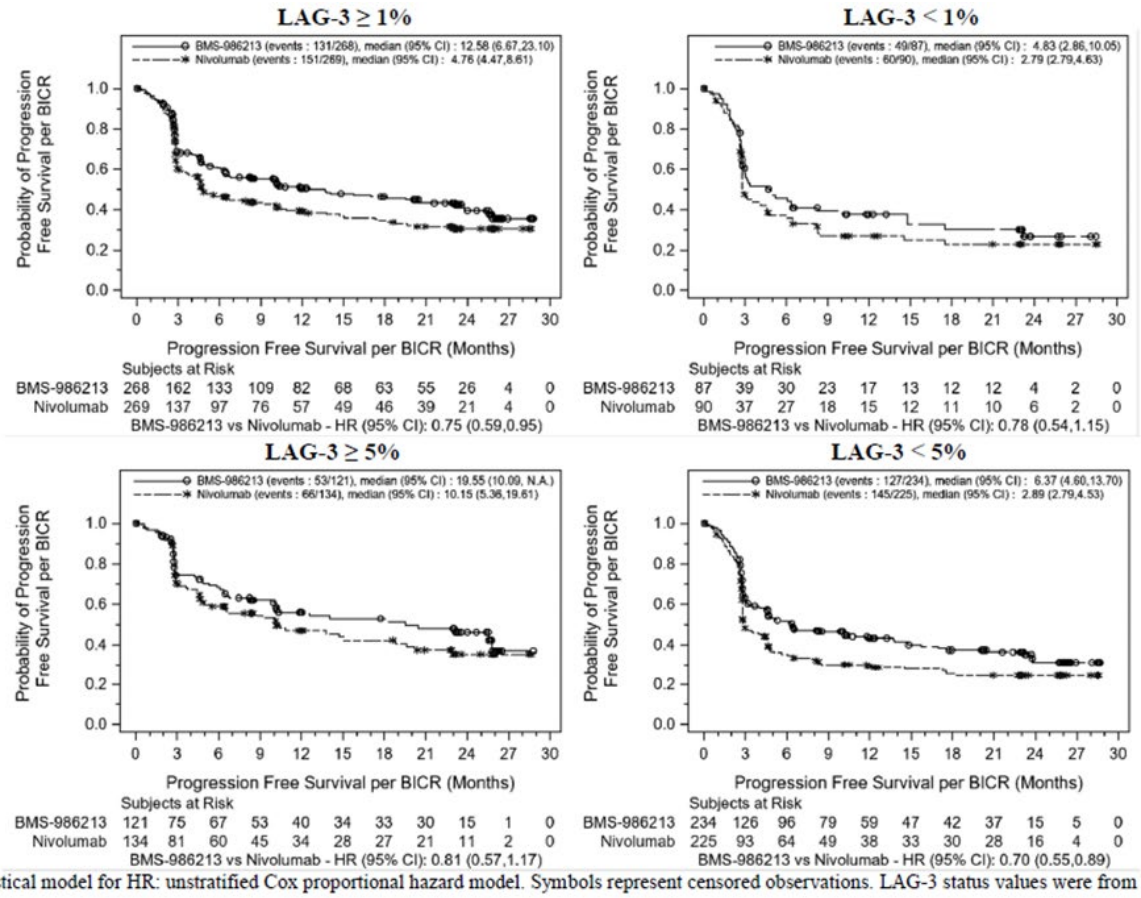
LAG-3 expression

The PFS HRs favoured rela+nivo FDC (BMS-986213) compared with nivolumab monotherapy regardless of LAG-3 expression (< 1%, ≥ 1%, < 5%, and ≥ 5%) (Table 23 and Figure 11). The largest absolute improvement in median PFS was observed with high LAG-3 expression (≥ 1%, and ≥ 5%).

Table 23. PFS by baseline LAG-3 expression levels – All randomised subjects Study CA224047

	LAG-3 < 1%		LAG-3 ≥ 1%		LAG-3 < 5%		LAG-3 ≥ 5%	
	BMS-986213 N = 87	Nivo N = 90	BMS-986213 N = 268	Nivo N = 269	BMS-986213 N = 234	Nivo N = 225	BMS-986213 N= 121	Nivo N = 134
HR (95% CI)	0.78 (0.54, 1.15)		0.75 (0.59, 0.95)		0.70 (0.55, 0.89)		0.81 (0.57, 1.17)	
Events, n	49	60	131	151	127	145	53	66
Median PFS, mo. (95% CI)	4.83 (2.86, 10.05)	2.79 (2.79, 4.63)	12.58 (6.67, 23.10)	4.76 (4.47, 8.61)	6.37 (4.60, 13.70)	2.89 (2.79, 4.53)	19.55 (10.09, N.A.)	10.15 (5.36, 19.61)

Figure 11. Kaplan-Meier plot of PFS by LAG-3 expression – All randomised subjects Study CA224047



Note: statistical model for HR: unstratified Cox proportional hazard model. Symbols represent censored observations. LAG-3 status values were from IRT.

PD-L1 expression

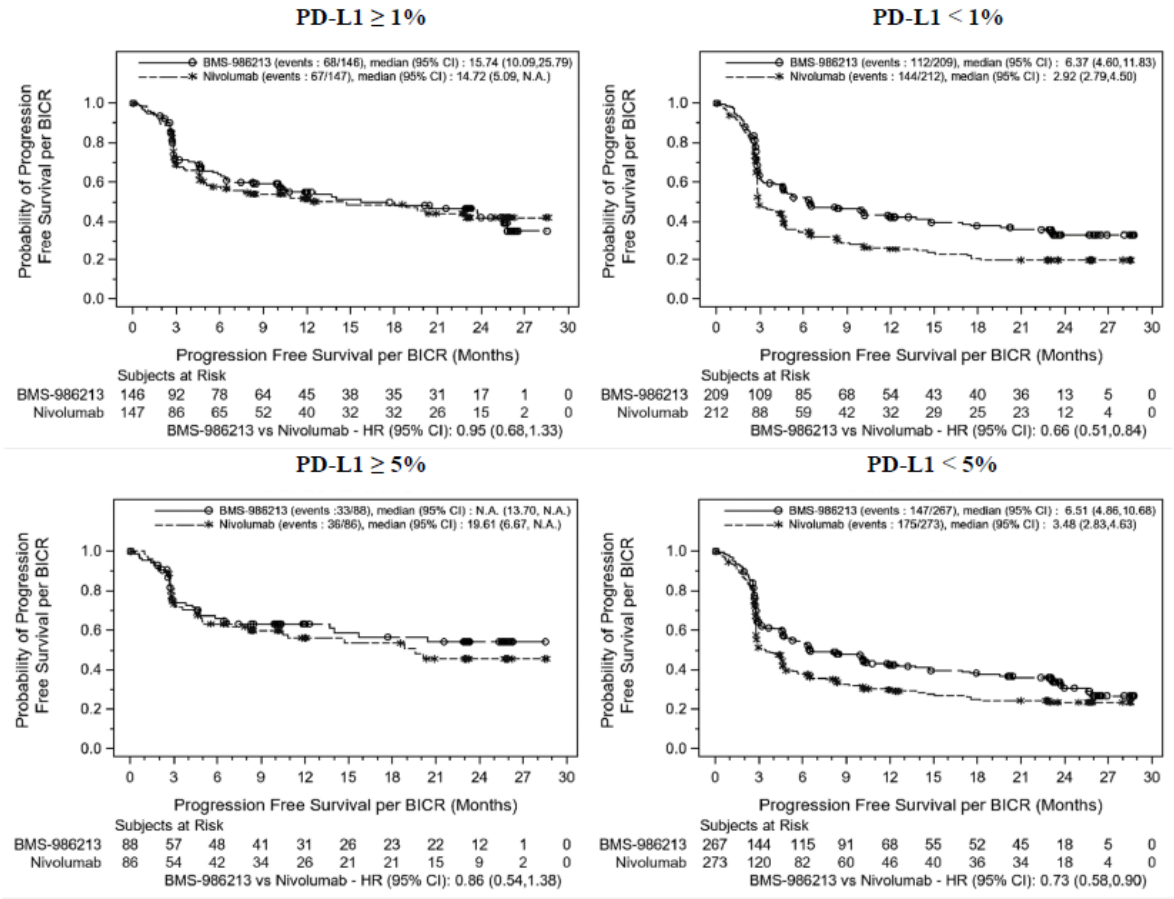
The PFS HRs and K-M curves for PFS for rela+nivo FDC (BMS-986213) compared with nivolumab monotherapy are shown in

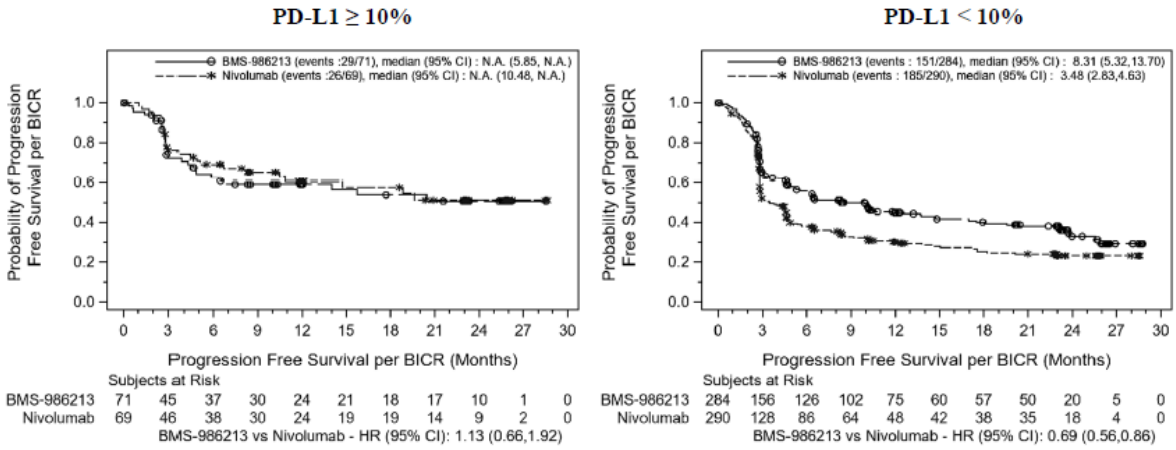
Table *24* and Figure 12. The largest absolute improvement in median PFS was observed with low PD-L1 expression (<1%) and HR was 0.66, whereas median PFS was comparable between treatment arms in the PD-L1 ≥ 1% group, HR was 0.95. K-M curves overlap in the subgroup with high PD-L1 expression. For subjects with high PD-L1 expression (≥ 5%, and ≥ 10%), median PFS was not reached in the rela+nivo FDC arm or in both treatment arms.

Table 24. PFS by baseline PD-L1 expression levels – All randomised subjects Study CA224047

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	BMS-986213 N = 209	Nivo N = 212	BMS-986213 N = 146	Nivo N = 147	BMS-986213 N = 267	Nivo N = 273	BMS-986213 N = 88	Nivo N = 86	BMS-986213 N = 284	Nivo N = 290	BMS-986213 N = 71	Nivo N = 69
HR (95% CI)	0.66 (0.51, 0.84)		0.95 (0.68, 1.33)		0.73 (0.58, 0.90)		0.86 (0.54, 1.38)		0.69 (0.56, 0.86)		1.13 (0.66, 1.92)	
Events, n	112	144	68	67	147	175	33	36	151	185	29	26
Median PFS, mo. (95% CI)	6.37 (4.60, 11.83)	2.92 (2.79, 4.50)	15.74 (10.09, 25.79)	14.72 (5.09, N.A.)	6.51 (4.86, 10.68)	3.48 (2.83, 4.63)	N.A. (13.70, N.A)	19.61 (6.67, N.A.)	8.31 (5.32, 13.70)	3.48 (2.83, 4.63)	N.A (5.85, N.A.)	N.A. (10.48, N.A.)

Figure 12. Kaplan-Meier plot of PFS per BICR by PD-L1 expression – All randomised subjects Study CA224047





Note: statistical model for HR: unstratified Cox proportional hazard model. Symbols represent censored observations. PD-L1 values were evaluated at LabCorp LA.

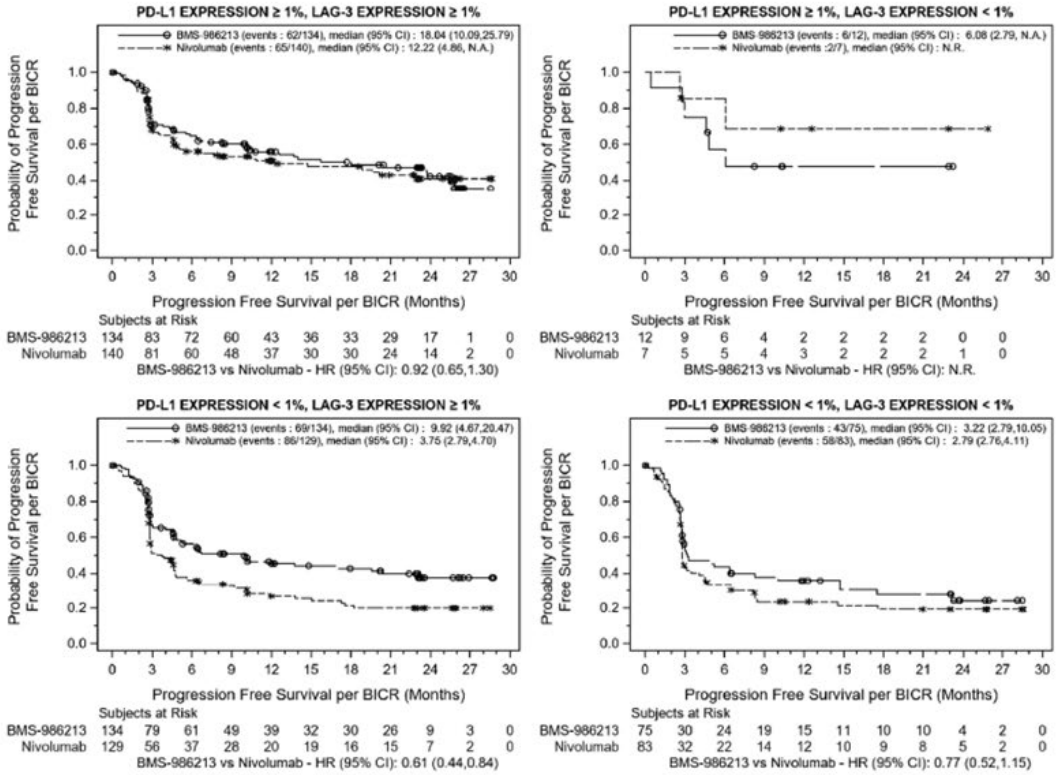
LAG-3/PD-L1 expression

The PFS HRs and K-M curves for PFS for rela+nivo FDC (BMS-986213) compared with nivolumab monotherapy are shown in Table 25 and Figure 13. There were few subjects in the PD-L1 ≥ 1%/LAG-3 < 1% subgroup (n=19) and no HR could be computed.

Table 25. PFS by baseline PD-L1/LAG-3 expression levels – All randomised subjects Study CA224047

	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	Nivo N = 140	BMS-986213 N = 12	Nivo N = 7	BMS-986213 N = 134	Nivo N = 129	BMS-986213 N = 75	Nivo N = 83
HR (95% CI)	0.92 (0.65, 1.30)		Not reported		0.61 (0.44, 0.84)		0.77 (0.52, 1.15)	
Events, n	62	65	6	2	69	86	43	58
Median PFS, mo. (95% CI)	18.04 (10.09, 25.79)	12.22 (4.86, N.A.)	6.08 (2.79, N.A.)	Not reported	9.92 (4.67, 20.47)	3.75 (2.79, 4.70)	3.22 (2.79, 10.05)	2.79 (2.76, 4.11)

Figure 13 Kaplan-Meier plot of PFS by BICR by baseline PD-L1/LAG-3 biomarker expression – All randomised subjects Study CA224047



Note: Statistical model for hazard ratio: Unstratified Cox proportional hazard model. Symbols represent censored observations. N.R.: Not reported when sample size is less than 10 subjects for the subgroup category. PD-L1 values were evaluated at LabCorp LA, and LAG-3 status values were from IRT.

Updated Efficacy analyses (28-Oc-2021 DBL) Biomarker subgroups

Updated efficacy analyses of PFS confirm the initial analyses (Table 26). Exploratory subgroup analyses for OS provided higher HR point estimates for the comparison between nivo+rela FDC and nivolumab monotherapy among tumour PD-L1 expressers relative to those with low or absent expression at the 1%, 5%, and 10% thresholds. As noted above, the OS data remain immature with OS maturity defined as deaths in 50% of subjects. There were approximately 42% (297/714) of deaths among all randomised subjects (34% and 46% of deaths among patients in the PD-L1 positive and PD-L1 negative subgroups based on 1% cut-off, respectively). An ORR difference of ~8% to 12% was observed in favour of nivo+rela FDC above nivolumab monotherapy across the majority of PD-L1 expression levels.

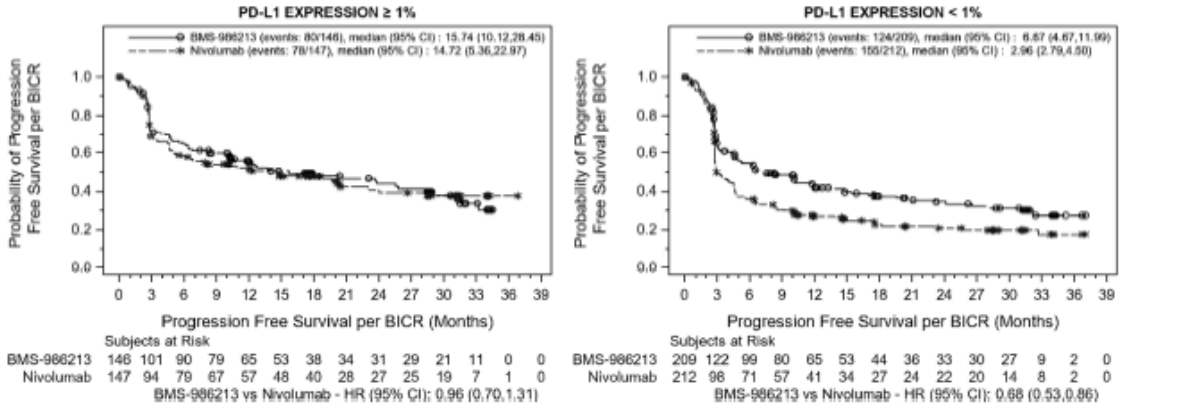
Table 26 Efficacy by baseline tumour cell PD-L1 expression levels – All randomised subjects (28-Oct-2021)

	PD-L1 < 1%		PD-L1 ≥ 1%		PD-L1 < 5%		PD-L1 ≥ 5%		PD-L1 < 10%		PD-L1 ≥ 10%	
	nivo+rela FDC N = 209	Nivo N = 212	nivo+rela FDC N = 146	Nivo N = 147	nivo+rela FDC N = 267	Nivo N = 273	nivo+rela FDC N = 88	Nivo N = 86	nivo+rela FDC N = 284	Nivo N = 290	nivo+rela FDC N = 71	Nivo N = 69
PFS per BICR												
HR (95% CI)	0.68 (0.53, 0.86)		0.96 (0.70, 1.31)		0.74 (0.60, 0.91)		0.94 (0.60, 1.48)		0.71 (0.58, 0.87)		1.23 (0.74, 2.04)	
Events, n	124	155	80	78	165	195	39	38	170	206	34	27
Median PFS, mo. (95% CI)	6.67 (4.67, 11.99)	2.96 (2.79, 4.50)	15.74 (10.12, 28.45)	14.72 (5.36, 22.97)	8.31 (5.32, 11.83)	3.48 (2.83, 4.63)	29.37 (12.22, NA)	19.61 (10.48, NA)	10.09 (6.28, 12.58)	3.48 (2.86, 4.63)	28.45 (6.77, NA)	NA (10.84, NA)
Overall Survival												
HR (95% CI)	0.78 (0.59, 1.04)		0.84 (0.57, 1.24)		0.75 (0.58, 0.96)		1.08 (0.65, 1.81)		0.72 (0.56, 0.92)		1.43 (0.79, 2.60)	
Events, n	89	104	48	56	107	132	30	28	112	141	25	19
Median OS, mo. (95% CI)	NA (27.43, NA)	27.04 (17.12, NA)	NA (NA, NA)	NA (31.97, NA)	NA (32.20, NA)	27.33 (19.55, NA)	NA (29.24, NA)	NA (34.73, NA)	NA (34.04, NA)	27.04 (19.55, NA)	NA (28.45, NA)	NA (36.80, NA)
ORR per BICR												
Events, n (%)	76 (36.4)	51 (24.1)	77 (52.7)	66 (44.9)	99 (37.1)	74 (27.1)	54 (61.4)	43 (50.0)	111 (39.1)	78 (26.9)	42 (59.2)	39 (56.5)
95% CI	29.8, 43.3	18.5, 30.4	44.3, 61.1	36.7, 53.3	31.3, 43.2	21.9, 32.8	50.4, 71.6	39.0, 61.0	33.4, 45.0	21.9, 32.4	46.8, 70.7	44.0, 68.4

Updated efficacy PFS analyses by combined baseline PD-L1/LAG-3 expression levels supported the initial analyses and the updated median PFS in the subgroup PD-L1 ≥1%/LAG-3 ≥1% was similar to that of the PD-L1 ≥1% subgroup (data not shown).

Tumour PD-L1 expression at the 1% threshold was a study randomisation stratification factor and defined the largest PD-L1 positive subgroup in Study CA224047. Therefore, additional analyses to further characterize the relationship between treatment efficacy and PD-L1 expression were focused on the PD-L1 ≥1% subgroup. KM-curves of PFS and OS per baseline PD-L1 expression are shown below (Figure 14 and Figure 15). Clear separation of curves is seen for PD-L1 <1%, whereas curves overlap for PD-L1 ≥1%.

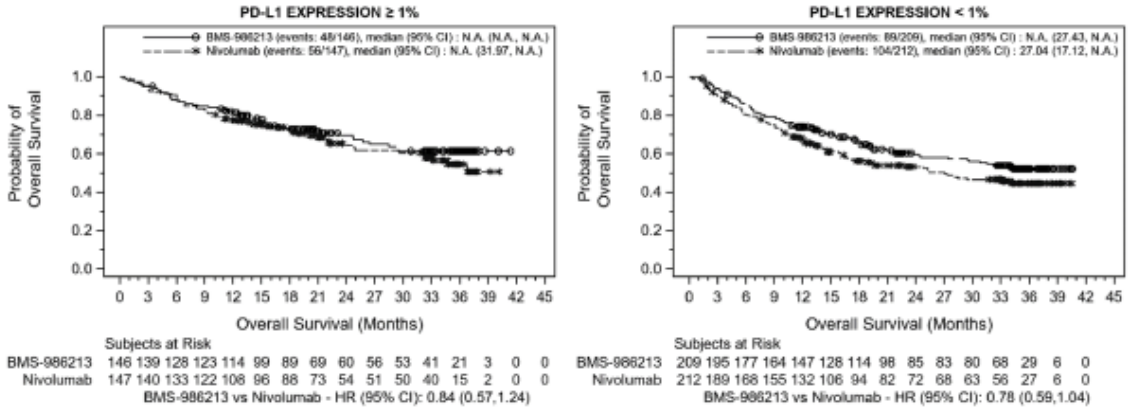
Figure 14 Kaplan-Meier plot of PFS per BICR by baseline PD-L1 expression – All randomised subjects (28-Oct-2021 DBL)



Statistical model for hazard ratio: Unstratified Cox proportional hazard model. Symbols represent censored observations. PD-L1 values were evaluated at LabCorp LA.

Source: Figure S.10.3.1 in the CA224047 CSR Addendum 01.[2]

Figure 15. Kaplan-Meier plot of OS by baseline PD-L1 expression – All randomised subjects (28-Oct-2021 DBL)

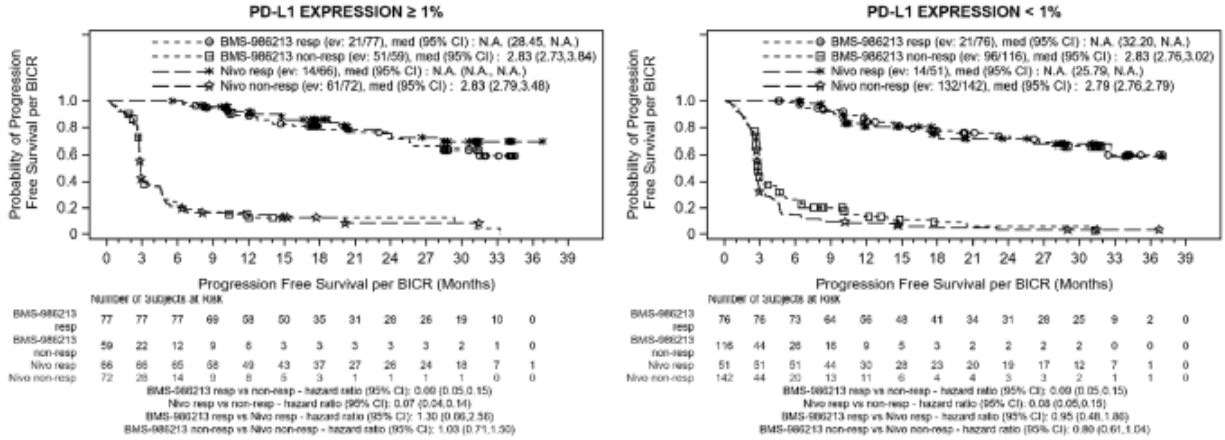


Note: statistical model for HR: unstratified Cox proportional hazard model. Symbols represent censored observations. PD-L1 values were evaluated at LabCorp LA.

Source: Figure S.10.3.4 in the CA224047 CSR Addendum 01.[2]

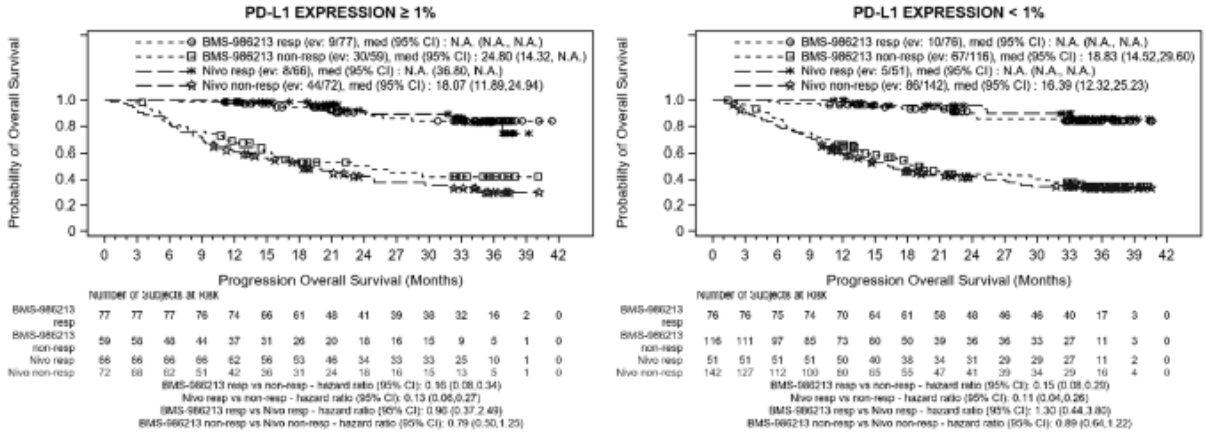
Exploratory analyses of PFS and OS by response showed that achievement of a tumour response (BOR of CR or PR) was associated with prolonged PFS and OS, irrespective of the treatment and PD-L1 expression subgroup (≥1% and < 1%) (Figure 16 and Figure 17).

Figure 16. Kaplan-Meier plot of PFS per BICR, primary definition, by responder/Non-responder per BICR, All randomised subjects by baseline PD-L1 expression (≥1% vs < 1%) (28-Oct-2021 DBL)



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; Nivo = Nivolumab; ev = events; med = median.
Updated PFS from 28OCT2021 database lock, at the time of response read-out.
Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Figures\EBR29DBL03
Program Name: rg-ef-pfsbicrbyresponderpdl13.sas

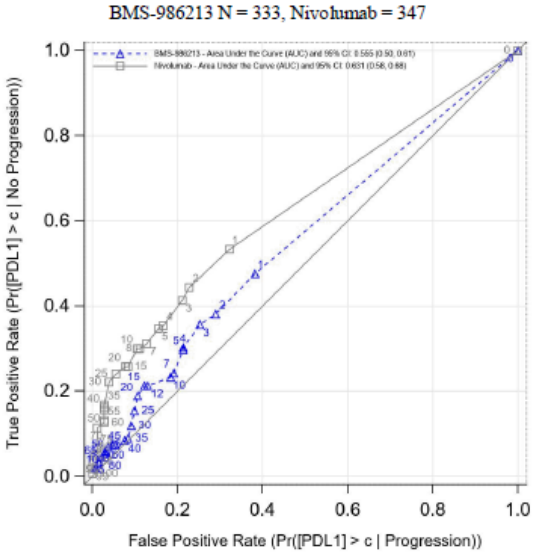
Figure 17. Kaplan-Meier plot of Overall Survival by responder/Non-responder per BICR, All randomised subjects by baseline PD-L1 expression (≥1% vs < 1%) (28-Oct-2021 DBL)



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; Nivo = Nivolumab; ev = events; med = median.
Data from 28OCT2021 database lock, at the time of OS and response read-out.
Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Figures\EBR29DBL03
Program Name: rg-ef-osbyresponderpdl13.sas

A receiver operating characteristic (ROC) curve for PD-L1 expression based on 6-month PFS was constructed, which was the closest landmark to the 8.7-month minimum study follow-up at the time of the latest DBL (Figure 18). The ROC analyses for PFS at 6 months and response per BICR demonstrated AUCs close to 0.5 for both nivo+rela FDC and nivolumab monotherapy, and the ROC analysis does not clearly define an optimal PD-L1 cut-off that maximizes sensitivity and specificity.

Figure 18. ROC curve based on 6-month progression-free survival per BICR, all randomised subjects with quantifiable baseline PDL1 values



Annotations represent the level of baseline PDL1 expression (%).
Best PDL1 cut-off based on Youden's J index is 2 for Nivolumab and 4 for BMS-986213.
Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Figures\EBR13DBL03
Program Name: rg-bm-rocpdl1pfsbicr6mos.sas

PFS2 per investigator

PFS2 was defined as the time from randomisation to progression date after the next line of therapy, per investigator assessment, or to death from any cause, whichever occurred first. Subjects who were alive and without progression after the next line of therapy were censored at last known alive date.

Median PFS2 per investigator were N.A. (95% CI: 21.75, N.A.) and 20.04 (95% CI: 15.44, 25.13) months for rela+nivo FDC (BMS-986213) vs nivolumab monotherapy, respectively. HR of rela+nivo FDC (BMS-986213) arm versus nivolumab monotherapy arm was 0.77 (95% CI: 0.61, 0.97).

Based on the 28-Oct-2021 DBL, PFS2 was 30.23 (95% CI: 23.72, NA) and 20.04 (95% CI: 15.44, 25.13) months for rela+nivo FDC vs nivolumab monotherapy, respectively (HR: 0.76, 95% CI: 0.61, 0.93).

Frequencies and type of subsequent anti-cancer therapy were comparable between treatment arms. A total of 35.5% and 37.3% of subjects received any type of subsequent systemic therapy in the rela+nivo FDC and nivolumab arm, respectively. PD1/CTLA4 inhibitors were given in 9.0% and 12.8% of subjects, and targeted BRAF/MEK mono or combination were given in 11.5% and 13.9% of subjects in the rela+nivo FDC and nivolumab arm, respectively.

Treatment-free interval and treatment-free survival

TFI and TFS are defined in a limited subgroup of randomised subjects who were off study treatment, and either on study or off study. Median TFI was 7.53 months (range: 0.1-30.4) in the rela+nivo FDC arm (n=167) and 4.21 months (range: 0.1-3.25) in the nivolumab arm (n=151). Median TFS was 3.98 months (range: 0.1-30.4+) and 1.45 months (range: 0.1-25.6+) for rela+nivo FDC and nivolumab, respectively.

Patient reported outcomes (PRO)

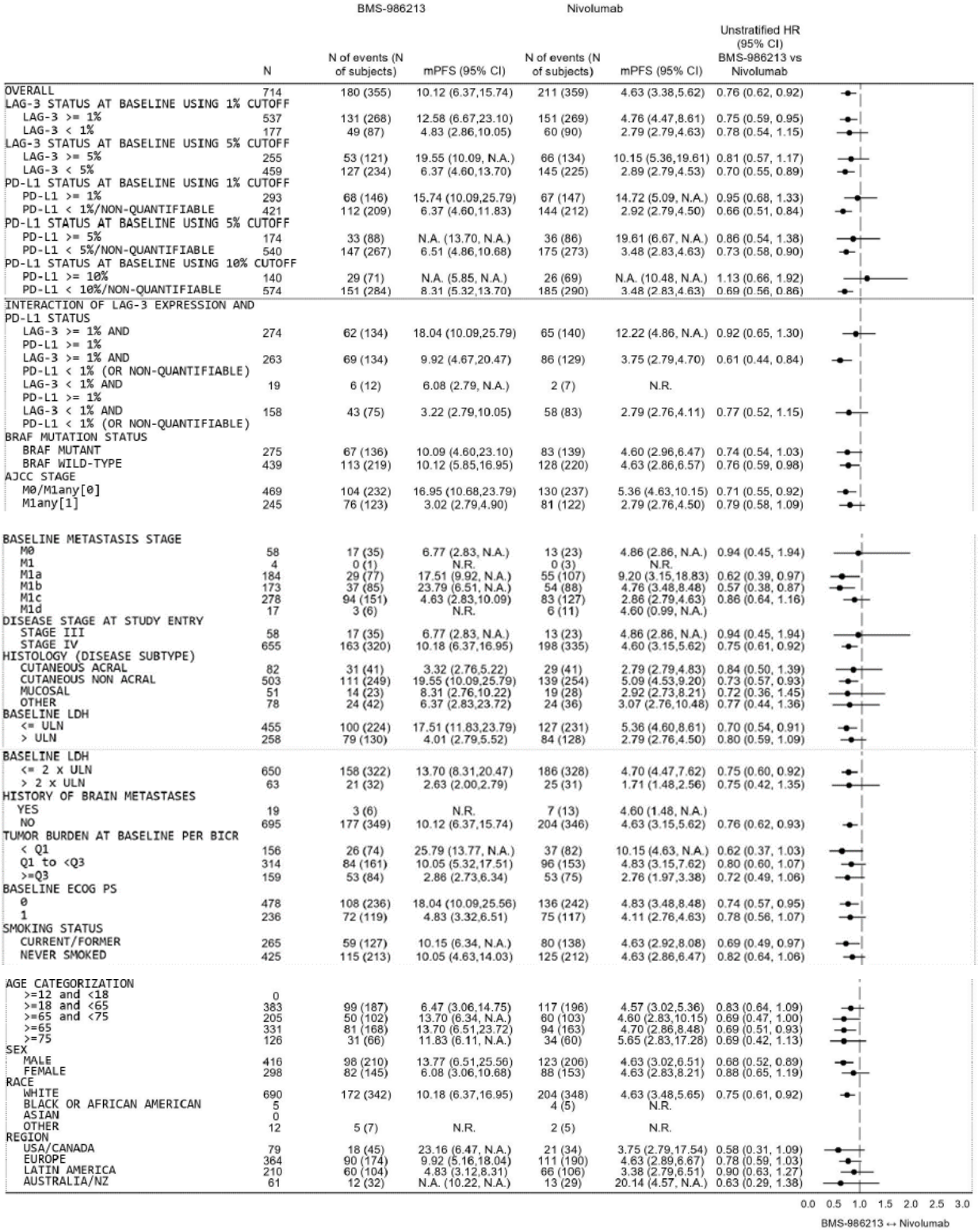
Various PRO tools were used to measure changes in quality of life, including change in health status (EuroQoL EQ-5D), change in cancer-related symptoms and quality of life (FACT-M score), and impact of symptomatic AEs (FACIT GP5 item). In general, quality of life remained stable in both treatment arms and observed changes did not reach minimal important differences. Numerically slightly higher scores for nivolumab monotherapy were observed in some domains of these scores, however no clinically meaningful differences in health-related quality of life were observed between both treatment arms.

- **Ancillary analyses**

Subgroup analyses for PFS per BICR (primary definition) are presented in Figure 19. Biomarker data have been discussed before. For almost all other subgroups, HR was below 1.

Additionally, subgroup analyses are shown for OS based on 28-Oct-2021 DBL (Figure 20) and results for most subgroups are in line with the ITT. However, data are considered preliminary as OS data are not yet fully mature.

Figure 19. Forest plot of treatment effect on PFS per BICR (primary definition) in predefined subsets – All randomised subjects Study CA224047

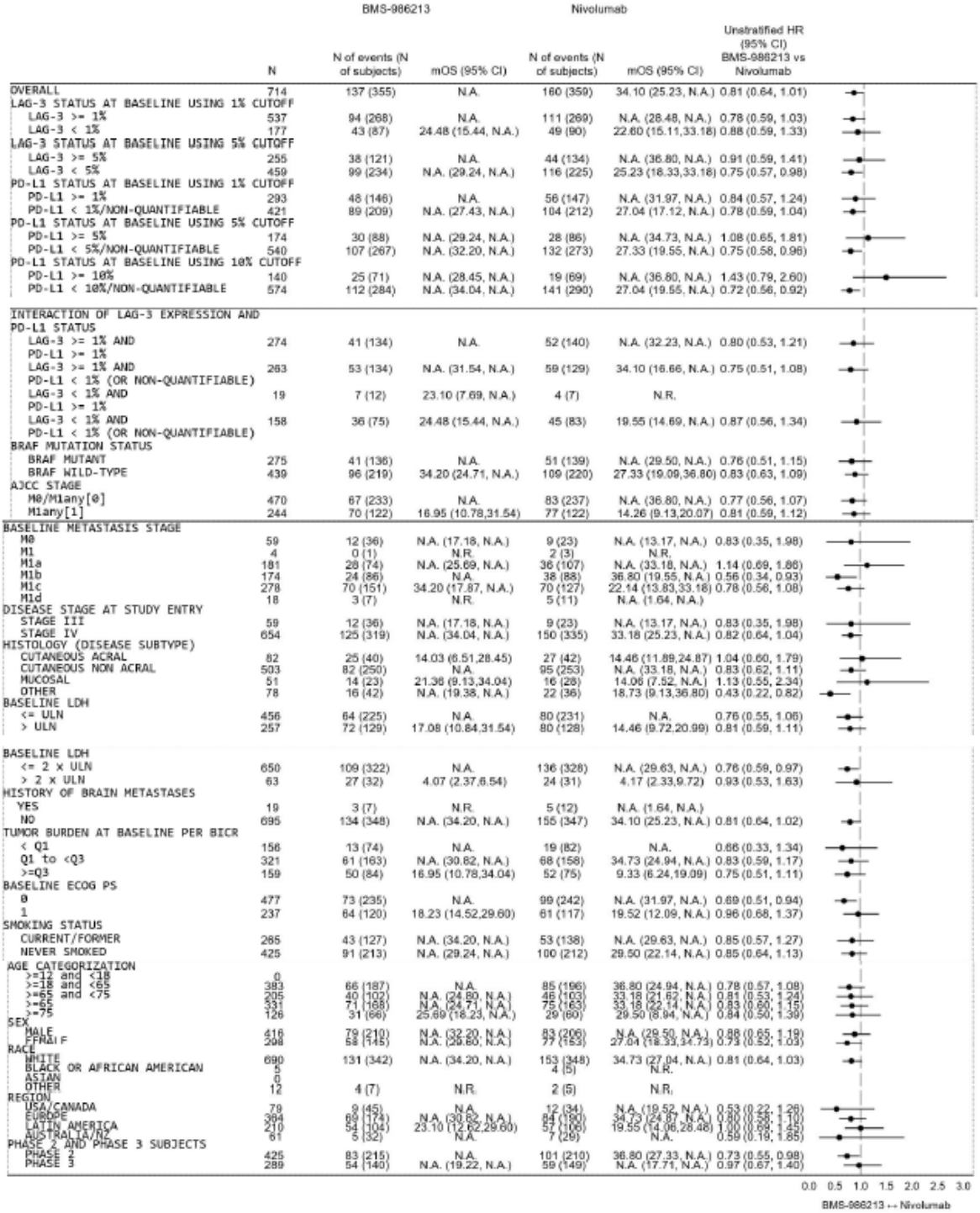


	N	BMS-986213 N of events (N of subjects)	BMS-986213 mPFS (95% CI)	Nivolumab N of events (N of subjects)	Nivolumab mPFS (95% CI)	Unstratified HR (95% CI) BMS-986213 vs Nivolumab
OVERALL	714	180 (355)	10.12 (6.37,15.74)	211 (359)	4.63 (3.38,5.62)	0.76 (0.62, 0.92)
LAG-3 STATUS AT BASELINE USING 1% CUTOFF						
LAG-3 >= 1%	537	131 (268)	12.58 (6.67,23.10)	151 (269)	4.76 (4.47,8.61)	0.75 (0.59, 0.95)
LAG-3 < 1%	177	49 (87)	4.83 (2.86,10.05)	60 (90)	2.79 (2.79,4.63)	0.78 (0.54, 1.15)
LAG-3 STATUS AT BASELINE USING 5% CUTOFF						
LAG-3 >= 5%	255	53 (121)	19.55 (10.09, N.A.)	66 (134)	10.15 (5.36,19.61)	0.81 (0.57, 1.17)
LAG-3 < 5%	459	127 (234)	6.37 (4.60,13.70)	145 (225)	2.89 (2.79,4.53)	0.70 (0.55, 0.89)
PD-L1 STATUS AT BASELINE USING 1% CUTOFF						
PD-L1 >= 1%	293	68 (146)	15.74 (10.09,25.79)	67 (147)	14.72 (5.09, N.A.)	0.95 (0.68, 1.33)
PD-L1 < 1%/NON-QUANTIFIABLE	421	112 (209)	6.37 (4.60,11.83)	144 (212)	2.92 (2.79,4.50)	0.66 (0.51, 0.84)
PD-L1 STATUS AT BASELINE USING 5% CUTOFF						
PD-L1 >= 5%	174	33 (88)	N.A. (13.70, N.A.)	36 (86)	19.61 (6.67, N.A.)	0.86 (0.54, 1.38)
PD-L1 < 5%/NON-QUANTIFIABLE	540	147 (267)	6.51 (4.86,10.68)	175 (273)	3.48 (2.83,4.63)	0.73 (0.58, 0.90)
PD-L1 STATUS AT BASELINE USING 10% CUTOFF						
PD-L1 >= 10%	140	29 (71)	N.A. (5.85, N.A.)	26 (69)	N.A. (10.48, N.A.)	1.13 (0.66, 1.92)
PD-L1 < 10%/NON-QUANTIFIABLE	574	151 (284)	8.31 (5.32,13.70)	185 (290)	3.48 (2.83,4.63)	0.69 (0.56, 0.86)
INTERACTION OF LAG-3 EXPRESSION AND PD-L1 STATUS						
LAG-3 >= 1% AND PD-L1 >= 1%	274	62 (134)	18.04 (10.09,25.79)	65 (140)	12.22 (4.86, N.A.)	0.92 (0.65, 1.30)
LAG-3 >= 1% AND PD-L1 < 1% (OR NON-QUANTIFIABLE)	263	69 (134)	9.92 (4.67,20.47)	86 (129)	3.75 (2.79,4.70)	0.61 (0.44, 0.84)
LAG-3 < 1% AND PD-L1 >= 1%	19	6 (12)	6.08 (2.79, N.A.)	2 (7)	N.R.	
LAG-3 < 1% AND PD-L1 < 1% (OR NON-QUANTIFIABLE)	158	43 (75)	3.22 (2.79,10.05)	58 (83)	2.79 (2.76,4.11)	0.77 (0.52, 1.15)
BRAF MUTATION STATUS						
BRAF MUTANT	275	67 (136)	10.09 (4.60,23.10)	83 (139)	4.60 (2.96,6.47)	0.74 (0.54, 1.03)
BRAF WILD-TYPE	439	113 (219)	10.12 (5.85,16.95)	128 (220)	4.63 (2.86,6.57)	0.76 (0.59, 0.98)
AJCC STAGE						
M0/M1any[0]	469	104 (232)	16.95 (10.68,23.79)	130 (237)	5.36 (4.63,10.15)	0.71 (0.55, 0.92)
M1any[1]	245	76 (123)	3.02 (2.79,4.90)	81 (122)	2.79 (2.76,4.50)	0.79 (0.58, 1.09)
BASELINE METASTASIS STAGE						
M0	58	17 (35)	6.77 (2.83, N.A.)	13 (23)	4.86 (2.86, N.A.)	0.94 (0.45, 1.94)
M1	4	0 (1)	N.R.	0 (3)	N.R.	
M1a	184	29 (77)	17.51 (9.92, N.A.)	55 (107)	9.20 (3.15,18.83)	0.62 (0.39, 0.97)
M1b	173	37 (85)	23.79 (6.51, N.A.)	54 (88)	4.76 (3.48,8.48)	0.57 (0.38, 0.87)
M1c	278	94 (151)	4.63 (2.83,10.09)	83 (127)	2.86 (2.79,4.63)	0.86 (0.64, 1.16)
M1d	17	3 (6)	N.R.	6 (11)	4.60 (0.99, N.A.)	
DISEASE STAGE AT STUDY ENTRY						
STAGE III	58	17 (35)	6.77 (2.83, N.A.)	13 (23)	4.86 (2.86, N.A.)	0.94 (0.45, 1.94)
STAGE IV	655	163 (320)	10.18 (6.37,16.95)	198 (335)	4.60 (3.15,5.62)	0.75 (0.61, 0.92)
HISTOLOGY (DISEASE SUBTYPE)						
CUTANEOUS ACRAL	82	31 (41)	3.32 (2.76,5.22)	29 (41)	2.79 (2.79,4.83)	0.84 (0.50, 1.39)
CUTANEOUS NON ACRAL	503	111 (249)	19.55 (10.09,25.79)	139 (254)	5.09 (4.53,9.20)	0.73 (0.57, 0.93)
MUCOSAL	51	14 (23)	8.31 (2.76,10.22)	19 (28)	2.92 (2.73,8.21)	0.72 (0.36, 1.45)
OTHER	78	24 (42)	6.37 (2.83,23.72)	24 (36)	3.07 (2.76,10.48)	0.77 (0.44, 1.36)
BASELINE LDH						
<= ULN	455	100 (224)	17.51 (11.83,23.79)	127 (231)	5.36 (4.60,8.61)	0.70 (0.54, 0.91)
> ULN	258	79 (130)	4.01 (2.79,5.52)	84 (128)	2.79 (2.76,4.50)	0.80 (0.59, 1.09)
BASELINE LDH						
<= 2 x ULN	650	158 (322)	13.70 (8.31,20.47)	186 (328)	4.70 (4.47,7.62)	0.75 (0.60, 0.92)
> 2 x ULN	63	21 (32)	2.63 (2.00,2.79)	25 (31)	1.71 (1.48,2.56)	0.75 (0.42, 1.35)
HISTORY OF BRAIN METASTASES						
YES	19	3 (6)	N.R.	7 (13)	4.60 (1.48, N.A.)	
NO	695	177 (349)	10.12 (6.37,15.74)	204 (346)	4.63 (3.15,5.62)	0.76 (0.62, 0.93)
TUMOR BURDEN AT BASELINE PER BICR						
< Q1	156	26 (74)	25.79 (13.77, N.A.)	37 (82)	10.15 (4.63, N.A.)	0.62 (0.37, 1.03)
Q1 to <Q3	314	84 (161)	10.05 (5.32,17.51)	96 (153)	4.83 (3.15,7.62)	0.80 (0.60, 1.07)
>=Q3	159	53 (84)	2.86 (2.73,6.34)	53 (75)	2.76 (1.97,3.38)	0.72 (0.49, 1.06)
BASELINE ECOG PS						
0	478	108 (236)	18.04 (10.09,25.56)	136 (242)	4.83 (3.48,8.48)	0.74 (0.57, 0.95)
1	236	72 (119)	4.83 (3.32,6.51)	75 (117)	4.11 (2.76,4.63)	0.78 (0.56, 1.07)
SMOKING STATUS						
CURRENT/FORMER	265	59 (127)	10.15 (6.34, N.A.)	80 (138)	4.63 (2.92,8.08)	0.69 (0.49, 0.97)
NEVER SMOKED	425	115 (213)	10.05 (4.63,14.03)	125 (212)	4.63 (2.86,6.47)	0.82 (0.64, 1.06)
AGE CATEGORIZATION						
>=12 and <18	0					
>=18 and <65	383	99 (187)	6.47 (3.06,14.75)	117 (196)	4.57 (3.02,5.36)	0.83 (0.64, 1.09)
>=65 and <75	205	50 (102)	13.70 (6.34, N.A.)	60 (103)	4.60 (2.83,10.15)	0.69 (0.47, 1.00)
>=65	331	81 (168)	13.70 (6.51,23.72)	94 (163)	4.70 (2.86,8.48)	0.69 (0.51, 0.93)
>=75	126	31 (66)	11.83 (6.11, N.A.)	34 (60)	5.65 (2.83,17.28)	0.69 (0.42, 1.13)
SEX						
MALE	416	98 (210)	13.77 (6.51,25.56)	123 (206)	4.63 (3.02,6.51)	0.68 (0.52, 0.89)
FEMALE	298	82 (145)	6.08 (3.06,10.68)	88 (153)	4.63 (2.83,8.21)	0.88 (0.65, 1.19)
RACE						
WHITE	690	172 (342)	10.18 (6.37,16.95)	204 (348)	4.63 (3.48,5.65)	0.75 (0.61, 0.92)
BLACK OR AFRICAN AMERICAN	5			4 (5)	N.R.	
ASIAN	0					
OTHER	12	5 (7)	N.R.	2 (5)	N.R.	
REGION						
USA/CANADA	79	18 (45)	23.16 (6.47, N.A.)	21 (34)	3.75 (2.79,17.54)	0.58 (0.31, 1.09)
EUROPE	364	90 (174)	9.92 (5.16,18.04)	111 (190)	4.63 (2.89,6.67)	0.78 (0.59, 1.03)
LATIN AMERICA	210	60 (104)	4.83 (3.12,8.31)	66 (106)	3.38 (2.79,6.51)	0.90 (0.63, 1.27)
AUSTRALIA/NZ	61	12 (32)	N.A. (10.22, N.A.)	13 (29)	20.14 (4.57, N.A.)	0.63 (0.29, 1.38)

Note: HR and median (displayed as N.R.) are not computed for subset category with less than 10 subjects per treatment arm. PD-L1 data was from LabCorp LA, LAG-3 and BRAF mutation status data was from IRT, and AJCC M-stage data was from RAVE and laboratory values.

N.A.: not applicable, median or limit of CI not estimable.

Figure 20. Forest plot of treatment effect on overall survival in predefined subsets – All randomised subjects (28-Oct-2021 DBL)

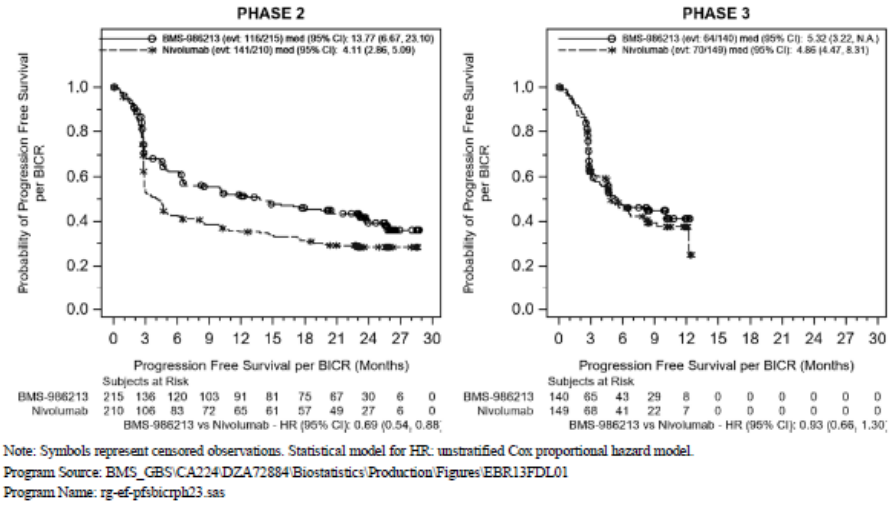


HR and median (displayed as N.R.) are not computed for subset category with less than 10 subjects per treatment group.
N.A.: Not Applicable, median or limit of CI not estimable
Source: Figure S.5.31.3 in the CA224047 CSR Addendum 01.[2]

Efficacy analyses were also performed for the phase 2 and 3 cohorts separately (Figure 21 and Table 27). As of the 28-Oct-2021 DBL, the HRs of PFS and OS were lower in the Phase 2 subgroup (PFS HR 0.69 [95% CI: 0.55, 0.88] and OS HR 0.73 [95% CI: 0.55, 0.98]) relative to the Phase 3 subgroup (PFS HR 0.96 [95% CI: 0.70, 1.31] and OS HR 0.97 [95% CI: 0.67, 1.40]). The ORR difference

between treatment arms favoured nivo+rela FDC in both subgroups (12.7 [95% CI: 3.5, 21.7] in the Phase 2 subgroup and 7.1 [95% CI: -3.9, 18.0] in the Phase 3 subgroup).

Figure 21. Kaplan-Meier plot of PFS per BICR (primary definition), all randomised subjects (09-Ma-2021 DBL)



Note: Symbols represent censored observations. Statistical model for HR: unstratified Cox proportional hazard model.
Program Source: BMS_GBS\CA224\DZA72884\Biostatistics\Production\Figures\EBR13FDL01
Program Name: rg-ef-pfsbicrph23.sas

Table 27. Treatment effect on PFS per BICR, OS and ORR for the phase 2 and phase 3 phase 3 part separately, all randomised subjects (28-Oct-2021 DBL)

		Rela+nivo FDC		Nivolumab monotherapy		Rela+nivo FDC vs Nivo
	N	**N of events (N of subjects)**	**mPFS (95% CI)**	**N of events (N of subjects)**	**mPFS (95% CI)**	**Unstratified HR (95% CI)**
Phase 2	425					
PFS		126 (215)	13.70 (6.67, 23.10)	151 (210)	3.61 (2.86, 4.70)	0.69 (0.55, 0.88)
OS		83 (215)	N.A.	101 (210)	36.80 (27.33, N.A.	0.73 (0.55, 0.98)
ORR		97 (215)	45.1 (38.3, 52.0)	68 (210)	32.4 (26.1, 39.2)	12.7 (3.5, 21.7)
Phase 3	289					
PFS		78 (140)	8.34 (4.63, 12.02)	82 (149)	6.44 (4.50, 11.86)	0.96 (0.70, 1.31)
OS		54 (150)	N.A. (19.22, N.A.)	59 (49)	N.A. (17.71, N.A.)	0.97 (0.67, 1.40)
ORR		56 (140)	40.0 (31.8, 48.6)	49 (149)	32.9 (25.4, 41.0)	7.1 (-3.9, 18.0)

- **Summary of main efficacy results**

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

Table 28. Summary of efficacy for trial CA224047

Title: A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with Nivolumab versus Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma.			
Study identifier	CA224047		
	CA224047 is a multicentre, seamless Phase 2/3, randomised, double-blind study of relatlimab + nivolumab (FDC at a 1:3 ratio; BMS-986213) vs nivolumab monotherapy in subjects with previously untreated metastatic or unresectable melanoma. Subjects (adults and adolescents ≥ 12 years of age) were randomised 1:1 to treatment with BMS-986213 (relatlimab + nivolumab 160/480 mg IV Q4W FDC) or nivolumab 480 mg IV Q4W and study treatment was continued until disease progression, treatment discontinuation, withdrawal of consent, or end of study. Randomisation was stratified by tumour PD-L1 expression (≥ 1% vs < 1%), LAG-3 expression (≥ 1% vs < 1%), BRAF mutation (V600 mutation positive vs V600 wild-type), and AJCCv8 M stage M0/M1any[0] vs M1any[1]). As the indication is restricted to the patient population with tumour PD-L1 expression <1%, results described below refer to this patient group.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	FPFV was on 11-April 2018, last subject randomised Dec 2020. Database lock: 09-March 2021. The study is ongoing. Additional follow-up for OS up to maximum 5 years after randomisation last subject. Not applicable Not applicable	
Hypothesis	Treatment with BMS-986213 will improve PFS when compared to nivolumab monotherapy in previously untreated participants with unresectable or metastatic melanoma.		
Treatments groups	Rela+nivo FDC (BMS-986213)	Relatlimab + nivolumab 160/480 mg IV Q4W FDC; median treatment duration 5.55 months; 355 subjects randomised No dose reductions allowed	
	Nivolumab	Nivolumab monotherapy 480 mg IV Q4W; median treatment duration 4.86 months; 359 subjects randomised No dose reductions allowed	
Endpoints and definitions	Primary endpoint / PFS	Progression-free survival defined as the time interval between the date of randomisation and the first date of documented progression or death due to any cause, whichever occurs first.	
	Secondary endpoint / OS	Overall survival defined as the time between the date of randomisation and the date of death due to any cause.	
	Secondary endpoint / ORR	Objective response rate defined as the proportion of subjects who achieved a best overall response (BOR) of complete response (CR) or partial response (PR) based on RECIST 1.1. Confirmation of response is required at least 4 weeks after the initial response.	
Database lock	9 March 2021 primary analysis PFS and 28 October 2021 for the secondary analyses of OS and ORR		
Results and Analysis			
Analysis description	**Primary Analysis - PFS**		
Analysis population and time point description	The final primary PFS analysis was performed when at least 365 PFS events occurred per BICR (9 March 2021 DBL). The analysis population is the randomised population. Reported data are in the PD-L1<1% subgroup based on the 28 October 2021 DBL.		
Descriptive statistics and estimate variability	Treatment group	Rela+nivo FDC	Nivolumab
	Number of subjects	N=209	N=212
	Median PFS (months)	6.7	3.0
	95% CI	4.7, 12.0	2.8, 4.5
	Median OS (months)	N.A.	27.0
	95% CI	27.4, N.A	17.1, NA
	ORR (%)	36.4	24.1
	95% CI	29.8, 43.3	18.5, 30.4

Title: A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with Nivolumab versus Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma.			
Study identifier	CA224047		
Effect estimate per comparison	Primary endpoint: PFS	Comparison groups	BMS-986213 vs nivolumab
		HR	0.68
		95% CI	0.53, 0.86
	Secondary endpoint: OS	Comparison groups	BMS-986213 vs nivolumab
		HR	0.78
		95% CI	0.59, 1.04
Notes	Results are supported by the updated PFS analysis at the time of the OS and ORR analyses (28-Oct-2021 DBL) Exploratory analyses of biomarker-defined subgroups showed a beneficial effect of the combination on PFS independent of LAG-3 expression (cut-off 1%).		

2.6.5.3. Clinical studies in special populations

There was no dedicated study in special populations.

A summary of the clinical trial by age is shown below.

Table 29. Subjects in studies CA224020 and CA224047 by age groups

Study	Total number of subjects	Age ≥ 65 - < 75	Age ≥ 75 - < 85	Age ≥ 85
CA224020, n (%)	1404	420 (29.9)	150 (10.7)	24 (1.7)
CA224047				
Nivo+rela FDC, n (%)	355	102 (28.7)	60 (16.9)	6 (1.7)
Nivolumab, n (%)	359	103 (28.7)	53 (14.8)	7 (1.9)

Source: Table S.3.1.1; Table S.3.2.1.1 in the CA224047 Primary CSR.[3]

Paediatric population

The applicant applies for the first line indication treatment of metastatic or unresectable (advanced) melanoma. This indication includes both adults and adolescents aged 12 to <18 years of age (weighing at least 40 kg), however no patients below the age of 18 years are included in the clinical studies for the fixed dose combination of relatlimab and nivolumab. The indication for adolescents will be based on extrapolation of adult data. Given the low incidence of advanced melanoma in the paediatric population it is difficult to enroll adolescents in clinical studies in this setting.

The following points are considered important for assessment of extrapolation in the context of the favourable and unfavourable effects:

- Confirmation that benefit/risk can be established and is positive in the source (adult) population

- Confirmation that disease, progression of disease, treatment and prognosis is similar between ages

- Confirmation that with the proposed dose, exposure in adolescents can be predicted and is comparable with adults

- Confirmation that the PK/response- relation is comparable for adults and adolescents, or relation can be predicted from adult data

- Evaluating the safety profile in adolescents

Similarity and differences in disease between adults and adolescents

Primary melanoma tumour characteristics are considered to be comparable between adolescent and adult melanoma patients. In an analysis of 1,255 children (age less than 20 years), the 10-19-year-old group had similar baseline characteristics compared with the group of 20-24-year-old young adults (Strousse JJ et al., J Clin Oncology 2005).

Similarity of advanced melanoma between adolescents and adults has been demonstrated by comparable general clinical characteristics:

- Histology: The frequency of histological subtypes, such as lentigo malignant melanoma, superficial spreading melanoma, acral lentiginous melanoma, and nodular melanoma in tumours of adolescent melanoma patients is comparable to melanoma tumours in adult patients.
- Clinical presentation: Primary tumour characteristics, such as the site of the primary tumour, stage at diagnosis, tumour thickness, or level of invasion were compared between paediatric and adult melanoma patients.
- Risk factors: Common risk factors for melanoma in paediatric and adult patients are intermittent intense sun exposure, tendency to sunburn, tendency to freckle, fair skin, blue or green eyes, and blond or red hair. Genetic predisposing conditions for developing melanoma, specifically in the paediatric population, do more frequently manifest in early childhood than in adolescence.
- Driver mutations: Among the paediatric melanomas, conventional melanoma, which predominantly occurs in adolescents, shares properties similar to adult melanomas, including mutation rates, high rate of single nucleotide variations that are characteristic of ultraviolet damage, and similar rate of activating BRAFV600 mutation (Lu C et al., J Invest Derm 2015; Newman S et al., Nat Med 2019; Bhram A et al., Pediatr Blood Cancer 2018)
- Survival: A literature search for studies investigating the survival in paediatric melanoma patients was conducted. The majority of publications show that the OS, including the subgroup of adolescent melanoma patients with regional or distant metastases, is similar to that from adult patients.
- Treatment: Current treatment strategies for paediatric and adolescent melanoma are based on clinical guidelines for adult patients (Bagnoni G et al., Pediatr Surg Int 2019). There are limited clinical studies evaluating treatment outcomes in these age groups. The number of patients in paediatric studies are generally small and the studies did not have a randomised design.
    - The few clinical studies with radiotherapy and chemotherapy in paediatric patients with melanoma showed a comparable safety profile to adult patients. Tumour shrinkages in individual patients were reported. However, the design of the reported studies and the small number of adolescent melanoma patients enrolled do not allow for a conclusive comparison of efficacy to adult studies.
    - Clinical studies with IFNα2b and high-dose IL-2 in paediatric patients showed the feasibility and overall comparable safety profile to adult patients. However, the number of enrolled paediatric melanoma patients in these studies is too small to make a conclusive statement about the efficacy of IL-2 or interferon treatment in paediatric melanoma in relation to adult patients. These treatment modalities have now largely been supplanted (Michielin O et al., Ann Oncol 2019)

- Targeted therapies: To date, there are limited data on the safety and efficacy of BRAF V600 targeted therapies (eg, vemurafenib and dabrafenib)26,27,28 in the paediatric population (ages 12-17 years). Similar to adult melanoma, paediatric CM is associated with a high somatic mutation load, high frequencies of activating BRAF mutations, and PTEN copy number changes, with resulting activation of MAPK and PI3K/AKT cellular signalling pathways (Davar D et al., J Invest Dermatol 2015). Real world data from the DMTR (n = 3775) showed that the proportion of adolescents and young adults initially treated with BRAF/MEK-inhibition and immune checkpoint inhibitors were 35.2% and 33.8%, respectively (van der Kooij MK et al., Cancer 2020). Suggesting that BRAF and MEK inhibitors might also be active against adolescent melanoma.
- CTLA-4 inhibitor: Ipilimumab was evaluated in 2 trials of paediatric patients: (1) a dose-finding study in 33 patients aged 2 to 21 years with relapsed or refractory solid tumours, and (2) an open-label, single-arm trial in 12 adolescents aged 12 to 16 years with previously treated or untreated, unresectable Stage III or IV malignant melanoma. The overall safety profile of ipilimumab in children and adolescents was consistent with the safety profile in adults.
- PD-(L)1 Inhibitor: Clinical study CA209070 (NCT02304458), is an ongoing Phase ½ study of nivolumab with or without ipilimumab in children, adolescents, and young adults with recurrent or refractory solid tumours or sarcomas. The study includes patients older than 12 months of age to 30 years of age with variety of tumours occurring in children, such as lymphoma, neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing Sarcoma as well as advanced melanoma. The study will eventually report on 242 patients.

  In addition, the Phase 1/2 study, KEYNOTE-051 (NCT02332668) (Geoerger B, et al., Lancet Oncol 2020), which evaluated the safety of pembrolizumab monotherapy in 154 paediatric patients with advanced melanoma (5.2%), lymphoma (11.7%), and PD-L1 positive advanced, relapsed/refractory solid tumours had shown that the safety profile was generally similar to that seen in adults. Pooled efficacy results for the solid tumours cohort reported an ORR of 5.9%, with no CRs and a PR rate of 8.9%.

Exposure in adolescents and adults

The applied indication for Opdualag is for patients ages 12 years and older. The dosing regimen for adolescent patients 12-18 years is based on popPK simulations.

With respect to nivolumab, limited PK data in children and adolescents were available for patients with solid tumours. These paediatric PK data were included in the nivolumab popPK model. Comparison of the exposure data in the nivolumab popPK model indicate that adolescent subjects had 24% lower CL0, 28% lower CLSS, and 28% lower VC than corresponding parameters of adult subjects.

Although limited nivolumab PK data in adolescent solid tumour patients indicate a reduced clearance of nivolumab in adolescents as compared to adults, with respect to relatlimab, no adolescent PK data were available. The consequences of either the presence or absence of a reduced clearance in adolescent patients on nivolumab and relatlimab exposure was further investigated. To this end, popPK simulations on the different scenarios, i.e., flat dose or weight-based dose, and decreased clearance in adolescents or comparable clearance in adolescents and adults. Based on these provided simulated exposure to relatlimab and nivolumab in adolescent and adult patients, applying a flat dose and taking into account either the presence or the absence of a reduced clearance in adolescents, sufficiently comparable exposure between adolescent and adults is demonstrated. Considering the comparable

pathophysiology of melanoma in adolescents and adults, the proposal for a flat dose for relatlimab and nivolumab, being the same in adolescents and adults, is therefore supported.

PK/response- relation for adults and adolescents

As relatlimab and nivolumab are immune checkpoint inhibitors, the E-R resulting from relatlimab + nivolumab in adult and adolescent subjects with advanced melanoma is expected to be similar, based on the following biological and empirical evidence:

- The immune system in adolescents is fully mature with adult levels of T cells (Th1, Th2, cytotoxic T cells), dendritic and B cells, and is known to obtain adult levels of protection against infections.
- Relatlimab and nivolumab are IgG4 mAb targeting the LAG-3 and PD-1 receptors, respectively. Similar systemic exposures in adolescents and adults will therefore result in similar antibody-target binding; therefore, the E-R of relatlimab in combination with nivolumab is expected to be the same.

The exposure-effect relationships only have been investigated in adults.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

LAG-3 and PD-L1 were determined in Formalin-Fixed Paraffin- Embedded (FFPE) Human Tissue Samples.

LAG-3 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. LAG-3 expression is scored on a continuous scale from 0, then increments of 1% from 1 – 5% (i.e. 1, 2, 3, 4, 5), followed by increments of 10 for samples with ≥ 10% of cells staining (i.e. 10, 20, 30, 40, 50, 60, 70, 80, 90, 100) LAG-3 positive cells. The final LAG-3 score is LAG-3 negative: <1% LAG-3 positive cells, or LAG-3 Positive: ≥1% LAG-3 positive cells.

LAG-3 analytical method

The analytical method for LAG-3 in FFPE human tissue is determined at LabCorp using Immunohistochemistry performed on the Leica Bond III Automated Staining System. This assay is labelled as Research Use Only (RUO). In order to remove or reduce melanin pigmentation, which could interfere with LAG-3 staining interpretation, tissue slides are pretreated with a 3% hydrogen perioxide/ 1x target retrieval solution pH9/methanol solution. Following the melanin removal process, tissue sections are incubated with a primary antibody that is directed specifically against the target epitope. In general, for this method, heat induced epitiope retrieval (HIER) pretreatment is used to enhance exposure of the epitope to the antibody. After incubating the tissue with the primary antibody, the bound antibody is detected using Bond Polymer Refine Detection reagents (Leica). This detection format uses a polymerbased, biotin-free system that complexes horseradish peroxidase (HRP) to the tissue-bound antibody. The antibody-HRP complexes are visualised using diaminobenzidine (DAB) which produces a brown reaction product. The specimen is then counterstained and coverslipped. Results are interpreted using a light microscope by a pathologist.

Validation of the LAG-3 IHC assay was performed at LabCorp CMBP in accordance with LabCorp Standard Operating Procedures (SOPs) and regulatory requirements to provide documentation of assay

performance characteristics and to ensure validity of the data produced. The original validation of LAG-3 IHC was completed 27-Nov-2017.

LAG-3 assay clinical validity

No information on clinical validation was provided. This assay is labelled as Research Use Only (RUO).

LAG-3 cut-point selection and validation

The LAG-3 IHC assay is validated for exploratory purposes and has been used to stratify randomisation of subjects at a cut-off of 1%. Clinical validation has not been performed. About 75% of patients had LAG-3 ≥1% at baseline.

No clinical cut-point has been selected and validated for this assay.

PD-L1 assay

PD-L1 positive staining is defined as complete circumferential and/or partial linear plasma membrane staining of tumour cells at any intensity. The entire specimen must be evaluated. All viable tumour cells on the entire PD-L1 stained patient slide must be evaluated and included in the PD-L1 scoring assessment. A minimum of 100 viable tumour cells should be present in the PD-L1 stained patient slide to determine the percentage of stained cells. Cytoplasmic staining, if present, is not considered for scoring purpose. Non-malignant cells and immune cells (e.g., infiltrating lymphocytes or macrophages) may also stain with PD-L1; however, these should not be included in the scoring for the determination of PD-L1 positivity.

PD-L1 assay analytical method

Two PD-L1 biomarker reports were submitted one for LabCorp CMBP NC which initially performed PD-L1 testing and one for LabCorp LA used for the primary analysis and described here. The analytical method for PD-L1 determined at LabCorp LA used the immunohistochemistry (IHC) assay for the detection of PD-L1 clone 28-8 (Dako) in human formalin fixed embedded (FFPE) tissues. PD-L1 IHC 28-8 pharmDx contains optimised reagents and protocol required to complete an IHC staining procedure of FFPE specimens using Dako Autostainer Link48 and PT Link Pre-treatment module. Following incubation with the primary monoclonal antibody to PD-L1 or the Negative Control Reagent (NCR), specimens are incubated with a linker antibody specific to the host species of the primary antibody and incubated with a ready-to-use visualisation reagent consisting of secondary antibody molecules and horseradish peroxidase molecules coupled to a dextran polymer backbone. The enzymatic conversion of the subsequently added chromogen results in precipitation of a visible reaction product at the site of antigen. The colour of the chromogenic reaction is modified by a chromogen enhancement reagent. The specimen may then be counterstained and coverslipped. Results are interpreted by a trained pathologist using a light microscope.

Validation of the PD-L1 assay was performed in CLS Los Angeles in accordance with Covance Standard Operating Procedures (SOPs) and approved for use in 06-Nov-2017 (Melanoma Samples). The Dako PD-L1 IHC 28-8 pharmDx™ assay is labeled for Investigational Use Only (IUO).

PD-L1 assay clinical validity

No information on clinical validation was provided. The analytical method for PD-L1 in Formalin-Fixed Paraffin Embedded Human Tissue is Immunohistochemistry performed on Dako Autostainer Link48. This assay is labelled as Investigational Use Only (IUO).

PD-L1 cut-point selection and validation

The PD-L1 IHC assay is validated for exploratory purposes and has been used to stratify randomisation of subjects at a cut-off of 1%. Clinical validation has not been performed. About 40% of patients had

PD-L1 ≥1% at baseline. PFS by baseline PD-L1 expression showed a beneficial effect of the combination over nivo monotherapy in subjects with low PD-L1 expression (<1%). No beneficial effect was seen in subjects with PD-L1 ≥1%. Comparable results were seen based on a cut-off of 5% or 10%.

No clinical cut-point has been selected and validated for this assay.

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

Not applicable.

2.6.5.6. Supportive study(ies)

The phase 1/2a study CA224020 provides support for antitumour activity of the combination treatment in the PD-L1 pretreated melanoma population, however this is not the current target population. Anti-tumour activity was shown in subjects with 1L melanoma (Part C, see section on dose response study), but these results cannot be fully interpreted in the absence of a nivolumab monotherapy arm.

Immunogenicity

In Study CA224047, the incidence of relatlimab and nivolumab treatment emergent ADA and Nab were low (< 6%) in subjects who received rela+nivo FDC and nivolumab monotherapy. The incidence of nivolumab treatment emergent ADA, persistent ADA and NAb was similar in the FDC arm as compared to nivolumab monotherapy. There was no apparent trend showing an effect of ADA or NAb (either anti-relatlimab or anti-nivolumab) on the efficacy of rela+nivo FDC based on the assessment of the presence of ADA and NAb in relation to PFS (per BICR). Comparable results were observed for the phase 1/2a study CA224020.

Biomarker analysis plan

The applicant presented a biomarker analysis plan, aimed to identify biomarkers that predict response to rela+nivo combination therapy and gain a better understanding of the mechanism of action of novel LAG-3 and PD1 dual checkpoint inhibition. The utility of LAG-3 and PD-L1 as predictive biomarkers is described above in section 2.6.5.4. Further investigations performed by the applicant are described here.

LAG-3 as biomarker for treatment selection

Retrospective analysis by LAG-3 status in CA209067 showed similar enrichment in efficacy by LAG-3 expression when treated with nivolumab monotherapy or nivolumab+ipilimumab combination as was shown in study CA224020 in patients previously treated with IO therapy. As LAG-3 expression was quantified as the percentage of LAG-3 positive lymphocytes among all nucleated cells, it is likely to correlate with overall infiltrating lymphocytes in the tumour. In CA224020, biomarker comparison revealed apparent correlation between LAG-3 IHC score and BMS-4 gene tumour inflammatory signature (data not shown). An "inflamed" tumour microenvironment and the presence of tumour infiltrating lymphocytes have been associated with improved response to anti-PD1 therapy in melanoma, so LAG-3 expression as presently quantified, reflecting tumour immune infiltrates, may be a general predictive marker for immune therapies that rely on the presence of infiltrating immune cells to mount anti-tumour response. According to the applicant, overall data support LAG-3 as a predictive marker for checkpoint blockade therapy but not specific to relatlimab.

Other exploratory biomarkers study CA224047

In CA224047, exploratory biomarker analyses characterizing tumour and immune microenvironment and interrogating LAG-3 pathway were planned and data generation are ongoing. Amongst others tumour expression of CD8, MHC class I and class II at baseline, gene expression signature for tumour inflammation, and tumour TMB as measured by whole exome sequencing will be evaluated for association with response to rela+nivo therapy. Projected timeline for most biomarkers is Q2-Q3 2022 (PAM-REC).

2.6.6. Discussion on clinical efficacy

This is a marketing authorisation application (MAA) for an intravenous (IV) fixed-dose combination (FDC) of relatlimab, a first in class human LAG-3 specific IgG4 antibody, and nivolumab. This application is based on the adaptive phase 2/3 pivotal clinical study CA224047, as described below. In addition, data from the phase 1/2 study CA224020 have been submitted to provide supportive evidence of efficacy for the proposed combination in unresectable or metastatic melanoma, including subjects with advanced (relapsed or refractory) melanoma previously treated with immunotherapies.

The initially applied indication was:

"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)."

The primary objective of Study CA224047 was to determine if relatlimab/nivolumab IV FDC improves PFS, assessed per BICR, compared with nivolumab, which is a current standard of care in this patient population (adults only).

Design and conduct of clinical studies

The rationale for the dual blockade is supported by co-expression of LAG-3 and PD-1 on infiltrated lymphocytes and synergistic anti-tumour activity in mouse tumour models. Relatlimab monotherapy up to 800 mg elicited only one PR (n=25) in the phase 1/2a study CA224020. Available data indicate that LAG-3 monotherapy will not lead to clinically meaningful benefit for the target population and the lack of a relatlimab monotherapy arm in the pivotal trial is acceptable. Overall, it is considered adequate to investigate the efficacy in the first line setting, as in the relapsed/refractory setting with PD-L1 pre-treated patients' outcomes did not appear promising, based on the results of the CA224020 study, with an expected ORR of around 10%.

The phase 2/3 recommended dose of rela+nivo FDC of 160/480 mg Q4W in adults was based on an integrated assessment of relatlimab and nivolumab data from in vitro and preclinical studies, as well as clinical PK, PD, safety, and efficacy results from the phase 1/2a study CA224020. Treatment with rela+nivo 80/240 mg Q2W induced responses in heavily pretreated advanced solid tumours. The dose of 160/480 mg Q4W was supported by model-based simulations predicting similar exposure and receptor occupancy between rela+nivo 80/240 mg Q2W and 160/480 mg Q4W. Exposure-response relationships suggest flat relationships for both efficacy and safety, including the full PK data from Part E investigating relatlimab 480 mg vs. 160 mg Q4W. The applicant presented preliminary efficacy and safety results of the two doses of relatlimab (480 mg vs. 160 mg Q4W) in the first line melanoma setting from part E. Preliminary efficacy results indicate that ORR was higher with the higher relatlimab dose, however, tolerability appeared lower. Overall, these findings support the phase 2/3 recommended dose to a sufficient extent although predominantly based on safety/tolerability. The lack of a nivolumab monotherapy within study CA224020 precludes conclusions on the efficacy of the combination treatment over monotherapy in the 1L melanoma setting (Part C). Treatment with the FDC showed comparable safety to co-administration of the single agents, supported by PK exposure

data. The FDC was selected to provide convenient infusion preparation and rapid administration, as well as to decrease dosing and administration errors. Such simplification of therapy is insufficient by itself for a complete justification of a FDC (FDC guideline, EMA/CHMP/158268/2017), however, there is also no objection in terms of limitation of dose adjustments for the individual components as no dose changes are allowed. The proposed infusion time is 30 minutes, whereas a 60-minute infusion time was used in the clinical studies. This is further discussed in the PK and safety section.

The pivotal trial study CA224047 was a global, double-blind, randomised, adaptive phase 2/3 study comparing rela+nivo FDC with nivolumab in patients with previously untreated, unresectable, or metastatic melanoma. The overall study design is acceptable, as also stated at the time of a first initial SA received in January 2020 (EMEA/H/SA/4345/1/2019/II). The study enrolled male and female subjects, sought to enrol ≥ 12 years of age, with histologically confirmed Stage III (unresectable) or Stage IV melanoma (AJCC 8th), with no prior systemic anticancer therapy for advanced melanoma. Specified prior adjuvant or neoadjuvant melanoma therapies were permitted. Patients with uveal melanoma, active or untreated brain metastases, active autoimmune disease, and a history of myocarditis, and those with a baseline elevated troponin > 2xULN were excluded from the study. The in- and exclusion criteria largely reflect the target population, although somewhat healthier, and resemble that of clinical studies in the same setting. Exclusion of subjects with a history of myocarditis and elevated troponin was based on preclinical findings, myocarditis being an IMAE for nivolumab, and a case of Grade 4 myocarditis reported in Study CA224020.

Subjects were randomised 1:1 to treatment with relatlimab + nivolumab 160/480 mg IV Q4W FDC (BMS-986213) or nivolumab 480 mg IV Q4W, and randomisation was stratified based on LAG-3 expression (≥ 1% vs < 1%), tumour cell PD-L1 expression (≥ 1% vs < 1%), BRAF mutation (V600 mutation positive vs V600 wild-type), and AJCC v8 M stage (M0/M1Any[0] vs M1Any[1]). BRAF mutation and elevated LDH (stage M1Any[1]) are well known prognostic factors. Stratification by LAG-3 and PD-L1 is supported given their potential predictive value. Nivolumab monotherapy or in combination with ipilimumab is the standard of care for the target population and an appropriate comparator, as is the recommended dose of 480 mg Q4W over 60 minutes iv infusion.

The phase 2/3 adaptive trial design is acceptable. As the PFS IA met the pre-specified HR of ≤ 0.8 after 425 subjects were enrolled, the study transitioned seamlessly to Phase 3. During a follow-up SA procedure, received in May 2020 (EMEA/H/SA/4345/1/FU/1/2020/II), a second interim analysis (PFS IA2) was proposed by the applicant. This was discouraged and the recommendation was followed by the applicant. The primary endpoint is PFS by BICR using RECIST v1.1 with OS as the key secondary endpoint. PFS is an acceptable endpoint provided mature OS data exclude a negative effect are available and the effect is homogenous across important sub-populations. ORR was also part of the hierarchical testing strategy after OS and was not considered mature until all subjects had the potential for 7 months of follow-up. For the primary analysis, a primary and secondary definition of PFS were defined. These differed by how subsequent anti-cancer medication prior to BICR-determined progression was handled (i.e. censored or not). Further definitions of events and censoring rules were standard, and a number of sensitivity analyses were pre-specified.

A total of 1,281 patients were enrolled in the study. Among them 714 (55.7%) were randomised in the study, 355 subjects received rela+nivo FDC and 359 received nivolumab monotherapy. The main reason for screening failure was "no longer meeting study criteria" (n=465; 36.3%). These included unevaluable PD-L1, LAG-3, and/or BRAF status, worsening of ECOG PS, and presence of exclusionary brain metastases with no single predominant reason.

Baseline demographic and disease characteristics were balanced across the treatment arms. The median age was 63 years (range: 20-94), 58.3% were male and 96.6% were white. ECOG performance status score was 0 (33.1%) or 1 (66.9%). The majority of the patients had AJCC stage IV

disease (91.7%); 38.9% had M1c disease at study entry. A slightly higher percentage was observed in the rela+nivo FDC arm. Thirty-eight percent of subjects had BRAF mutation-positive melanoma, 36.1% had baseline LDH level greater than ULN at study entry, and 2.7% had a history of brain metastases. Forty-one percent of subjects had PD-L1 ≥1% tumour cell membrane expression and 75.2% had LAG-3 ≥1% expression. Eight percent of subjects received prior adjuvant therapy.

Study enrolment was paused for the PFS IA of phase 2, thereafter enrolment was slowed down for about 6 months due to the pandemic. Demographic and baseline disease characteristics were largely comparable between the phase 2 and phase 3 part, except for a higher proportion of subjects with ECOG 1 in the phase 3 part (42.9% vs 26.4%). Differences (<10%) were also seen for baseline LDL>ULN (higher in phase 3 part) and metastasis M1c (lower in phase 3 part). In addition, more patients were included from Latin America in the phase 3 part compared to the phase 2 part (42.9% vs 20.5%) due to additional recruitment from this region. PFS analyses were also presented separately for the phase 2 and phase 3 part of the study to rule out, to the extent possible, that the decision to proceed to phase 3 was not based on over-optimistic phase 2 results. Divergent results were seen between the two phases with clearly separating KM-curves in the phase 2 part and (party) overlapping curves in the phase 3 part of the study. Though differences in baseline characteristics and follow-up may partly explain this divergent result, there was no single baseline characteristic that could explain the observed differences. As the decision to proceed to phase 3 was made by the DMC independently of the company and in a blinded manner, it appears reasonable to conclude that the decision was not based on over-optimistic phase 2 results.

Changes in primary endpoint for the phase 2 part (PFS instead of ORR) and the order of statistical testing of the phase 3 part secondary endpoints were driven by external evidence and not considered to impact the study integrity or outcome. There were, in general, no issues raised during the assessment concerning the conduct of the studies submitted. The majority of subjects had any important protocol deviation, however a limited number had deviations that could potentially impact study outcomes. GCP inspections from competent authorities support GCP compliance.

Study CA224020 provides limited supported evidence for efficacy of the combination treatment in the 1L target population (Part C) as a nivolumab monotherapy arm was not included.

Efficacy data and additional analyses

At the time of the database lock (9 March 2021), 33.0% and 35.1% subjects remained on treatment in the rela+nivo FDC and nivolumab arms, respectively. The most common reason for treatment discontinuation in both groups was progressive disease; a higher percentage within the nivolumab arm discontinued due to disease progression (46.0%) compared with the rela+nivo FDC arm (36.3%), while discontinuation due to study drug toxicity was more frequent in those receiving rela+nivo FDC (17.7% vs 8.9% in the nivolumab arm).

At the time of the final PFS the median duration of follow-up was 13.21 months (range: 0-33.1); the median duration of therapy was 5.55 months (range: 0.0, 31.5) and 4.86 months (range: 0.0, 32.2), for the rela+nivo FDC and nivolumab monotherapy arm, respectively. In all randomised subjects, rela+nivo FDC showed a statistically significant improvement in PFS vs nivolumab monotherapy, HR: 0.75 (95% CI: 0.62, 0.92). Median PFS improved from 4.63 (95% CI: 3.38, 5.62) to 10.12 (95% CI: 6.37, 15.74) months; the improvement in median PFS of 5.5 months is considered of clinical relevance. The primary PFS analysis is supported by several sensitivity analyses and investigator assessed PFS.

As of 9 March 2021, about 40-50% of subjects are censored and remain in follow up and median treatment duration is low. An updated PFS analysis, including sensitivity analyses, was performed at the time of the OS analysis, 28-Oct-2021 DBL, with a median extent of follow-up of 19.27 months, and

the median duration of therapy was 8.3 months in the nivo+rela FDC arm and 6.5 months in the nivolumab monotherapy arm. This analysis included an additional 46 PFS events and supported the primary analysis.

Additional sensitivity analyses were performed post-hoc to justify the assumption of non-informative censoring, including subsequent anticancer therapy as PFS event, combining investigator assessment and BICR for PFS events, counting non-administrative censored times as events, as well as further information after treatment discontinuation. These analyses were reassuring that any potentially informative censoring did not have an influence on the results and related conclusions of efficacy in the ITT population (both for the 09-Mar-2021 DBL and 28-Oct-2021 DBL).

The observed median PFS in the control arm is somewhat lower than expected based on the results in study CA209067 (median PFS of 4.6 months vs. 6.9 months), although based on an indirect comparison. Potential reasons for the observed difference are differences in study design (e.g. BICR vs investigator assessment and need for confirmation) as well as differences in patient characteristics. Median OS appears comparable and there are no concerns on the (external) validity of the obtained results.

The primary endpoint PFS in the ITT population is supported by the key secondary endpoints OS and ORR (28-Oct-2021 DBL). With a median follow-up of 19.27 months, 39% OS events with rela+nivo FDC and 45% with nivo monotherapy were observed. The OS results did not reach statistical significance (final OS analysis). Median OS was not reached (95% CI: 34.20, NR) in the nivo+rela FDC arm and 34.10 (95% CI: 25.23, NR) months in the nivolumab monotherapy arm. Nevertheless, the KM curves showed that the nivo+rela FDC arm was well above the nivolumab monotherapy arm throughout the follow-up period for the ITT population, supporting a trend for an OS benefit and excluding a detrimental effect. In addition, confirmed ORR per BICR showed a 10.3% (95% CI: 3.4, 17.3) increase in ORR for the combination treatment over nivolumab. However, statistical testing was not performed due to the hierarchical testing strategy (ORR after OS).

Median PFS2 was not yet reached with combination treatment and about 20 months for the nivolumab monotherapy arm (HR: 0.77; 95% CI: 0.61, 0.97). However, results should be interpreted cautiously as this was an exploratory endpoint. About 30% of patients in both treatment arms received subsequent systemic therapy during follow-up, predominantly targeted BRAF/MEK inhibitors or PD1/CTLA4 inhibitors. Updated analysis confirmed the previous analysis with a median PFS2 of 30.23 months and 20.04 months for rela+nivo FDC and nivolumab monotherapy, respectively (28-Oct-2021 DBL; HR 0.76 (95% CI: 0.61, 0.93)).

A beneficial effect of rela+nivo FDC over nivo monotherapy on PFS was shown independent of LAG-3 status (either cut-off ≥ 1% or ≥ 5%). Comparable HRs were observed for LAG-3 low expression (<1%, HR: 0.78; 95% CI: 0.54, 1.15) and LAG-3 high expression (≥ 1%, HR: 0.75; 95% CI: 0.59, 0.95), supported by a clear separation of KM-curves. These data suggest clinical benefit from rela+nivo FDC irrespective of LAG-3 expression level and do not support the utility of LAG-3 as a biomarker selecting differential benefit by rela+nivo FDC over nivolumab monotherapy. In subjects with PD-L1 low expression the use of the combination appears to offer additional benefit while there is little 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%). In the subgroup with PD-L1 ≥ 1%, median PFS was comparable for both treatment arms (15.74 months vs 14.72 months) and KM-curves overlap. These results suggest that PD-L1 status modifies the treatment effect of rela+nivo FDC compared to nivo monotherapy. Based on the current PFS results, patients with a high PD-L1 expression respond well to nivolumab monotherapy and there is little additional benefit of relatlimab in combination with nivolumab. For the low PD-L1 expression group, patients on nivolumab monotherapy performed poorly, with a large proportion having experienced a PFS event (presumably death) before the first

assessment for progression scheduled at 12 weeks. In this patient subgroup, there is some benefit to the addition of relatlimab particularly for the LAG-3 ≥ 1% group.

As of the 28-Oct-2021 DBL, similar PFS results were obtained for PD-L1 positive patients (cut-off >1%) with a HR 0.96 (95% CI: 0.70, 1.31) and median PFS of 15.74 months versus 14.72 months for nivo+rela FDC and nivolumab monotherapy, respectively, and overlapping K-M curves. Exploratory analyses showed that PFS and OS were longer in responders compared to non-responders in both subgroups. However, these analyses are based on post-randomisation events of CR and PR and inference of PFS/OS gain from these data is questionable. It is acknowledged that at the time of the MAA of the combination treatment of nivolumab + ipilimumab (EPAR EMEA/H/C/002213/II0055 and EMEA/H/C/003985/II/003 and 0032) a 10% difference in ORR, in the absence of an effect on PFS and OS, was considered potentially of clinical relevance in the PD-L1 positive subgroup based on similar analyses. At that time there was uncertainty, amongst others, related to the available IHC PD-L1 assay not being able to provide a clear demarcation of a bimodal population that could be defined by a dichotomous cut-off and potential heterogeneity within the subjects' tumours. Ultimately, an "all-comer" population was granted and the differential efficacy based on PD-L1 subgroup was reflected in the indication. This approach is no longer deemed acceptable. Of more importance, long term data up till 60 months of follow-up do not indicate a PFS/OS benefit for ipi+nivo in the PD-L1 ≥1% subgroup (see SmPC Yervoy), questioning the prior assumption that the observed ORR difference translates into long term benefit (at least within a reasonable timeframe). Overall, a clinical benefit of the addition of relatlimab to nivolumab over nivolumab monotherapy has not been made plausible/demonstrated in the PD-L1≥1% subgroup.

The current understanding of LAG-3 is still very limited, including its signalling mechanism and the ligands involved. It also remains unclear whether LAG-3 could be a predictive or prognostic biomarker in melanoma. In addition, the exact mechanisms of the synergistic or additive action of LAG-3 with PD-1 remains unknown. Additional data presented by the applicant suggest that LAG-3 expression as presently quantified, reflecting tumour immune infiltrates, may be a general predictive marker for immune therapies that rely on the presence of infiltrating immune cells to mount an anti-tumour response. The current data showing a beneficial effect of the combination independent of LAG-3 expression, do not support the utility of LAG-3 for patient selection for efficacy. Initially the applicant did not consider PD-L1 suitable for patient selection of efficacy based on the confidence intervals of HR, encompassing the point estimates of HR for low and high PD-L1 expression and the all-comer HR. Further, receiver operating characteristic analyses indicate that PD-L1 is not a reliable predictor of efficacy for either treatment, at any threshold. However, these analyses do not provide insight into the PD-L1 cut-off for which the added benefit of relatlimab is demonstrated. Experience with PD-1/L1 inhibitors has increased over the past years and there are several examples in which indications are restricted based on PD-1/L1. It is acknowledged that biomarker-defined subgroups were not alpha-controlled in the current study, in contrast to other cases, however these were still pre-planned in the SAP. In addition, the PD-L1 cut off of 1% was chosen as a stratification factor based on previous data showing an association between PD-L1 expression and outcomes. Therefore, PD-L1 of 1% is considered a reasonable cut-off point. Overall, it was considered that the clinical benefit of the addition of relatlimab to nivolumab monotherapy has not been made plausible/demonstrated in the PD-L1 ≥1 subgroup. The applicant has restricted the indication by tumour PD-L1<1%.

Additional analyses of biomarker data from study CA224047 are ongoing and the applicant will submit these data when available to better understand the role of LAG-3 inhibition in combination with PD-1 inhibition and a further insight into potential responders/non-responders (PAM-REC).

Exploratory subgroup analyses for PFS support a beneficial effect of rela+nivo FDC over nivo monotherapy in most important subgroups as HR was below 1. This includes important subgroups with a worse prognosis like BRAF mutation, high HDL and baseline metastasis stage of M1c.

Adolescents

There were no adolescents included in the phase 1/2a or the phase 2/3 studies. Efficacy assessment is based on the extrapolation concept, assuming that disease, progression of disease, treatment and prognosis is similar for adolescents and adults. Furthermore, the proposed doses should lead to comparable exposure and PK/response relation should be similar as well.

The applicant has submitted data to address these issues support the extrapolation of adult data to the adolescent population.

Indeed, disease histology, genetic background, treatment and prognosis of metastatic melanoma appears to be comparable for adults and adolescents, therefore comparable efficacy of anti-melanoma therapies might be expected in these patients populations. Nivolumab and relatlimab, are both check point inhibitors stimulating the anti-tumour immune response. As the immune system in adolescents are mature, it can be assumed that these agents simulate the immune system in adolescents in a comparable manner as in adults.

The added benefit of relatlimab appears dependent on the level of PDL1 expression. The indication is restricted by tumour PD-L1<1%, which is also applicable to adolescents.

No paediatric efficacy data for nivolumab and relatlimab combination therapy and only very limited efficacy data for other treatments, is available to support the expected similar efficacy. For the treatment of advanced melanoma in adolescents only ipilimumab is approved. Approval of ipilimumab for adolescents was based on extrapolation of adult efficacy data which was accepted given a similar course of the disease and an overlapping PK in combination with limited efficacy data showing a similar trend of efficacy in adolescents and adults with advanced melanoma.

One of the principles of the extrapolation concept is that comparable drug exposure will lead to comparable efficacy.

Limited nivolumab PK data in adolescent solid tumour patients indicate a reduced clearance and volume of distribution of nivolumab in adolescents as compared to adults. However, with respect to relatlimab, no adolescent PK data were available. The consequences of either the presence or absence of a reduced clearance and volume of distribution in adolescent patients on nivolumab and relatlimab exposure was further investigated. To this end, popPK simulations on the different scenarios, i.e., flat dose or weight-based dose, and decreased clearance and volume of distribution in adolescents or comparable clearance and volume of distribution in adolescents and adults were conducted. Based on these provided simulated exposure to relatlimab and nivolumab in adolescent and adult patients, applying a flat dose and taking into account either the presence or the absence of a reduced clearance in adolescents, sufficiently comparable exposure between adolescent and adults is demonstrated. Considering the comparable pathophysiology of melanoma in adolescents and adults, the proposal for a flat dose for relatlimab and nivolumab, being the same in adolescents and adults, is therefore supported.

Furthermore, for extrapolation PK/response relation for adults and adolescents need to be comparable.

Considering the mode of action of relatlimab and nivolumab which are immune checkpoint inhibitors and that the immune system of adolescents is fully mature with adult levels of T cells dendritic and B cells, the exposure response relation for relatlimab + nivolumab in adult and adolescent is expected to be comparable, provided that PDL1 expression is similar in adult and adolescent tumours and that with the proposed dosing the receptor binding (occupancy) is comparable.

The exposure-effect relationships, only based on adult patients, have been investigated.

With respect to the *exposure-peripheral receptor occupancy* (OR), the predicted peripheral LAG-3 RO was similar between relatlimab/nivolumab 80/240 mg Q2W regimen and the requested relatlimab/nivolumab 160/480 mg Q4W dose regimen. LAG-3 RO was higher following a dose of relatlimab/nivolumab 480/480 mg Q4W as compared to 160/480 mg Q4W; The clinical relevance of this increased RO at higher dose is not completely clear, considering the flat exposure-PFS analysis, but at the same time the dose-dependent exposure-OR relationship.

With respect to the exposure-efficacy, PFS, OS, and OR were significantly associated with relatlimab exposure, resulting in a longer PFS or OS and higher OR compared to nivolumab monotherapy. The efficacy for all the PFS and OS endpoints was similar across the range of relatlimab exposures (Cavgd28) produced by nivolumab/relatlimab 240/80 mg Q2W, 480/160 mg Q4W, and 480/480 mg Q4W suggesting a flat E-R for efficacy. This flat E-R was shown to be applicable both for 1L and prior-IO melanoma patients. Some uncertainty on the E-R comes from the exposure-OR analyses, where OR is predicted to be higher with higher doses of relatlimab (480 mg vs. 160 mg and 80 mg Q4W). However, tolerability also appears lower with the higher relatlimab dose.

With respect to the *exposure-Grade 2+ immune-mediated adverse events,* as well as the *exposure Grade 3+ drug-related adverse events*, the risk of these Gr2 and Gr3 AEs was significantly associated with relatlimab and nivolumab exposure, resulting in a higher risk in relatlimab + nivolumab combination compared with nivolumab monotherapy. Nivolumab exposure was not significantly associated with the risk of Gr3+ Drug-related adverse events. The risk for these Gr2 and Gr3 AEs was similar across the range of relatlimab exposures produced by the studied combination dosing regimen in Studies CA224020 and CA224047, supporting a flat relatlimab E-R relationship over this exposure range.

2.6.7. Conclusions on the clinical efficacy

The improvement in median PFS of 5.5 months for the combination treatment compared to monotherapy could be considered clinically relevant in the ITT population. The primary endpoint is supported by a trend for OS benefit whereas a detrimental effect is excluded. However, the effect in the ITT population is driven by the subgroup of PD-L1 <1%; a beneficial effect of adding relatlimab to nivolumab has not been demonstrated/made plausible in the PD-L1 ≥1% subgroup which responds well to nivolumab monotherapy.

Regarding to adolescents, based on similarity of disease and response to treatment, extrapolation of efficacy from adults to adolescents can be acceptable, provided exposures between adults and adolescent (≥ 12 years) are similar. Based on the provided simulated exposure to relatlimab and nivolumab in adolescent and adult patients, applying a flat dose and taking into account either the presence or the absence of a reduced clearance and volume of distribution in adolescents, sufficiently comparable exposure between adolescent and adults is demonstrated. Considering the comparable pathophysiology of melanoma in adolescents and adults, the proposal for a flat dose regimen for relatlimab and nivolumab, being the same in adolescents and adults, is therefore supported.

The finally agreed indication 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 with PD-L1 <1%."

2.6.8. Clinical safety

The primary safety data presented in this AR are from:

- pivotal Study CA224047, a Phase 2/3, randomised, double-blind study of rela+nivo FDC versus nivolumab in subjects with unresectable or metastatic melanoma. Safety data in adult subjects treated with rela+nivo FDC (N = 355) and nivolumab monotherapy (N = 359) are based on a 09-Mar-2021 DBL.
- CA224020 (supportive Phase 1/2a study): Supportive safety data from the relatlimab monotherapy cohort (CA224020 Part A) and relatlimab plus nivolumab combination cohorts (CA224020 Part B, Part C, Part D [D1 and D2], and Part E, including the safety from rela+nivo 160/480 mg Q4W and 80/240 mg Q2W) are presented; safety data are presented based on a DBL of 25-Feb-2021.

The all treated population from Study CA224047 was the primary population for safety analysis. There was no pooling of safety data from CA224047 and CA224020 due to the differences in study design (see Table *2*). Data from the higher dose of rela+ nivo 480 mg/480 mg Q4w from part E of study CA22402 were not included in the safety database.

The issues that warranted increased attention during the conduct of Studies CA224047 and CA224020 included:

- *Myocarditis* was initially identified as a potential safety concern due to the observation of early, lethal myocarditis in LAG-3/PD-1 double knockout mouse models, coupled with emerging literature describing a low risk of severe checkpoint inhibitor-associated myocarditis in the post approval setting. Myocarditis was also identified as an IMAE for Nivolumab in 2016. A case of Grade 4 myocarditis was reported in May 2016 in Study CA224020 at the rela+nivo dose of 240/240 mg IV Q2W. Troponin monitoring was included in Study CA224047 as a pilot to determine if increased surveillance could support identification of early myocarditis, and to permit characterisation of the frequency and severity of myocarditis with rela+nivo FDC compared with an established anti-PD-1 monotherapy. The timeframe of 2 months was selected based on the median time-to-onset of observed myocarditis cases within Study CA224020 at the time of implementation and the safety data from Nivolumab programme. Both myocarditis and troponin elevation terms are OESIs, permitting characterisation of the potential risk of myocarditis identified in the pre-clinical setting.
- *CNS vasculitis* and mild inflammation of the choroid plexus and brain vasculature were observed during pre-clinical general toxicity testing in cynomolgus monkeys. Due to the rare, but known, risk of immune-mediated events of the CNS with established immuno-oncology agents, CNS adverse event terms were added to the OESI category to support detection and reporting, including demyelination, meningitis and encephalitis. There are no routine laboratory or imaging evaluations that would enhance safety monitoring for CNS events within these clinical studies beyond clinical observation.
- *Hypersensitivity/infusion reactions*: Because both relatlimab and nivolumab contain only human immunoglobulin protein sequences, they have a low risk of inducing immunogenicity or associated infusion or hypersensitivity reactions. Given a theoretical risk of infusion reactions with the new FDC formulation, a safety lead-in in Study CA224047 was employed for the first 18 subjects randomised to monitor for Grade 3 or 4 infusion reactions; no risks were identified in the safety lead-in study.

2.6.8.1. Patient exposure

The majority of subjects in both treatment arms received ≥ 90% of the intended dose intensity (87% and 85%), and approximately one-third of subjects received ≥ 12 months of study drug, which was comparable between the BMS-986213 and nivolumab monotherapy treatment (29% and 28%). Median treatment duration was about 5 months (Table 30 and Table 31).

Table 30. Cumulative dose and relative dose intensity - All treated subjects study CA224047

	BMS-986213 N = 355	Nivolumab N = 359
NUMBER OF DOSES RECEIVED		
MEAN (SD)	10.2 (8.67)	10.5 (9.73)
MEDIAN (MIN - MAX)	7.0 (1 - 35)	6.0 (1 - 35)
CUMULATIVE DOSE (MG)		
MEAN (SD)	6555.055 (5549.6498)	5043.354 (4674.8113)
MEDIAN (MIN - MAX)	4480.000 (640.00 - 22400.00)	2880.000 (480.00 - 16800.00)
RELATIVE DOSE INTENSITY (%)		
>= 110%	0	1 (0.3)
90% to < 110%	309 (87.0)	304 (84.7)
70% to < 90%	41 (11.5)	45 (12.5)
50% to < 70%	5 (1.4)	9 (2.5)
< 50%	0	0
NOT REPORTED	0	0

Table 31. Duration of study therapy summary - All treated subjects study CA224047

	BMS-986213 N = 355	Nivolumab N = 359
DURATION OF THERAPY (MONTHS)		
MEAN (MIN, MAX)	9.0 (0.0, 31.5)	9.2 (0.0, 32.2)
MEDIAN	5.55	4.86
>= 3 MONTHS (%)	239 (67.3)	241 (67.1)
>= 6 MONTHS (%)	175 (49.3)	159 (44.3)
>= 9 MONTHS (%)	143 (40.3)	131 (36.5)
>= 12 MONTHS (%)	104 (29.3)	101 (28.1)
>= 15 MONTHS (%)	71 (20.0)	76 (21.2)

2.6.8.2. Adverse events

The overall safety data of study CA224047 are summarised in *Table 32*.

The most frequently reported any grade AEs (≥ 15% of subjects, regardless of causality) were:

- Rela+nivo FDC: fatigue (28.7%), pruritus (24.8%), arthralgia (23.7%), diarrhoea (22.8%), headache (17.5%), nausea (16.9%), rash (16.6%), and hypothyroidism (15.2%);
- Nivolumab: fatigue (20.1%), diarrhoea (16.7%), and pruritus (17.3%).

The most frequently reported Grade 3-4 AEs (≥ 1% of subjects) were:

- Rela+nivo FDC: malignant neoplasm progression (3.1%), anaemia (2.0%), arthralgia (1.7%), back pain, increased ALT, increased AST, weight decreased, fatigue, and dyspnoea (1.4% each), diarrhoea, and hypertension, (1.1% each);
- Nivolumab: malignant neoplasm progression (3.9%), anaemia (3.1%), and diarrhoea and hyperglycaemia (1.4% each), increased ALT and hypertension (1.1% each).

Table 32. Summary of safety - AlltTreated subjects in study CA224047

	No. of Subjects (%)			
Safety Parameters	**Rela+nivo FDC N = 355**		**Nivolumab N = 359**	
Deaths at any time during the study	108 (30.4)		119 (33.1)	
Primary Reason for Death				
Disease	90 (25.4)		99 (27.6)	
Study Drug Toxicity[a]	3 (0.8)		2 (0.6)	
Unknown	1 (0.3)		2 (0.6)	
Other[b]	14 (3.9)		16 (4.5)	
	Adverse Event Grades			
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	121 (34.1)	91 (25.6)	105 (29.2)	74 (20.6)
Drug-related SAEs	50 (14.1)	33 (9.3)	28 (7.8)	17 (4.7)
All-causality AEs leading to DC	69 (19.4)	41 (11.5)	41 (11.4)	23 (6.4)
Drug-Related AEs leading to DC	52 (14.6)	30 (8.5)	24 (6.7)	11 (3.1)
All-causality AEs	345 (97.2)	143 (40.3)	339 (94.4)	120 (33.4)
≥ 10% of Subjects in Any Treatment Arm				
Fatigue	102 (28.7)	5 (1.4)	72 (20.1)	2 (0.6)
Pruritus	88 (24.8)	0	62 (17.3)	2 (0.6)
Arthralgia	84 (23.7)	6 (1.7)	53 (14.8)	2 (0.6)
Diarrhea	81 (22.8)	4 (1.1)	60 (16.7)	5 (1.4)
Headache	62 (17.5)	1 (0.3)	42 (11.7)	1 (0.3)
Nausea	60 (16.9)	2 (0.6)	52 (14.5)	0
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	54 (15.2)	0	43 (12.0)	0
Decreased appetite	52 (14.6)	2 (0.6)	26 (7.2)	1 (0.3)
Anemia	48 (13.5)	7 (2.0)	34 (9.5)	11 (3.1)
Cough	48 (13.5)	1 (0.3)	37 (10.3)	0
Back pain	47 (13.2)	5 (1.4)	29 (8.1)	1 (0.3)
Asthenia	44 (12.4)	2 (0.6)	32 (8.9)	0
Vitiligo	39 (11.0)	0	36 (10.0)	0
Pyrexia	39 (11.0)	0	32 (8.9)	1 (0.3)
Constipation	38 (10.7)	2 (0.6)	22 (6.1)	0
Urinary tract infection	37 (10.4)	2 (0.6)	29 (8.1)	2 (0.6)

Safety Parameters	No. of Subjects (%)			
	Rela+nivo FDC N = 355		Nivolumab N = 359	
Drug-related AEs	288 (81.1)	67 (18.9)	251 (69.9)	35 (9.7)
≥ 5% of Subjects in Any Treatment Group				
Pruritus	83 (23.4)	0	57 (15.9)	2 (0.6)
Fatigue	82 (23.1)	4 (1.1)	46 (12.8)	1 (0.3)
Rash	55 (15.5)	3 (0.8)	43 (12.0)	2 (0.6)
Arthralgia	51 (14.4)	3 (0.8)	26 (7.2)	1 (0.3)
Hypothyroidism	51 (14.4)	0	43 (12.0)	0
Diarrhea	48 (13.5)	3 (0.8)	33 (9.2)	2 (0.6)
Vitiligo	37 (10.4)	0	35 (9.7)	0
Nausea	29 (8.2)	0	15 (4.2)	0
Alanine aminotransferase increased	28 (7.9)	5 (1.4)	11 (3.1)	2 (0.6)
Asthenia	28 (7.9)	0	14 (3.9)	0
Myalgia	25 (7.0)	1 (0.3)	14 (3.9)	0
Hyperthyroidism	21 (5.9)	0	22 (6.1)	0
All-causality Select AEs[c]				
Endocrine	93 (26.2)	7 (2.0)	76 (21.2)	2 (0.6)
Gastrointestinal	84 (23.7)	7 (2.0)	62 (17.3)	5 (1.4)
Hepatic	70 (19.7)	18 (5.1)	49 (13.6)	10 (2.8)
Pulmonary	16 (4.5)	4 (1.1)	9 (2.5)	1 (0.3)
Renal	27 (7.6)	6 (1.7)	19 (5.3)	1 (0.3)
Skin	160 (45.1)	5 (1.4)	135 (37.6)	6 (1.7)
Hypersensitivity/Infusion Reactions	23 (6.5)	0	15 (4.2)	1 (0.3)
Drug-Related Select AEs[c]				
Endocrine	85 (23.9)	5 (1.4)	69 (19.2)	2 (0.6)
Gastrointestinal	51 (14.4)	6 (1.7)	34 (9.5)	2 (0.6)
Hepatic	43 (12.1)	14 (3.9)	26 (7.2)	4 (1.1)
Pulmonary	15 (4.2)	3 (0.8)	9 (2.5)	1 (0.3)
Renal	14 (3.9)	5 (1.4)	6 (1.7)	1 (0.3)
Skin	150 (42.3)	5 (1.4)	122 (34.0)	6 (1.7)
Hypersensitivity/Infusion Reactions	23 (6.5)	0	15 (4.2)	1 (0.3)
All-causality Non-endocrine IMAEs within 100 days of last dose Treated with Immune Modulating Medication[d]				
Diarrhea/Colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Nephritis/Renal Dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Hypersensitivity/Infusion Reactions	4 (1.1)	0	4 (1.1)	0

Safety Parameters	No. of Subjects (%)			
	Rela+nivo FDC N = 355		Nivolumab N = 359	
All-causality Endocrine IMAEs within 100 days of last dose With or Without Immune Modulating Medication[d]				
Adrenal Insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Hypothyroidism	59 (16.6)	0	47 (13.1)	0
Thyroiditis	10 (2.8)	0	5 (1.4)	0
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Diabetes Mellitus	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
All-causality OESIs within 100 days of last dose With or Without Immune Modulating Medication[e]				
Troponin Event	41 (11.5)	1 (0.3)	36 (10.0)	2 (0.6)
Uveitis	6 (1.7)	1 (0.3)	5 (1.4)	2 (0.6)
Myocarditis	6 (1.7)	2 (0.6)	2 (0.6)	0
Pancreatitis	4 (1.1)	0	4 (1.1)	1 (0.3)
Encephalitis	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)
Myositis/Rhabdomyolysis	2 (0.6)	1 (0.3)	0	0
Guillain-Barre Syndrome	1 (0.3)	0	0	0
Myasthenic Syndrome	0	0	0	0
Demyelination	0	0	0	0
Other meningitis	0	0	0	0
Graft Versus Host Disease	0	0	0	0

[a] The causes of death per investigator were as follows:

Rela+nivo FDC arm: hemophagocytic lymphohistiocytosis, acute edema of lung, and pneumonitis

Nivolumab arm: sepsis and myocarditis, and worsening of pneumonia.

[b] The verbatim terms reported for the 'other' reasons for death were as follows:

Rela+nivo FDC arm: death not specified, aspiration pneumonia, myocardial infarction, septic shock (3 subjects), aspiration pneumonia (septicemy), medical history and respiratory failure not related to study treatment, respiratory failure aggravated by disease progression, neoplasm progression and SARS COV2 infection, pneumonia, suspected COVID-19, COVID-19 infection, and acute myocardial infarction;

Nivolumab arm: inadvertent pain medication overdose, acute respiratory insufficiency, arteria basiliaris thrombosis, progressive pulmonary insufficiency, coronavirus, COVID-19 (2 subjects), COVID-19 complications, sudden death, complications of cerebrovascular event, acute myocardial infarction (2 subjects), coronary ischemia, cardiac shock, septic shock and atypical pneumonia, and respiratory insufficiency.

[c] See Section 1.1.2.1 for the analysis of select AEs.

[d] See Section 1.1.2.2 for the analysis of IMAEs.

[e] See Section 1.1.2.3 for the analysis of OESIs.

MedDRA version 23.1 CTCAE version 5.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Common Adverse Events

There is a higher numerical incidence of grade 3-4 AEs in the rela+nivo FDC group vs nivo, 39.4% vs. 31.8%. There is no specific adverse event to which this increased incidence might be attributed.

Drug-Related Adverse Events

The most frequently reported any grade drug-related AEs (≥ 15% of subjects) were (*Table 32*):

- Rela+nivo FDC: pruritus (23.4%), fatigue (23.1%), rash (15.5%);
- Nivolumab: pruritus (15.9%).

The most frequently reported drug-related Grade 3-4 AEs (≥ 1% of subjects) were:

- Rela+nivo FDC: lipase increased (1.7%), ALT increased (1.4%), AST increased (1.4%), fatigue (1.1%);

- Nivolumab: None; all drug-related Grade 3-4 AEs by PT occurred in < 1% of subjects.

Select Adverse Events (select AEs)

Select AEs have been defined as AEs that:

- differ from non-immunotherapies
- may require immunosuppression
- early recognition may mitigate severe toxicity
- for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterisation

The majority of select AEs reported were Grade 1 or 2 and most were considered drug-related by the investigator. The most frequently reported drug-related select AEs by PT (any grade; rela+nivo FDC vs nivo; ≥ 10% of rela+nivo FDC subjects) were:

- pruritus (23.4% vs 15.9%)
- rash (15.5% vs 12.0%)
- hypothyroidism (14.4% vs 12.0%)
- diarrhoea (13.5% vs 9.2%)
- vitiligo (10.4% vs 9.7%).

The most frequently reported Grade 3-4 drug-related select AEs by PT (rela+nivo FDC vs nivo; ≥ 1% of rela+nivo FDC subjects) were increased ALT (1.4% vs 0.6%) and increased AST (1.4% vs 0.3%).

Most of drug-related select AEs resolved, except for endocrine AEs that made endocrine suppletion or suppression permanently necessary (Table 33).

Table 33. Onset, management, and resolution of drug-related select AEs, Rela+Nivo FDC (N = 355) and Nivolumab (N = 359) treated subjects in study CA224047

Category/ Total # of Subj. with an Event	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), wks	% Treated Subj. with Drug-related Select AE Leading to DC	% Subj. with Drug-related Select AE Treated with IMM/ High-dose Corticosteroids[a]	Median Time[b] to Resolution of Drug-related Select AE (range), weeks[c,d,e]	% Subj. with Drug-related Select AE that Resolved[d,e]
Rela+nivo FDC						
Endocrine N = 85	23.9/1.4	12.29 (1.0 - 71.0)	1.1	29.4/7.1	N.A (0.1+ - 138.1+)	23.5*
Gastrointestinal N = 51	14.4/1.7	11.86 (0.1 - 95.6)	2.0	45.1/35.3	4.50 (0.1 - 103.9+)	84.0
Hepatic N = 43	12.1/3.9	9.00 (2.0 - 104.0)	1.4	41.9/39.5	4.71 (0.7 - 54.0)	79.1
Pulmonary N = 15	4.2/0.8	20.00 (3.6 - 94.4)	1.7	73.3/60.0	12.00 (2.3 - 18.6+)	80.0
Renal N = 14	3.9/1.4	18.36 (1.9 - 98.1)	1.1	42.9/28.6	12.43 (0.9 - 51.0+)	85.7
Skin N = 150	42.3/1.4	6.50 (0.1 - 97.9)	0.3	31.3/3.3	N.A. (0.1 - 142.6+)	42.7
Hypersensitivity/ Infusion Reaction N = 23	6.5/0	4.14 (0.1 - 37.7)	0	34.8/17.4	0.14 (0.1 - 8.1)	100.0
Nivolumab						
Endocrine N = 69	19.2/0.6	8.14 (2.0 - 120.3)	0	10.1/1.4	N.A. (0.7 - 125.3+)	30.4
Gastrointestinal N = 34	9.5/0.6	8.71 (0.1 - 92.4)	0.3	23.5/17.6	2.64 (0.1 - 65.7)	85.3
Hepatic N = 26	7.2/1.1	11.21 (1.9 - 100.3)	1.1	34.6/19.2	4.21 (0.1 - 98.4+)	76.9
Pulmonary N = 9	2.5/0.3	28.14 (4.3 - 67.9)	0.3	55.6/44.4	14.29 (1.6+ - 40.4+)	55.6
Renal N = 6	1.7/0.3	26.00 (9.0 - 31.9)	0.6	33.3/16.7	9.14 (1.0 - 19.0)	83.3
Skin N = 122	34.0/1.7	11.50 (0.1 - 108.7)	0.6	30.3/4.9	N.A. (0.3 - 126.1+)	38.5
Hypersensitivity/ Infusion Reaction N = 15	4.2/0.3	4.14 (0.1-12.1)	0.6	53.3/6.7	0.14 (0.1 - 0.4)	100.0

* Average resolution rate for the non-endocrine category was driven by hypothyroidism that prompted life-long treatment, and was often deemed as an AE that was ongoing.

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

[b] From Kaplan-Meier estimation.

[c] Symbol + indicates a censored value.

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

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

Immune-mediated Adverse Events (IMAEs)

IMAEs are defined as events

- within 100 days of the last dose and
- treated with immunosuppression or
- any endocrine AEs

The most frequently reported IMAEs (any grade; rela+nivo FDC vs nivo; ≥ 5% of rela+nivo FDC subjects) were:

- hypothyroidism (16.6% vs 13.1%)
- rash (9.3% vs 6.7%)
- diarrhoea/colitis (6.8% vs 3.1%)
- hyperthyroidism (6.2% vs 6.7%)

- hepatitis (5.6% vs 2.5%).

The most frequently reported Grade 3-4 IMAEs (rela+nivo FDC vs nivo; ≥ 1% of rela+nivo FDC subjects) were:

- hepatitis (3.9% vs 1.1%)

- adrenal insufficiency (1.4% vs 0.8%)

- nephritis/renal dysfunction (1.1% vs 1.1%)

- diarrhoea/colitis (1.1% vs 1.4%).

Most drug-related select AEs and all causality IMAEs (except for endocrine events) had resolved at the time of database lock. Across the categories, the median time to resolution of drug-related select AEs ranged from 0.14 (range 0.1-8.1) weeks to 12.43 (range: 0.9-51.0+) weeks, and the median time to resolution of IMAEs ranged from 0.14 (range: 0.1- 0.1) weeks to 25.43 (0.6+-104.0+) weeks.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

As of the 09-Mar-2021 DBL, 30.4% subjects in the rela+nivo FDC arm and 33.1% of subjects in the nivolumab monotherapy arm died during the study (*Table 34*). Disease progression was the most common cause of death in both arms. A similar proportion of subjects in the rela+nivo FDC (0.8%; 3 subjects) and nivolumab (0.6%; 2 subjects) arms died due to study drug toxicity during the study. Per Investigator, causes of death due to study drug toxicity in the rela+nivo FDC arm were haemophagocytic lymphohistiocytosis, acute oedema of lung, and pneumonitis.

Table 34. Death summary, All treated subjects in study CA224047

	Rela+Nivo FDC (N = 355)	Nivolumab (N = 359)	Total N = 714
NUMBER OF SUBJECTS WHO DIED (%)	108 (30.4)	119 (33.1)	227 (31.8)
PRIMARY REASON FOR DEATH (%)			
DISEASE	90 (25.4)	99 (27.6)	189 (26.5)
STUDY DRUG TOXICITY	3 (0.8)	2 (0.6)	5 (0.7)
UNKNOWN	1 (0.3)	2 (0.6)	3 (0.4)
OTHER	14 (3.9)	16 (4.5)	30 (4.2)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	10 (2.8)	18 (5.0)	28 (3.9)
PRIMARY REASON FOR DEATH (%)			
DISEASE	1 (0.3)	8 (2.2)	9 (1.3)
STUDY DRUG TOXICITY	1 (0.3)	1 (0.3)	2 (0.3)
UNKNOWN	1 (0.3)	2 (0.6)	3 (0.4)
OTHER	7 (2.0)	7 (1.9)	14 (2.0)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	51 (14.4)	60 (16.7)	111 (15.5)
PRIMARY REASON FOR DEATH (%)			
DISEASE	35 (9.9)	42 (11.7)	77 (10.8)
STUDY DRUG TOXICITY	3 (0.8)	1 (0.3)	4 (0.6)
UNKNOWN	1 (0.3)	2 (0.6)	3 (0.4)
OTHER	12 (3.4)	15 (4.2)	27 (3.8)

Deaths attributed to other reasons were reported in 14 (3.9%) subjects in the rela+nivo FDC arm and 16 (4.5%) subjects in the nivolumab arm. Deaths due to AEs considered unrelated to study drug by investigators were balanced between treatment arms, including deaths attributed to COVID-19 (3 in the rela+nivo FDC arm and 4 in the nivolumab monotherapy arm). Of the subjects who died due to COVID-19, 5 subjects had already experienced disease progression per BICR prior to death.

Table 35. Verbatim terms for deaths attributed to "other" reasons - All treated subjects in study CA224047

Rela+nivo FDC	Nivolumab
Death NOS	Inadvertent pain medication overdose
Aspiration pneumonia	Acute respiratory insufficiency
Myocardial infarction	Arteria basiliaris thrombosis
Septic shock	Progressive pulmonary insufficiency
Aspiration pneumonia (septicemy)	Coronavirus
Septic shock	COVID-19
Septic shock	Sudden death at home, found dead by daughter, no autopsy performed
Suspected COVID-19	Patient got worst due to complications of the cerebrovascular event
Medical history (diabetes mellitus 2) and respiratory failure not related to study treatment	Acute myocardial infarction
Respiratory failure aggravated by disease progression	The patient died due to complications from COVID-19
PI considered patient's death was because of malignant neoplasm progression and SARS COV2 infection	COVID-19
Pneumonia	Coronary ischemia
COVID-19 infection	Cardiac shock
Acute myocardial infarction	Septic shock, atypical pneumonia
	Acute myocardial infarction
	Respiratory insufficiency

Serious Adverse Events (SAEs)

Overall, 34% and 29% of patients in rela+nivo FDC and nivo, respectively, experienced a SAE (any grade). The most frequently reported (≥ 1% of subjects) any-grade SAEs were:

- Rela+nivo FDC: malignant neoplasm progression (3.7%), adrenal insufficiency, myocarditis, back pain, colitis, and diarrhoea (1.1% each);

- Nivolumab: malignant neoplasm progression (5.3%).

The frequency of specific drug-related SAEs was so low (<2%), that no pattern of drug-related SAEs could be established.

Of SAEs attributed to study drug by the investigator, there were 4 reported events total that were considered rare for immuno-oncology agents in the rela+nivo FDC arm affecting individual subjects (haemolytic anaemia, Guillain-Barré syndrome, Vogt-Koyanagi-Harada disease and hemophagocytic lymphohistiocytosis), and 1 event in the nivolumab arm (acquired haemophilia).

Other Events of Special Interest (OESIs)

OESIs are events that do not fulfil all criteria to qualify as select AEs or IMAEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. OESIs included the following categories: demyelination, encephalitis, Guillain Barré syndrome, myasthenic syndrome, pancreatitis, uveitis, myositis/rhabdomyolysis, myocarditis, graft versus host disease, troponin elevation, and meningitis.

Overall, OESIs were reported in 62/355 subjects (17.5%; 83 OESIs) in the rela+nivo FDC arm and 49/359 subjects (13.6%; 75 OESIs) in the nivolumab arm.

In the *rela+nivo FDC* arm, the OESIs reported were Guillain Barré syndrome (1 [0.3%] subject; 1 event), pancreatitis (4 [1.1%] subjects; 5 events), uveitis (6 [1.7%] subjects; 9 events), encephalitis (2 [0.6%] subjects; 3 events), myositis/rhabdomyolysis (2 [0.6%] subjects; 3 events), myocarditis (6

[1.7%] subjects; 9 events), and troponin elevation (41 [11.5%] subjects; 53 events). There were no events in the categories of myasthenic syndrome, demyelination, meningitis, and graft versus host disease. Of the 83 OESIs, 76 OESIs in the rela+nivo FDC arm were resolved at the time of DBL: 45 troponin events, 9 myocarditis events, 8 uveitis events, 3 encephalitis events, 3 myositis events, 3 pancreatitis events, and 1 Guillain Barré Syndrome.

All resolved events of myocarditis, uveitis, encephalitis, myositis, pancreatitis, and Guillain Barré Syndrome were resolved with immune-modulating medication (IMM); only 3/45 troponin events were resolved with IMM.

In the *nivolumab* arm, the OESIs reported were pancreatitis (4 [1.1%] subjects; 6 events), uveitis (5 [1.4%] subjects; 13 events), encephalitis (2 [0.6%] subjects; 2 events), myocarditis (2 [0.6%] subjects; 3 events), and troponin elevation events (36 [10.0%] subjects; 51 events). There were no events in the categories of Guillain Barré syndrome, myositis/rhabdomyolysis, myasthenic syndrome, demyelination, meningitis, and graft versus host disease. Of the 75 OESIs, 64 OESIs in the nivolumab arm were resolved at the time of DBL: 46 troponin events, 11 uveitis events, 2 myocarditis events, and 5 pancreatitis events.

All resolved events of uveitis, myocarditis, and pancreatitis were resolved with IMM; only 1/46 troponin event was resolved with IMM.

Myocarditis and Troponin Elevation

Myocarditis was reported infrequently at 1.7% and 0.6% in the rela+nivo FDC and nivolumab arms, respectively, and a minority were high grade (Grade 3-4) events (0.6% vs 0%, respectively). The majority of myocarditis events occurred in the first 2 months. In the rela+nivo FDC arm, all observed myocarditis events were manageable within established IMAE management practices and resolved. There were no overall differences in the median time to resolution or median duration of immunosuppression between the study arms.

There was 1 fatal event in the nivolumab arm; the cause of death was attributed to a combination of myocarditis and bacterial sepsis due to immune suppression for management of myocarditis. This subject died despite early observed myocarditis events were associated with other symptoms or signs (eg, fatigue, nausea, diffuse body aches, dizziness, dyspnoea, and hepatitis).

Adverse events of troponin elevation were observed more commonly than myocarditis events, and were reported in 41 (11.5%) subjects in the rela+nivo FDC arm and 36 (10.0%) subjects in the nivolumab arm, in the context of a protocol requirement for cardiac assessment in subjects with raised troponin values. In addition to a subject in the rela+nivo FDC arm who was recorded as treated with steroids for both myocarditis and elevated troponin and therefore appears in both OESI categories, 3 subjects with troponin elevation events were treated with immune-modulating medications: 2 (0.6%) subjects vs 1 (0.3%) subject in the rela+nivo FDC and nivolumab arms, respectively. One of these 3 subjects, treated with corticosteroids in the rela+nivo FDC, had myocardial inflammation on MRI but was asymptomatic; the other 2 subjects did not have radiographic confirmation of myocarditis and a clinical decision was made to treat with corticosteroids. However, these 3 events represented a minority of the troponin elevation events observed within the study, most of which required no immunosuppression.

CNS AEs

OESIs of the central nervous system, including encephalitis, meningitis, and demyelination events were uncommon and balanced between treatment arms.

CNS AEs were reported infrequently in both treatment arm: 2 subjects each in the rela+nivo FDC and nivolumab arms experienced encephalitis OESIs. No subjects in either arm reported meningitis and

demyelination events. Of the encephalitis OESIs reported in the rela+nivo arm, all events were manageable with established IMAE management practices and resolved after 6-60 days. One subject in the nivolumab arm had a concurrent COVID-19 infection, which was fatal.

Hypersensitivity/infusion-related reactions

All hypersensitivity/infusion-related reactions were drug-related and of low frequency, with less than 2.5% difference in all grade events (6.5% vs 4.2% in the rela+nivo FDC arm vs nivolumab arms, respectively). The proportion of hypersensitivity/infusion-related reactions treated with immune-modulating medication was higher in the nivolumab arm (53.3% vs 34.8%), of which 17.4% in the rela+nivo FDC arm vs 6.7% in the nivolumab arm were treated with high dose steroids. The events were manageable with no high grade or serious hypersensitivity/infusion-related reactions in the rela+nivo FDC arm, compared with 0.3% high grade events and 0.6% serious events in the nivolumab arm. The two infusion reaction events that led to discontinuation were in the nivolumab arm with no infusion reaction events leading to discontinuation of treatment with rela+nivo FDC.

2.6.8.4. Laboratory findings

Haematology

The on-treatment haematologic parameters that worsened to Grade 3-4 relative to baseline in ≥ 1% of subjects in both treatment arms included decreased haemoglobin (rela+nivo FDC: 2.7%, nivolumab: 3.5%) and decreased absolute lymphocyte count (rela+nivo FDC: 3.8%, nivolumab: 1.2%). There were no Grade 3 or 4 haematologic abnormalities reported in >5% of subjects in both treatment arms.

Liver Tests

Increased ALT was reported more frequently with rela+nivo FDC (30.1% Grade 1-4; 2.3% Grade 3-4) compared with nivolumab (22.0% Grade 1-4; 1.4% Grade 3-4).

During the treatment period, abnormalities in hepatic parameters (all increases) were primarily Grade 1-2). There were no Grade 3 or 4 hepatic abnormalities reported in > 5% of subjects in both treatment arms. A total of 2/342 (0.6%) subjects in the rela+nivo FDC arm and 1/345 (0.3%) subject in the nivolumab arm had concurrent ALT or AST > 3 > ULN with total bilirubin > 2 > ULN within 1 day and within 30 days based on laboratory results reported after the first dose and within 30 days of last dose of study therapy, suggestive of a potential drug induced liver injury.

There were 3 additional subjects in the rela+nivo FDC arm that had concurrent elevation of ALT or AST > 3x ULN with total bilirubin > 2x ULN within 100 days after the first dose of study therapy that could suggest a potential DILI. Liver toxicity was confounded by progressive disease in 2 subjects and Gilbert's disease in 1 subject. In 1 subject, liver toxicity could have been in the context of concurrently elevated creatinine kinase/myositis.

Thyroid Function Tests

TSH increases (> ULN) from baseline (> ULN) were reported in 84/354 (23.7%) subjects in the rela+nivo FDC arm, and 82/357 (23.0%) subjects in the nivolumab arm. TSH decreases (< LLN) from baseline were reported in 79/327 (24.2%) subjects in the rela+nivo FDC arm, and 78/331 (23.6%) subjects in the nivolumab arm.

Electrolytes

Grade 3-4 hyponatremia and hyperkalemia were reported more frequently with rela+nivo FDC (1.2% and 1.8%, respectively) compared with nivolumab (0.6% and 0.9%, respectively).

Most subjects had normal electrolyte levels during the treatment reporting period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity. No Grade 3 or 4 abnormalities in electrolytes were observed in ≥ 5% of treated subjects in both treatment arms.

Selected Laboratory Abnormalities that Worsened Relative to Baseline in Study CA224047

In CA224047, laboratory abnormalities that worsened relative to baseline in ≥ 15% of rela+nivo FDC treated subjects are presented in Table 36 below.

Table 36. Laboratory abnormalities worsening from baseline occurring in ≥ 15% of subjects on Rela+Nivo FDC - All treated subjects in CA224047

Laboratory Abnormality	Percentage (%) of Subjects with Worsening Laboratory Test from Baseline[a]			
	Rela+nivo FDC		Nivolumab	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Chemistry				
Increased AST	103 (30.1)	8 (2.3)	76 (22.0)	5 (1.4)
Increased ALT	88 (25.7)	11 (3.2)	85 (24.6)	7 (2.0)
Hyponatremia	82 (24.1)	4 (1.2)	70 (20.3)	2 (0.6)
Increased creatinine	66 (19.4)	0	54 (15.7)	0
Increased alkaline phosphatase	65 (19.2)	2 (0.6)	60 (17.4)	3 (0.9)
Hematology				
Anemia	126 (37.4)	9 (2.7)	106 (30.9)	12 (3.5)
Lymphopenia	21 (26.3)	3 (3.8)	25 (29.4)	1 (1.2)

Toxicity Scale: CTC Version 5.0

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

[a] Each test incidence is based on the number of subjects who had both baseline and at least one on-study laboratory measurement available: Rela+nivo FDC (range: 80 to 342 subjects); Nivolumab (range: 85 to 345 subjects).

Vital signs and ECG parameters

Vital Signs

In CA224047, on-study safety assessments of vital signs were required at screening and within 3 calendar days prior to each dose of study treatment. Median baseline vital sign values (blood pressure, heart rate, and temperature) were in the normal range, with no clinically meaningful differences between the nivo+rela FDC and nivolumab monotherapy arms. No substantial changes in the longitudinal vital sign assessments were seen for subjects within the two treatment arms of CA224047, and there were no remarkable differences seen between treatment arms across all measured parameters.

Electrocardiograms

In CA224047, ECG assessments were required at screening and within 3 calendar days prior to each dose of study treatment. ECGs were read locally by investigators and results entered into the eCRF by the site. Median baseline ECG values (HR, PR Interval, QRS duration, QT interval, and QTcB and/or QTcF) were in the normal range, and were comparable between the nivo+rela FDC and nivolumab monotherapy arms. No clinically important difference was seen in the median change from baseline for any measured ECG parameter in either treatment arm (across treatment cycles including at least 10% randomised subjects), and there were no remarkable differences between the treatment arms.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Overall, the safety profile of rela+nivo FDC among subgroups of age, gender, race, and geographic region was generally similar to the total rela+nivo FDC treated population.

Intrinsic and Extrinsic Factors

The frequencies of all-causality and drug-related AEs in the rela+nivo FDC arm and nivolumab arm for subgroups of gender, race, age, and geographic region were generally similar to the AE frequencies reported for the overall study populations by treatment.

Race: Most subjects were clustered in a single category (White), consistent with the geographical distribution of study subjects. Very low sample sizes in other categories of race limit the interpretability of potential differences (data not shown).

Age: The overall safety profile of rela+nivo FDC was comparable between subjects ≥ 65 years of age and those < 65 years of age. No substantial differences in AEs (all-causality or drug-related; any grade) were reported in older subjects (≥ 65 and < 75 and ≥ 75 years) compared with younger subjects (< 65 years) treated with rela+nivo FDC, although the small number of subjects above the age of 85 limited comparisons (table below).

Table 37. Summary of on-treatment adverse events by age Ggoup - All randomised subjects treated with Nivo+rela FDC (28-Oct-2021 DBL)

	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 187	65–74 N = 102	75–84 N = 60	>= 85 N = 6	Total N = 355
TOTAL SUBJECTS WITH AN EVENT	186 (99.5)	100 (98.0)	60 (100.0)	6 (100.0)	352 (99.2)
SERIOUS AE - TOTAL	61 (32.6)	40 (39.2)	26 (43.3)	4 (66.7)	131 (36.9)
FATAL	7 (3.7)	7 (6.9)	3 (5.0)	0	17 (4.8)
HOSPITALIZATION/PROLONGATION	54 (28.9)	35 (34.3)	23 (38.3)	4 (66.7)	116 (32.7)
LIFE THREATENING	3 (1.6)	4 (3.9)	2 (3.3)	0	9 (2.5)
CANCER	12 (6.4)	3 (2.9)	2 (3.3)	0	17 (4.8)
DISABILITY/INCAPACITY	4 (2.1)	2 (2.0)	0	0	6 (1.7)
IMPORTANT MEDICAL EVENT	17 (9.1)	8 (7.8)	6 (10.0)	2 (33.3)	33 (9.3)
AE LEADING TO DISCONTINUATION	39 (20.9)	18 (17.6)	15 (25.0)	2 (33.3)	74 (20.8)
PSYCHIATRIC DISORDERS	27 (14.4)	15 (14.7)	6 (10.0)	0	48 (13.5)
NERVOUS SYSTEM DISORDERS	72 (38.5)	42 (41.2)	21 (35.0)	2 (33.3)	137 (38.6)
ACCIDENT AND INJURIES	18 (9.6)	8 (7.8)	4 (6.7)	2 (33.3)	32 (9.0)
CARDIAC DISORDERS	16 (8.6)	16 (15.7)	7 (11.7)	1 (16.7)	40 (11.3)
VASCULAR DISORDERS	23 (12.3)	22 (21.6)	8 (13.3)	2 (33.3)	55 (15.5)
CEREBROVASCULAR DISORDERS	3 (1.6)	2 (2.0)	0	0	5 (1.4)
INFECTIONS AND INFESTATIONS	76 (40.6)	44 (43.1)	32 (53.3)	2 (33.3)	154 (43.4)
ANTICHOLINERGIC SYNDROME	56 (29.9)	34 (33.3)	17 (28.3)	3 (50.0)	110 (31.0)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	24 (12.8)	12 (11.8)	5 (8.3)	2 (33.3)	43 (12.1)

Gender: The overall safety profile of rela+nivo FDC was comparable between males and females. All-causality AEs of headache, nausea, and UTIs were more common in females, while arthralgia was more common in males; this pattern was similar to the differences between genders for the nivolumab arm. The frequency of drug-related AEs was similar between males and females for both the rela+nivo FDC and nivolumab (data not shown).

Region: The frequencies of overall AEs was generally higher in the US and Australia than Europe or Latin America for both the rela+nivo FDC and the nivolumab treatment arms. There were no differences in the nature of AEs reported between regions (data not shown).

Safety in relation to PD-L1- and LAG-3-expression

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 (1% and 10% cut-offs) or LAG-3 expression subgroups (1% cut-off). A safety summary for LAG-3 and PD-L1 subgroups with a 1% cut-off are provided in Table 38 and Table 39, respectively.

Table 38. Summary of safety by LAG-3 expression - All treated subjects

Safety Parameters	No. of Subjects (%)							
	Rela+nivo FDC				Nivolumab			
	LAG-3 < 1% N = 87		LAG-3 ≥ 1% N = 268		LAG-3 < 1% N = 90		LAG-3 ≥ 1% N = 269	
Deaths	3 (3.4)		7 (2.6)		6 (6.7)		12 (4.5)	
	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	31 (35.6)	22 (25.3)	90 (33.6)	69 (25.7)	27 (20.0)	21 (23.3)	78 (29.0)	53 (19.7)
Drug-related SAEs	11 (12.6)	7 (8.0)	39 (14.6)	26 (9.7)	7 (7.8)	5 (5.6)	21 (7.8)	12 (4.5)
All-causality AEs leading to DC	15 (17.2)	10 (11.5)	54 (20.1)	31 (11.6)	9 (10.0)	7 (7.8)	32 (11.9)	16 (5.9)
Drug-Related AEs leading to DC	11 (12.6)	7 (8.0)	41 (15.3)	23 (8.6)	4 (4.4)	2 (2.2)	20 (7.4)	9 (3.3)
All-causality AEs	86 (98.9)	37 (42.5)	259 (96.6)	106 (39.6)	86 (95.6)	32 (35.6)	253 (94.1)	88 (32.7)
Drug-related AEs	67 (77.0)	16 (18.4)	221 (82.5)	51 (19.0)	59 (65.6)	9 (10.0)	192 (71.4)	26 (9.7)

MedDRA version 23.1 CTCAE version 5.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Table 39. Summary of safety by PD-L1 expression - All treated subjects

Safety Parameters	No. of Subjects (%)							
	Rela+nivo FDC				Nivolumab			
	PD-L1 < 1%/non-quantifiable N = 209		PD-L1 ≥ 1% N = 146		PD-L1 < 1%/non-quantifiable N = 212		PD-L1 ≥ 1% N = 147	
Deaths	5 (2.4)		5 (3.4)		11 (5.2)		7 (4.8)	
	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	76 (36.4)	56 (26.8)	45 (30.8)	35 (24.0)	65 (30.7)	49 (23.1)	40 (27.2)	25 (17.0)
Drug-related SAEs	30 (14.4)	19 (9.1)	20 (13.7)	14 (9.6)	16 (7.5)	10 (4.7)	12 (8.2)	7 (4.8)
All-causality AEs leading to DC	39 (18.7)	25 (12.0)	30 (20.5)	16 (11.0)	17 (8.0)	9 (4.2)	24 (16.3)	14 (9.5)
Drug-Related AEs leading to DC	28 (13.4)	16 (7.7)	24 (16.4)	14 (9.6)	8 (3.8)	3 (1.4)	16 (10.9)	8 (5.4)
All-causality AEs	204 (97.6)	89 (42.6)	141 (96.6)	54 (37.0)	201 (94.8)	76 (35.8)	138 (93.9)	44 (29.9)
Drug-related AEs	165 (78.9)	36 (17.2)	123 (84.2)	31 (21.2)	142 (67.0)	19 (9.0)	109 (74.1)	16 (10.9)

MedDRA version 23.1 CTCAE version 5.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

2.6.8.7. Immunological events

Incidence of Immunogenicity

The incidence of relatlimab and nivolumab treatment emergent ADA and NAb were low (< 6%) when relatlimab was administered with nivolumab as the FDC or nivolumab was administered alone, and the incidence of nivolumab treatment emergent ADA and NAb was similar in both treatment arms (*Table 40*). In the rela+nivo FDC arm, there were only 2 subjects that were NAb positive (1 to relatlimab and 1 to nivolumab), and in the nivolumab arm, there was only 1 subject that was NAb positive. In the rela+nivo FDC arm, no subjects were PP positive to relatlimab and 2 subjects were PP positive to nivolumab. In the nivolumab arm, 2 subjects were PP positive.

Table 40. ADA assessments summary - All treated subjects with baseline and at least one post-baseline assessment in study CA224047

	Rela+nivo FDC	Nivolumab
Subject ADA Status (%)	ADA status for RELATLIMAB N = 286	ADA status for NIVOLUMAB N = 288	ADA status for NIVOLUMAB N = 272
BASELINE ADA POSITIVE	4 (1.4)	15 (5.2)	25 (9.2)
ADA POSITIVE	16 (5.6)	11 (3.8)	16 (5.9)
PERSISTENT POSITIVE (PP)	0	2 (0.7)	2 (0.7)
NOT PP LAST SAMPLE POSITIVE	6 (2.1)	5 (1.7)	7 (2.6)
OTHER POSITIVE	10 (3.5)	4 (1.4)	7 (2.6)
NEUTRALIZING POSITIVE	1 (0.3)	1 (0.3)	1 (0.4)
ADA NEGATIVE	270 (94.4)	277 (96.2)	256 (94.1)

Baseline ADA Positive: A subject with baseline ADA-positive sample.
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment.
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA positive samples are at least 16 weeks apart.
Not PP-Last Sample Positive: Not persistent but with ADA-positive sample at the last sampling timepoint.
Other Positive: Not persistent but some ADA-positive samples with the last sample being negative.
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline.
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Note: Post-baseline assessments are assessments reported after initiation of treatment.

Effect of Immunogenicity on Safety

The occurrence of either relatlimab or nivolumab ADA did not have an effect on safety of the regimens. None of the relatlimab ADA positive subjects had hypersensitivity/infusion reactions. There were only 1 and 2 subjects with hypersensitivity/ infusion reactions who were nivolumab ADA positive in the rela+nivo FDC and nivolumab arms, respectively. Most of the hypersensitivity/infusion reactions occurred after the first dose, were transient, and independent of ADA status.

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

Drug Interactions

Since mAb are not direct inhibitors/inducers of metabolizing enzymes and are eliminated by metabolic pathways (ie, degradation by catabolism/proteolysis [mainly by enzymes in the cells of reticuloendothelial system], Fc gamma receptor-mediated clearance, target-mediated clearance, nonspecific endocytosis, and formation of immune-complexes followed by complement- or Fc receptor-mediated clearance mechanism) that are different from small molecules, direct drug-drug interactions (DDIs) between mAb and small molecules are unlikely. Therefore, no formal PK DDI studies have been conducted with rela+nivo FDC. However, therapeutic proteins that are modulators of cytokines may indirectly affect the expression of cytochrome P450 enzyme. Levels of cytokines quantified in CA224020 and CA224047 including IL6, IL10 IL1β, IL12p70 and TNFα are near or below the assay lower limit of quantification in rela+nivo treated patients. Rela+nivo treatment resulted in increases in IFNγ and IFNγ-induced chemokines; however, clinically meaningful effects of IFNγ and IFNγ-induced chemokines on the expression or stability of CYP enzymes have not been reported. Overall, rela+nivo FDC is considered to have a low potential to affect the PK of other drugs eliminated by CYP450 enzymes, based on the lack of any clinically relevant effect on cytokines in the peripheral circulation.

Relatlimab and nivolumab are IgG4 monoclonal antibodies, which are likely to be eliminated via several pathways similar to that of other antibodies, ie degradation by catabolism/proteolysis (mainly by enzymes in the cells of reticuloendothelial system), Fc gamma receptor-mediated clearance, target-

mediated clearance, nonspecific endocytosis, and formation of immune-complexes followed by complement- or Fc receptor-mediated clearance mechanism. These enzymes or pathways are not known to be inhibited or induced by drugs; therefore, it is unlikely that other drugs will have an impact on the PK of relatlimab and nivolumab. Food-drug interactions are not applicable as rela+nivo FDC is administered as an IV infusion.

Use in Pregnancy and Lactation

There are no available data on rela+nivo FDC use in pregnant women to evaluate a drug-associated risk. There was one reported case of inadvertently exposure to rela+nivo FDC during pregnancy that resulted in spontaneous abortion, which was considered related to rela+nivo FDC by the investigator. Human IgG4 is known to cross the placenta; and rela+nivo FDC therapy has the potential to be transmitted from the mother to the developing fetus. Therefore, rela+nivo FDC should not be used during pregnancy. If a patient becomes pregnant while taking this drug, they should be advised of the potential risk to the fetus. It is unknown whether relatlimab and/or nivolumab are secreted in human milk. Because antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue from rela+nivo FDC therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Overdose

Higher doses of relatlimab up to 1440 mg in combination with nivolumab have been studied and were well-tolerated by patients without increased toxicity. Therefore, the observed physiological effect is minimal. However, in case of over dosage, the patient should be closely monitored for immune-adverse reactions and treated appropriately. There is no known antidote for relatlimab and/or nivolumab overdose.

Drug Abuse

There is no evidence that suggest a risk for a potential drug abuse for rela+nivo FDC as the combination drug is dispensed by pharmacies and administered in medical settings.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Relatlimab and/or nivolumab may have a minor influence on the ability to drive and use machines due to fatigue, which is a very common side effect of rela+nivo FDC.

2.6.8.9. Discontinuation due to adverse events

A total of 39.4% of subjects in the rela+nivo FDC arm and 36.2% of subjects in the nivolumab monotherapy arm had at least 1 dose delayed, mainly due to an AE (no specific ones), but dose delays accounted for only approximately 6-7% of all doses received by subjects. Most dose delays lasted ≤ 42 days. Very few dose delays were due to COVID-19 (27 total in the rela+nivo FDC 3 arm and 34 total in the nivolumab monotherapy arm).

The majority of "other" reasons for IV rate reduction were more specifically due to previous infusion reaction, infusion reaction prophylaxis, and infusion reaction. Infusion interruption occurred in a low percentage of subjects and was similar between the two treatment arms (6.2% and 5.6% in the rela+nivo FDC and nivolumab arms, respectively). The most common cause of infusion interruption was hypersensitivity reaction (73.3% and 62.5% in the rela+nivo FDC and nivolumab arms, respectively).

The overall frequencies of AEs leading to discontinuation (all-causality and drug-related) were higher in the rela+nivo FDC arm (19.4%) compared with the nivolumab arm (11.4%). Drug-related any grade AEs leading to discontinuation were 14.6% and 7.8%, and grade 3-4 8.5% and 3.1%, respectively.

2.6.8.10. Post marketing experience

No post-marketing data were provided.

SUPPORTIVE SAFETY - CA224020

An overview of extent of exposure in all treated subjects with rela+nivo 160/480 mg Q4W (N = 412, FDC or non-FDC) is provided in Table 41.

Table 41. Dose information summary - All treated subjects with relatlimab + nivolumab 160/480 mg Q4W in study CA224020

	All Subjects Treated with Rela+Nivo 160/480 mg N = 412		
	All non-FDC Rela+Nivo 160/480 mg N = 330		Rela+Nivo 160/480 mg FDC Part D1 N = 82
	Relatlimab	Nivolumab	Rela+Nivo FDC
Number of Doses			
Mean	7.4	7.4	8.9
Median	4.0	4.0	5.0
Min - Max	1 - 37	0 - 37	1 - 29
SD	8.05	8.05	8.48
Duration of Therapy, weeks			
Mean	30.9	30.9	37.0
Median	16.0	16.0	19.8
Min- Max	2 - 158	2 - 158	4 - 128
SD	33.44	33.49	35.67
Cumulative Dose per Subject, mg			
Mean	1192.2	3574.5	5596.9
Median	640.0	1920.0	2880.0
Min - Max	160 - 5920	480 - 17760	640 - 17920
SD	1288.17	3862.92	5407.15
Relative Dose Intensity, n (%)			
< 50%	1 (0.3)	2 (0.6)	2 (2.4)
50% to < 70%	5 (1.5)	5 (1.5)	0
70% to < 90%	25 (7.6)	27 (8.2)	11 (13.4)
90% to < 110%	299 (90.6)	295 (89.4)	68 (82.9)
≥ 110%	0	0	0
Not Reported	0	1 (0.3)	1 (1.2)

Duration of therapy(weeks) for Q4W= (last dose date - first dose date +28)/7
Cumulative dose is the sum of all actual doses that a subject received.
Relative dose intensity is defined as actual dose a subject received divided by planned dose.

Median duration of therapy was 16 weeks for single agent vials and 19.8 weeks for rela+nivo FDC. Drug-related SAEs grade 3-4 varied between 4.9% and 15.8%. Drug-related AEs leading to discontinuation varied between 4.9% and 10.5%. The most frequently reported any-grade drug-

related select AE categories were skin (31.6%), endocrine (23.7%), gastrointestinal (7.9%), and hypersensitivity/infusion reaction (5.3%).

OESIs were infrequently reported (5 subjects reported 6 OESIs). The OESIs reported were uveitis, meningitis, myositis/rhabdomyolysis, and myocarditis (1 subject [1 event] each), and Guillain-Barre syndrome (1 subject [2 events]). Of the 5 OESIs, 1 event was resolved with IMM and 4 events were continuing at the time of DBL.

Of all subjects treated with rela+nivo 160/480 mg Q4W who were evaluable for ADA, hypersensitivity/infusion reaction select AEs were experienced by 1/13 (7.7%) relatlimab ADA-positive subject, 11/316 (3.5%) relatlimab ADA-negative subjects, and 12/323 (3.7%) nivolumab ADA-negative subjects; none of the nivolumab ADA-positive subjects experienced hypersensitivity/infusion reaction.

Overall, hypersensitivity/infusion reactions occurred in 11 (2.7%) subjects in the pooled group of subjects who received at least one dose of rela+nivo 160/480 mg Q4W (N = 412), and in 8 (5.7%) subjects who received at least one dose of rela+nivo 480/480 mg Q4W (N = 140) in Study CA224020.

Hypersensitivity/infusion reaction events were manageable. Due to Grade 3-4 AEs 2 subjects treated with rela+nivo 160/480 mg Q4W and none of the subjects treated with rela+nivo 480/480 mg Q4W with hypersensitivity/infusion reactions were treated with immune modulating medication.

2.6.9. Discussion on clinical safety

The main safety data for relatlimab+nivolumab (rela+nivo) FDC (160 mg + 480 mg Q4W) is based on the pivotal study CA224047. Safety data from study CA224020 was also included, but there was no pooling of safety data from these studies due to a difference of study designs, e.g. high percentage of IO-pre-treated patients and various tumour types. The safety profile of 412 patients that were comparable to the pivotal patients was supportive for the safety data of the pivotal study.

The pivotal Study CA224047 is a Phase 2/3, randomised, double-blind study of rela+nivo FDC (n=355) versus nivolumab (nivo) monotherapy (N = 359) in subjects with unresectable or metastatic melanoma. Safety data is based on a 09-Mar-2021 DBL.

Based on the MOA of relatlimab and nivolumab, the key expected drug toxicities were related to immune activation; therefore, particular attention was paid to detecting and reporting select AEs, IMAEs, and OESIs.

Exposure

The study population included 18% of subjects ≥ 75 years of age, including almost 2% who were above the age of 85 years and no patients < 18 years of age. The median follow-up time was 13.2 months. The median duration of therapy was comparable for both treatment arms, being 5.5 months for rela+nivo FDC and 4.8 months for nivo monotherapy, as was relative dose intensity 90-110% in 87% and 85%, respectively. Most patients received >90% intensity in both treatment arms, which is indicative of manageable adverse events. However, median duration of treatment is 5 months with a median follow-up time of 13 months, which is short to conclude on long-term safety. The applicant provided updated data with 28-Oct-2021 DBL (with a median follow-up of 19.27 months) (data not shown). The median treatment duration was 8.31 months for nivo+rela FDC treated subjects and 6.47 months for nivolumab monotherapy treated subjects, and nearly 40% subjects have been treated ≥ 12 months. This follow-up data was consistent with the previously provided data and is considered of sufficient duration to have an adequate understanding of safety.

Patients included in the study may have received prior adjuvant or neo-adjuvant therapy if, at least, it had happened 6 months (6 weeks for interferon) before recurrence. In Study CA224047, 31 (8.7%) and 26 (7.2%) subjects had received prior adjuvant therapy in the combination and monotherapy arm, respectively; and 2 (0.6%) and 1 (0.3%) patients, respectively, had received prior therapy in the neo-adjuvant setting. As per inclusion criteria these subjects were allowed to enter the study if all related AEs have either returned to baseline or stabilised. There were no predefined objective criteria to consider non-resolved AEs from adjuvant therapy as stabilised and this was up to the investigator. The percentage of patients receiving prior systemic therapy has been added to section 5.1 SmPC.

Adverse events (AEs)

Almost all patients experienced all-causality AEs, any grade at 97% and 94%, and grade 3-4 at 40% and 33%, for rela+nivo FDC and nivo monotherapy, respectively. Regarding drug-related AEs, the reported incidence of any grade AEs was 81.1% in the rela+nivo FDC arm and 69.9% in the nivo arm, while grade 3-4 drug-related AEs were reported by 18.9% and 9.7% of subjects, respectively.

The most frequently (>15%) reported any grade AEs were fatigue (29% vs 20%), pruritus (25% vs 17%), arthralgia (24% vs 15%), diarrhoea (23% vs 17%), headache (18% vs 12%), nausea (17% vs 15%), rash (17% vs 13%) and hypothyroidism (15% vs 12%).

The most frequently reported drug-related AEs (rela+nivo FDC vs nivo monotherapy; ≥ 10% of rela+nivo FDC subjects) were pruritus (23.4% vs 15.9%), fatigue (23.1% vs 12.8%), rash (15.5% vs 12.0%), arthralgia (14.4% vs 7.2%), hypothyroidism (14.4% vs 12.0%), diarrhoea (13.5% vs 9.2%), and vitiligo (10.4% vs 9.7%); these AEs were predominantly of low grade.

The most frequently reported Grade 3-4 drug-related AEs (rela+nivo FDC vs nivo monotherapy; ≥ 1% of rela+nivo FDC subjects) were increased lipase (1.7% vs 0.8%), increased ALT (1.4% vs 0.6%), increased AST (1.4% vs 0.3%), and fatigue (1.1% vs 0.3%).

In general, rela+nivo showed more toxicity than nivo monotherapy, as was to be expected since two drugs can cause more adverse events than just one. Therefore, the numerical incidence of grade 3-4 drug-related SAEs is higher in the rela+nivo FDC patients (9.3%) versus nivo monotherapy (4.7%). Although the overall frequencies of all causality and drug-related AEs were higher in the rela+nivo FDC arm, the majority were of low grade (Grades 1-2), and the safety profile of rela+nivo FDC was manageable using well established AE management guidelines.

Serious adverse events (SAEs) and deaths

As of the 09-Mar-2021 DBL, 30.4% subjects in the rela+nivo FDC arm and 33.1% of subjects in the nivo monotherapy arm died during the study. Disease progression was the most common cause of death in both arms. A similar proportion of subjects in the rela+nivo FDC (0.8%; 3 subjects) and nivo monotherapy (0.6%; 2 subjects) arms died due to study drug toxicity during the study. This was caused by haemophagocytic lymphohistiocytosis, acute oedema of the lung and pneumonitis in the rela+nivo FDC group and in the nivo monotherapy group sepsis+myocarditis and worsening pneumonia. The numbers are too low to reveal any trend or indication for a systematic causal relationship on the contribution of relatlimab.

Although a higher numerical percentage of patients in the rela+nivo FDC group (34%) than in the nivo monotherapy group (29%) suffered from any grade SAEs, no individual SAE was reported with a frequency > 2% except malignant neoplasm progression in either arm. The majority of SAEs in both groups were considered not drug-related by the investigator, which is an acceptable explanation with respect to the wide variety and type of SAEs.

Drug-related SAE of myocarditis was infrequent in both treatment arms (1.1% rela+nivo FDC and 0.3% nivolumab monotherapy), as were high grade myocarditis SAEs (0.6% in the rela+nivo FDC arm

vs 0% in the nivolumab monotherapy arm). There seems to be no specific relationship between drug-related SAEs and one of the treatment arms.

Deaths attributed to other reasons were reported in 14 (3.9%) subjects in the rela+nivo FDC arm and 16 (4.5%) subjects in the nivolumab monotherapy arm, which is balanced between study arms. The verbatim terms might be consistent with events expected in this study population and none were considered related to the study drugs. This might be acceptable as explanation for the variety of causes of death. However, 6 patients of all randomised patients died of ischemic cardiac failure and 2 patients died of a cerebrovascular event. From the details of the cardiovascular death cases it is understood that most patients had a pre-existing risk factor for cardiovascular disease and that it is unlikely that the death was attributable to the study drug. This seems acceptable.

Other Serious Adverse Events

Of SAEs attributed to study drug by the investigator, there were 4 reported events that are considered rare for immuno-oncology agents in the rela+nivo FDC arm affecting individual subjects (haemolytic anaemia, Guillain-Barré syndrome, Vogt-Koyanagi-Harada disease and haemophagocytic lymphohistiocytosis), and 1 event in the nivo monotherapy arm (acquired haemophilia).

The most frequently reported (≥ 1% of patients) any-grade drug-related SAEs were:

- Rela+nivo FDC: colitis, diarrhoea, and myocarditis (1.1% each);

- Nivolumab: None; all drug-related SAEs by PT occurred in < 1% of subjects.

No individual SAE was reported with a frequency > 2% except malignant neoplasm progression in either arm. The majority of SAEs in both groups were considered not drug-related by the investigator. Drug-related SAE of myocarditis was infrequent in both treatment arms (1.1% rela+nivo FDC and 0.3% nivolumab), as were high grade myocarditis SAEs (0.6% in the rela+nivo FDC arm vs 0% in the nivolumab arm). There seems to be no specific relationship between overall SAEs and one of the treatment arms.

The applicant has outlined some SAEs that were considered rare for immuno-oncology agents: haemolytic anaemia, Guillain-Barré syndrome, Vogt-Koyanagi-Harada disease and haemophagocytic lymphohistiocytosis (with concomitant hypohysitis) in the rela+nivo arm and a case of acquired haemophilia in the nivo arm. Except for haemolytic anaemia and acquired haemophilia, the rest of them have been already identified as nivolumab ADRs and are included in the PI of Opdivo. Haemolytic anaemia was resolved after long treatment with corticosteroids and resolution of concomitant infective arthritis according to the submitted patient narrative.

Adverse Events Leading to Discontinuation of Study Therapy

The overall frequencies of AEs leading to discontinuation (all-causality and drug-related) were higher in the rela+nivo FDC arm (19%) compared with the nivo monotherapy arm (11%) as was the case for Grade 3-4 events in both treatment arms (11.5% vs 6.4%).

The most frequently reported any grade AEs leading to discontinuation (≥ 1% of patients) were:

- Rela+nivo FDC: pneumonitis, malignant neoplasm progression, and myocarditis (1.4% each);
- Nivolumab monotherapy: malignant neoplasm progression (2.5%).

The most frequently reported any grade drug-related AEs leading to discontinuation (≥ 1% of subjects) were:

- Rela+nivo FDC (14.6%): pneumonitis and myocarditis (1.4% each);
- Nivolumab (6.7%): None; all events by PT occurred in < 1% of subjects.

Recommended treatment modifications are properly addressed in section 4.2 of the SmPC.

The proportion of AEs leading to discontinuation represented by Grade 3-4 events in both treatment arms were 11.5% and 6.4%, respectively, as well as for Drug-Related Adverse Events Leading to Discontinuation (14.6% vs 6.7%). There is a non-negligible difference of about 8% in drug-related discontinuation of treatment.

Select Adverse Events

Across the select AE categories, the majority of events in the rela+nivo FDC and nivolumab monotherapy arm were manageable using the established algorithms, with resolution occurring for the majority of non-endocrine AEs (ranging from 42.7% - 100% across categories) when immune-modulating medications (mainly systemic corticosteroids) were administered. Although there is a higher incidence of select AEs in the rela+nivo patients, this difference is acceptable from a clinical point of view.

Immune-mediated Adverse Events (IMAEs)

The most frequently reported IMAEs (any grade; ≥ 5% of subjects) were as follows in each treatment arm:
- Rela+nivo FDC: hypothyroidism (16.6%), rash (9.3%), diarrhoea/colitis (6.8%), hyperthyroidism (6.2%), and hepatitis (5.6%);
- Nivolumab monotherapy: hypothyroidism (13.1%), hyperthyroidism (6.7%), and rash (6.7%).
Incidence and duration of IMMs in subjects who experienced IMAEs did not appear to be consistently different between treatment arms. The percentage of subjects with an IMAE leading to dose discontinuation was comparable between both treatment arms.
IMAEs and implications are well described in section 4.4 of SmPC, as are the class effects.

Other Events of Special Interest (OESIs)

Events defined as OESIs for rela+nivo included the following categories: myasthenic syndrome, demyelination, Guillain-Barré syndrome, pancreatitis, uveitis, encephalitis, myositis/rhabdomyolysis, myocarditis, GVHD, meningitis and troponin increase.

Specific attention was paid to:

- *Myocarditis*. Early, lethal myocarditis in LAG-3/PD-1 double knockout mouse models was observed, together with emerging literature describing a low risk of severe checkpoint inhibitor-associated myocarditis in the post approval setting. Monitoring of troponin has been implemented adequately in the study protocol
- *CNS vasculitis* and mild inflammation of the choroid plexus and brain vasculature were observed during pre-clinical general toxicity testing in cynomolgus monkeys. There are no routine laboratory or imaging evaluations that would enhance safety monitoring for CNS events within these clinical studies beyond clinical observation and awareness of the treating physician, which is acceptable.
- *Hypersensitivity/infusion reactions*: Because both relatlimab and nivolumab contain only human immunoglobulin protein sequences, they have a low risk of inducing immunogenicity or associated infusion or hypersensitivity reactions. Given a theoretical risk of infusion reactions with the new FDC formulation, a safety lead-in was employed in Study CA224047 for the first 18 subjects randomised to monitor for Grade 3 or 4 infusion reactions; no risks were identified in the safety lead-in study.

Overall, OESIs were reported in 17.5% of patients in the rela+nivo FDC arm and 13.6% in the nivolumab arm. In the rela+nivo FDC arm 76 of the 83 OESIs, were resolved at the time of DBL: 45 troponin events, 9 myocarditis events, 8 uveitis events, 3 encephalitis events, 3 myositis events, 3 pancreatitis events, and 1 Guillain Barré Syndrome. All resolved events of myocarditis, uveitis,

encephalitis, myositis, pancreatitis, and Guillain Barré Syndrome were resolved with IMM; only 3/45 troponin events were resolved with IMM.

In the nivolumab monotherapy arm 64 of the 75 OESIs were resolved at the time of DBL: 46 troponin events, 11 uveitis events, 2 myocarditis events, and 5 pancreatitis events. All resolved events of uveitis, myocarditis, and pancreatitis were resolved with IMM; only 1/46 troponin event was resolved with IMM.

Myocarditis was reported infrequently at 1.7% and 0.6% in the rela+nivo FDC and nivolumab arms, respectively, and a minority were high grade (Grade 3-4) events (0.6% vs 0%, respectively). The majority of myocarditis events occurred in the first 2 months. In the rela+nivo FDC arm, all observed myocarditis events were manageable within established IMAE management practices and resolved. There was 1 fatal event in the nivolumab arm due to a combination of myocarditis and bacterial sepsis due to immune suppression for management of myocarditis. There were no overall differences in the median time to resolution or median duration of immunosuppression between the study arms.

Troponin elevation was reported in 41 (11.5%) subjects in the rela+nivo FDC arm and 36 (10.0%) subjects in the nivo monotherapy arm, in the context of a protocol requirement for cardiac assessment in subjects with raised troponin values. 3 subjects with troponin elevation events were treated with immune-modulating medications: 2 (0.6%) subjects vs 1 (0.3%) subject in the rela+nivo FDC and nivo monotherapy arms, respectively. One of these 3 subjects, treated with corticosteroids in the rela+nivo FDC, had myocardial inflammation on MRI but was asymptomatic; the other 2 subjects did not have radiographic confirmation of myocarditis and a clinical decision was made to treat with corticosteroids. However, these 3 events represented a minority of the troponin elevation events observed within the study, most of which required no immunosuppression. Overall, the rate, duration, or grade of troponin elevation events were similar between the study arms. Troponin elevation does not seem to be of clinical importance. However, troponin elevation might be indicative for myocardial damage and since there is no difference between both treatment groups it might be related to 'any' immunotherapy. According to the applicant, study CA224047 is the first randomised, double-blind immuno-oncology (IO) trial to incorporate prospective troponin monitoring as a tool to determine if increased surveillance could support identification of myocarditis and to permit characterisation of the risk of myocarditis with nivo+rela FDC compared to an established immune check-point inhibitor (ICI), nivolumab. Data from cohort studies recently published in literature indicate that the clinical relevance and aetiology of troponin elevations for patients receiving checkpoint inhibitors are currently ill-defined and multi-factorial. Overall, as only very few patients with an isolated troponin evaluation in the CA224047 study might have suffered from myocarditis with clinical symptoms, it might be concluded, that troponin elevation is not a reliable predictive value for myocarditis and should only be used as diagnostic in case of clinical suspicion of myocardial damage. The current information in the SmPC and package leaflet is considered sufficient to take care of patient and prescriber awareness of cardiac toxicity.

In this respect, as the key immune-mediated cardiac toxicity for checkpoint inhibitors including nivo+rela FDC, and due to the need for early identification and appropriate clinical management of this event, myocarditis has been included in the proposed SmPC within Sections 4.8 and Section 4.4 (Special Warnings and Precautions) to support patient safety. These measures are considered adequate.

CNS AEs were reported infrequently in both treatment arms: 2 subjects each in the rela+nivo FDC and nivo monotherapy arms experienced encephalitis OESIs. Of the encephalitis OESIs reported in the rela+nivo arm, all events were manageable with established IMAE management practices and resolved (in the 2 cases in the nivo monotherapy arm it did not resolve). Overall, there is no clinical important difference in incidence and outcome of OESIs between both treatment arms. Encephalitis is listed in

Section 4.4 of the SmPC, Special warnings and Precautions for use, along with other rarely reported immune-related adverse reactions, and with adequate treatment guidelines. 'Encephalitis' was positioned within Table 2 under the 'Nervous system disorders' instead of the 'Infections and infestations' heading, in accordance with the non-infectious aetiology of this type of encephalitis.

With respect to OESIs it was noted, that in nivo+rela FDC 76 out of 83 OESIs and in the nivo group 64 out of 75 were resolved. To address the question "which OESIs were not resolved", an analysis was performed to evaluate the proportion of subjects experiencing each OESI in whom the event resolved within 100 days of last dose, based on the updated safety information from the DBL of 28-Oct-2021. Overall, the proportion of subjects with ongoing OESIs was similar between the nivo+rela FDC and nivolumab arms. Although there were some differences between treatment arms in the proportion with resolved events for individual OESI categories, these differences are likely attributable to small numbers of impacted subjects and there was no consistent trend.

SUPPORTIVE SAFETY data of study CA224020

Study CA224020 is an ongoing Phase 1/2 trial evaluating safety, tolerability, and efficacy of multiple dosing regimens of relatlimab monotherapy and relatlimab in combination with nivolumab in subjects with selected advanced or recurrent malignancies, including melanoma:

n=412 for rela+nivo 160/480 mg Q4W, median duration of therapy varies from 16-19.8 weeks; median follow-up varies from 9.4-13.4 months;

n=743 for rela+nivo 80/240 mg Q2W, median duration of therapy 16 weeks; median follow-up varies from 12-30.3 months.

Data on safety and immunogenicity of study CA224020 for all subjects who received at least one dose of rela+nivo 160/480 mg Q4W (the proposed dosing regimen, N = 412) was generally consistent with the safety findings from study CA224047. Since there is no control group in the CA224020 study no comparison can be made between single and combined therapy. No additional safety signals were noticed.

Laboratory findings

Haematology

There were no Grade 3 or 4 haematologic abnormalities reported in >5% of subjects in both treatment arms.

Liver tests, creatinine and electrolytes

Only a very small percentage of patients had concurrent ALT or AST > 3 ULN with total bilirubin > 2 ULN. Since there were only 3 patients involved, and 2 of them had contributing factors to elevated liver enzymes, no conclusions can be drawn on this reversible high grade hepatic toxicity. Moreover, the incidence of drug-induced high grade hepatic toxicity is very low.

There were no Grade 4 increased creatinine levels in either arm. No Grade 3 or 4 abnormalities in electrolytes were observed in > 5% of treated subjects in both treatment arms.

Thyroid Function Tests

TSH increases (>ULN) and decreases (<LLN) were equally distributed between both study arms, 23% and 24%, respectively.

Overall, incidence of grade 3-4 laboratory toxicity was low and no unexpected signals were noticed.

Vital signs

No remarkable differences were noted between treatment arms across all measured parameters.

Safety by Biomarkers (LAG-3 and PD-L1 Expression)

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 (1% and 10% cut-offs) or LAG-3 expression subgroups (1% cut-off).

SAFETY IN SPECIAL GROUPS AND SITUATIONS - CA224047

Overall, the safety profile of rela+nivo FDC among subgroups of age, gender, race, and geographic region was generally similar to the total rela+nivo FDC treated population.

PREGNANCY - CA224047

One patient who received two doses of rela+nivo FDC on Study Day 1 and Day 30 had a positive pregnancy test at day 54 and most probably had an early spontaneous abortion. There is no other data on pregnancy, which is addressed in SmPC 4.6.

Immunogenicity

Like in other PD-(L)1 inhibitor trials and prior nivolumab-trials ADAs were found in a relatively low and stable percentage of patients. ADA positivity was found for relatlimab (5.6%, n=286) and nivo monotherapy (3.8%, n=288) in the FDC group and nivolumab (5.9%, n=272) in the nivo monotherapy group. Almost none were persistently positive and Nab was only found in 0.3%. No new safety signal due to ADA for nivolumab was noted and no detrimental ADA-related safety effect for relatlimab.

Proposed 30-minute infusion rate

The applicant proposes a 30-minute infusion rate within the SmPC, whereas a 60 minute infusion rate was used in the pivotal study. This is acceptable as a clinically relevant increase of immunogenicity and adverse events is considered unlikely given the limited differences in exposure based on popPK simulations. In addition, both nivolumab and relatlimab have a low immunogenic potential and a limited number of patients experienced hypersensitivity/infusion-related reactions (11/412 pooled data) at the recommended dose. There were no apparent associations between dose (maximum rela SAV + nivo dose up to 1440/480 mg Q4W) and infusion or hypersensitivity reactions in study CA224020.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Assessment of paediatric data on clinical safety

Safety extrapolation from adults to adolescents

There is a need for new therapeutic modalities for advanced melanoma given the limited options and poor outcomes in adolescent patients. Currently only ipilimumab is approved for the treatment of advanced (unresectable or metastatic) melanoma in adolescents. Although survival benefit for ipilimumab in adults is established, the toxicity of this drug is considerable, by which the medical need for adolescent advanced melanoma patients is considered not fulfilled. The applied indication for the FDC of relatlimab and nivolumab includes both adults and adolescents aged 12 to <18 years old, however no patients below the age of 18 years were included in the clinical studies. Given the low incidence of advanced melanoma in the paediatric population it is difficult to enroll adolescents in clinical studies in this setting. Therefore, the indication for adolescents is based on extrapolation from adult data.

Prognosis for adolescent patients is poor, and advanced melanoma is rare in adolescents, by which the number of patients that could be available to participate in a (paediatric) clinical study is too limited for generation of robust efficacy and safety data needed for benefit/risk assessment, therefore the proposed approach by the applicant to support the adolescent indication by extrapolation from adult data is agreed.

Regarding young adults, in Study CA224047, 11 subjects treated with rela+nivo FDC were 18 to ≤ 30 years of age. In Study CA224020, of the 412 treated subjects receiving the same study drug dose and schedule (relatlimab 160 mg + nivolumab 480 mg Q4W), 8 subjects treated with relatlimab + nivolumab were 18 to ≤ 30 years of age. No substantial differences in incidence of AEs including grade 3-4 AEs, SAEs IMAEs, were reported for young adults or the ITT population.

To facilitate the extrapolation approach, clinical data in subjects with advanced melanoma receiving relatlimab 160 mg + nivolumab 480 mg Q4W (SAV and FDC formulations) in Studies CA224047 and CA224020 were analysed by body weight (data not shown). There were 6 subjects with low body weight (< 50 kg) in Study CA224047 and 10 subjects with low body weight (< 50 kg) in Study CA224020. The safety profile of the combination of relatlimab and nivolumab in subjects with advanced melanoma with low body weight (< 50 kg) was generally similar to the safety profile in subjects with a body weight ≥ 50 kg, and no consistent trend was seen for higher frequency or severity of AEs with decreasing body weight. The cut-off of 50 kg was used because the analysis using a 40 kg cut-off would not be feasible due to negligible numbers enrolled in the studies. The number of subjects < 40 kg at baseline enrolled in CA224047 and CA224020 are 0 and 1, respectively.

For the only product that is currently approved for the treatment of adolescents with advanced melanoma, ipilimumab, only limited safety data for adolescents treated were available at the time of approval. No new safety concerns and no new adverse drug reactions for ipilimumab were reported in adolescents 12 years of age and older during this procedure (EMEA/H/C/002213/II/0044). However, the CHMP concluded that ipilimumab seemed to be less well tolerated in adolescents compared to adults as a numeric high number of SAEs and AEs leading to treatment discontinuation, were reported. To further characterize the safety profile in children and mitigate the uncertainties surrounding a negative effect of ipilimumab on endocrine-related ADRs which may affect hormonal and sexual development in adolescents, the CHMP requested to collect post-marketing paediatric safety data, through joining the existing Dutch Melanoma Treatment Registry (DMTR) as additional pharmacovigilance activities. Similarly, to obtain more adolescent data for the relat+nivo FDC the study CA224122 will be initiated. This is a voluntary post-authorisation safety study and pertains to a long-term follow-up of paediatric patients exposed to relatlimab + nivolumab fixed dose combination (FDC) in the DMTR (see RMP).

Considering the lack of safety data of nivolumab and relatlimab monotherapy and for nivolumab in combination with relatlimab in adolescents, the applicant submitted further safety data from two studies (CA209070 and CA209908, data not shown), which included children who were treated with nivolumab monotherapy or nivolumab in combination with ipilimumab. In general, the short-term safety profile of nivolumab for children appears to be comparable to the known safety profile of nivolumab in adults. As both nivolumab and relatlimab are checkpoint inhibitors, also for relatlimab the toxicity profile is expected to be comparable in adolescents and adults, as comparable exposure has been established.

Selected AEs and IMAEs, including those that were severe appeared to be manageable and the majority of drug related select AEs and IMAEs resolved. An exception is endocrine select AEs and endocrine IMAEs, that were managed by hormone replacement therapy.

Hardly any long-term toxicity data for any immune checkpoint inhibitor is available for adolescents. Considering the endocrine AEs that are managed with hormone replacement therapy and the unknown

impact of these AEs on growth and development, the lack of information on long term toxicity is a concern. On the other hand, it is acknowledged that the prognosis of adolescents with metastatic or unresectable (advanced) melanoma is poor and have a high unmet medical need. The long-term safety for checkpoints in adolescents will be further studied, specifically for the nivolumab+ relatlimab combination therapy, additional safety data will become available from children with haematological malignancies treated with this combination. Moreover, adolescent melanoma patients treated with nivolumab+relatlimab will be included in the DMTR study, which may also provide long term safety follow up data. Critical attention should be given to several potential long-term toxicities associated to treatment with check point inhibitors (like autoimmune endocrine, hepatic and renal toxicity) in the adolescent population. These aspects are reflected in the RMP.

2.6.10. Conclusions on the clinical safety

In general, no new safety signals were found from the phase 3 study comparing rela+nivo FDC with nivo monotherapy for first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents. As was to be expected, adverse events were observed in a higher incidence in the (combined treatment) study arm, although there was only a small difference in grade 3-4 toxicity. The most common serious adverse reactions are colitis, diarrhoea, back pain, myocarditis, and adrenal insufficiency, though in low frequency. An extended follow-up at median 19.3 months showed consistent results with the primary analysis (data not shown).

Drug-related adverse events lead to discontinuation of treatment in almost 15% of patients in the rela+nivo FDC group versus almost 7% in the nivo group. Nevertheless, drug-related AEs were generally manageable with treatment guidelines and are adequately addressed in SmPC 4.2.

The issue of troponin elevation and myocarditis that has been raised in non-clinical studies does not seem to play a clinically important role. While there is a quite high incidence of troponin elevation in both study arms of around 10%, it is noticed that troponin elevation is not a reliable predictive value for myocarditis. There is not enough knowledge about the causal mechanism of troponin elevation, and it is not justified yet neither to screen for troponin elevation during treatment nor to make a specific guideline for the situation of isolated elevated troponin. Instead, elevated troponin should only be used as a diagnostic marker in case of clinical suspicion of myocardial damage. SmPC sections 4.2, 4.4 and 4.8 provide adequate information on immune-related myocarditis.

No adolescents have been included in the pivotal phase 3 study. In general, the safety profile of nivolumab in adolescents seems to be comparable to the known safety profile of nivolumab in adults. As both nivolumab and relatlimab are check point inhibitors, also for relatlimab comparable toxicity for adults and adolescents can be expected as comparable exposure has been established. No long-term safety data for adolescents treated with checkpoint inhibitors is however available. The long-term safety of nivolumab+relatlimab in adolescents will be followed post-approval (cat 3 study in the RMP).

In conclusion, there are no new clinically relevant safety issues.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 42 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
Missing information	Long term safety (including growth and development disorders) in paediatric patients ≥ 12 years of age

2.7.2. Pharmacovigilance plan

Table 43 On-going and planned additional pharmacovigilance activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA224122: Long-term follow-up of paediatric patients exposed to nivolumab + relatlimab FDC in the DMTR. Planned Voluntary PASS	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.	1. Protocol synopsis submission 2. Full Protocol submission 3. Interim reports[a] 4. Final report	13-Sep-2021 2Q2023 4Q2026 4Q2029 4Q2032 4Q2035 4Q2038

2.7.3. Risk minimisation measures

Table 44. 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	**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	**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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 18 March 2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Opdualag (relatlimab / nivolumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Opdualag is indicated 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%.

3.1.2. Available therapies and unmet medical need

Melanoma is a heterogeneous and complex disease with various clinical factors and molecular defects playing a key role in outcomes. Cutaneous melanoma is by far the most common melanoma subtype and approximately 50% of cutaneous melanomas bear an oncogenic driver mutation in the BRAF gene which is associated with a worse prognosis. Clinical factors associated with poor survival include elevated LDH, visceral metastases (notably liver and brain), multiple metastatic sites, and poor performance status.

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. The main aim of treatment in this setting is to prolong progression-free survival and improve overall survival. The current first-line standard of care treatments for unresectable stage III/IV are PD-1 blockade (nivolumab, pembrolizumab), PD-1 blockade (nivolumab) combined with CTLA-4 blockade (ipilimumab) and, in addition for BRAFV600-mutated melanoma, BRAF inhibition (vemurafenib, dabrafenib, encorafenib) combined with MEK inhibition (cobimetinib, trametinib, binimetinib). Patients for whom immunotherapy can be delivered safely for the first few months, i.e. patients with tumours not progressing very quickly and not immediately threatening an important organ or function, should be considered for immunotherapy first, preserving targeted therapies for the subsequent lines.

Combination treatment of ipilimumab and nivolumab has markedly improved survival with a 5-year OS rate of 52%. 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 is a need for more effective therapies as part of the patient population fail to respond to these therapies or respond but then later 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

Pivotal study CA224047 is a seamless 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%.

3.2. Favourable effects

The primary objective was to compare PFS (per BICR) of rela+nivo FDC to nivolumab monotherapy with OS and ORR as key secondary endpoints (ITT).

At the time of the database lock (9 March 2021) and a median duration of follow-up of 13 months, rela+nivo FDC showed a statistically significant improvement in PFS vs. nivolumab monotherapy, HR: 0.75 (95% CI: 0.62, 0.92, log-rank p-value 0.0055). Median PFS was 10.12 months with rela+nivo FDC versus 4.63 months with nivolumab monotherapy. An updated PFS analysis with a median follow-up of 19.27 months (at the time of OS analysis 28-Oct-2021 DBL) supported the primary analysis,

OS data were not statistically significant at the time of the final analysis (28-Oct-2021 DBL); HR of 0.80 (95% CI: 0.64, 1.01). Median OS was not reached for rela+nivo FDC (95% CI: 34.20, N.A.) and 34.10 months (95% CI: 25.23, N.A.) for nivolumab monotherapy.

ORR was 43.1% (95% CI: 37.9, 48.4) vs 32.6% (95% CI: 27.8, 37.7) in the rela+nivo FDC and nivolumab monotherapy arm, respectively (28-Oct-2021 DBL).

In subjects with PD-L1 low expression the use of the combination appears to offer additional PFS benefit while there is little 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. KM-curves for OS only start to separate late (30 months) in the PD-L1 positive subgroup where there is still extensive censoring.

ORR data showed an increase in ORR for the combination treatment over monotherapy of 8% and 12% for PD-L1 ≥1% and PD-L1 <1% subgroup, respectively.

Exploratory subgroup analyses for PFS supported a beneficial effect of rela+nivo FDC over nivo monotherapy in most important subgroups as HR was below 1. This includes important subgroups with a worse prognosis like BRAF mutation, high HDL and baseline metastasis stage of M1c. Comparable HRs were observed for LAG-3 low expression (<1%, HR: 0.78; 95% CI: 0.54, 1.15) and LAG-3 high expression (≥ 1%, HR: 0.75; 95% CI: 0.59, 0.95).

3.3. Uncertainties and limitations about favourable effects

Though OS results were not statistically significant and have not reached full maturity, KM-curves show a clear separation between treatment arms supporting the primary endpoint and excluding a detrimental effect in the ITT population. ORR data could not be formally tested due to the hierarchical testing strategy (OS first). Nevertheless, response rates numerically favour the combination treatment over monotherapy and are also considered supportive for the primary endpoint in the ITT population. The applicant was recommended to provide additional descriptive OS data. Survival follow-up continues for approximately 5 years and will be submitted when available.

Efficacy in adolescents ≥12-18 years was uncertain as no adolescents were included in the pivotal study. An extrapolation approach from adults to adolescents using relatlimab and nivolumab exposures based on similarity of disease and expected similarity of outcome to treatment is acceptable, as exposures between adults and adolescent (≥ 12 years) with the adult and adolescent posology are similar. The latter accounts for relatlimab as well as for nivolumab (see clinical pharmacology part of this AR). Therefore, based on sufficiently comparable exposure to relatlimab and nivolumab in adolescents and adults weighing 30 kg or more and considering comparable pathophysiology between the two patient populations, the proposed inclusion of adolescents 12 years of age and older on the therapeutic indication is considered acceptable. In the SmPC section 4.2, the 30 kg cut-off used in the popPK simulations is referred to with a cross reference to section 5.2 (see SmPC).

3.4. Unfavourable effects

Almost all patients experienced all-causality AEs, any grade 97% and 94%, grade 3-4 40% and 33% for rela+nivo FDC and nivo, respectively. Regarding drug-related AEs, the reported incidence of any grade AEs was 81.1% in the rela+nivo FDC arm and 69.9% in the nivo arm while grade 3-4 drug-related AEs were reported by 18.9% and 9.7% of subjects, respectively.

The most frequently (>15%) reported *any grade AEs* in the rela+nivo FDC were fatigue (29%), pruritus (25%), arthralgia (24%), diarrhoea (23%), headache (18%), nausea (17%), rash (17%) and hypothyroidism (15%).

The most frequently reported *drug-related AEs* (rela+nivo FDC) were pruritus (23.4%), fatigue (23.1%), rash (15.5%), arthralgia (14.4%), hypothyroidism (14.4%), diarrhoea (13.5%), and vitiligo (10.4%); these AEs were predominantly of low grade.

The most frequently reported *Grade 3-4 drug-related AEs* (rela+nivo FDC) were increased lipase (1.7%), increased ALT (1.4%), increased AST (1.4%), and fatigue (1.1%).

As of the 09-Mar-2021 DBL, 30.4% subjects in the rela+nivo FDC arm and 33.1% of subjects in the nivolumab monotherapy arm died during the study. Disease progression was the most common cause of *death* in both arms. A similar proportion of subjects in the rela+nivo FDC (0.8%; 3 subjects) and nivolumab (0.6%; 2 subjects) arms died due to study drug toxicity during the study. This was caused by haemophagocytic lymphohistiocytosis, acute oedema of the lung and pneumonitis in the rela+nivo FDC group and in the nivo group sepsis+myocarditis and worsening pneumonia.

SAEs were reported by 34.1% of subjects in the rela+nivo arm and 29.2% in the nivolumab arm and the most common drug-related SAEs in the combination arm were colitis, diarrhoea and myocarditis (1.1% each).

The overall frequencies of *AEs leading to discontinuation* (all-causality and drug-related) were higher in the rela+nivo FDC arm (19%) compared with the nivolumab arm (11%) as was the case for Grade 3-4 events in both treatment arms (11.5% vs 6.4%).

Regarding IMAEs, all categories presented a higher number of subjects from the rela+nivo treatment arm although the type of events were similar between both arms.

OESIs were reported in 17.5% in the rela+nivo FDC arm and 13.6% in the nivolumab arm. In the rela+nivo FDC arm 76 of the 83 OESIs, were resolved at the time of DBL. In the nivolumab arm 64 of the 75 OESIs were resolved at the time of DBL. *Myocarditis* was reported infrequently at 1.7% and 0.6% in the rela+nivo FDC and nivolumab arms, respectively. *Troponin* elevation was reported in 11.5% of subjects in the rela+nivo FDC arm and 10.0% of subjects in the nivolumab arm. *CNS* AEs (including encephalitis, meningitis, and demyelination) were reported: 2 subjects each in the rela+nivo FDC and nivolumab arms experienced encephalitis. Also, some events of Guillain-Barré Syndrome, pancreatitis, uveitis and myositis were reported with the combination. AEs of pancreatitis and uveitis were also reported in the nivolumab arm.

3.5. Uncertainties and limitations about unfavourable effects

Safety data in adolescents is missing and long-term safety effect in this patient population is unknown. Available safety data for nivolumab in adolescents, suggest a similar short term toxicity profile in adults and adolescents. Safety follow up in adolescents is planned in a post-authorisation safety study, i.e. CA224122 (DMTR) (cat 3 RMP).

3.6. Effects Table

Table 45. Effects Table for Opdualag for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents ≥12 yrs (Study CA224047, data cut-off 9 March 2021)

Effect	Short Description	Unit	Rela+nivo FDC (n=209)	Nivolumab (n=212)	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS (PD-L1<1)	Patients alive and free of progression (all randomised patients)	Median (months)	6.7 (95% CI: 4.7, 12)	3.0 (95% CI: 2.8. 4.5)	HR: 0.68 (95% CI: 0.53, 0.86) Results confirmed with longer follow-up (28-Oct-2021 DBL)	09-March-2021 DBL
OS (PD-L1<1)	Overall survival	Median (months)	N.A. (95% CI: 27.4, N.R.)	27.0 (95% CI: 17.1, N.R.)	HR: 0.78 (95% CI: 0.59, 1.04) Data not fully mature. Trend for OS benefit in the PD-L1<1% patient population	28-Oct-2021 DBL
ORR (PD-L1<1)	Overall response rate	%	36.4 (95% CI: 29.8, 43.3)	24.1 (95% CI: 18.5, 30.4)		28-Oct-2021 DBL
Unfavourable Effects						

Effect	Short Description	Unit	Rela+nivo FDC (n=209)	Nivolumab (n=212)	Uncertainties/ Strength of evidence	References
AEs gr. 3-4	All causality Drug-related	%	25.6 9.1	20.6 4.7		
AEs leading to discontinuation	All causality Drug-related	%	19.4 14.6	11.4 6.7		
SAEs grade 3-4	Serious AEs	%	25.4	19.5		
IMAEs non endocrine	Immune mediated AEs (IMM treated)	%	28.5	16.5	Majority of IMAEs resolved at DBL	
IMAEs endocrine		%	32.5	23.4	Majority of IMAEs resolved at DBL	
OESIs	Other Events of Special Interest	%	18.1	13.7	Rare events of increased troponin, myocarditis, encephalitis equally distributed over both groups	

Abbreviations: CI: confidence interval; HR: Hazard rate; ORR: overall response rate; OS: overall survival; PFS: progression free survival; IMAEs: Immune-mediated Adverse Events; OESIs: other event of special interest; DBL: database lock; SAE: serious adverse event, N.R.: not reached.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The median PFS results of 10.12 months with rela+nivo FDC versus 4.63 months with nivolumab monotherapy and a HR of 0.75 (95% CI: 0.62, 0.92, log-rank p-value 0.0055), in the overall population could be considered a clinically relevant benefit. OS data, though not statistically significant and not fully mature, show a trend for a clinical benefit of the combination treatment over monotherapy as well. A detrimental effect can be excluded. In addition, ORR data numerically favour the combination treatment over monotherapy and is in line with the primary endpoint in the ITT population.

In general, a beneficial effect on PFS was observed among important (prognostic) subgroups and independent of LAG-3 expression. However, the effect in the ITT population appears to be driven by the PD-L1 <1% subgroup as no PFS benefit of relatlimab in combination with nivolumab was shown in the subgroup of patients with high PD-L1 expression (cut-off 1%). As seen for PFS, KM-curves of OS separate in the PD-L1 <1% subgroup but overlap in the PD-L1 ≥1% subgroup. ORR is numerically in favour of the combination treatment in both PD-L1 defined subgroups, however it is uncertain whether this translates into clinical benefit for these patients, while it is known that the PD-L1 subgroup ≥1% responds well to nivolumab monotherapy. Notably, similar results for the PD-L1 defined subgroups were seen at the time of the MAA of the combination of ipilimumab and nivolumab in the same target population. Long-term follow-up data on OS up till 5 years did not show a benefit of ipi+nivo in the PD-L1 ≥1% subgroup over nivolumab monotherapy, despite a 10% difference in ORR (see Opdivo SmPC).

In the dossier at hand the PD-L1 subgroup analysis was not alpha-controlled, but exploratory analysis were pre-planned in the SAP and randomisation was stratified for PD-L1 with a cut-off of 1% based on previous data. Therefore, in combination with the available efficacy results and the plausible biological rationale for nivolumab monotherapy inferring clinical benefit in patients expressing PD-L1, it is concluded that only for patients with no or low PD-L1 expression (<1%), benefit of the combination therapy is demonstrated. The applicant has restricted the indication by tumour PD-L1<1%.

The qualitative safety profile of the combination was comparable to that known for nivolumab monotherapy and no new safety signals were identified. In general, rela+nivo showed more toxicity than nivolumab monotherapy, as to be expected from a combination treatment, e.g. the numerical incidence of grade 3-4 drug-related SAEs is higher in the rela+nivo FDC patients versus nivo. Although the overall frequencies of all causality and drug-related AEs were also higher in the rela+nivo FDC arm, the majority were of low grade (Grades 1-2), and the safety profile of rela+nivo FDC was manageable using well established AE management guidelines. Notably, in the rela+nivo FDC group 14.6% versus nivo 6.7% of patients had to discontinue treatment because of drug-related adverse events.

The *median treatment duration* of patients was 5 months, which is rather short to assess the safety over time. However, around 30% of patients in both treatment arms have been treated over 12 months. At time of DBL the median follow-up was 13 months. An update of the safety data with a median follow-up of 19.3 months supported the previous analyses and no new safety signals were identified.

3.7.2. Balance of benefits and risks

Relatlimab+nivolumab FDC has demonstrated a statistically significant and clinically relevant improvement in PFS in the ITT population. This is supported by a trend for benefit in OS and numerically higher ORR, whereas an OS detriment can be excluded. However, considering the lack of 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% patients. For the patient population with PD-L1<1%, the benefit/risk ratio is considered positive based on a clinically relevant improvement in terms of PFS and manageable toxicity.

3.7.3. Additional considerations on the benefit-risk balance

No adolescents were included in the clinical studies. Given the similarity of disease histology, genetic background, treatment and prognosis of metastatic melanoma for adults and adolescents, and sufficiently comparable predicted drug exposure in adults and adolescents, based on popPK simulations in patients weighing at least 30 kg, extrapolation of efficacy and safety from adults to the adolescent population is considered acceptable. In these simulations, both the situation of a reduced clearance and volume of distribution of relatlimab and nivolumab, as well as the situation of a comparable clearance and volume of distribution in adolescents and adults, was simulated. In both cases the exposure is considered sufficiently comparable between adolescent and adult patients. Therefore, inclusion of adolescents 12 years of age and older in the indication is considered approvable.

The available safety data of nivolumab in adolescents, indicate a comparable short term safety profile for adolescents as for adults. Given that nivolumab and relatlimab are both check-point inhibitors, also for relatlimab a comparable short term safety profile for adolescents and adults may be expected in case of comparable exposure. Long term safety data are missing, especially the long-term effect of endocrine AEs might be different between adults and adolescents. Given the poor prognosis of adolescents with metastatic or unresectable (advanced melanoma), the uncertainty regarding the long-term toxicity profile is not considered a major concern. In addition, long-term safety will be followed-

up post approval (cat 3 study).

3.8. Conclusions

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

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Opdualag is favourable in the following indication(s):

Opdualag is indicated 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 CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where 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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that relatlimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0070/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.