Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Opdualag

Active ingredients: Nivolumab and Relatlimab

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

December 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event(s)
ALT	Alanine transaminase
AJCC	American Joint Committee on Cancer
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AST	Aspartate transferase
AUC	Area under the concentration versus time curve
BICR	Blinded independent central review
CMI	Consumer Medicines Information
$C_{max,ss}$	Maximum concentration at steady state
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CTLA-4	Cytotoxic T-lymphocyte antigen-4
DLP	Data lock point
EC_{50}	Half-maximal effective concentration
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration (United States of America)
HLH	Haemophagocytic lymphohistiocytosis
HR	Hazard ratio
IMAE	Immune-mediated adverse events
LAG-3	Lymphocyte-activation gene 3
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
OESI	Other events of special interest
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death receptor-1
PD-L (1 or 2)	Ligands for programmed death receptor-1
PFS	Progression-free survival

Abbreviation	Meaning
PI	Product Information
PSUR	Periodic safety update report
RMP	Risk management plan
TGA	Therapeutic Goods Administration
US(A)	United States (of America)
UV	Ultraviolet

Product submission

Submission details

Type of submission:	New combination
Product name:	Opdualag
Active ingredients:	Nivolumab and Relatlimab
Decision:	Approved
Date of decision:	5 October 2022
Date of entry onto ARTG:	7 October 2022
ARTG number:	372783
▼*Black Triangle Scheme*	Yes
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd Level 2, 4 Nexus Court Mulgrave VIC 3170
Dose form:	Concentrate solution for intravenous infusion
Strength:	Nivolumab 240 mg and Relatlimab 80 mg
Container:	Vial
Pack size:	20 mL
Approved therapeutic use for the current submission:	*Opdualag is indicated for the treatment of patients with unresectable or metastatic melanoma who are at least 12 years old.*
Route of administration:	Intravenous
Dosage:	Treatment must be initiated and supervised by physicians experienced in the treatment of cancer. The recommended dose of Opdualag for adult patients, or for paediatric patients who are 12 years or older and weigh at least 40 kg, is 480 mg nivolumab and 160 mg relatlimab administered as a 30 minute intravenous infusion once every 4 weeks, until disease progression or unacceptable toxicity. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to register Opdualag (nivolumab 240 mg and relatlimab 80 mg) concentrate solution for intravenous infusion in a vial for the following proposed indication:[1]

> *Opdualag is indicated for the treatment of adult and adolescent patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma.*

Mechanism of action

The molecular biology of immune recognition and activation includes regulatory mechanisms, called 'checkpoints', that prevent autoimmune injury to normal tissue.[2] Lymphocyte activation gene 3 (*LAG-3*) and programmed death receptor-1 (PD-1) are inhibitory co-receptors involved in such checkpoint functions.[3] Drugs that block interaction between PD-1 and its ligand (PD-L1) reduce this mechanism of immune tolerance and are thereby believed to facilitate tumour recognition by immune effector cells.[4]

LAG-3 is an inhibitory immune checkpoint co-receptor, and is expressed on activated CD4+ T-cells and CD8+ T-cells, especially those that are 'exhausted', that is, in settings of chronic antigen exposure.[3] LAG-3 is also expressed on inhibitory regulatory T-cells in patients with cancer (including melanoma), which suppress anti-tumour T-cell activity.[5] Conversely, loss of LAG-3 function exacerbates autoimmune disease.[6] LAG-3 therefore presents a potential drug target in both cancer and autoimmune disease. The precise molecular mechanisms by which LAG-3 regulates T-cell activation remain to be characterised, however, recent data suggest the major functional ligand of LAG-3 is stable peptide-major histocompatibility complex Class II (pMHCII) (and not fibrinogen-like protein 1).[7] LAG-3 has also been reported to disrupt T-cell receptor signalling by interfering with immune synapse pH in a major histocompatibility complex (MHC)

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

[2] Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nat Rev Immunol* 2020; 20(11): 651-668. doi: 10.1038/s41577-020-0306-5.

[3] Maruhashi T, Sugiura D, Okazaki IM, et al. LAG-3: from molecular functions to clinical applications. *J Immunother Cancer* 2020; 8(2): e001014. doi:10.1136/jitc-2020-001014.

[4] Alsaab HO, Sau S, Alzhrani R, et al. PD-1 and PD-L1 Checkpoint Signaling Inhibition for Cancer Immunotherapy: Mechanism, Combinations, and Clinical Outcome. *Front Pharmacol* 2017; 8:561. doi:10.3389/fphar.2017.00561.

[5] Camisaschi C, Casati C, Rini F, et al. LAG-3 expression defines a subset of CD4(+)CD25(high)Foxp3(+) regulatory T cells that are expanded at tumor sites. *J Immunol* 2010; 184(11): 6545-6551. doi: 10.4049/jimmunol.0903879.

[6] Jones BE, Maerz MD, Bahnson HT, et al. Fewer LAG-3+ T Cells in Relapsing-Remitting Multiple Sclerosis and Type 1 Diabetes. *J Immunol* 2022; 208(3): 594-602. doi: 10.4049/jimmunol.2100850.

[7] Maruhashi T, Sugiura D, Okazaki IM, et al. Binding of LAG-3 to stable peptide-MHC class II limits T cell function and suppresses autoimmunity and anti-cancer immunity. *Immunity* 2022; 55(5): 912-924.e8. doi: 10.1016/j.immuni.2022.03.013.

Class II-independent fashion.[8] As the mechanisms by which LAG-3 and PD-1 contribute to immune tolerance may be distinct from each other, there could be synergism of dual blockade in rescuing antitumour immunity.[9]

Condition

Melanomas are malignant neoplasms of melanocytic origin. The term 'melanoma' is generally taken to refer to cutaneous melanoma unless otherwise specified, as this makes up the vast majority of melanoma (around 90%).[10] It is associated with mutations in the mitogen-activated protein kinase pathway (notably, *BRAF* and *NRAS*), lymphatic dissemination (mostly to lung, brain, lymph node, and soft tissue), and the highest tumour mutational burden among major cancer types.[11,12] Disseminated disease first manifests in regional lymph nodes in about half of cases, as satellite or in-transit metastases for around 20%, and as distant metastases for around 30%.[13]

Exposure (especially intense, intermittent exposure) to ultraviolet (UV) light has a causal association with the development of melanoma, evidenced by a specific genetic mutational signature.[14,15] Other independent risk factors include pale skin (phototype 1 or 2), large and irregular atypical or dysplastic naevi, and personal or family history: around 10% are seen in a familial setting.[14] Men have a higher incidence (possibly attributable to higher average occupational and recreational UV exposure) and worse survival rates than women.[16] Based on data from the Victorian Cancer Registry, the median age at diagnosis is 63 years in males and 59 years in females.[17] The mean age of diagnosis among Australian patients is 65.7 years for males and 62.4 years for females.[16]

[8] Guy C, Mitrea DM, Chou PC, et al. LAG3 associates with TCR–CD3 complexes and suppresses signaling by driving co-receptor–Lck dissociation. *Nat Immunol* 2022; 23: 757–767. doi: 10.1038/s41590-022-01176-4.

[9] Andrews LP, Cillo AR, Karapetyan L, et al. Molecular Pathways and Mechanisms of LAG-3 in Cancer Therapy. *Clin Cancer Res* 2022; 28(23): 5030-5039. doi: 10.1158/1078-0432.CCR-21-2390.

[10] Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer* 1998; 83(8): 1664–1678.
doi: 10.1002/(sici)1097-0142(19981015)83:8<1664::aid-cncr23>3.0.co;2-g.

[11] van der Kooij MK, Speetjens FM, van der Burg SH, et al. Uveal Versus Cutaneous Melanoma; Same Origin, Very Distinct Tumor Types. *Cancers (Basel)* 2019; 11(6): 845. doi:10.3390/cancers11060845.

[12] Jager MJ, Shields CL, Cebulla CM, et al. Uveal melanoma. *Nat Rev Dis Primers* 2020; 6(1): 24.
doi: 10.1038/s41572-020-0158-0. Erratum in: *Nat Rev Dis Primers* 2022; 8(1): 4.

[13] Leiter U., Meier F., Schittek B, et al. The natural course of cutaneous melanoma. *J Surg Oncol* 2004; 86: 172–178.
doi: 10.1002/jso.20079.

[14] Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. *Lancet* 2014; 383(9919): 816-27.
doi: 10.1016/S0140-6736(13)60802-8.

[15] Rabbie R, Ferguson P, Molina-Aguilar C, et al. Melanoma subtypes: genomic profiles, prognostic molecular markers and therapeutic possibilities. *J Pathol* 2019; 247(5): 539-551. doi:10.1002/path.5213.

[16] Australian Institute of Health and Welfare 2021. Cancer in Australia 2021. Cancer series no. 133. Cat. no. CAN 144. Canberra: AIHW. doi:10.25816/ye05-nm50.

[17] Victorian Cancer Registry. Melanoma factsheet. Published 10 May 2021. Available at: https://www.cancervic.org.au/research/vcr/fact-sheets-and-annual-reports/melanoma-factsheet.html.

Factors associated with worse prognosis for melanoma include the (Breslow) thickness of primary tumour, ulceration, mitotic rate, extent and sites of nodal and metastatic disease, and lactate dehydrogenase level.[18,19]

Molecular genetic features may also be prognostic. Based on driver mutations, melanomas are considered under four genomic subtypes: *BRAF*-mutant, *NRAS*-mutant, *NF1*-loss and triple wild-type.[20,21] These subtypes account for approximately 50%, 30%, 10 to 15%, and 5 to 10% of cutaneous melanomas, respectively, and show differing clinical associations. However, whilst it is clear that *BRAF*-mutation confers a poorer prognosis,[22,23] there are conflicting reports on the prognostic significance of *NRAS*, and the clinical utility of a promising 31-gene expression profile panel remains to be confirmed.[15]

Cutaneous melanoma is very rare in paediatric patients (under 18 years of age), with an Australian incidence likely less than 1 in 100,000.[24] Melanoma in paediatric patients can be considered within four age groups, each with different epidemiology and risk factors: congenital (*in utero* to birth), infantile (birth to one year), childhood (one year to puberty), and adolescent (postpuberty).[25] Around 2% of melanomas overall occur in paediatric patients, but they mostly occur in adolescents and are very rare in patients under the age of 14 (perhaps 5 cases per million in Australia).[26] The incidence of melanoma during the second decade of life is probably 7 to 10 times higher than during the first decade.[27]

While the age cut-off (puberty) is ultimately arbitrary, prepubertal and postpubertal melanomas are meaningfully different.[28] In prepubertal patients, melanomas are mostly spitzoid or can arise from congenital naevi, whilst the majority of postpubertal melanomas are conventional melanoma, that is, similar morphologically to adult melanoma.[29] Spitzoid melanoma does occur in adolescents but is much less common (perhaps 10%),[30] and behaves differently.[29]

[18] Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. *Expert Rev Anticancer Ther* 2018; 18(8): 775-784. doi:10.1080/14737140.2018.1489246.

[19] Wasif N, Bagaria SP, Ray P, et al. Does metastasectomy improve survival in patients with Stage IV melanoma?. A cancer registry analysis of outcomes. *J Surg Oncol* 2011; 104(2): 111–115. doi: 10.1002/jso.21903.

[20] Hayward NK, Wilmott JS, Waddell N, et al Whole-genome landscapes of major melanoma subtypes. *Nature* 2017; 545: 175–180. doi: 10.1038/nature22071.

[21] Cancer Genome Atlas Network . Genomic classification of cutaneous melanoma. *Cell* 2015; 161: 1681–1696. doi 10.1016/j.cell.2015.05.044.

[22] Long GV, Menzies AM, Nagrial AM, et al Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 2011; 29: 1239–1246. doi: 10.1200/JCO.2010.32.4327.

[23] Nagore E, Requena C, Traves V, et al. Prognostic value of BRAF mutations in localized cutaneous melanoma. *J Am Acad Dermatol* 2014; 70(5): 858-62.e2. doi: 10.1016/j.jaad.2013.10.064.

[24] Ryan AL, Burns C, Gupta AK, et al. Malignant Melanoma in Children and Adolescents Treated in Pediatric Oncology Centers: An Australian and New Zealand Children's Oncology Group (ANZCHOG) Study. *Front Oncol* 2021; 11: 660172. doi: 10.3389/fonc.2021.660172.

[25] Jen M, Murphy M, Grant-Kels JM. Childhood melanoma. *Clin Dermatol* 2009; 27: 529–536. doi: 10.1016/j.clindermatol.2008.09.011.

[26] Ferlay J, Shin HR, Bray F, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2010. *Int J Cance*r 2010; 127(12): 2893–2917. doi: 10.1002/ijc.25516.

[27] Brecht IB, De Paoli A, Bisogno G, et al. Pediatric patients with cutaneous melanoma: A European study. *Pediatr Blood Cancer* 2018; 65(6) :e26974. doi: 10.1002/pbc.26974.

[28] Strouse JJ, Fears TR, Tucker MA, et al, Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. *J Clin Oncol* 2005; 23 (21): 4735–4741. doi: 10.1200/JCO.2005.02.899.

[29] Bahram A, Barnhill RL. Pathology and genomics of pediatric melanoma: A critical reexamination and new insights. *Pediatr Blood Cancer* 2018; 65(2):10.1002/pbc.26792. doi: 10.1002/pbc.26792.

[30] Lu C, Zhang J, Nagahawatte P, et al. The genomic landscape of childhood and adolescent melanoma. *J Invest Dermatol* 2015; 135(3): 816–823. doi: 10.1038/jid.2014.425.

While clinicopathological characteristics of melanoma in adolescent patients (but not pre-pubescent patients) are comparable to those in adult patients, melanoma in adolescents shows a female preponderance and a higher proportion of nodular melanomas and amelanotic melanomas than for adults.[25]

Importantly, conventional melanomas in paediatric patients (which occur mostly in adolescents) have been demonstrated to show genomic similarity to those in adults.[31] They demonstrate high mutation rates, a high frequency of single nucleotide variations typical of UV-related damage, and a similar rate of activating *BRAF* V600 mutation to adult melanoma.[30]

Skin cancer is often referred to as Australia's 'national cancer',[32] and Australia has the highest incidence of melanoma in the world.[33] The age-standardised incidence of melanoma in Australia approximately doubled between 1982 and 2002, and although the rate of increase appears to have slowed, the most recent data and estimates from the Australian Institute of Health and Welfare (AIHW) indicate it continuing to rise, with a predicted age-standardised incidence of 55.3 per 100,000 in 2021.[34]

In 2021, melanoma was predicted to be the second most common cancer diagnosed in Australian males (after prostate cancer), and the third most common diagnosed in females (after breast and colorectal carcinoma) and in people regardless of sex (after breast and prostate cancer).[16]

Incidence does, however, appear to be decreasing in younger Australian patients. Between 2001 and 2021 the age-specific rate of melanoma dropped from 1.9 to 0.4 per 100,000 in people aged 10 to 19 years, and from 23.3 to 14.9 in people aged 20 to 39 years.[16] Evidence from Queensland is also supportive: the incidence of thin invasive melanoma has decreased since the 1990s in people born after the inception of state primary prevention and early detection programs.[35] Changes in incidence and mortality rates over time might be related to public health education and primary prevention campaigns.[36]

Despite its relatively high incidence, melanoma is only the eleventh most deadly cancer in Australia in 2021, with a predicted age-standardised mortality of around 4 per 100,000.[16] This is largely attributable to the frequency with which they are diagnosed at an early stage (around 90% in Victoria are Stage 1 or 2 at diagnosis),[17] making them amenable to excision-based treatment with curative intent. For Australians with melanoma overall, the 5 year relative survival between 2007 and 2011 was 90%.[37]

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[31] Pappo AS. Pediatric melanoma: the whole (genome) story. *Am Soc Clin Oncol Educ Book* 2014; :e432-5. doi: 10.14694/EdBook_AM.2014.34.e432.

[32] House of Representatives Standing Committee on Health. Skin cancer in Australia: our national cancer. Report on the Inquiry into Skin Cancer in Australia. Canberra: Parliament of the Commonwealth of Australia; 2015. Available at: www.aph.gov.au/Parliamentary_Business/Committees/House/Health/Skin_Cancer/Report.

[33] Olsen CM, Green AC, Pandeya N, et al. Trends in Melanoma Incidence Rates in Eight Susceptible Populations through 2015. *J Invest Dermatol* 2019; 139(6): 1392-1395. doi: 10.1016/j.jid.2018.12.006.

[34] Australian Institute of Health and Welfare. AIHW Cancer Data in Australia 2021: Book 1a – Cancer incidence (age-standardised rates and 5-year age groups). Australian Government, Canberra, Australia: AIHW. Available at https://www.aihw.gov.au/getmedia/e8779760-1b3c-4c2e-a6c2-b0a8d764c66b/AIHW-CAN-122-CDiA-2021-Book-1a-Cancer-incidence-age-standardised-rates-5-year-age-groups.xlsx.aspx.

[35] Iannacone MR, Youlden DR, Baade PD, et al. Melanoma incidence trends and survival in adolescents and young adults in Queensland, Australia. *Int J Cancer* 2015; 136(3): 603-609. doi: 10.1002/ijc.28956.

[36] Erdmann F, Lortet-Tieulent J, Schüz J, Zeeb H, Greinert R, Breitbart EW, Bray F. International trends in the incidence of malignant melanoma 1953-2008--are recent generations at higher or lower risk? *Int J Cancer* 2013; 132(2): 385-400. doi: 10.1002/ijc.27616.

[37] Australian Institute of Health and Welfare 2016. Skin cancer in Australia. Cat. no. CAN 96. Canberra: AIHW.

For patients whose disease is locally advanced and not considered resectable, or is metastatic, systemic treatment is indicated.[38] Prognosis for these patients had historically been dismal with a median overall survival (OS) of around 7 to 9 months, and a 5-year survival rate of around 5%.[39] This has dramatically changed over the last decade with the advent of new treatment options.[40] In 2016, 5-year survival rates for Australians with metastatic melanoma were 26% for patients with metastatic disease and 61% for those with regional spread.[41] More recent Australia-specific survival data is not yet reported.

Current treatment options

In 2010, for patients with advanced, unresectable melanoma, single agent chemotherapy with dacarbazine had been considered the standard-of-care for three decades, with response rates of 7 to 15%,[42] and no demonstrated effect on survival time.[43] A new era for advanced melanoma treatment began that year, when an inhibitor of cytotoxic T-lymphocyte antigen-4 (CTLA4) – an immune checkpoint receptor – became the first drug to demonstrate significant prolongation of median OS in patients with advanced melanoma.[44] The following year, an inhibitor of the melanoma-associated oncoprotein, BRAF, was shown to prolong OS significantly in those with a *BRAF* V600E mutation.[45] Ipilimumab[46] and vemurafenib[47] have regulatory approval in Australia. Acquired resistance to anti-BRAF monotherapy was found to emerge after around 6 months in around half of patients receiving it, but in 2014, combination treatment with the addition of a mitogen-activated protein kinase (MEK) inhibitor was found to delay such resistance and increase OS.[48]

Meanwhile, the research base supporting immune checkpoint inhibition was also expanding. In 2015, monoclonal antibodies against programmed death receptor-1 (PD-1), another checkpoint molecule, demonstrated not only longer survival but a better toxicity profile than anti-CTLA4 monotherapy.[49,50] Extended follow up has confirmed the durability of such benefit, with 5-year survival rates and median survival times of 44% and 36.9 months (nivolumab) versus 26% and

[38] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Melanoma: Cutaneous Version 3.2022. 11 Apr 2022; National Comprehensive Cancer Network. Available at NCCN website.
[39] Essner R, Lee JH, Wanek LA, et al. Contemporary surgical treatment of advanced-stage melanoma. *Arch Surg* 2004; 139(9): 961-966; discussion 966-7. doi: 10.1001/archsurg.139.9.961.
[40] Pasquali S, Hadjinicolaou AV, Chiarion Sileni V, et al. Systemic treatments for metastatic cutaneous melanoma. Cochrane Database Syst Rev 2018; 2(2): CD011123. doi:10.1002/14651858.CD011123.pub2.
[41] Australian Institute of Health and Welfare. AIHW Cancer Data in Australia 2021: Book 8 – Cancer incidence and survival by stage. Australian Government, Canberra, Australia: AIHW. Available at https://www.aihw.gov.au/getmedia/9b861a57-82b2-455b-8228-7cfbcf4bd057/AIHW-CAN-122-CDiA-2021-Book-8-Cancer-incidence-and-survival-by-stage.xlsx.aspx.
[42] Fricker J. New era in metastatic melanoma. *Mol Oncol* 2010; 4(2): 91-97. doi:10.1016/j.molonc.2010.02.001.
[43] Sandru A, Voinea S, Panaitescu E, et al. Survival rates of patients with metastatic malignant melanoma. *J Med Life* 2014; 7(4): 572-576.
[44] Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363(8): 711–723. doi: 10.1056/NEJMoa1003466.
[45] Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364(26): 2507-2516. doi: 10.1056/NEJMoa1103782.
[46] Ipilimumab was first registered in Australia on 4 July 2011 (ARTG number: 174319).
[47] Vemurafenib was first registered in Australia on 10 May 2012 (ARTG number:183674).
[48] Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014; 371(20): 1867–1876. doi: 10.1056/NEJMoa1408868.
[49] Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; 372(4): 320-330. doi: 10.1056/NEJMoa1412082.
[50] Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015; 372(26): 2521-2532. doi: 10.1056/NEJMoa1503093.

19.9 months (ipilimumab) in one study (the CheckMate 067 trial),[51,52] and 39% and 32.7 months (pembrolizumab) versus 31% and 15.9 months (ipilimumab) in the other (the KEYNOTE-006 trial).[53] Patients treated with a PD-1 inhibitor in combination with a CTLA4 inhibitor in the third treatment arm in the CheckMate 067 trial have demonstrated a 5 year survival rate of 52%,[52] and a 6.5 year survival rate of 49%.[54] Unfortunately, the combination is also associated with increased toxicity compared to anti-PD-1 monotherapy: rates of treatment related adverse events that were high grade and of those that led to treatment discontinuation were more than doubled (59% versus 23%, and 42% vs 13%, respectively).[52]

For patients with an actionable *BRAF* mutation, immunotherapy and BRAF/MEK inhibitor therapy both present therapeutic options, as OS benefit with immunotherapy has been demonstrated to be independent of *BRAF* mutation status.[55,56] A direct randomised comparison between single agent immunotherapy and BRAF/MEK inhibitor therapy is not yet available,[57] however, data comparing anti-CTLA4/PD-1 doublet therapy directly against BRAF/MEK inhibitor therapy became available in November 2021, when the DREAMseq randomised trial was ceased early based on results demonstrating a 2-year OS rate of 72% for patients in Arm A (who received CTLA4 plus PD-1 inhibition first-line and BRAF plus MEK inhibition second-line), and 52% for those in Arm B (who received the same two combinations in the reverse order); rates of toxicity were similar between arms.[58] However, both the progression-free survival (PFS) and the OS Kaplan-Meier curve were biphasic, with crossover at 6 and 10 months, respectively.[58] This appearance of non-proportional hazards has been seen in multiple previous studies comparing immunotherapy-only regimens to treatments with a faster onset of action.[59] For patients with rapidly progressive, symptomatic, *BRAF* mutation-positive disease, therefore, initial BRAF/MEK inhibitor therapy may be preferable.[60] For the remainder of *BRAF* mutation-positive tumours, however, it appears based on DREAMseq that anti-CTLA4/PD-1

[51] Wolchock JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017; 377(14): 1345-1356. doi: 10.1056/NEJMoa1709684.

[52] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2019; 381: 1535-1546. doi: 10.1056/NEJMoa1910836.

[53] Robert C, Ribas A, Schachter J, et al. 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; 20(9): 1239-1251. doi: 10.1016/S1470-2045(19)30388-2.

[54] Bristol Myers Squibb - Six-and-a-Half-Year Outcomes for Opdivo (nivolumab) in Combination with Yervoy (ipilimumab) Continue to Demonstrate Durable Long-Term Survival Benefits in Patients with Advanced Melanoma (bms.com).

[55] Larkin J, Lao CD, Urba WJ, et al. Efficacy and Safety of Nivolumab in Patients With BRAF V600 Mutant and BRAF Wild-Type Advanced Melanoma: A Pooled Analysis of 4 Clinical Trials. *JAMA Oncol* 2015; 1(4): 433-440.doi: 10.1001/jamaoncol.2015.1184.

[56] Shahabi V, Whitney G, Hamid O, et al. Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. *Cancer Immunol Immunother* 2012; 61: 733-737. doi: 10.1007/s00262-012-1227-3.

[57] Rogala P, Czarnecka AM, Cybulska-Stopa B, et al. Long-Term Outcomes of Targeted Therapy after First-Line Immunotherapy in BRAF-Mutated Advanced Cutaneous Melanoma Patients—Real-World Evidence. *J Clin Med* 2022; 11(8): 2239. doi: 10.3390/jcm11082239.

[58] Atkins MB, Lee SJ, Chmielowski B, et al. DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): a phase III trial—ECOG-ACRIN EA6134. (Abstract 356154). *J Clin Oncol* 2021; 39(36): 356154. doi: 10.1200/JCO.2021.39.36_suppl.356154.

[59] Mick R, Chen TT. Statistical Challenges in the Design of Late-Stage Cancer Immunotherapy Studies. *Cancer Immunol Res* 2015; 3(12): 1292-1298. doi: 10.1158/2326-6066.CIR-15-0260.

[60] Ascierto PA, Mandala M, Ferrucci PF, et al. SECOMBIT: the best sequential approach with combo immunotherapy [ipilimumab (I)/nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma: a phase II randomized study. *Ann Oncol* 2021; 32(Suppl 5): S1316–S1317. doi: 10.1016/j.annonc.2021.08.2118.

immunotherapy is the preferred first-line option.[61] A complication of interpreting this data is that in recent years, adjuvant therapy with either BRAF/MEK or CTLA4/PD-1 inhibition has become the standard of care and may affect tumour microenvironment at relapse, subsequent response, and ultimately survival.[61] In DREAMseq, only 14% of patients had received prior systemic therapy, and this was almost exclusively adjuvant interferon: none had received adjuvant immune checkpoint inhibitor or BRAF/MEK-targeted therapy.[61]

Combinations of checkpoint inhibitors and BRAF/MEK inhibitors have also been investigated for the first-line treatment of *BRAF* mutated advanced melanoma: early evidence of high toxicity with regimens containing an anti-CTLA4 drug led to a focus on those containing a PD-1 or PD-L1 inhibitor. Of four randomised clinical trials, a significant PFS benefit of anti-PD-(L)1 add-on to BRAF/MEK inhibitor therapy has only been demonstrated by one trial (IMspire150).[62] Randomised comparison of these triplets to single agent PD-(L)1 inhibitor therapy have not been made, and a major limitation of the data on triplet therapies is the lack of an anti-PD-(L)1/CTLA4 comparator arm, which was not standard-of-care at the time of trial design.[63]

Treatment of advanced melanoma in adolescents is based on the approach for adults, extrapolating evidence from adult studies.[64,65] Data evaluating treatment outcomes in adolescents is limited but suggests comparable efficacy and toxicity of available therapies.[66]

Regulatory status

OPDUALAG is a new fixed-dose combination for Australian regulatory purposes.

This evaluation was facilitated through Project Orbis, an initiative of the United States of America (USA) Food and Drug Administration (FDA) Oncology Center of Excellence. Under this project, the FDA, Swissmedic (Switzerland) and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

During the time the TGA was considering this submission, similar submissions were approved in the USA on 18 March 2022 and in the European Union on 15 September 2022. A similar submission was under consideration in Switzerland (submitted on 16 August 2021).

The following table summarises these submissions and provides the indications where approved.

[61] Gyorki DE. Spoiled for Choice: Do We Finally Have Clarity on Optimal Treatment Sequencing for Patients with Metastatic Melanoma Harboring an Actionable BRAF Mutation? *Ann Surg Oncol* 2022; 29: 4014–4015. doi: 10.1245/s10434-022-11611-3.

[62] Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF(V600) mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020; 395(10240):1835–1844. doi: 10.1016/S0140-6736(20)30934-X.

[63] Dixon-Douglas J, Patel R, Somasundram P, et al. Triplet Therapy in Melanoma — Combined BRAF/MEK Inhibitors and Anti-PD-(L)1 Antibodies. *Curr Oncol Rep* 2022; 24: 1071-1079. doi: 10.1007/s11912-022-01243-x.

[64] Kumar RS, Messina JL, Sondak VK, et al. Treating melanoma in adolescents and young adults: challenges and solutions. *Clinical Oncology in Adolescents and Young Adults* 2015; 5: 75-86. doi: 10.2147/COAYA.S90563.

[65] Del Fiore P, Russo I, Ferrazzi B, et al. Melanoma in Adolescents and Young Adults: Evaluation of the Characteristics, Treatment Strategies, and Prognostic Factors in a Monocentric Retrospective Study. *Front Oncol* 2021; 11: 725523. doi: 10.3389/fonc.2021.725523. Erratum in: Front Oncol. 2021 Oct 27;11:793169.

[66] Bagnoni G, Fidanzi C, D'Erme, AM, et al. Melanoma in children, adolescents and young adults: anatomo-clinical features and prognostic study on 426 cases. *Pediatr Surg Int* 2019; 35(1): 159–165. doi: 10.1007/s00383-018-4388-0.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	19 July 2021	Approved on 18 March 2022	*Opdualag is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.*
European Union	13 September 2021	Approved on 15 September 2022	*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 less than 1%.*
Switzerland	16 August 2021	Under consideration	Under consideration

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2021-03689-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	30 September 2021
First round evaluation completed	30 March 2022
Sponsor provides responses on questions raised in first round evaluation	2 May 2022
Second round evaluation completed	21 June 2022
Delegate's Overall benefit-risk assessment[67]	31 August 2022
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	5 October 2022

[67] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who approved the product under section 25 of the Act.

Description	Date
Administrative activities and registration on the ARTG completed	7 October 2022
Number of working days from submission dossier acceptance to registration decision*	221

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in TGA's evaluation reports, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

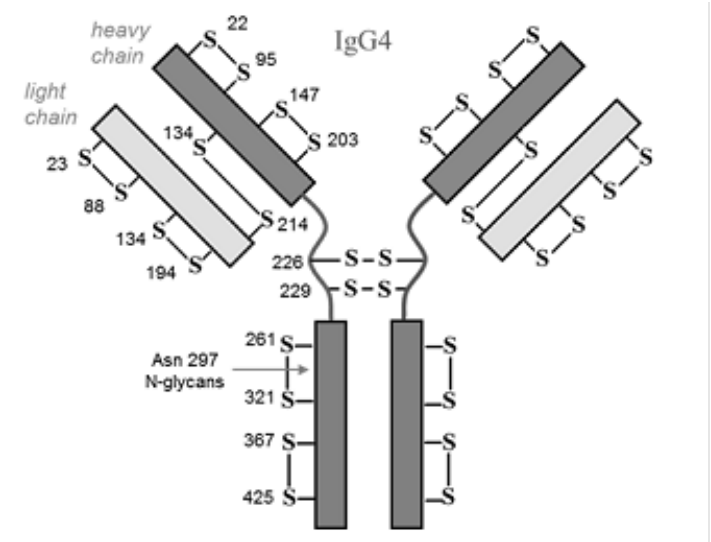
Quality

Nivolumab and relatlimab are human immunoglobulin G4 monoclonal antibodies.

Nivolumab has been previously evaluated by the TGA;[68] information on its chemistry and quality has been published.[69] Compared to the earlier product, nivolumab for Opdualag is formulated in a histidine-based buffer rather than a citrate-based buffer.

Relatlimab is a new biological entity and has not been previously evaluated by the TGA. Relatlimab consists of 2 identical heavy chains and 2 identical light chains, and its schematic representation is shown in Figure 1. Relatlimab has a calculated molecular mass of 148 kDa.

Figure 1: Schematic representation of relatlimab



Nivolumab and relatlimab are expressed in a Chinese hamster ovary cell line by recombinant DNA technology and purified using standard chromatography and filtration steps.

[68] Nivolumab (tradename Opdivo) was first registered in Australia on 11 January 2016 (ARTG number: 318057).

[69] AusPAR for nivolumab as a new medicine is available at Australian Public Assessment Report for Nivolumab (tga.gov.au).

Review of the submission was completed with no outstanding issues with registration of the product from a quality perspective. The proposed shelf life for the drug product of 36 months when stored at 2°C to 8°C with the storage conditions 'do not freeze', 'protect from light' and 'do not shake' was considered acceptable.

Sufficient evidence was provided to demonstrate that the risks related to adventitious agents in the manufacturing of Opdualag have been managed to an acceptable level. An evaluation of sterility aspects concluded that there were no objections from a microbiological perspective to approval of the application to register Opdualag. Container safety aspects were adequate.

Standard quality-related conditions of registration are proposed.

Nonclinical

The submitted nonclinical data support the following statements for relatlimab.

- *In vitro,* relatlimab:
  - bound the D1 domain of human LAG-3 with a dissociation constant of 0.12 nM; recombinant human LAG-3-mFc fusion protein with a half-maximal effective concentration (EC_{50}) of 0.49 nM; and LAG-3 in activated human T-cells with a dissociation constant of 0.51 nM
  - inhibited interaction between LAG-3 and MHC Class II at an EC_{50} of 0.67 nM; and between LAG-3 and fibrinogen-like protein 1 at an EC_{50} of 0.02 nM
  - stimulated T-cell activation in human LAG-3 T-cell hybridoma 349 cells (EC_{50} 1.05-1.39 nM) when co-cultured with MHC Class II matched antigen-presenting cells
  - did not induce antibody-dependent cellular toxicity or complement-dependent cytotoxicity on LAG-3+ activated human T-cells
  - did not significantly induce T-cell, B-cell, or natural killer cell activation or cytokine release in human peripheral blood mononuclear cells, alone or in combination with nivolumab.
- No off-target effects or interaction with hERG channels are expected with relatlimab as it is a monoclonal antibody.
- *In vivo,* in syngeneic mouse tumour models (MC38 colon adenocarcinoma and Sa1N fibrosarcoma), nivolumab and relatlimab inhibited tumour growth more when given in combination than compared to either one given as a monotherapy.
- In a 4-week intravenous repeat-dose toxicity study, moderate inflammation of the central nervous system (CNS) (including spinal cord, perivascular brain parenchyma, choroid plexus, and meninges) and CNS vasculitis resulting in moribundity were seen in Cynomolgus monkeys who received nivolumab in combination with relatlimab at exposures 3 and 27 times, respectively, the human exposure (by steady state area under the concentration versus time curve (AUC)) at the recommended dose.. These data indicate immune-mediated CNS toxicity can occur in monkeys when relatlimab is added to nivolumab. As a result, CNS events were given specific attention in the clinical review.
- No genotoxicity or carcinogenicity studies were submitted. Given the protein nature of the medicine and the proposed indication, this is considered acceptable.
- Fertility, pregnancy and lactation:

- In accordance with ICH guideline S9,[70] no studies of fertility and early embryonic development or pre-postnatal development were conducted with relatlimab. In a 4-week intravenous repeat dose toxicity study, mixed cell inflammation of the epididymis, seminal vesicles, testes, and mineralisation of seminal vesicles were seen in Cynomolgus monkeys who received nivolumab in combination with relatlimab at exposures 3 and 27 times, respectively, the human exposure (by steady state AUC) at the recommended dose.
- Based on its mechanism of action, and data from earlier animal studies of nivolumab, relatlimab in combination with nivolumab is expected to pose a risk to embryofetal development. The sponsor has proposed Pregnancy Category D,[71] which is appropriate based on the above.
- No studies were conducted to investigate the presence of relatlimab in breast milk or placental transfer. As immunoglobulin G4 antibodies, both relatlimab and nivolumab may cross the placenta and potentially transfer through milk during lactation.

The nonclinical evaluation came to the following conclusions:

- No major deficiencies were identified in the nonclinical dossier. No new nonclinical data were submitted for nivolumab.
- Findings from the primary pharmacology studies adequately support the proposed indication.
- Repeat dose toxicity studies with nivolumab and relatlimab in combination identified inflammation/infiltration affecting the brain and spinal cord as a potential toxicity.
- No embryofetal development studies were performed with relatlimab and based on its mechanism of action and data from animal studies of nivolumab alone and relatlimab in combination with nivolumab can cause embryo-fetal risk. Therefore, Pregnancy Category D is considered appropriate.
- There are no nonclinical objections to approval of the nivolumab and relatlimab fixed-dose combination provided the clinical studies provide adequate dosing and efficacy data.

Clinical

Summary of clinical studies

The clinical dossier consisted of:

- one Phase I/IIa study, Study CA224020 (also known as the RELATIVITY-020 trial), which was an open label study that investigated a range of doses of relatlimab (alone and in combination with nivolumab) in adults with various solid tumours and adolescents 12 years and older with melanoma. No patients with previously untreated melanoma received Opdualag in this study.
- one Phase II/III study, Study CA224047 (also known as the RELATIVITY-047 trial), a seamless, randomised (1:1), double blind study of Opdualag versus nivolumab monotherapy

[70] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals, EMA/CHMP/ICH/646107/2008, May 2010.

[71] **Pregnancy Category D:** Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

in adult or paediatric patients at least 12 years old with previously untreated metastatic or unresectable melanoma.

Pharmacology

Pharmacokinetics

Nivolumab pharmacokinetics

The pharmacokinetics of nivolumab have been previously characterised, including in the setting of advanced melanoma, as assessed during earlier regulatory submissions to the TGA. Consistent with what has been previously described, when given in combination with relatlimab, nivolumab pharmacokinetics (PK) were described by a linear 2-compartment model with time varying clearance, a geometric mean volume of distribution of 6.65 L (coefficient of variation 19%), and elimination half-life of 26.5 days.

Relatlimab pharmacokinetics

Relatlimab exhibited nonlinear (approximately 31% of total relatlimab clearance at the recommended dose) and time varying PK. The nonlinear component (not seen with nivolumab) was considered likely due to a higher level of target receptors compared to nivolumab. The model predicted average serum relatlimab concentration after the first dose increased dose proportionally with doses at and above 160 mg every 4 weeks. At the recommended dose (with nivolumab), serum relatlimab steady state concentrations were reached by approximately 16 weeks with about two-fold systemic accumulation, a geometric mean volume of distribution of 6.65 L (coefficient of variation 20%), and 97% clearance within 69 days. Steady state LAG-3 receptor occupancy is estimated to be 74% at trough concentration and 84% at average concentration.

Intrinsic factors

A number of covariates in the population pharmacokinetic model showed statistically significant effects on baseline clearance of nivolumab, relatlimab, or both. Most effects were small (less than 20%) and therefore considered clinically irrelevant.

Serum albumin (for nivolumab only) and body weight had a greater than 20% effect on clearance but these factors are not expected to be clinically relevant effects, given the flat exposure-response relationships for efficacy and safety. Relatlimab steady state exposure was 31% lower in patients at the 95th body weight percentile, and 26% higher in patients at the 5th percentile relative to the median body weight (75 kg).

The effect of race on nivolumab and relatlimab PK was not able to be characterised due to an insufficient representation of non-Caucasian people among the study participants who contributed data to the population pharmacokinetics datasets (5% to 8%).

Mild or moderate hepatic or renal impairment did not significantly affect the PK of nivolumab or relatlimab. Opdualag has not been studied in patients with severe renal or hepatic impairment; however, both drugs are monoclonal antibodies, and therefore not expected to be subject to hepatic metabolism or renal clearance but expected to be catabolised into small peptides and amino acids.

Time-varying clearance

Clearance of both nivolumab and relatlimab decreased over the duration of therapy: clearance at steady state was around 20% and 10% lower, respectively, than after the first dose. Time-

varying clearance has been described for multiple therapeutic monoclonal antibodies used in oncology and is a known feature of nivolumab PK. Decreased tumour-related catabolism with treatment efficacy is likely part of the explanation for this phenomenon, and as a possible confounding factor of exposure-response analyses, is the reason that such analyses are generally undertaken using exposure after the first dose, rather than at steady state.[72]

Baseline nivolumab clearance was not significantly different in patients who had received immunotherapy in prior lines of treatment compared to those being treated first-line.

Interactions

No PK interaction between the two active substances was observed when given in combination.

No interactions with other drugs are predicted as both active substances are monoclonal antibodies which are highly specific.

Due to the low incidence of treatment-emergent anti-drug antibodies and treatment-emergent neutralising antibodies (see Summary of key data), their effect on the pharmacokinetics or pharmacodynamics exposures of nivolumab with relatlimab could not be meaningfully analysed.

Exposure-response analyses

Pooled data from patients with melanoma across the two RELATIVITY trials indicated that, when given in combination with nivolumab 480 mg every 4 weeks, higher doses of relatlimab (480 mg versus 160 mg every 4 weeks) are not associated with significantly better efficacy (progression-free survival (PFS) or objective response).

A flat exposure-toxicity relationship had previously been seen with nivolumab monotherapy at doses of 0.1 to 10 mg per kg every 2 weeks, in earlier nivolumab submissions.

Pooled data from the RELATIVITY-020 and RELATIVITY-047 trials also indicated a flat exposure-response relationship for toxicity of the combination (including infusion reactions), based on assessment of Common Terminology Criteria adverse event (CTCAE) Grade 2 and higher immune related adverse reactions,[73] and Grade 3 and higher adverse reactions for relatlimab up to 1440 mg every 4 weeks when given in combination with nivolumab.

Exploratory analyses conducted by the FDA of safety metrics by body weight category were not indicative of worse toxicity in patients lighter than 50 kg compared to those weighing 50 to 80 kg or more than 80 kg.[74]

Dosing

The sponsor proposed the following doses, given every 4 weeks by 30 minute intravenous infusion, and continued until disease progression or unacceptable toxicity:

- Adults: 480 mg nivolumab and 160 mg relatlimab

[72] Dai HI, Vugmeyster Y, Mangal N. Characterizing Exposure-Response Relationship for Therapeutic Monoclonal Antibodies in Immuno-Oncology and Beyond: Challenges, Perspectives, and Prospects. *Clin Pharmacol Ther* 2020; 108(6): 1156-1170. doi:10.1002/cpt.1953.

[73] The **Common Terminology Criteria (CTC)** is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life threatening; Grade 5 = Death. The CTCAE is published by the National Cancer Institute (United States).

[74] See pages 107-108 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

- Patients 12 years or older and weighing at least 40 kg: 6 mg per kg nivolumab and 2 mg per kg relatlimab (up to a maximum of 480 mg nivolumab and 160 mg relatlimab).

Justification for fixed-dose combination

The sponsor's justification for taking a fixed-dose approach was that nivolumab and relatlimab have distinct immune checkpoint targets, and based on biological rationale, nonclinical and early phase clinical data, may act synergistically or at least additively.

The proposed benefit of a single combination product was that it simplifies therapy, with reduced total infusion time, simpler dose calculation and reduced opportunity for dosing error, and a single PI document, reducing the likelihood of confusion.

The sponsor stated that the safety profile of the fixed-dose combination as studied in the pivotal trial was acceptable given the clinical setting. The lack of ability to reduce the dose of one active agent separately from the other was not specifically addressed. Due to the apparent flat exposure-response relationship for safety for both nivolumab and relatlimab, this is not of concern.

Justification for proposed adult dose

The existing approved dose of nivolumab for advanced melanoma is a flat dose of 240 mg every 2 weeks or 480 mg every 4 weeks, based on similar benefit-risk to the studied 3 mg per kg every 2 weeks dosing regimen.

In the RELATIVITY-020 trial, a range of doses or regimens for the combination of relatlimab plus nivolumab were tested:

- relatlimab monotherapy: 20 to 800 mg every 2 weeks
- nivolumab with relatlimab:
  - nivolumab 80 to 240 mg every 2 weeks with relatlimab 20 to 240 mg every 2 weeks
  - nivolumab 480 mg every 4 weeks with relatlimab 160 to 1440 mg every 4 weeks.

Based on preliminary data from the RELATIVITY-020 trial, the initial dose studied in melanoma subjects was nivolumab 240 mg with relatlimab 80 mg every 2 weeks. As a higher and less frequent relatlimab 160 mg every 4 weeks dose was predicted to provide similar relatlimab exposure and peripheral receptor occupancy to that of 80 mg every 2 weeks, the nivolumab 480 mg with relatlimab 160 mg every 4 weeks dosing regimen was chosen for evaluation in the pivotal RELATIVITY-047 trial.

Justification for shortened infusion time

In both RELATIVITY studies, relatlimab was administered as monotherapy or in combination with nivolumab over a 60 minute infusion duration. The sponsor proposes a shorter, 30 minute infusion time for Opdualag, for patient, caregiver, and health care provider convenience.

There are no direct clinical data to support this infusion time, however:

- both nivolumab and relatlimab contain only human immunoglobulin protein sequences, so are considered to have a low risk of inducing immunogenicity or associated infusion or hypersensitivity reactions
- infusion reactions were uncommon with the 60 minute infusion in the pivotal trial (6%) and there were no high-grade events or discontinuations. The duration of treatment in the pivotal trial (median 5.6 months, mean 9.0 months, maximum 31.5 months) is adequate to support this assessment

- there was not an apparent correlation between relatlimab dose and incidence of infusion or hypersensitivity reactions
- the rate of relatlimab infusion would be approximately 5 mg/min if Opdualag was given over a duration of 30 minutes. A much higher relatlimab infusion rate of 24 mg/min (1440 mg given over 60 minutes) was received by 19 patients in the RELATIVITY-020 trial Part B. The safety profile in patients receiving this dose was not notably different from other doses and there was no apparent correlation between higher doses and safety outcomes
- the total protein infusion rate with a 30 minute infusion of the proposed Opdualag dose would be 21 mg/min, which is the same as the total protein infusion rate for the highest dose that was tested in the RELATIVITY-020 trial (480 mg nivolumab with 1440 mg relatlimab every 4 weeks given sequentially over 90 minutes)
- population pharmacokinetic analysis predicts less than 1% difference in exposure metrics for systemic exposures (that is, maximum concentration, minimum concentration and average concentration) between a 30 minute and a 60 minute infusion time.

Justification for proposed paediatric dose

The pivotal trial did not include patients younger than 12 years, and conventional melanoma is not expected to occur in such patients. Direct data to inform PK or efficacy and safety of relatlimab in adolescents is not available, because although the RELATIVITY clinical trials both allowed paediatric patients over the age of 12 years to enrol, only one such patient did so (a 17-year-old patient in the RELATIVITY-020 trial).

The sponsor conducted modelling of PK data from studies in which 26 patients under the age of 12 years, and 24 patients between the ages of 12 and 17 years received nivolumab (including the 17-year-old in the RELATIVITY-020 trial).

Based on overall PK similarity of nivolumab and relatlimab, the sponsor applied the paediatric effect on nivolumab clearance to the linear component of relatlimab clearance and the paediatric effect on nivolumab volume of distribution to the relatlimab volume of distribution, to predict relatlimab exposure in adolescent patients (paediatric patients aged at least 12 years).

The model predicted a weight-independent decrease in baseline clearance for paediatric patients, and was applied to four possible paediatric dosing scenarios to try and obtain close to adult exposures:

- Scenario 1: nivolumab 6 mg/kg with relatlimab 2 mg/kg (for patients below 40 kg body weight) or nivolumab 480 mg with relatlimab 160 mg (for patients 40 kg and over) every 4 weeks
- Scenario 2: nivolumab 6 mg/kg with relatlimab 2 mg/kg up to a maximum of nivolumab 480 mg with relatlimab 160 mg every 4 weeks
- Scenario 3: nivolumab 7.5 mg/kg with relatlimab 2.5 mg/kg up to a maximum of nivolumab 480 mg with relatlimab 160 mg every 4 weeks
- Scenario 4: nivolumab 9 mg/kg with relatlimab 3 mg/kg up to a maximum of nivolumab 480 mg with relatlimab 160 mg every 4 weeks.

Dosing regimens in Scenarios 1, 3, and 4 were ruled out as:

- predicted median exposures (maximum concentration at steady state ($C_{max,ss}$)) for nivolumab were higher than the adult range for adolescents between 40 and 60 kg under Scenario 1
- predicted median exposures ($C_{max,ss}$) for relatlimab were higher than the adult range for adolescents between 60 and 70 kg under Scenario 3

- predicted median exposures ($C_{max,ss}$) for relatlimab were higher than the adult range for adolescents between 40 and 70 kg under Scenario 4.

Scenario 2 gave the closest predicted exposure for adolescent patients, and this is the dose proposed by the sponsor for paediatric patients over 12 years of age. Patients with body weight lower than 40 kg were excluded from the sponsor's proposed indication, as the predictions for median relatlimab exposures in such patients were below the range of adult median exposures, raising concerns for lack of efficacy, and the estimates are also unreliable because the paediatric patients aged 12 years or older who contributed nivolumab exposure data to the population pharmacokinetic model were 40 kg or heavier (median 60 kg, minimum 39.7 kg).

Efficacy

Pivotal study – Study CA224047 (RELATIVITY-047 trial)

The pivotal data supporting efficacy come from Study CA224047, also known as the RELATIVITY-047 trial. The study is included in a major US clinical trial directory,[75] and its design has been described in the literature and in the publicly available FDA label.[76,77,78]

The primary clinical study report dated 25 May 2021 from the RELATIVITY-047 trial was submitted in support of the proposed registration of Opdualag. The date of database lock for the clinical study report was 9 March 2021.

An updated clinical study report addenda document with database lock date of 28 October 2021, with additional data on secondary endpoints, was provided by the sponsor in January 2022.

Design

The RELATIVITY-047 trial is a seamless Phase II/III, randomised (1:1), double blind study of Opdualag versus nivolumab monotherapy in adult or paediatric patients at least 12 years old with previously untreated metastatic or unresectable melanoma.

Prior (neo)adjuvant treatment was allowed: with an anti-PD-1, anti-CTLA4, or *BRAF*-MEK containing regimen, as long as recurrence occurred at least 6 months after the last dose; and with interferon, as long as the last dose was at least 6 weeks before randomisation.

[75] RELATIVITY-047 listing at clinicaltrials.gov, accessed 31 May 2022 at: https://clinicaltrials.gov/ct2/show/NCT03470922.
[76] FDA approved label for BLA 761234 (Opdualag). Approval date 18 Mar 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000lbl.pdf.
[77] Lipson EJ, Long GV, Tawbi H, et al. CA224-047: A Randomized, Double-Blind, Phase 2/3 Study of Relatlimab (anti-LAG-3) in Combination With Nivolumab (anti-PD-1) Versus Nivolumab Alone in Previously Untreated Metastatic or Unresectable Melanoma. *Ann Oncol* 2018; 29(supp 8): VIII464–VIII466. doi: 10.1093/annonc/mdy289.058.
[78] Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med* 2022; 386: 24–34. doi: 10.1056/NEJMoa2109970.

Patients with a poor performance status (Eastern Cooperative Oncology Group (ECOG) 2 or higher,[79] or Lansky score less than 80% for patients aged 12 to 17 years[80]), uveal melanoma, active and untreated brain metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, a history of prior malignancy active within 3 years (except locally cured cancers), a history of myocarditis, and those with a baseline elevated troponin more than twice the upper limit of normal, were excluded.

Patients were randomised (1:1) to receive either Opdualag (nivolumab 480 mg plus relatlimab 160 mg) intravenously every 4 weeks (n = 355) or nivolumab monotherapy 480 mg intravenously every 4 weeks (n = 359). The infusion products were matched in presentation for the purpose of maintaining double blinding. Dose modifications were not permitted. Randomisation was stratified by tumour PD-L1 expression (1% and over versus less than 1%), LAG-3 expression (1% and over versus less than 1%), *BRAF* mutation status (V600 mutation positive versus V600 wild-type), and presence of metastasis based on American Joint Committee on Cancer (AJCC) staging system (version 8)[81,82] (M0 and M1 with normal lactate dehydrogenase (LDH) versus M1 with elevated LDH).

Under the seamless design 425 patients were first randomised as an initial Phase II step, and after a recruitment pause (to allow for adequate follow-up for an interim PFS analysis) if the result met the criteria for continuation, a further 289 patients would be randomised to complete the Phase III portion of the study.

[79] **ECOG Performance Status**: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following ECOG status are used: Grade 0 = Fully active, able to carry on all pre-disease performance without restriction; Grade 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house-work, office work; Grade 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; Grade 3 = Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; Grade 4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; Grade 5 = Dead. See: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47. doi: 10.1016/j.ejca.2008.10.026.

[80] The **Lansky Performance Status** is a method for describing functional status in paediatric cancer patients, or possibly other children with serious chronic or life-threatening diseases. It was derived and internally validated in children with cancer to assess response to therapies and overall status. A Lansky Performance Status of 80% is 'active, but tires more quickly'. See Lansky SB, List MA, Lansky LL, et al. The measurement of performance in childhood cancer patients. *Cancer* 1987; 60:1651–1656. doi: 10.1002/1097-0142(19871001)60:7<1651::AID-CNCR2820600738>3.0.CO;2-J.

[81] The **American Joint Committee on Cancer (AJCC) staging system**, better known as the TNM Staging System is a widely used cancer staging system, developed and maintained by the AJCC and the Union for International Cancer Control (UICC). The TNM Staging System is based on the extent of the tumour (T), extent of spread to lymph nodes (N) and presence of metastasis (M). The T category describes the original (primary) tumour: TX = Primary tumour cannot be evaluated; T0 = No evidence of primary tumour; Tis = Carcinoma in situ (early cancer that has not spread to neighbouring tissue); T1 to T4: Size and/or extent of the primary tumour. The N category describes whether or not the cancer has reached nearby lymph nodes: NX = Regional lymph nodes cannot be evaluated; N0 = No regional lymph node involvement (no cancer found in the lymph nodes); N1 to N3 = Involvement of regional lymph nodes (number and/or extent of spread). The M category describes whether there are distant metastases (spread of cancer to other parts of the body): M0 = No distant metastasis (cancer has not spread to other parts of the body); M1 = Distant metastasis (cancer has spread to distant parts of the body). In version 8, M1a = Distant metastasis to skin, soft tissue including muscles, and/or nonregional lymph node; M1b = Distant metastasis to lung with or without M1a sites of disease; M1c = Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease; M1d = Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease.

[82] The sponsor clarified that the staging on metastases was M0/M1 with normal lactate dehydrogenase (LDH) versus M1 with elevated LDH.

Study treatment was ceased on disease progression per RECIST v1.1 criteria,[83] or for unacceptable toxicity, however, treatment beyond initial investigator assessed radiographic progression was permitted (to allow for the phenomenon of pseudo-progression described to occur in immuno-oncology).[84] Criteria for allowing treatment beyond radiographic progression (around investigator-assessed clinical benefit and tolerance of study treatment) were specified in the protocol.

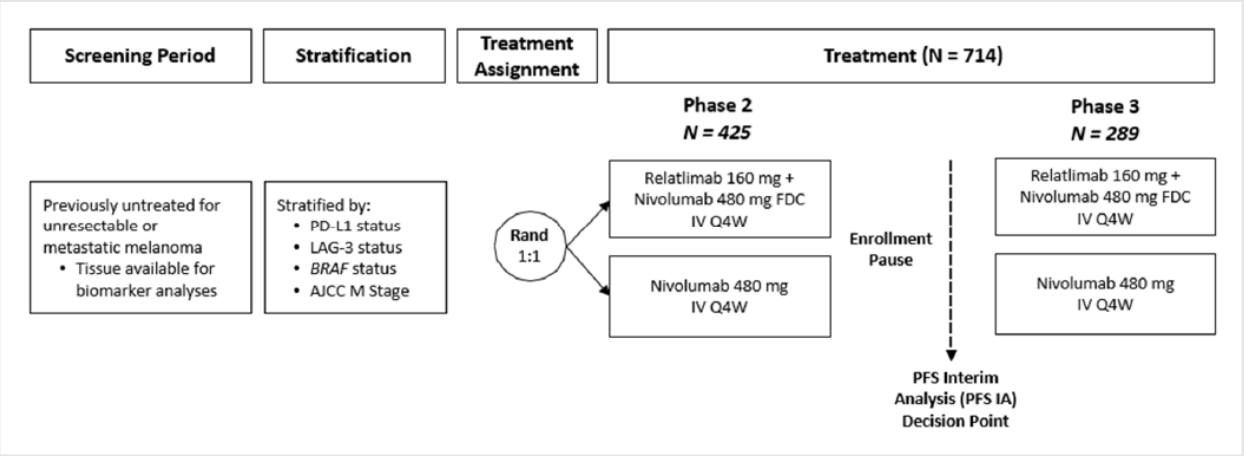
Tumour assessments were conducted at Week 12 (post-randomisation), then every 8 weeks until Week 52, then every 12 weeks thereafter until the blinded independent central review (BICR) confirmed disease progression or treatment discontinuation, whichever occurred later.

A summary of the design of the RELATIVITY-047 trial is included in Figure 2 below.

The primary efficacy outcome was PFS by BICR, and the key secondary endpoints (with hierarchical testing) were overall survival (OS) and objective response rate per BICR. Progression-free survival per investigator, PFS by biomarkers (LAG-3, PD-L1, PD-L1/LAG-3), PFS after the next line of subsequent therapy, and treatment free interval/treatment free survival were all exploratory endpoints.

The statistical analysis plan and changes to it are described in detail in the FDA multidisciplinary review document.[85] No concerns have emerged about the interpretability of the study results with regard to protocol amendments, good clinical practice issues or protocol deviations.

Figure 2: RELATIVITY-047 Schematic of the study design



Abbreviations: AJCC = American Joint Committee on Cancer; BRAF = B-Raf proto-oncogene; FDC = fixed-dose combination; IV = intravenous; LAG-3 = lymphocyte-activation gene 3; M = metastases; N = number of subjects; Q4W = every 4 weeks; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; Rand = randomised.

[83] The **Response Evaluation Criteria In Solid Tumours (RECIST)** is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

[84] Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol* 2016; 34(13): 1510-1517. doi: 10.1200/JCO.2015.64.0391.

[85] See pages 124-128 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

Population

Patients were randomised across 114 sites in 25 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, New Zealand, Norway, Poland, Romania, Russian Federation, Spain, Sweden, United Kingdom, and United States of America). In total, 61 patients (almost a tenth of the study population) were randomised at sites in Australia or New Zealand: 32 to Opdualag and 29 to nivolumab.

Demographics and baseline disease characteristics were generally similar between treatment arms (suggestive of intact randomisation), and in keeping with what would be expected for a first-line advanced melanoma population in Australia. The median age was 63 years (range: 20 to 94 years), 58% of patients were male, 97% were Caucasian, 7% were Hispanic, and two-thirds had an ECOG Performance Status of 0. Of their tumours, PD-L1 expression was at least 1% in 41% of cases, LAG-3 expression was at least 1% in 75% of cases, and 39% had a *BRAF* V600 mutation. Almost all patients (92%) had AJCC stage IV disease, 39% had M1c disease (39%), 2.4% had M1d disease, and 36% had elevated LDH. Overall, 9% of patients had received a prior systemic therapy for their melanoma, mostly adjuvant interferon (6%); 1% had received anti-CTLA4 treatment; 1% had received anti-PD-1 treatment; and 0.1% had received combined anti-CTLA4/anti-PD-1 treatment.

Disposition

Disposition across the two arms showed around two thirds (67% of the Opdualag arm and 65% of the nivolumab arm) of subjects had discontinued treatment at time of database lock.[86] A higher proportion of the Opdualag arm discontinued treatment due to study drug toxicity, and a higher proportion of the nivolumab arm discontinued treatment due to disease progression. Study discontinuation due to death was 3% higher in the nivolumab arm.

The proportion of patients who received subsequent anticancer therapy (radiation, surgery, or systemic agents) was similar between arms.

Efficacy outcomes

At the time of database lock for the primary analysis, the median duration of follow-up was 13 months (range: 0 to 33 months), with coronavirus disease 2019 (COVID-19) responsible for an enrolment slowdown contributing to the wide range and low minimum. Results for the RELATIVITY-047 trial are summarised in Table 3 and Figure 3.

The primary efficacy endpoint showed a statistically significant and clinically meaningful increase in PFS by BICR of 5.5 months with the addition of relatlimab to nivolumab treatment, corresponding to a hazard ratio of 0.75 (95% CI: 0.62, 0.92) and a 2-sided p-value less than the pre-specified alpha level of 0.049.

Exploratory landmark analyses indicated an approximately 12 to 13% higher Kaplan-Meier estimated PFS rate at arbitrary 6 month and 12 month time points with Opdualag compared to relatlimab.

At time of final analysis, a statistically significant difference between arms was not detected for the key secondary endpoint (overall survival), with cumulative design power of 69%. Among all randomised subjects, there were 137 deaths in the Opdualag arm and 160 deaths in the nivolumab arm, corresponding to a hazard ratio of 0.80 (95% CI: 0.64, 1.01) with a nominal

[86] See pages 130-131 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

p-value of 0.0593 (2-sided O'Brien Fleming boundary for statistical significance less than 0.04302).

No other endpoints were formally analysed. The objective response rate was 43% (95% CI: 38, 48) in the Opdualag arm and 33% (95% CI: 28, 38) in the nivolumab arm. The rates of partial response and progressive disease, respectively, were 27% and 30% in the Opdualag arm; and 18% and 42% in the nivolumab arm. Rates of complete response, times to response and durations of response were not appreciably different between arms.

Table 3: RELATIVITY-047 Primary efficacy results of progression-free survival (all randomised participants)

	Nivolumab with Relatlimab (n = 355)	**Nivolumab (n = 359)**
Patients with death or progression events, n (%)	180 (51%)	211 (59%)
Patients with progression events, n (%)	*156 (44%)*	*194 (54%)*
Patients who died without progression being recorded, n (%)	*24 (7%)*	*17 (5%)*
Median PFS (95% CI),[a] months	10.1 (6.4, 15.7)	4.6 (3.4, 5.6)
Hazard Ratio (95% CI) (p-value)[b]	0.75 (0.62, 0.92) (p = 0.0055)	

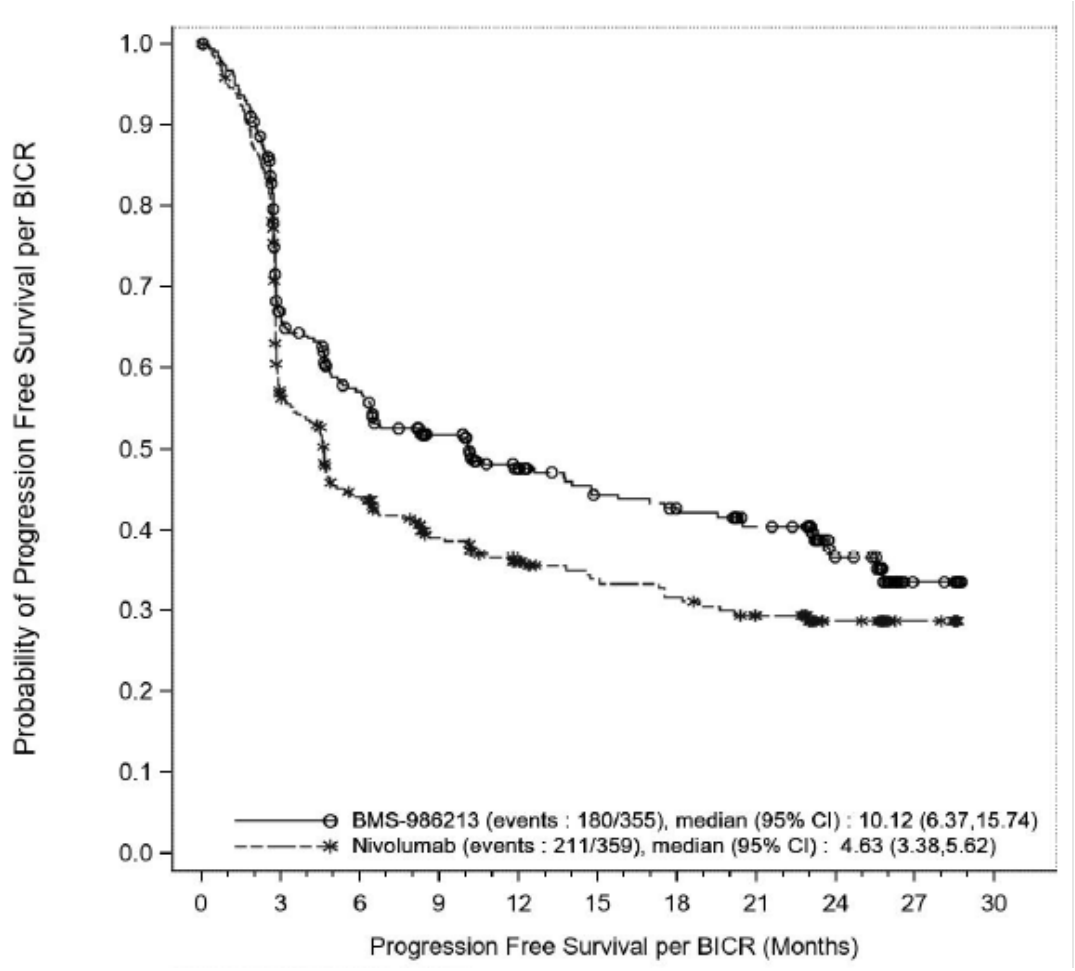
Abbreviations: CI = confidence interval; n = number of subjects; PFS = progression-free survival.

a Kaplan-Meier estimate

b Cox proportional hazards model and log-rank test: stratified by LAG-3 (1% and over versus less than 1%), *BRAF* (mutation positive versus mutation wild-type), and American Joint Committee on Cancer (AJCC) M-stage (M0 and M1 with normal lactate dehydrogenase (LDH) versus M1 with elevated LDH). PD-L1 was removed from stratification (as pre-specified in the statistical analysis plan v2.1) because it led to subgroups with fewer than 10 subjects.

Database lock date: 9 March 2021

Figure 3: RELATIVITY-047 Kaplan-Meier plot of progression-free survival (all randomised participants)



Abbreviations: BICR = blinded independent central review; BMS-986213 = Opdualag; CI = confidence interval.

Database lock date: 9 March 2021

Sensitivity and subgroup analyses

Exploratory sensitivity and subgroup analyses performed by the sponsor and FDA are available.[87] The results of these analyses were generally consistent with the primary analysis (by BICR) in the entire randomised population. Their interpretation is limited by their post-hoc nature and the lack of alpha control.

Subgroup results for PFS are shown in Figure 4. Of particular interest were the subgroup analyses with regard to PD-L1 status, as the association of this biomarker with efficacy has been heterogeneous across studies of therapeutic regimens containing an anti-PD-1 or anti-PD-L1 drug. Biological rationale supports that patients with higher PD-L1 might have sufficient efficacy with nivolumab alone such that the addition of relatlimab may do more harm than good.

The point estimate for PFS hazard ratio at the 10% PD-L1 cut-off is above 1, however, this is not the case at cut-offs of 5% or 1%, and the confidence interval is very wide (0.66 to 1.92). This reflects the small subgroup size (140 patients) and the small absolute difference in number of PFS events between arms (26 with nivolumab alone and 29 with Opdualag).

[87] See pages 139 to 148 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

Exploratory subgroup analysis of the OS results similarly showed a hazard ratio point estimate above 1 for subgroups based on a PD-L1 cut-off of 5% and also 10%. Again the confidence intervals are wide and include 1.

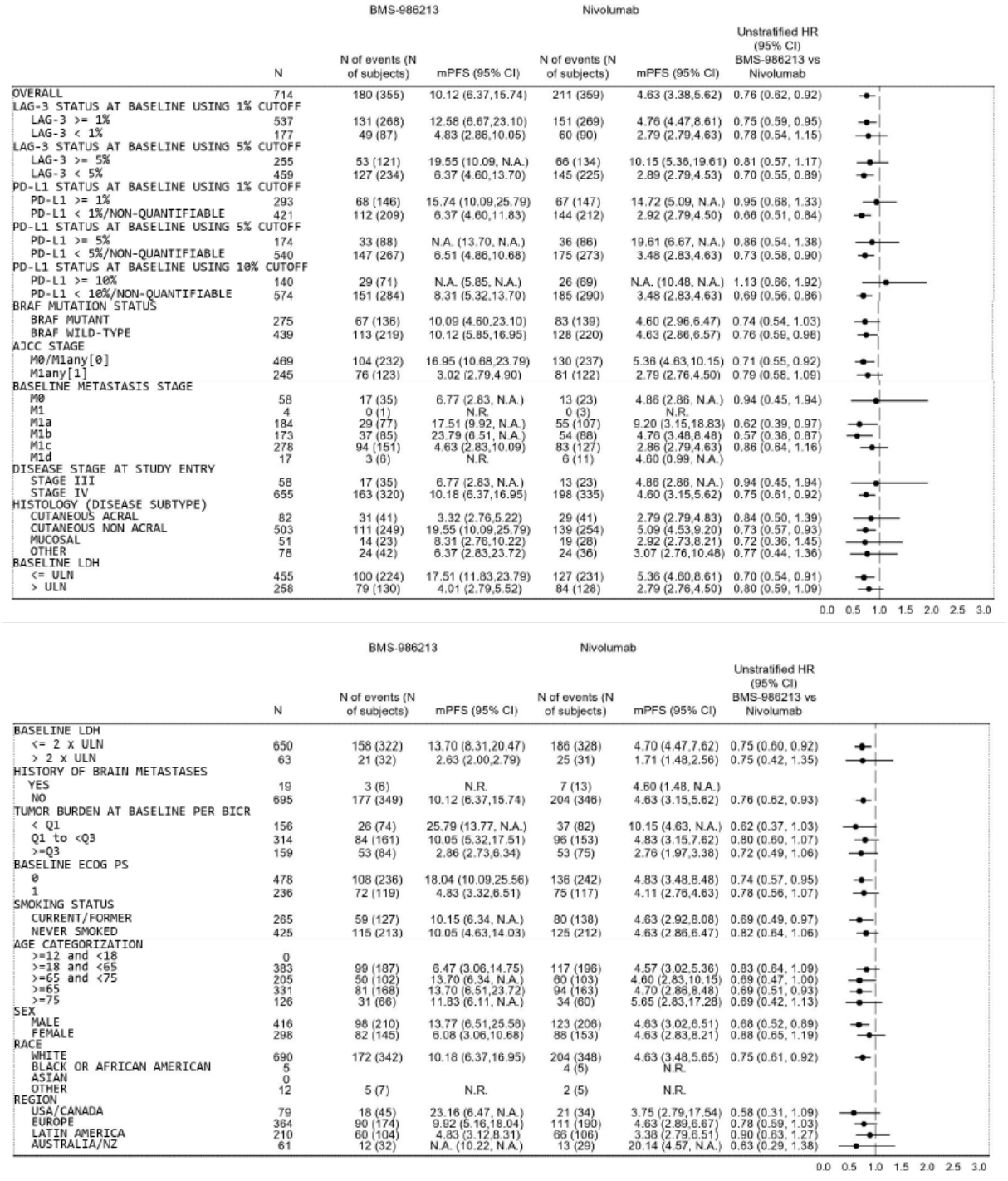
As randomisation was stratified by PD-L1 using the cut-off of 1%, subgroups based on other PD-L1 cut-offs are not congruent with randomisation strata and prognostic baseline characteristics may be meaningfully imbalanced between such groups, more likely so in subgroups of smaller size. Baseline characteristics for PD-L1 subgroups show notable imbalances between arms[88], particularly baseline LDH and M stage at the 10% cut-off, that could have affected the PFS and OS subgroup results.

An exploratory FDA analysis of safety in subgroups based on PD-L1 status[89] did not identify a toxicity-related explanation for the trend towards higher hazard ratios in patients with positive PD-L1 status; see Figure 4.

[88] See pages 144 to 148 of the FDA multidisciplinary review (MDR) document for OPDUALAG. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

[89] See Table 69 on page 217 of the FDA multidisciplinary review (MDR) document for OPDUALAG. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

Figure 4: RELATIVITY-047 Forest plots representing exploratory subgroup analyses of progression-free survival per blinded independent review committee (all randomised patients)



Abbreviations: BICR = blinded independent review committee; BMS-986213 = Opdualag; CI = confidence interval; HR = hazard ratio; LDH = lactate dehydrogenase; mPFS = median progression-free survival per RECIST v1.1; N = number; N.A. = not applicable, median or limit of CI not estimable; ULN = upper limit of normal.

Note: HR and median (displayed as N.R.) are not computed for subset category with less than 10 subjects per treatment group.

Supporting study – Study CA224020 (RELATIVITY-020 trial)

The RELATIVITY-020 trial is an international (14 countries) Phase I/II study of relatlimab administered alone (n = 25) and in combination with nivolumab (n = 1,379) in advanced solid tumours (except primary CNS tumours), incorporating dose escalation (parts A and B of the study) and cohort expansion (parts A1, C, D1, D2 and E). An interim clinical study report dated 9 June 2021 (with a database lock of 25 February 2021) was submitted.

Design

The following table provides a summary of the study design.

Table 4: RELATIVITY-020 Summary of study design for parts A through E

Part	Population inclusion criteria	Nivolumab dose (IV)	Relatlimab dose (IV)	Given	Dose frequency	N
A	Solid tumours, immunothera	-	20 to 800 mg [a]	As monother apy	Q2W	17
A1	NSCLC/RCC, prior anti-PD-(L)1 allowed	-	800 mg	As monother apy	Q2W	8
B	Solid tumours	80 to 480 mg [b]	20 to 1440 mg [b]	Sequentia lly	Q2W or Q4W [b]	107
C	MEL, prior anti-PD-1	240 mg	80 mg	Sequentia lly	Q2W	151
	MEL, first-line					66
	Solid tumours					329
	Bladder cancer, immunothera py naive	480 mg	160 mg	Sequentia lly	Q4W	37
D1	MEL, prior anti-PD-1; focused eligibility[d] Randomised to one of three doses	240 mg	80 mg	Co-administe red from separate vials	Q2W	189 [c]
		480 mg	160 mg	Co-administe red from separate vials	Q4W	83
		480 mg	160 mg	**As the fixed-dose combinat ion**	Q4W	82
D2	MEL, prior anti-PD-1; expanded eligibility	480 mg	160 mg	Co-administe red from separate vials	Q4W	164

Part	Population inclusion criteria	Nivolumab dose (IV)	Relatlimab dose (IV)	Given	Dose frequency	N
E	MEL, prior anti-PD-1	480 mg	480 mg	Co-administered from separate vials	Q4W	95
	MEL, first-line MEL Randomised to one of two doses	480 mg	160 mg	Co-administered from separate vials	Q4W	38 [e]
		480 mg	480 mg	Co-administered from separate vials	Q4W	38 [e]

Abbreviations: IV = intravenously; MEL = melanoma; N = number of patients randomised or treated; DP-1 = programmed death receptor-1; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; Q2W = every 2 weeks; Q4W = every 4 weeks.

A Relatlimab monotherapy dose escalation levels: 20 mg, 80 mg, 240 mg, and 800 mg every 2 weeks.

B Nivolumab with relatlimab dose escalation levels: 80/20, 240/20, 240/80, 240/160, and 240/240 mg every 2 weeks; 480/160, 480/240, 480/320, 480/480, 480/960, and 480/1440 mg every 4 weeks. Note: per protocol doses could go up to 480/1600 mg every 4 weeks; however, the highest dose studied was 480/1440 mg every 4 weeks.

C One adolescent subject was treated.

D Included: refractory or relapsed disease within 3 months of last dose of anti-PD-1 therapy, documented progression on the prior regimen that contained anti-PD-1 treatment, and, for those with *BRAF* mutations, progression on a single line of a *BRAF* inhibitor.

E First-line melanoma cohorts in Part E are currently enrolling (as at June 2021). This part aims to assess exposure-response.

Efficacy outcomes

Selected efficacy outcomes from the RELATIVITY-020 trial are presented in Table 5 below, for patients with advanced melanoma that had previously been treated with an immunotherapy agent, who received combination treatment with nivolumab and relatlimab in Part D1 or Part D2.

Table 5: RELATIVITY-020 Response rates and durations with nivolumab plus relatlimab treatment (patients who had previously received an immunotherapy for advanced melanoma)

Part	Dose	Given	ORR (95% CI) responses	mDOR	mTTR (min, max)
D1 (arm 1)	240 mg nivolumab plus 80 mg relatlimab Q2W (n = 189)	Co-administered from separate vials	12% (8, 17) 4% CR 8% PR	NR*	15 weeks (6, 39)

Part	Dose	Given	ORR (95% CI) responses	mDOR	mTTR (min, max)
D1 (arm 2)	480 mg nivolumab plus 160 mg relatlimab Q4W (n = 83)	Co-administered from separate vials	6% (2, 14) 4% CR 2% PR	NR	15 weeks (8, 71)
D1 (arm 3)	480 mg nivolumab plus 160 mg relatlimab Q4W (n = 82)	**As the fixed-dose combination**	18% (11, 28) 5% CR 13% PR	18 months	16 weeks (7, 55)
D2	480 mg nivolumab plus 160 mg relatlimab Q4W (n = 83)	Co-administered from separate vials	9% (5, 15) 2% CR 7% PR	13 months	16 weeks (7, 40)

Abbreviations: CI = confidence interval; CR = complete response; max = maximum; mDOR = median duration of responses; min = minimum; mTTR = median time to response; NR = not reached; ORR = objective response rate confirmed per blinded independent central review; PR = partial response; Q4W = every four weeks.

* There were 55% of patients ongoing at 28 months minimum follow-up.

Safety

Safety analysis methodology

The safety analysis population consists of all patients who received at least one dose of the fixed=dose combination of nivolumab with relatlimab in the RELATIVITY-047 trial. The main safety analysis was performed on data from the same database lock date as the primary efficacy analysis (9 March 2021). A 120-day safety update (with an additional 4 months of follow-up) and safety data at time of final OS analysis were also reviewed.

The protocol for the RELATIVITY-047 trial contained detailed criteria for delay, resumption, and discontinuation of study treatment for specific adverse events.

Adverse events (AE) were reported in the study using Medical Dictionary for Regulatory Activities (MedDRA)[90] and are described in the submission using Preferred Terms (PT)[91]. For the purposes of meaningful clinical inference, the regulatory review of safety data has used clinically meaningful groups of PTs (grouped terms).

Based on the mechanism of action for Opdualag, immune-mediated adverse events (IMAE) and other events of special interest (OESI) were a particular focus of the safety review.

Exploratory subgroup analyses were conducted by the FDA and did not indicate a different safety profile based on age, sex, or region.[92]

[90] The **Medical Dictionary for Regulatory Activities (MedDRA)** is an internationally used set of terms relating to medical conditions, medicines and medical devices. It was created to assist regulators with sharing information. It is also used by industry, academics, health professionals and other organisations that communicate medical information.

[91] In MedDRA, Preferred Terms (PT) are single concepts for symptoms, signs, disease diagnosis, therapeutic indications, investigations, procedures, and characteristics. There are over 20,000 Preferred Terms.

[92] See page 215 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

Treatment duration and exposure

Exposure to study treatment for the safety analysis population at the database lock date of 9 March 2021 for the primary analysis is summarised in the following table. Exposure was similar between treatment arms.

The recruitment pause for interim PFS analysis and a COVID-19 related enrolment slowdown, explain the notable proportion (around one-third) of patients in the RELATIVITY-047 trial who had 3 months or less duration of treatment at the time of primary PFS analysis.

Table 6: RELATIVITY-047 Treatment duration and exposure (safety analysis population)

		Nivolumab with relatlimab (n = 355)	**Nivolumab (n = 359)**
Treatment duration and exposure			
Median treatment duration, months (range)		6 (0, 31)	5 (0, 32)
Mean treatment duration, months (standard deviation)		9 (8)	9 (9)
Percentage of patients with a minimum duration of therapy	3 months	67	67
	6 months	49	44
	9 months	40	36
	12 months	29	28
	15 months	20	21
Mean relative dose intensity (standard deviation)		96 (7)	96 (8)

Database lock date: 9 March 2021

Deaths

An analysis of deaths in the RELATIVITY-047 trial is detailed by the FDA.[93] An overview of deaths in the study is summarised in Table 7.

Three deaths (0.8%) in the nivolumab with relatlimab arm were reported as treatment related by the reporting investigator: one case each of haemophagocytic lymphohistiocytosis (HLH), pulmonary oedema, and pneumonitis. HLH and pneumonitis are known risks with nivolumab.

The case of pulmonary oedema occurred in a 75-year-old male, and the narrative does not allow for meaningful clinical inference:

> On Day 41 the patient experienced dyspnea and signs of lobar pneumopathy; 20 days after the 2nd infusion day, the patient died of pulmonary edema (related). An autopsy was not performed. The study therapy was discontinued with the last dose received on Day 29.

Case narratives were individually reviewed for all deaths not recorded as due to disease progression and did not reveal additional attributable deaths.

Table 7: RELATIVITY-047 Deaths (safety analysis population)

	Nivolumab with Relatlimab (n = 355)		Nivolumab (n = 359)	
Deaths	N	%	N	%
Total	**108**	**30**	**119**	**33**
Disease progression	90	25	99	28
Study drug toxicity	3	0.8	2	0.6
Unknown	1	0.3	2	0.6
Other	14	3.9	16	4.5

Abbreviations: N = number of cases, n = total number of patients

[93] See page 176 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

Database lock date: 9 March 2021.

Dose interruptions and permanent discontinuations

The sponsor's analysis of dose delay, dose infusion interruption, and infusion rate reduction in the RELATIVITY-047 trial is available with a list of AEs that led to treatment discontinuation.[94] A brief summary of these metrics is included in the following table. Below.

Table 8: RELATIVITY-047 Dose modifications and permanent discontinuations (safety analysis population)

		Nivolumab with Relatlimab (n = 355)		Nivolumab (n = 359)	
		N	%	N	%
Dose delays and infusion interruptions					
Patients with at least one dose delayed* due to AE		140	39	130	36
Patients with at least one AE that led to dose delay or infusion interruption**		160	45	136	38
Infusion rate reduction					
Patients with at least one infusion during which the rate was reduced		15	4	8	2
AEs leading to permanent discontinuation					
Patients with at least one AE leading to discontinuation		69	19	41	11
AEs leading to discontinuation with a incidence at least 1% different between arms	diarrhoea	7	2	1	0.3
	pneumonitis	6	1.7	1	0.3
	myocarditis	6	1.7	0	0

Abbreviations: AE = adverse event; N = number of cases, n = total number of patients

* Delay of at least 3 days longer than the expected 28 days between doses, based on exposure data.

** Based on 'action taken with drug' data from adverse event reports; includes delays of any duration.

Database lock date: 9 March 2021

Dose delays occurred in a similar proportion of each arm but were generally longer in the nivolumab with relatlimab arm: the proportion of delays lasting 15 to 42 days was 10% higher, and the proportion of delays lasting 4 to 7 days was 12% lower, than for nivolumab monotherapy. A higher proportion of delays in the nivolumab with relatlimab arm were attributed to adverse events.

The AEs that most frequently led to dose delay in the nivolumab with relatlimab arm were: troponin increased (3.9%), diarrhoea (3.9%), aspartate aminotransferase (AST) increased (2.8%), troponin T increased (2.8%), alanine aminotransferase (ALT) increased (2.3%), arthralgia (2.3%), and hypothyroidism (2.3%).

Common and high-grade adverse events

The approved FDA label contains the following description of common adverse events and laboratory abnormalities with nivolumab with relatlimab in the RELATIVITY-047 trial:

> The most common (≥20%) adverse reactions that occurred in patients treated with OPDUALAG were musculoskeletal pain (45%), fatigue (39%), rash (28%), pruritus (25%), and diarrhea (24%).

[94] See page 185 to 188 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

> The most common (≥20%) laboratory abnormalities that occurred in patients treated with OPDUALAG were decreased hemoglobin (37%), decreased lymphocytes (32%), increased AST (30%), increased ALT (26%), and decreased sodium (24%).[76]

Using clinically rational grouped AE terms, the most common Grade 3 and 4 AE in the nivolumab with relatlimab arm was musculoskeletal pain (4.2%), while fatigue, diarrhoea and anaemia each occurred in 2% of patients.[95] Grade 3 and 4 adverse events occurred in 39% of the Opdualag arm and 32% of the nivolumab monotherapy arm. Toxicity grades were assessed in accordance with the CTCAE Version 5.0.[73]

Serious adverse events

According to the sponsor's analysis, serious adverse events (SAE) in the RELATIVITY-047 trial occurred in 34% of the nivolumab with relatlimab arm and 29% of the nivolumab arm.

The overall rate of SAE in the nivolumab with relatlimab arm cited in the approved FDA label is 36%. Their analysis of SAE excluded disease progression related terms (such as 'malignant neoplasm progression') and did not exclude events that occurred 30 to 100 days after last dose of study treatment, in keeping with the known possibility for IMAE to occur in such a time frame.

As expected, based on the rate of higher-grade events, there were more immune-mediated SAEs in the nivolumab with relatlimab arm, including colitis or diarrhoea, myocarditis, and adrenal insufficiency. Of note were SAEs of Grade 3 haemolytic anaemia, Grade 2 Guillain-Barré syndrome, Grade 3 Vogt-Koyanagi-Harada disease, and Grade 4 HLH in the nivolumab with relatlimab arm. These are described in the approved Australian PI for nivolumab[96] (and are therefore expected adverse reactions for Opdualag) and should be included in Section 4.8 of the Australian PI for Opdualag. Each of these events were seen in a single patient in the study, and based on the infrequency, separate text in Section 4.4 Special warnings and precautions for use (in addition to Section 4.8) is not required at this time.

Immune-mediated adverse events and other events of special interest

Immune-mediated adverse events (IMAEs) are known to occur with nivolumab and other immuno-oncology drugs. They can occur in just about any organ system, and (uncommonly) have late onset, even weeks to months after drug cessation. For this reason, the 30-day post-cessation window traditionally used as a cut-off for the assessment of adverse events in a trial may not be ideal for the assessment of IMAEs.

Immune-mediated adverse events were defined in the RELATIVITY-047 trial protocol as treatment-emergent adverse events that occurred within 100 days of the last dose; that were assessed by the investigator to be consistent with an immune-mediated mechanism or immune-mediated component, for which non-inflammatory aetiologies (for example, infection or tumour progression) had been ruled out; and that were treated with immune-modulating medication. Endocrine AEs such as adrenal insufficiency, hypothyroidism, thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis were included regardless of use of immune-modulating medication, because they are often managed without it.

Immune-mediated adverse events considered in the safety analysis of the RELATIVITY-047 trial included endocrinopathies, diarrhoea or colitis, hepatitis, pneumonitis, interstitial nephritis, and rash. MedDRA Preferred Terms describing each of these IMAEs were grouped into system

[95] See Table 61 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.
[96] Australian Product Information document for nivolumab, dated 1 Mar 2022. Available from the TGA website.

categories for analysis (endocrine, gastrointestinal, hepatic, pulmonary, renal, skin, and hypersensitivity or infusion reaction).

Other events of special interest (OESIs) were defined as events that do not fulfil all criteria to qualify as select AEs or IMAEs but are still considered clinically significant. Other events of special interest included the following categories: myositis or rhabdomyolysis, myocarditis, demyelination, Guillain-Barré syndrome, pancreatitis, uveitis, encephalitis, myasthenic syndrome, graft-versus-host disease, troponin elevation, and meningitis.

Based on the sponsor's summary of IMAEs and OESI (see Table 9), high grade events of immune-mediated hepatitis and adrenal insufficiency appeared notably more common with the nivolumab-with-relatlimab combination than nivolumab monotherapy. Rates of IMAEs overall were more common with Opdualag than nivolumab, with the exception of hyperthyroidism and diabetes mellitus. The use of immune-modulating medications reflected this, with 50% of the nivolumab with relatlimab arm and 35% of the nivolumab arm requiring corticosteroid or immunosuppressant treatment for AEs.

A higher percentage of patients in the Opdualag arm were treated with corticosteroids or immunosuppressants for AEs (50.4% versus 35.4% in the nivolumab arm), but the duration of treatment required was not appreciably different. The categories of all-grade events most frequently requiring immune-modulating treatment were similar:

- nivolumab with relatlimab: rash (6.2%), arthralgia (5.1%), pruritus (4.8%), and diarrhoea (4.2%)
- nivolumab: rash (3.6%), pruritus (3.3%), diarrhea (2.2%), and arthralgia (2.2%).

The FDA describes individual immune related adverse event category review findings,[97] and accordingly the approved FDA label includes detailed warnings and precautions for immune related pneumonitis, colitis, hepatitis, endocrinopathies, nephritis (with renal dysfunction), dermatological reactions, myocarditis, and a list of rarer immune-mediated adverse reactions.[76]

Table 9: RELATIVITY-047 Summary of treatment-emergent immune-mediated adverse events and other events of special interest (safety analysis population)

	Nivolumab with relatlimab (n = 355)				Nivolumab (n = 359)			
	Any grade		Grade 3-4		Any grade		Grade 3-4	
Safety parameters	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
IMAEs within 100 days of last dose that were treated with immune-modulating medication								
Diarrhoea/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	0	4	1.1	0	0
Endocrine IMAEs within 100 days of last dose								
Adrenal insufficiency	15	4.2	5	1.4	3	0.8	0	0
Hypophysitis	9	2.5	1	0.3	3	0.8	1	0.3
Hypothyroidism	59	16.6	0	0	47	13.1	0	0
Thyroiditis	10	2.8	0	0	5	1.4	0	0
Hyperthyroidism	22	6.2	0	0	24	6.7	0	0
Diabetes mellitus	1	0.3	1	0.3	2	0.6	1	0.3
OESIs within 100 days of last dose*								

[97] FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

	Nivolumab with relatlimab (n = 355)				Nivolumab (n = 359)			
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	0
Pancreatitis	4	1.1	0	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	0	0
Guillain-Barré syndrome	1	0.3	0	0	0	0	0	0

Abbreviations: IMAE = immune-mediated adverse events; N = number of cases, n = total number of patients; OESI = other events of special interest.

*No events of myasthenic syndrome, demyelination, graft versus host disease, or meningitis were reported.

Database lock date: 9 March 2021. Analysis by sponsor.

Hypersensitivity or infusion reactions

The incidence and severity of hypersensitivity or infusion reactions was not notably higher with the nivolumab with relatlimab combination (7.0%) than with nivolumab monotherapy (4.2%), or with higher doses of relatlimab when given with nivolumab in the RELATIVITY-020 trial.[98] This is a known risk of nivolumab and has been included by the sponsor in the proposed Australian PI for Opdualag as a warning or precaution.

Cardiac safety

No clinically relevant effect on the QTc interval duration was seen with nivolumab plus relatlimab treatment, [99] and there was no apparent relationship between serum relatlimab concentration and change in QT interval duration (corrected for heart rate according to Fridericia's formula) in patients with solid tumours.

Myocarditis is a known risk of checkpoint inhibition.[96] Myocarditis was included as an OESI in the RELATIVITY-047 trial due to the observation of early, lethal myocarditis in LAG-3/PD-1 double knockout mouse models, and in context of post-market evidence of rare (0.1% incidence or less) severe checkpoint inhibitor-associated myocarditis. The incidences of myocarditis and troponin increase in the RELATIVITY-047 trial with Opdualag were 1.7% and 12%, and with nivolumab monotherapy were 0.3% and 10%, respectively. The sponsor has proposed a stand-alone warning or precaution paragraph in the Opdualag PI for myocarditis, in line with that included in the approved FDA label. Whilst the magnitude of difference between arms may not appear very large, the excess of 5 cases of myocarditis in the Opdualag arm represents a meaningful difference, given that this event has been reported only rarely with nivolumab monotherapy. In light of the rate of observed myocarditis in the trial, and the nonclinical data suggesting additive or synergistic effects of nivolumab and relatlimab on this risk, the sponsor's proposal for a dedicated warning paragraph is appropriate.

Troponin monitoring was included in the RELATIVITY-047 trial as a pilot to determine if increased surveillance could support identification of asymptomatic myocarditis. A testing timeframe of 2 months from start of therapy was selected, based on the median time-to-onset for previously observed cases. The outcomes of the trial do not suggest troponin monitoring for

[98] Page 212 of FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

[99] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave on an electrocardiogram. It approximates to the time taken for ventricular depolarisation and repolarisation, that is, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The **corrected QT interval (QTc)** estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

asymptomatic myocarditis would be advisable. The rate of troponin elevation was 12% in the nivolumab with relatlimab arm and 10% in the nivolumab arm.

Central nervous system effects

Neurological adverse event terms were included in the OESI list for the RELATIVITY-047 trial based on nonclinical data (CNS vasculitis in cynomolgus monkeys) and the known risk of immune-mediated CNS events with checkpoint inhibitor treatment.

Overall, the incidence of CNS adverse events was higher with nivolumab with relatlimab (31%) than nivolumab (23%), however there were low rates of higher-grade events (6 (1.7%) with nivolumab with relatlimab and 1 (1.1%) with nivolumab). The FDA concluded:

> CNS adverse events were manageable and not unexpected in patients treated with immunotherapy. CNS toxicity does not meet evidentiary standards for inclusion in the label under Warnings and Precautions.[100]

This approach is also appropriate for the Australian PI.

Immunogenicity

The immunogenicity profile of Opdualag and nivolumab seen in the RELATIVITY-047 trial is summarised in the approved FDA label as follows:

> During the initial 24-month treatment period in [the RELATIVITY-047 trial], the incidence of:
>
> - anti-nivolumab antibodies and neutralising antibodies in the OPDUALAG group was 3.8% (11/288) and 0.3% (1/288), respectively, which was similar to that observed in the nivolumab group: 5.9% (16/272) and 0.4% (1/272), respectively.
> - anti-relatlimab antibodies and neutralising antibodies in the OPDUALAG group was 5.6% (16/286) and 0.3% (1/286), respectively.
>
> Because of the low incidence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, or effectiveness of OPDUALAG is unknown.[76]

Diagnostic testing considerations

The proposed indication does not require identification of a biomarker for selection of a subgroup of patients with melanoma for treatment with Opdualag.

Risk management plan

The European risk management plan (RMP) version 1.0 (dated 18 August 2021; data lock point 9 March 2021) and Australia-specific annex (ASA) version 2.0 (dated 8 July 2022) were submitted.

The summary of safety concerns and their associated risk monitoring and mitigation strategies from the RMP are presented in Table 10. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

[100] See pages 211 to 212 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

Table 10: Summary of safety concerns

Safety concern		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	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	✓	-	✓	✓†
	Immune-related neurological ARs	✓	-	✓	✓†
	Other immune-related ARs #	✓	-	✓	✓†
Important potential risks	Embryofetal toxicity	✓	-	✓	-
Missing information	Long term safety (including growth and development disorders) in paediatric patients 12 years of age and older	✓	✓*	✓	-

*Study CA224122

† Patient Card

Includes risk of graft-versus-host disease after allogeneic haematopoietic stem cell transplantation. The sponsor has committed to providing an updated ASA including immune related neurological adverse reactions as an important identified risk.

Routine risk minimisation activities are proposed for all safety concerns, as well as a patient card regarding immune-related adverse reactions. In addition, the sponsor plans to conduct Study CA224122, on long-term follow-up of paediatric patients exposed to Opdualag in the Dutch Melanoma Treatment Registry.

The TGA suggested a similar register for Australian paediatric patients should be considered. The sponsor provided information to justify why, at this point in time, long-term systematic data collection in Australian adolescent patients is not feasible, which was accepted by the TGA. The sponsor committed to continue to explore other options for collecting long-term safety data in adolescent populations besides the Dutch Melanoma Treatment Registry and will conduct its routine pharmacovigilance responsibilities. This has been noted and the proposed pharmacovigilance plan is acceptable from an RMP perspective.

Conditions of registration related to the RMP are proposed.

Risk-benefit analysis

Delegate's consideration

Summary of key data

Advanced (locally advanced and unresectable, or metastatic) melanoma is a serious and life-threatening condition. Despite remarkable progress of systemic therapies since 2010, 5-year survival rates remain around 50%.

Nivolumab and relatlimab are both inhibitors of 'checkpoint' molecules that downregulate activation of immune effector cells (PD-1 and LAG-3, respectively). Nivolumab as a monotherapy is already registered for the treatment of advanced melanoma and was the comparator in the pivotal study.

Study CA224047 (RELATIVITY-047) is an ongoing, double-blind, randomised, multicentre study in 714 patients with advanced unresectable or metastatic melanoma, who had not received prior systemic therapy in the metastatic setting. Patients were randomised (1:1) to receive Opdualag (nivolumab 480 mg plus relatlimab 160 mg) intravenously once every 4 weeks (n = 355) or nivolumab monotherapy 480 mg intravenously once every 4 weeks (n = 359) until radiographic progression or unacceptable toxicity.

Paediatric patients aged at least 12 years were allowed to enrol but no paediatric patient was enrolled. Efficacy and safety in paediatric patients must therefore be extrapolated from adult data.

The RELATIVITY-047 trial demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint: progression-free survival (PFS) in patients treated with nivolumab with relatlimab compared to nivolumab (hazard ratio of 0.75 (0.62, 0.92), p = 0.0055). The difference in median PFS between arms was 5.5 months.

The safety of Opdualag for the treatment of advanced melanoma appears acceptable for a therapy used for the treatment of a serious and life-threatening disease, with a toxicity profile, as for that of nivolumab monotherapy, dominated by immune-related adverse events. The rates of adverse events were generally higher with Opdualag than with nivolumab monotherapy, but the difference between arms was generally less than 10%. Grade 3 and 4 adverse events were 7% more frequent, serious adverse events were 6% more frequent, and adverse events leading to permanent discontinuation were 8% more frequent in the Opdualag arm. Myocarditis was of particular note as it is rare with nivolumab monotherapy but occurred in 1.7% of patients in the Opdualag arm, while nonclinical data had predicted that this event may be a particular risk with the combination. The most common adverse events leading to discontinuation of Opdualag were immune-related diarrhoea, pneumonitis or myocarditis. Deaths related to study drug toxicity occurred in 0.8% of the Opdualag arm and 0.6% of the nivolumab arm.

Immunogenicity was rare (neutralising antibodies occurred in 0.3% of patients receiving Opdualag), precluding conclusions regarding its effect on pharmacokinetics, efficacy or safety. Infusion reactions were uncommon (7%) but as for nivolumab monotherapy these warrant precautionary PI text.

The exploratory subgroup analyses do not allow robust conclusions comparing efficacy of the combination against tumours with higher PD-L1 compared to lower PD-L1, and limitation of the indication to PD-L1 negative (less than 1%) tumours is not considered required for Australia. However, the results in these subgroups are of particular clinical interest, given the scientific rationale for the activity of nivolumab, and the relevance of PD-L1 in considering treatment choices amongst the existing standard-of-care treatment options. As PD-L1 status using the 1%

cut-off was a stratification factor, subgroups based on this status should be balanced with regard to baseline factors (known and unknown) that may affect outcomes. Therefore, although not alpha-controlled and exploratory, the subgroup results at the 1% PD-L1 cut-off should be included with the trial results in the Australian PI (noting their limitations).

Choice of comparator arm in the pivotal study

Available regimens in use for first-line systemic treatment of advanced melanoma in Australia are summarised by the FDA.[101] For a randomised clinical trial studying nivolumab with relatlimab in patients regardless of *BRAF* mutation status, an anti-BRAF agent would not have been a suitable comparator. Of the remaining options, none have been directly compared head-to-head. In the CheckMate 067 trial,[102] nivolumab monotherapy and nivolumab plus ipilimumab were each compared against ipilimumab monotherapy, but the trial was not powered nor alpha controlled to compare nivolumab monotherapy to nivolumab plus ipilimumab. Informal comparisons suggest the combination is more efficacious, but at the cost of higher toxicity than anti-PD-1 therapy alone. Nivolumab monotherapy is therefore considered a current standard-of-care option, and a reasonable choice of comparator for study against Opdualag. It also allows for inferential assessment of the contribution of effect of relatlimab to Opdualag.

Relevance to patients who have received prior (neo)adjuvant therapy

Adjuvant therapy with either BRAF/MEK or CTLA4/PD-1 inhibition has become standard-of-care and may affect tumour microenvironment at relapse, subsequent response, and ultimately survival.[103] Prior systemic treatment for melanoma had been received by 9% of patients in the RELATIVITY-047 trial, mostly adjuvant interferon. Around 2% of patients had received prior immunotherapies or anti-BRAF/MEK treatment.

Parts D1 and D2 of the RELATIVITY-020 trial enrolled patients who had previously received treatment with at least an anti-PD-1 drug in the metastatic setting for their advanced melanoma, and response rates (between 6 and 18%; see Table 5) were far lower than those seen in the RELATIVITY-047 trial (43%). Responses that did occur, however, showed good durability, with medians of 13 or 18 months, or not reached (with minimum 28 months follow-up), across various cohorts.

The available data do not directly address whether the efficacy of Opdualag in the first-line metastatic setting would be affected by (neo)adjuvant therapy but do suggest that a decreased likelihood of response is possible. This is not considered a barrier to registration, because it also remains unknown at present:

- what effect (neo)adjuvant treatment has on the efficacy of other therapies that are registered for use in the first-line metastatic setting
- the ideal sequencing of treatments across neoadjuvant, adjuvant and metastatic settings.

[101] See page 33 of the FDA multidisciplinary review (MDR) document for Opdualag. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000MultidisciplineR.pdf.

[102] Wolchock JD, Chiarion Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017; 377(14): 1345 1356. doi: 10.1056/NEJMoa1709684.
Larkin J, Chiarion Sileni V, Gonzalez R, et al. Five year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2019; 381: 1535 1546. doi: 10.1056/NEJMoa1910836.

[103] Gyorki DE. Spoiled for Choice: Do We Finally Have Clarity on Optimal Treatment Sequencing for Patients with Metastatic Melanoma Harboring an Actionable BRAF Mutation? *Ann Surg Oncol* 2022; 29: 4014–4015. doi: 10.1245/s10434-022-11611-3.

It seems rational to predict that alternating use of BRAF/MEK inhibition and immunotherapy might be preferable (for patients with *BRAF* mutations), but this is conjecture.

Extrapolation to paediatric patients

No paediatric patients enrolled in the pivotal study, in keeping with the rarity of melanoma in patients under the age of 18 years. However, as noted previously, genetic studies of conventional melanomas in paediatric patients (aged 10 to 20 years; 87% over 13 years) have demonstrated that this type of paediatric melanoma shows clinicopathological and genetic similarity to melanoma in adults.

Biological and empirical evidence supports an expectation that the exposure-response relationship in adolescent patients to immunotherapy treatment should be similar to that seen in adults: the immune system in human adolescence is fully mature,[104] therefore target receptor levels and drug target binding for a given systemic exposure should be comparable.

The FDA approval letter for Opdualag states that the US requirement for mandatory paediatric studies have been waived for patients aged 0 to 11 years based on the rarity and different biology (impeding extrapolation of adult data) of melanoma in this age group.[105]

In line with the trial inclusion criteria, the sponsor has proposed that the Australian indication be worded to include an adolescent population based on age (12 to 18 years), in keeping with the group in whom conventional paediatric melanoma is most commonly seen. Patients below this age would also be more likely to have a body weight too low to allow a dosing recommendation.

Based on the above, it appears acceptable to extrapolate the efficacy data from the pivotal trial to paediatric patients with conventional melanoma.

While 12 years is an arbitrary lower age cut-off, cases of conventional melanoma (that is, those in which disease similarity would support extrapolation of the pivotal trial data) would be expected to be exceptionally rare below this age. Another approach could have been to consider limiting the indication directly based on histology. However, the sponsor's proposed approach of limiting the indication (and the trial inclusion criteria) based on age is rational, because the diagnosis of paediatric melanoma can be complicated by histologic uncertainty.[106]

Paediatric (adolescent) dosing

The sponsor proposes a weight-based dose for adolescents, derived from pharmacokinetic extrapolation (from nivolumab to relatlimab) and modelling. They also propose that patients with body weight lower than 40 kg be excluded, as the model estimates for exposure in such patients are unreliable: the paediatric effect in the nivolumab population pharmacokinetic model was based on adolescents who were all 40 kg or heavier.

The nature of modelling is that it involves assumptions and uncertainty. In this case, the main uncertainties are a lack of direct paediatric data for relatlimab PK and the reliability of

[104] Jaspan HB, Lawn SD, Safrit JT, et al. The maturing immune system: implications for development and testing HIV-1 vaccines for children and adolescents. *AIDS* 2006; 20: 483–494. doi: 10.1097/01.aids.0000210602.40267.60.

[105] FDA approval letter for Opdualag dated 18 March 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761234Orig1s000Approv.pdf.

[106] Pappo AS. Pediatric melanoma: the whole (genome) story. Am Soc Clin Oncol Educ Book 2014; :e432 5. doi: 10.14694/EdBook_AM.2014.34.e43.

Kumar RS, Messina JL, Sondak VK, et al. Treating melanoma in adolescents and young adults: challenges and solutions. Clinical Oncology in Adolescents and Young Adults 2015; 5: 75 86. doi: 10.2147/COAYA.S90563.

Wechsler J, Bastuji-Garin S, Spatz A, et al. Reliability of the histopathologic diagnosis of malignant melanoma in childhood. *Arch Dermatol* 2002; 138(5): 625-628. doi: 10.1001/archderm.138.5.625.

extrapolating the paediatric effect on nivolumab PK to relatlimab PK. Due to the uncertainty, there is a risk that body weight-based dosing could be subtherapeutic for adolescent patients with weights towards the lower end of the paediatric weight range for which dosing is supported by PK modelling (40 kg).

Importantly, exploratory exposure-response analyses suggest flat relationships for both efficacy and safety.

Based on the flat exposure-efficacy and exposure-toxicity relationships at relevant exposures for both active ingredients in Opdualag, and the potential risk of subtherapeutic dosing in paediatric patients (given the life-threatening nature of the condition), the Delegate considers it more appropriate to use the adult flat dosing regimen for paediatric patients 12 to 18 years of age, rather than body weight-based dosing. This would be in keeping with the FDA decision to approve the same dose for adults as for patients aged between 12 and 18 years.

The Delegate's view is that a dose recommendation cannot be made with confidence for patients lighter than 40 kg.

Two studies of Opdualag in patients with lymphoma including patients aged 12 to 17 years were not complete at the time the FDA were ready to approve the adult indication, and these studies have been made post-market requirements of the US approval in order to support PK in paediatric patients. The updated nivolumab with relatlimab modelling for PK in adolescents using paediatric PK data from these studies should be submitted to TGA, when available.

Infusion duration

Although a 30-minute infusion time has not been studied, this is the infusion time proposed for registration. The sponsor provided a justification, discussed earlier. The Delegate considers the proposed infusion time of 30 minutes acceptable.

Proposed action

Overall, Opdualag has demonstrated a clinically meaningful efficacy advantage over nivolumab monotherapy, and an acceptable toxicity profile for patients with advanced melanoma. The benefit-risk balance of Opdualag for the proposed usage, taking into account the uncertainties, is positive. Expert input is sought to confirm that the explicit inclusion of paediatric patients aged at least 12 years in the indication is appropriate.

Independent expert advice

The Delegate received the following independent expert advice from Australian oncologist(s) with melanoma and/or paediatric expertise.

1. ***Do you agree with the Delegate's preliminary opinion regarding extrapolation of the pivotal trial data? Do you have any comments on the rationale for this, as described under Extrapolation to paediatric patients?***

Obtaining data from patients 12 years and older in the 12 to 18 year age group is not feasible due to the low incidence of advanced melanoma in that subgroup. It is not surprising that no patients in that age bracket were enrolled in the RELATIVITY-047 trial (Study CA224047). Extrapolating the data from the adult population to the 12 to 18 year old subgroup is reasonable. The expert(s) agreed with the assumption that the 12 to 18 year age group have a fully mature immune system and would be expected to respond similarly to adults to immune checkpoint inhibition. The expert(s) agreed with the expectation that target receptor levels and drug-target binding for a given systemic exposure should be comparable. The expert(s) agreed that

diagnosis of paediatric melanoma can be complicated by histologic uncertainty. Conventional melanomas in the age group requested for the indication (12 to 18 year olds) have been demonstrated to show clinicopathological and genetic similarity to those in adults. This is not true for melanomas that arise before puberty. In paediatric melanoma before puberty, melanomas have higher rates of spitzoid histologic features and have different genomic features that also includes lower tumour mutation burden, one predictor of response to anti-PD1 based therapies.[30]

2. ***Do you have any comments on the rationale for approving the adult dose for paediatric patients, as described under Paediatric (adolescent) dosing?***

Nivolumab with relatlimab displays flat exposure-efficacy and exposure-toxicity relationships. There is more certainty in this conclusion for monotherapy with nivolumab based on a larger body of data. These exposure relationships are the key assumption in concluding that dosing per kilogram of body weight would not lead to inadequate exposure. The Delegate's recommendation (that the adult flat dosing regimen be used in patients aged 12 to 18 years, rather than a per kg dosing approach) is in line with the dose approved by the FDA. The expert(s) agreed with the Delegate that the adult flat dosing regimen may be used in the 12 to 18 year old subgroup based on no evidence of different immune biology in this patient subgroup and the flat exposure-efficacy and exposure-toxicity relationships. The expert(s) also agreed that the uncertainty created by the limited data is more acceptable in the setting of the proposed indication, that is, a life-threatening disease.

3. ***Gyorki mentions that in recent years, adjuvant therapy with either BRAF/MEK or CTLA4/PD-1 inhibition has become standard-of-care for melanoma patients. Is this the case in Australia?***

Regarding the statement by Gyorki that *'adjuvant therapy has become standard-of-care for many patients with stage III melanoma'*,[107] the expert(s) agreed that currently the combination of BRAF plus MEK inhibitors or monotherapy with anti-PD-1 (nivolumab or pembrolizumab) are a standard-of-care for resected stage 3B-D or resected stage 4 melanoma. In the RELATIVITY-047 trial (Study CA224047) only approximately 2% of patients had received prior immunotherapies or BRAF inhibitor plus MEK inhibitor treatment. As such the relative efficacy of nivolumab with relatlimab versus nivolumab monotherapy in patients that have received prior immunotherapies or BRAF inhibitor plus MEK inhibitor treatment remains uncertain. Nonetheless the expert(s) supported the Delegate's recommendations to approve the registration of the product.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines for advice.

Proposed action following independent expert advice

The Delegate proposed to approve the registration of the product for the requested indication.

In addition to the standard conditions, and the specific conditions proposed by the RMP evaluation which include the application of the Black Triangle Scheme, the Delegate proposed the following additional specific conditions of registration:

[107] Gyorki DE. Spoiled for Choice: Do We Finally Have Clarity on Optimal Treatment Sequencing for Patients with Metastatic Melanoma Harboring an Actionable BRAF Mutation? *Ann Surg Oncol* 2022; 29: 4014–4015. doi: 10.1245/s10434-022-11611-3.

- Submit results from Study 2 (modelling and simulation/extrapolation study), to further characterise the pharmacokinetics and evaluate the dose regimen of nivolumab and relatlimab combination therapy in paediatric lymphoma, when available.
- Provide any new safety information emerging from the completed Study CA224122 (long term follow up of paediatric patients enrolled in an adolescent Dutch Melanoma Treatment Registry) in a revised RMP, when available.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Opdualag (nivolumab 240 mg and relatlimab 80 mg) concentrate solution for intravenous infusion in a vial, indicated for:

> *Opdualag is indicated for the treatment of patients with unresectable or metastatic melanoma who are at least 12 years old.*

Specific conditions of registration applying to these goods

- Opdualag (nivolumab and relatlimab) is to be included in the Black Triangle Scheme. The PI and CMI for Opdualag must include the black triangle symbol and mandatory accompanying text for 5 years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Opdualag EU-risk management plan (RMP) (version 1.0, dated 18 August 2021, data lock point 9 March 2021), with Australia-specific annex (ASA) (version 2.0, dated 8 July 2022), included with Submission PM-2021-03689-1-4, and any subsequent revisions as agreed with the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than 3 years from the date of the approval letter. The annual submission may be made up of two PSURs each covering 6 months. If the sponsor wishes, the 6-monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the 3 year period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than 3 years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Revision 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within 90 calendar days of the data lock point for that report.
- [The sponsor is to] submit results from Study 2 (modelling and simulation/extrapolation study), to further characterise the pharmacokinetics and evaluate the dose regimen of nivolumab and relatlimab combination therapy in paediatric lymphoma, when available.

- [The sponsor is to] provide any new safety information emerging from the completed Study CA224122 (long term follow up of paediatric patients enrolled in an adolescent Dutch Melanoma Treatment Registry) in a revised RMP, when available.

Attachment 1. Product Information

The PI for Opdualag approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #