Relatlimab/nivolumab (Opdualag®) for the first line treatment of advanced melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%

General information [1]

Drug description	Indication
The active substances of Opdualag® are nivolumab and relatlimab, two monoclonal antibodies. Nivolumab is a programmed death-1 inhibitor (anti-PD-1) and relatlimab is a lymphocyte-activation gene-3 inhibitor (anti-LAG-3). Their combined use increases T cell activation and cytokine secretion to inhibit tumour growth and promote tumour regression.	Relatlimab/nivolumab (Opdualag®) is indicated for the first line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%.

Current treatment [2]

- For stage III melanoma, NICE guidelines advise the following:
  - Talimogene laherparepvec is recommended, in adults, as an option for treating unresectable, regionally or distantly metastatic (Stage IIIB or IIIC) melanoma that has not spread to bone, brain, lung or other internal organs, only if the treatment with systemically administered immunotherapies is not suitable and the company provides talimogene laherparepvec with the discount agreed in the patient access scheme.
- For stage IV melanoma, the following NICE guidelines state:
  - Talimogene laherparepvec is recommended, in adults, as an option for treating unresectable, regionally or distantly metastatic (Stage IVM1a) melanoma that has not spread to bone, brain, lung or other internal organs, only if the treatment with systemically administered immunotherapies is not suitable and the company provides talimogene laherparepvec with the discount agreed in the patient access scheme.
  - Dacarbazine for people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable.
  - Ipilimumab is recommended, within its marketing authorisation, as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.
  - Nivolumab as monotherapy is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults.
  - Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults, only when the company provides ipilimumab with the discount agreed in the patient access scheme.

Regulatory status

EMA [1]	FDA [3]
Approval status for this indication: On 21 July 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Opdualag®. <u>The full indication is:</u> ❖ Opdualag® is indicated for the first line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%. **Other indications**: none ✓ Medicine under additional monitoring	**Approval status for this indication**: not approved **Other indications**: On 18 March 2022, the FDA approved nivolumab and relatlimab-rmbw (Opdualag®) for adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma. ✓ Priority review ✓ Fast track designation ✓ Orphan drug designation

Costs

Currently, there is no cost information available.

Posology/ Method of administration [4]

- ❖ Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.
- ❖ Patients treated with Opdualag® must be given the patient card and be informed about the risks of Opdualag® (please see also package leaflet).
- ❖ PD-L1 testing
  - Patients should be selected for treatment with Opdualag® based on the tumour expression of PD-L1 confirmed by a validated test.
- ❖ The recommended dose for adults and adolescents 12 years of age and older is 480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as an intravenous infusion over 30 minutes. This dose is established for adolescent patients weighing at least 30 kg.
- ❖ Treatment with Opdualag® should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in the product information. Detailed guidelines for the management of immune-related adverse reactions are described in the product information.
- ❖ Opdualag® is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 minutes. Opdualag® must not be administered as an intravenous push or bolus injection. Opdualag® can be used without dilution, or may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection. For instructions on the preparation and handling of the medicinal product before administration, please see product information.

Warnings and precautions [4]

- ❖ Traceability
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- ❖ Assessment of PD-L1 status
  - When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.
- ❖ Immune-related adverse reactions
  - Immune-related adverse reactions can occur with nivolumab in combination with relatlimab which require appropriate management, including initiation of corticosteroids and treatment modifications.
  - Immune-related adverse reactions affecting more than one body system can occur simultaneously. Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with Opdualag® may occur at any time during or after discontinuation of therapy.
  - For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, Opdualag® should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.
  - Opdualag® should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics may be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.
  - Opdualag® must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.
  - Immune-related pneumonitis
    - Severe pneumonitis or interstitial lung disease, including a fatal case, has been observed with nivolumab in combination with relatlimab. Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g. focal ground glass opacities, patchy infiltrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.
    - For Grade 3 or 4 pneumonitis, Opdualag® must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.
    - For Grade 2 (symptomatic) pneumonitis, Opdualag® should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, Opdualag® may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents, and Opdualag® must be permanently discontinued.
  - Immune-related colitis
    - Severe diarrhoea or colitis has been observed with nivolumab in combination with relatlimab. Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus and/or blood in stool. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Infectious and other aetiologies of diarrhoea should be ruled out, therefore appropriate laboratory tests and additional examinations must be performed. If diagnosis of corticosteroid-refractory immune-related colitis is confirmed, addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy should be considered.
    - For Grade 4 diarrhoea or colitis, Opdualag® must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
    - Opdualag® should be withheld for Grade 3 diarrhoea or colitis, and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, Opdualag® may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, Opdualag® must be permanently discontinued.

- For Grade 2 diarrhoea or colitis, Opdualag® should be withheld. Persistent diarrhoea or colitis should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, Opdualag® may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and Opdualag® must be permanently discontinued.

- Immune-related hepatitis
  - Severe hepatitis has been observed with nivolumab in combination with relatlimab. Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.
  - For AST or ALT increases to more than 5 times ULN regardless of baseline, total bilirubin increases to more than 3 times ULN, or concurrent AST or ALT increase to more than 3 times ULN and total bilirubin increase to more than 2 times ULN, Opdualag® must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
  - For AST/ALT increases to more than 3 and up to 5 times ULN, or total bilirubin increases to more than 1.5 and up to 3 times ULN, Opdualag® should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, Opdualag may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and Opdualag® must be permanently discontinued.
- Immune-related nephritis and renal dysfunction
  - Severe nephritis and renal dysfunction have been observed with nivolumab in combination with relatlimab. Patients should be monitored for signs and symptoms of nephritis or renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.
  - For Grade 4 serum creatinine elevation, Opdualag® must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
  - For Grade 2 or 3 serum creatinine elevation, Opdualag® should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, Opdualag® may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and Opdualag® must be permanently discontinued.
- Immune-related endocrinopathies
  - Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), and diabetes mellitus have been observed with nivolumab in combination with relatlimab. Cases of diabetic ketoacidosis have been observed with nivolumab monotherapy and could potentially occur with nivolumab in combination with relatlimab.
  - Patients should be monitored for clinical signs and symptoms of endocrinopathies, and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

❖ Thyroid dysfunction
- For symptomatic hypothyroidism, Opdualag® should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, Opdualag® should be withheld and antithyroid treatment should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, Opdualag® may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Opdualag® must be permanently discontinued for life-threatening (Grade 4) hyperthyroidism or hypothyroidism.

❖ Adrenal insufficiency
- Opdualag® must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. For symptomatic Grade 2 adrenal insufficiency, Opdualag® should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.

❖ Hypophysitis
- Opdualag® must be permanently discontinued for life-threatening (Grade 4) hypophysitis. For symptomatic Grade 2 or 3 hypophysitis, Opdualag® should be withheld, and hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, Opdualag® may be resumed after corticosteroid taper, if needed. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

❖ Diabetes mellitus
- For symptomatic diabetes, Opdualag® should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Opdualag® must be permanently discontinued for life-threatening diabetes.

❖ Immune-related skin adverse reactions

- Severe rash has been observed with nivolumab in combination with relatlimab. Opdualag® should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.
- Rare cases of SJS and TEN, some of them with fatal outcome, have been observed with nivolumab monotherapy and could potentially occur with nivolumab in combination with relatlimab. If symptoms or signs of SJS or TEN are suspected, Opdualag® should be withheld and the patient referred to a specialised unit for assessment and treatment. If the patient has confirmed SJS or TEN with the use of Opdualag®, permanent discontinuation of treatment is recommended.
- Caution should be used when considering the use of Opdualag® in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

❖ Immune-related myocarditis

- Severe immune-related myocarditis has been observed with nivolumab in combination with relatlimab. The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, Opdualag® should be withheld or permanently discontinued.
- For Grade 3 or 4 myocarditis, Opdualag® must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.
- For Grade 2 myocarditis, Opdualag® should be withheld and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalent. Upon improvement, resumption of Opdualag® may be considered after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents, and Opdualag® must be permanently discontinued.

❖ Other immune-related adverse reactions

- The following clinically significant immune-related adverse reactions have been rarely reported in patient treated with nivolumab in combination with relatlimab: uveitis, pancreatitis, Guillain-Barré syndrome, myositis/rhabdomyolysis, encephalitis, haemolytic anaemia, Vogt-Koyanagi-Harada syndrome.
- The following additional clinically significant immune-related adverse reactions have been rarely reported with nivolumab monotherapy or nivolumab in combination with other approved agents: demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis, myasthenic syndrome, aseptic meningitis, gastritis, sarcoidosis, duodenitis, hypoparathyroidism, and cystitis noninfective.
- For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, Opdualag® should be withheld and corticosteroids administered. Upon improvement, Opdualag® may be resumed after corticosteroid taper. Opdualag® must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

❖ Other important warnings and precautions, including class effects

- Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab in combination with relatlimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab in combination with relatlimab versus the risk of possible organ rejection should be considered in these patients.
- Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy, nivolumab in combination with relatlimab and nivolumab in combination with other agents with a fatal event reported with nivolumab in combination with relatlimab. Caution should be taken when administering nivolumab in combination with relatlimab. If HLH is confirmed, administration of nivolumab in combination with relatlimab should be discontinued and treatment for HLH initiated.
- In patients treated with nivolumab before or after allogeneic HSCT, rapid-onset and severe graft-versus-host disease (GVHD), some with fatal outcome, have been reported. Treatment with nivolumab in combination with relatlimab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab in combination with relatlimab versus the possible risk should be considered in these patients.

❖ Infusion reactions

- Severe infusion reactions have been reported in clinical studies of nivolumab in combination with relatlimab. In case of a severe or life-threatening infusion reaction, Opdualag® infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive Opdualag® with close monitoring and preventative treatment according to local guidelines for prophylaxis of infusion reactions.

❖ Patients excluded from pivotal advanced melanoma clinical study

- Patients with active autoimmune disease, medical conditions requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medicinal products, uveal melanoma, active or untreated brain, or leptomeningeal metastases, and those with a history of myocarditis, elevated troponin levels > 2 times ULN or ECOG performance status score ≥ 2, were excluded from the pivotal clinical study of nivolumab in combination with relatlimab. In the absence of data, nivolumab in combination with relatlimab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

❖ Patient card

- The prescriber must discuss the risks of Opdualag® therapy with the patient. The patient will be provided with the patient card and instructed to carry the card at all times.

Study characteristics [5-8]								
Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
RELATIVITY-047, (CA224-047) NCT03470922	714 (1:1)	160 mg of relatlimab and 480 mg of nivolumab in a fixed-dose combination in a single 60-minute IV infusion every 4 weeks	480 mg of nivolumab in a single 60-minute IV infusion every 4 weeks	PFS[1]	**ongoing[2]**, global, double-blind, randomised phase 2–3 trial	PD-L1	Bristol Myers Squibb	[7]

Efficacy (I vs. C)	Safety (I vs. C)
Median PFS: 10.1 months (95% CI, 6.4-15.7) vs. 4.6 months (95% CI, 3.4-5.6); HR for progression or death, 0.75 (95% CI, 0.62-0.92); p=0.006 by the log-rank test **Patients with PFS at 12 months**: 47.7% (95% CI, 41.8-53.2) vs. 36.0% (95% CI, 30.5-41.6) **Median PFS among patients with PD-L1 expression of ≥1%:** 15.7 months (95% CI, 10.1-25.8) vs. 14.7 months (95% CI, 5.1-not reached); HR for progression or death 0.95 (95% CI, 0.68-1.33) **Median PFS among patients with PD-L1 expression of ≤1%:** 6.4 months (95% CI, 4.6-11.8) vs. 2.9 months (95% CI, 2.8-4.5); HR 0.66 (95% CI, 0.51-0.84) **Median PFS in the subgroup of patients with BRAF mutations**: 10.1 months (95% CI, 4.6-23.1) vs. 4.6 months (95% CI, 3.0-6.5); HR for progression or death, 0.74 (95% CI, 0.54-1.03) **Median PFS in the subgroup of patients with wild-type BRAF**: 10.1 months (95% CI, 5.9-17.0) vs. 4.6 months (95% CI, 2.9-6.6); HR 0.76 (95% CI, 0.59-0.98) HRQoL ❖ The percentage of patients with completed HRQoL assessments was high (≥86% of the number of patients expected at all on-treatment visits) and was similar in the two treatment groups. ❖ Within each treatment group, least-squares mean changes from baseline over time in the FACT-M total score and the EQ-5D-3L utility index remained stable and did not exceed the minimal clinically important differences. ❖ Overall, no substantial differences in HRQoL were noted between the treatment groups. Efficacy results in patients with PD-L1 < 1% tumour cell expression from an exploratory analysis with median follow-up of 17.78 months (n=209 vs. n=212) [4]: **Median PFS**: 6.7 months (95% CI, 4.7-12.0) vs. 3.0 months (95% CI, 2.8-4.5); HR 0.68 (95% CI, 0.53-0.86) **PFS rate at 12 months**: 42.3% (95% CI, 35.1-49.4) vs. 26.9 months (95% CI, 20.9-33.3) **Median OS[3]**: NR (95% CI. 27.4-NR) vs. 27.0 months (17.1-NR); HR 0.78 (95% CI, 0.59-1.04) **OS rate at 12 months**: 73.9% (95% CI, 67.4-79.4) vs. 67.4 (95% CI, 60.6-73.3)	**Infusion-related adverse reactions:** 5.9% vs. 3.6% **Treatment-related AEs Grade 3 or 4:** 18.9% vs. 9.7% **Treatment-related AEs (of any grade) leading to discontinuation:** 14.6% vs. 6.7% **Deaths considered to be treatment-related by investigators:** 0.8% (hemophagocytic lymphohistiocytosis, acute pulmonary edema, and pneumonitis) vs. 0.6% (sepsis and myocarditis in one patient and pneumonia in one patient)

[1] Assessed according to RECIST, version 1.1,10 by blinded independent review.
[2] The RELATIVITY-047 trial is currently ongoing; estimated study completion date is 11/2023.
[3] **OS results are not yet mature.**

OS rate at 24 months: 59.6 (95% CI, 52.2-66.2) vs. 53.1 (95% CI, 45.8-59.9) **Overall response rate:** 36.4% (95% CI, 29.8-43.3) vs. 24.1 (95%CI, 18.5-30.4) **Complete response rate**: 12.0% vs. 9.4% **Partial response rate**: 24.4% vs. 14.6% **Stable disease rate**: 19.6% vs. 14.6%	

ESMO-MCBS version 1.1 [9]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2b	≤6 months	PFS: +5.5 months	0.75 (0.62-0.92)	HR≤0.65 AND gain ≥1.5 months	3	-	-	-	3
Adapted	NC	2b	≤6 months	PFS: +5.5 months	0.75 (0.62-0.92)	HR>0.65	1	-	-	-	1

Risk of bias (RCT) [10]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	Risk of bias
yes	yes	yes	unclear[4]	yes[5]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, AST=aspartate aminotransferase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, ECOG= Eastern Cooperative Oncology Group, EMA=European Medicines Agency, EQ-5D-3L=three-level version of the EuroQol Group–5 Dimensions, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-M=Functional Assessment of Cancer Therapy–Melanoma, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GVHD=graft-versus-host disease, HLH=haemophagocytic lymphohistiocytosis, HR=hazard ratio, HRQoL=health-related quality of life, HSCT=haematopoietic stem cell transplantation, I=intervention, Int.=intention, IV=intravenous, LAG-3=lymphocyte-activation gene 3, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, OS=overall survival, PD-1=programmed death 1, PD-L1=programmed death ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SJS= Stevens-Johnson syndrome, ST=standard treatment, TEN=toxic epidermal necrolysis, ULN=upper limit of normal

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[4] The RELATIVITY-047 trial is ongoing; currently, only interim analysis results are available.
[5] The trial was designed by the sponsor, in conjunction with the trial steering committee. Data were collected by the sponsor and analysed in collaboration with the authors. Professional medical writing and editorial assistance with an earlier version of the manuscript were funded by the sponsor.

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