Indication	For the first line treatment of unresectable stage III or stage IV melanoma in patients who have not have received prior systemic treatment for melanoma unless they received: • Prior adjuvant therapy with nivolumab or pembrolizumab or • Prior immune checkpoint inhibitors for advanced disease if given as part of a clinical trial either as monotherapy or in combination with ipilimumab or • BRAF/MEK inhibitor targeted therapy for adjuvant disease or • BRAF/MEK inhibitor targeted therapy as 1st line treatment for advanced disease.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days. Continue until disease progression, unacceptable toxicity or patient choice or for a maximum total treatment duration of 2 calendar years, whichever occurs first. A formal medical review as to whether treatment should continue or not will be scheduled to occur by the start of the 3rd cycle of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, U&Es, LFTs, random blood glucose at each cycle. • If PLT <75 or neuts <1.0 d/w consultant. • Thyroid function must be assessed at baseline then every 8 weeks or as clinically indicated. • Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose. • **Renal impairment:** No specific dose adjustment is necessary in patients with mild to moderate renal impairment. Severe renal impairment, limited data, d/w consultant. • **Hepatic impairment:** No dose adjustment in mild or moderate hepatic impairment, total bilirubin </=3 times ULN and any AST. Severe hepatic impairment, limited data, d/w consultant. • **Infusion-related reactions:** In the event of severe infusion-related reactions, discontinue and administer appropriate treatment. In the event of a mild or moderate reaction, treatment may be continued with close monitoring. Pre-medication with paracetamol and chlorphenamine should be considered for subsequent treatment. • **Dose Modification:** Dose escalation or reduction is not appropriate. Dosing delay or discontinuation may be required based on individual safety and tolerability, see table 1. • **Immune- related reactions:** o Most common reactions are pneumonitis, colitis, nephritis, hepatitis, hyperthyroidism, hypothyroidism, hypophysitis, diabetes, diabetic ketoacidosis and immune-related rash. o Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, Opdualag® should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, treatment should be permanently discontinued. o Cases of myocarditis have been reported, if a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment. Once a diagnosis of myocarditis is established, treatment should be withheld or permanently discontinued: for grade 3 or 4 myocarditis Opdualag® must be

	permanently discontinued, for grade 2 myocarditis treatment should be withheld upon improvement treatment may be restarted. ○ Treatment must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction. ○ If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month. Treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy. ○ See SPC and guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/ • **Haemophagocytic lymphohistiocytosis** (HLH) has been observed with nivolumab in combination with relatlimab. Caution should be taken when nivolumab is administered in combination with relatlimab. If HLH is confirmed, administration should be discontinued and treatment for HLH initiated. • Treatment with nivolumab in combination with relatlimab may increase the risk of severe graft-versus-host disease (GVHD) and death in patients who have had prior allogeneic Haematopoietic Stem Cell Transplantation (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. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ No interaction studies have been conducted. ○ The use of systemic corticosteroids and other immunosuppressants at baseline, before starting treatment, should be avoided, however, systemic corticosteroids and other immunosuppressants can be used after starting treatment to treat immune-related adverse reactions. • **Driving:** Opdualag® (nivolumab/relatlimab) can potentially cause fatigue in some patients and therefore use caution when driving or using machines. • The patient should be provided with the Opdualag® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment). • Patients must be advised to contact the oncology team or the 24 hour hot-line immediately they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment. • Patients should be monitored (for at least up to 5 months after the last dose) for immune related adverse reactions as these can occur any time during or after stopping treatment.
References	SPC accessed online 10.01.2024 CDF list V1.293 accessed online 21.02.2024 Blueteq form V1.0 accessed online 21.02.2024

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Recommended treatment modifications for Opdualag

Immune-related adverse reaction	**Severity**	**Treatment modification**
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue treatment
Immune-related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increases to more than 3 and up to 5 times upper limit of normal (ULN) or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	AST or ALT increases to more than 5 times ULN regardless of baseline. or 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	Permanently discontinue treatment
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue treatment
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue treatment
Immune-related skin adverse reactions	Grade 3 rash	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s)

	Grade 4 rash Confirmed SJS/TEN	Permanently discontinue treatment (see section 4.4)
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[b]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Other immune-related adverse reactions	Grade 3 (first occurrence)	Withhold dose(s)
	Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day	Permanently discontinue treatment

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5).

[b] The safety of re-initiating Opdualag in patients previously experiencing immune-related myocarditis is not known.

Repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	OPDUALAG® (nivolumab /relatlimab)	**480mg/160mg**	IV	30 minutes	Can be given undiluted or diluted. If diluted, give in 100ml Sodium Chloride 0.9% via in-line low- protein binding 0.2 micrometre filter. The diluted solution should have a final concentration ranging from 3mg/ml-12mg/ml of nivolumab and 1mg/ml-4mg/ml of relatlimab. * **Flush the line with sodium chloride 0.9% for injection at the end of the infusion**
	* the total volume of infusion must not exceed 160ml. For patients weighing less than 40 kg, the total volume of infusion should not exceed 4ml per kilogram of patient weight.				
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	TDS PRN Do not take for more than 5 days continuously. Dispense on cycle 1 only.	