Chemotherapy Protocol

SKIN CANCER

Nivolumab in combination with Relatlimab (Opdualag)

Regimen

- Skin – Nivolumab in in combination with Relatlimab (Opdualag)

Indication

The treatment of unresectable or metastatic melanoma in patients aged 12 years or more where the following criteria are met:

- the patient has unresectable stage III or stage IV histologically confirmed melanoma
- the prescribing clinician is fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to checkpoint inhibitor treatments including pneumonitis, colitis, nephritis, endocrinopathies, hepatitis, myocarditis and skin toxicities.
- the patient is aged 12 years or older.
- the patient has not received previous treatment for this indication of unresectable or metastatic melanoma with any of the following: anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibodies.
- the patient is completely treatment naïve for systemic therapy for melanoma or has only received specifically allowed prior systemic therapy (allowed therapies include: prior adjuvant therapy with adjuvant nivolumab or pembrolizumab, prior immune checkpoint inhibitors for the advanced disease indication only when given as part of a clinical trial either as monotherapy or in combination with ipilimumab, BRAF/MEK inhibitor targeted therapies when given for the adjuvant indication or BRAF/MEK inhibitor targeted therapies when given as 1st line treatment for the advanced disease indication.
- the patient is of ECOG performance status (PS) 0 or 1 or if aged 12-17 years is of Lansky performance score of 80% or more.
- the patient has no symptomatic brain metastases or leptomeningeal metastases currently requiring steroids for symptom control.

Toxicity

Drug	Adverse Effect
Nivolumab in combination with Relatlimab (Opdualag)	Anaemia, lymphopaenia, neutropaenia, leucopaenia, urinary tract infection, hypothyroidism, decreased appetite, headache, dyspnoea, cough, diarrhoea, vomiting, nausea, abdominal pain, constipation, rash, vitiligo, pruritus, muscoskeletal pain, arthralgia, fatigue, pyrexia, increased transaminases, increased creatinine, electrolyte disturbances

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- FBC, LFTs and U&Es prior to day of each cycle
- Thyroid function tests prior to starting treatment and then every 6 weeks or when clinically indicated.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.

Please discuss all dose delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

Proceed with treatment on Day 1 if:

Criteria	Eligible Level
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L

If this criteria is not met, please discuss with an appropriate clinician.

Hepatic Impairment

No dose adjustment is required in patients with pre-existing mild or moderate hepatic impairment. Data from patients with severe pre-existing hepatic impairment are too limited to draw conclusions on this population.

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, Nivolumab in in combination with Relatlimab (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, Nivolumab in in combination with Relatlimab (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 Nivolumab in in combination with Relatlimab (Opdualag) must be permanently discontinued.

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, Nivolumab in in combination with Relatlimab (Opdualag) must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Renal Impairment

No dose adjustment is required in patients with pre-existing mild or moderate renal impairment. Data from patients with pre-existing severe renal impairment are too limited to draw conclusions on this population.

For Grade 2 or 3 serum creatinine elevation, Nivolumab in in combination with Relatlimab (Opdualag) should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, Nivolumab in in combination with Relatlimab (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 Nivolumab in in combination with Relatlimab (Opdualag**)** must be permanently discontinued.

For Grade 4 serum creatinine elevation, Nivolumab in in combination with Relatlimab (Opdualag) must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Other

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 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[a] 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
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete.
	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

Regimen

28 day cycle for 2 years

Drug	Dose	Days	Route
Nivolumab in combination with Relatlimab (Opdualag)	480mg/160mg	1	Intravenous in 100ml sodium chloride 0.9% over 30 minutes

Dose Information

- Nivolumab in combination with relatlimab is a flat dose. Doses are delayed, not reduced, for toxicity.

Administration Information

Extravasation

• Nivolumab in combination with relatlimab – neutral

Other

- Use of an infusion set and an in-line or add-on, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm) is recommended.
- Nivolumab in combination with Relatlimab (Opdualag) infusion is compatible with EVA, PVC and polyolefin containers, PVC infusion sets and in-line filters with polyethersulfone (PES), nylon, and polyvinylidene fluoride (PVDF) membranes with pore sizes of 0.2 µm to 1.2 µm.
- After administration of the Nivolumab in combination with Relatlimab (Opdualag) dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Do not co-administer other medicinal products through the same infusion line.
- Flush intravenous line at the end of infusion with either sodium chloride 0.9% or glucose 5% solution for injection

Additional Therapy

- No antiemetics required
- As required for the treatment of infusion related reactions:
    - Chlorphenamine 10mg intravenous
    - Hydrocortisone 100mg intravenous
    - Paracetamol 1000mg oral

Additional Information

- 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.

References

1. Bristol Myers Squibb pharmaceuticals limited. Opdualag summary of product characteristics. Available from: Opdualag 240 mg/80 mg concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Accessed 04/03/2024. Last updated 27/12/2023.
2. Blessing Opawole for The Clatterbridge Cancer Centre (2024) *Systemic Anti Cancer Therapy Protocol Nivolumab with Relatlimab Advanced Metastatic Melanoma*. Available at: https://www.clatterbridgecc.nhs.uk/application/files/8815/9593/3784/Nivolumab_Metastatic_Colorectal_Cancer_Protocol_V1.0.pdf (Accessed: 06 June 2024).
3. Bristol Myers Squibb (2024) *Opdulag- Dosing Guide*. Bristol Myers Squibb.

REGIMEN SUMMARY

Day One

1. Nivolumab 480mg in combination with Relatlimab 160mg intravenous infusion over 30 minutes in sodium chloride 0.9% 100ml
   Administration instructions:
   Use of an infusion set and an in-line or add-on, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm) is recommended

2. Chlorphenamine 10mg intravenous when required for the treatment of infusion related reactions

3. Hydrocortisone sodium succinate 100mg intravenous when required for the treatment of infusion related reactions

4. Paracetamol 1000mg oral when required for the relief of infusion related reactions

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	March 2024	None	Alexandra Pritchard Pharmacist	Dr Sarah Ellis Consultant

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.