Nivolumab-Relatlimab Protocol

Indication
Palliative treatment for metastatic melanoma

ICD-10 codes
Dependant on tumour site

Regimen details

Day	Drug	Dose	Route
1	Nivolumab-relatlimab	480mg/160mg	IV infusion

Cycle frequency
Given every 4 weeks

Number of cycles
Given until disease progression, unacceptable toxicity or 2 years since the date of first treatment with nivolumab-relatlimab

Administration
Nivolumab-relatlimab is given as an intravenous infusion in 100ml 0.9% sodium chloride over 30 minutes
Administer via a 0.2µm filter
Patients should be monitored for signs of infusion reactions.

Pre-medication
Nil

Emetogenicity
Low

Additional supportive medication
None required routinely

Extravasation
Neutral

Investigations – pre first cycle
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

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days

LFT inc AST	14 days
LDH (melanoma only)	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	14 days
Luteinizing hormone	14 days
Follicle stimulating hormone	14 days
Testosterone	14 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	48 hours
U+E (including creatinine)	48 hours
LFT inc AST	48 hours
LDH (melanoma only)	48 hours
Thyroid function	Every 6 weeks unless otherwise clinically indicated
Glucose	As clinically indicated
Calcium	As clinically indicated
Cortisol	At consultant discretion

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Serum Creatinine	≤1.5 X ULN
Bilirubin	Serum total bilirubin ≤1.5 X ULN or direct bilirubin ≤ULN for patient with total bilirubin level >1.5 ULN
ALT/AST	≤2.5 X ULN or ≤5 X ULN with liver metastases
Alkaline Phosphatase	< 5 x ULN

Dose modifications

Do not amend the dose of nivolumab-relatlimab

Consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns.

- **Haematological toxicity**

Discuss with the consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment/toxicity**

No dose adjustment is required in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population
Discuss with consultant if CrCl <30mL/min.

- **Hepatic impairment/toxicity**

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

- **Endocrine toxicity**

Dose delays are not routinely required for abnormalities in endocrine function. Please seek advice from patient's

treating clinican.

- **Other toxicities**

Patients must be advised to seek specialist advice if they experience side effects as these can worsen rapidly.

Immune reactions may occur during or after completion of treatment. Patients should be monitored for at least 5 months following cessation of treatment.

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

Treatment of toxicities

Immunotherapy toxicities should be aggressively managed as can cause permanent and life threatening complications.
Refer to UKONS and ESMO guidance for treatment of immune related toxicities.
Available at:

https://www.healthierlsc.co.uk/download_file/8276/10020

- **Toxicity monitoring and dose delays/discontinuation.**

All toxicities should be actively management and monitored. Any dose delays or discontinuation should be supervised by the treating clinician and made on an individual patient basis.

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[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 (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

Nivolumab-relatlimab should be permanently discontinued if:
- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose
- Any event occurs a second time at Grade ≥ 3 severity
- Grade 3 or 4 myocarditis
- Grade 3 or 4 encephalitis
- Grade 3 or 4 Guillain-Barré syndrome

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Pneumonitis
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Myelosuppression
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Diarrhoea
Nausea
Rash
Fatigue
Hyperglycaemia
Hypocalcaemia

- **Other side effects**

Arthralgia

Significant drug interactions – for full details consult product literature/ reference texts

Corticosteroids: use of systemic corticosteroids at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of nivolumab-relatlimab. However, systemic corticosteroids or other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions.

Additional comments

Women of child bearing potential should use effective contraception during treatment and for at least 4 months after the last dose.

References
Opdualag SPC Accessed 23/02/24 at https://www.medicines.org.uk/emc/product/15383/

THIS PROTOCOL HAS BEEN DIRECTED BY PROFESSOR BOARD, DESIGNATED LEAD CLINICIAN FOR MELANOMA

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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