

Nivolumab and Ipilimumab (advanced melanoma)

Indication

Advanced (unresectable or metastatic) melanoma

Regimen details

Drug	Fluid	Route	Time
Nivolumab 1mg/kg	50ml Sodium chloride 0.9%	IV	30 mins
Ipilimumab 3mg/kg	100ml Sodium chloride 0.9%	IV	30 mins

Repeat every 3 weeks for 4 cycles

Followed by single agent nivolumab:

Drug	Fluid	Route	Time
Nivolumab 480mg	100ml Sodium chloride 0.9%	IV	60 mins
Or			
Nivolumab 240mg	50ml sodium chloride 0.9%	IV	30 mins

(1st dose of single agent nivolumab should be given 6 weeks after the last dose of combination treatment)

Repeat every 4 weeks as long as clinical benefit is observed or until treatment is no longer tolerated by the patient

Cycle frequency

Combination treatment: every 21 days

Single agent nivolumab: every 14 or 28 days

Number of cycles

Combination treatment given for 4 cycles

Single agent nivolumab given until disease progression or unacceptable toxicity

Administration

Combination treatment: nivolumab should be given first, followed by ipilimumab.

Nivolumab may be administered without dilution as a 10mg/mL solution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-10mg/mL over 60 minutes. Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

Ipilimumab may be administered without dilution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-4mg/mL over 90 minutes. Ipilimumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

Monotherapy: Nivolumab may be administered without dilution as a 10mg/mL solution or in sodium chloride 0.9% or glucose 5% at a concentration between 1-10mg/mL over 30 minutes (240mg dose) or 60 minutes (480mg dose).

Nivolumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 1.2µm).

Pre-medication

N/A

Emetogenicity

Low

Additional supportive medication

None routinely required

Extravasation

Neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
LDH	14 days
Bone profile	14 days
Glucose	14 days
Cortisol	14 days
LH/FSH	14 days
Testosterone	14 days
HbA1c	Baseline
TFTs	Baseline
Creatine kinase	Baseline
Hepatitis screen	Baseline
Magnesium	Baseline
Trop T	Baseline
proBNP	Baseline
Quantiferon Gold	Baseline
ECG	Baseline

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), bone profile, random glucose, LDH

TFTs (including T4 and TSH) every 4-6 weeks

Review in clinic prior to first 4 cycles then on at least alternate cycles

If adrenal insufficiency suspected check 9am cortisol, LH, FSH, testosterone, ACTH

Repeat Troponin/proBNP/CK if cardiac toxicity suspected

Repeat CRP/ESR if inflammatory condition eg PMR suspected

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	$\geq 1.0 \times 10^9/\text{L}$
Platelet count	$\geq 75 \times 10^9/\text{L}$
Creatinine clearance	$\geq 30 \text{ mL/min}$
Creatinine	$< 2 \times \text{ULN}$
Bilirubin	$\leq 1.5 \times \text{ULN}$
AST/ALT	$< 2.5 \times \text{ULN}$ if no liver mets, $< 5 \times \text{ULN}$ if liver mets

Dose modifications

Dose reductions are not permitted. Doses should be delayed until an adverse reaction resolves to $\leq$ grade 1.

For management of immune-related adverse reactions, see network guidelines:

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

https://www.healthierlsc.co.uk/download_file/1291/10020

Adverse effects –

for full details consult product literature/ reference texts

Fatigue

Rash

Immune-related adverse reactions

Infusion reactions

Significant drug interactions

– for full details consult product literature/ reference texts

Anticoagulants: increased risk of haemorrhage – avoid or closely monitor

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

Additional comments

References

National Institute for Health and Clinical Excellence TA400. Accessed 29/1/24 via

<https://www.nice.org.uk/guidance/ta400>

SPC for Yervoy. Accessed 29/1/24 via <https://www.medicines.org.uk/emc/product/4683>

SPC for Opdivo. Accessed 29/1/24 via <https://www.medicines.org.uk/emc/product/6888/smpc>

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

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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