# 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 | 30 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 30 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.

## 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 | ≥ 1.0 x $10^9$/L |
| Platelet count | ≥ 75 x $10^9$/L |
| Creatinine clearance | ≥ 30 mL/min |
| Creatinine | <2x ULN |
| Bilirubin | ≤ 1.5 x ULN |
| AST/ALT | < 2.5 x ULN if no liver mets, <5x ULN if liver mets |

## Dose modifications

Dose reductions are not permitted. Doses should be delayed until an adverse reaction resolves to ≤ 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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