# Avelumab

## Indication

Treatment of metastatic Merkel cell carcinoma in adults, for patients who have had 1 or more lines of chemotherapy for metastatic disease.

Recommended for use within the Cancer Drugs Fund as an option for treating metastatic Merkel cell carcinoma in adults, only if they have not had chemotherapy for metastatic disease.

(NICE TA517)

## ICD-10 codes

Codes with a pre fix C43

## Regimen details

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 | Avelumab | 10mg/kg | IV infusion |

## Cycle frequency

14 days

## Number of cycles

Continued until unacceptable toxicity or disease progression.

## Administration

Avelumab is administered in 250mL sodium chloride 0.9% over 60 minutes. It should be given via a sterile, non pyrogenic, low protein binding 0.2micron filter.

Patients should be monitored for infusion related reactions including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. For Grade 1 reactions, decrease the infusion rate to 50% and closely monitor. For Grade 2 infusion-related reactions, the infusion should be temporary discontinued until Grade 1 or resolved, then restart at a 50% slower infusion rate. If Grade 1-2 reactions, subsequent infusions may be given with premedication as below. For Grade 3 or Grade 4 infusion-related reactions, the infusion should be stopped and avelumab should be permanently discontinued.

## Pre-medication

Patients should receive an antihistamine (e.g chlorphenamine 10mg IV) and paracetamol 500mg-1g PO prior to the first 4 infusions. If these are completed without infusion related reactions, premedication for subsequent doses should be given at the consultants discretion.

## Emetogenicity

This regimen has low emetogenic potential

## Additional supportive medication

Loperamide if required.

## Extravasation

Avelumab is neutral (Group 1)

## Investigations – pre first cycle

| **Investigation** | **Validity period** (or as per local policy) |
|---|---|
| FBC | 7 days |
| U+E (including creatinine) | 7 days |
| LFT | 7 days |
| Thyroid function | 7 days |
| Calcium | 7 days |
| Glucose | 7 days |
| Cortisol | 7 days |

## Investigations – pre subsequent cycles

| **Investigation** | **Validity period** (or as per local policy) |
|---|---|
| FBC | 72 hours |
| U+E (including creatinine) | 72 hours |
| LFT | 72 hours |
| Calcium | As clinically indicated |
| Thyroid function* | 72 hours |
| Glucose* | 72 hours |
| Cortisol* | 72 hours |

* every cycle for the first 24 weeks, then every other cycle.

## Standard limits for administration to go ahead

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

| **Investigation** | **Limit** |
|---|---|
| Haemoglobin | > 90 g/L |
| Neutrophils | ≥ 1.0 x $10^9$/L |
| Platelets | ≥ 75 x $10^9$/L |
| Creatinine Clearance (CrCl) | ≥ 30mL/min |
| Bilirubin | ≤ 1.5 x ULN |
| ALT/AST | < 1.5 ULN |
| Alkaline Phosphatase | < 5 x ULN |

## Dose modifications

Dose reductions or escalations are not recommended. Doses should be delayed until an adverse reaction resolves to ≤ grade 1.

## Toxicity

Immune related toxicities may affect any organ system and should be considered for any new symptoms. Grade 1 toxicities should be managed symptomatically with close monitoring. Specific management guidelines for immune-related adverse reactions are described in full in the summary of product characteristics

- **Haematological toxicity**

Discuss with consultant if:

| | |
|---|---|
| Haemoglobin | ≤ 90 g/L |
| Neutrophils | < 1.0 x $10^9$/L |
| Platelets | < 75 x $10^9$/L |

- **Renal impairment**

No modifications are required for patients with mild or moderate renal impairment. There is insufficient data regarding administration in severe renal impairment.

Note: worsening renal failure can be a sign of toxicity and so investigation of the cause of worsening renal impairment should be considered before go ahead.

- **Hepatic impairment**

No modifications are required for patients with mild hepatic impairment. There is insufficient data regarding administration in moderate-severe hepatic impairment.

Note: worsening hepatic function can be a sign of toxicity and so investigation of the cause of hepatic impairment should be considered before go ahead.

- **Other toxicities**

**Immune-related adverse reactions**

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, avelumab should be withheld and corticosteroids administered. If corticosteroids are used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. In patients, whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants may be considered.

**Immune-related pneumonitis**

Patients should be monitored for signs and symptoms of immune-related pneumonitis and causes other than immune-related pneumonitis should be ruled out. Suspected pneumonitis should be confirmed with radiographic imaging eg high resolution CT. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1 to 2 mg/kg/day prednisolone or equivalent, followed by a corticosteroid taper). Avelumab should be withheld for Grade 2 immune-related pneumonitis until resolution, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 immune-related pneumonitis.

**Immune-related hepatitis**

Patients should be monitored for changes in liver function and symptoms of immune-related hepatitis and causes other than immune-related hepatitis should be ruled out. Corticosteroids should be administered for Grade ≥ 2 events (initial dose 1 to 2 mg/kg/day prednisolone or equivalent, followed by a corticosteroid taper). Avelumab should be withheld for Grade 2 immune-related hepatitis until resolution and permanently discontinued for Grade 3 or Grade 4 immune-related hepatitis.

**Immune-related colitis**

Patients should be monitored for signs and symptoms of immune-related colitis and causes other than immune-related colitis should be ruled out. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1 to 2 mg/kg/day prednisolone or equivalent followed by a corticosteroid taper). Avelumab should be withheld for Grade 2 or Grade 3 immune-related colitis until resolution, and permanently discontinued for Grade 4 or recurrent Grade 3 immune-related colitis.

**Immune-related endocrinopathies**

Immune-related thyroid disorders, immune-related adrenal insufficiency, and Type 1 diabetes mellitus have been reported in patients receiving avelumab. Patients should be monitored for clinical signs and symptoms of endocrinopathies. Avelumab should be withheld for Grade 3 or Grade 4 endocrinopathies until resolution.

**Thyroid disorders (hypothyroidism/hyperthyroidism)**
Thyroid disorders can occur at any time during treatment. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Hypothyroidism should be managed with replacement therapy and hyperthyroidism with anti-thyroid medicinal product, as needed. Avelumab should be withheld for Grade 3 or Grade 4 thyroid disorders.

**Adrenal insufficiency**
Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment. Corticosteroids should be administered (1 to 2 mg/kg/day prednisolone intravenously or oral equivalent) for Grade ≥ 3 adrenal insufficiency followed by a taper until a dose of less than or equal to 10 mg/day has been reached. Avelumab should be withheld for Grade 3 or Grade 4 symptomatic adrenal insufficiency.

**Type 1 diabetes mellitus**
Avelumab can cause Type 1 diabetes mellitus, including diabetic ketoacidosis. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Initiate treatment with insulin for Type 1 diabetes mellitus. Avelumab should be withheld and anti-hyperglycaemics in patients with Grade ≥ 3 hyperglycaemia should be administered. Treatment with avelumab should be resumed when metabolic control is achieved on insulin replacement therapy.

**Immune-related nephritis and renal dysfunction**
Avelumab can cause immune-related nephritis. Patients should be monitored for elevated serum creatinine prior to and during treatment. Corticosteroids (initial dose of 1 to 2 mg/kg/day prednisolone or equivalent followed by a corticosteroid taper) should be administered for Grade ≥ 2 nephritis. Avelumab should be withheld for Grade 2 or Grade 3 nephritis until resolution to ≤ Grade 1 and permanently discontinued for Grade 4 nephritis.

**Other immune-related adverse reactions**
Other clinically important immune-related adverse reactions were reported in less than 1% of patients: myocarditis including fatal cases, myositis, hypopituitarism, uveitis, and Guillain-Barré syndrome.

For suspected immune-related adverse reactions, ensure adequate evaluation to confirm aetiology or to rule out other causes. Based on the severity of the adverse reaction, avelumab should be withheld and corticosteroids be administered. Avelumab should be resumed when the immune-related adverse reaction returns to Grade 1 or less following corticosteroid taper. Avelumab should be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for Grade 4 immune-related adverse reaction.

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

- **Serious side effects**

Myocarditis
Pneumonitis
Hepatitis
Nephritis
Colitis
Infusion related reactions

- **Frequently occurring side effects**

Anaemia
Hypothyroidism
Reduced appetite
Headache, dizziness
Hypertension, hypotension
Cough, dyspnoea
Nausea, vomiting
Constipation
Arthralgia

- **Other side effects**

Uveitis
Rash

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

No interaction studies have been conducted.

Avelumab is primarily metabolised through catabolic pathways, therefore, it is not expected that avelumab will have pharmacokinetic drug-drug interactions with other medicinal products.

## Additional comments

## References


- National Institute for Health and Care Excellence. NICE TA517. Accessed 19 April 2018 via www.nice.org.uk
- Summary of Product Characteristics Avelumab (Merck) accessed 19 April 2018 via www.medicines.org.uk
- Patel MR, et al. A Phase II, Open-Label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab in Subjects With Merkel Cell Carcinoma. Lancet Oncology 2016 Oct;17(10):1374-1385.



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