# Pembrolizumab (RCC)

## Indication

Adjuvant treatment of renal cell carcinoma at increased risk of recurrence after nephrectomy, with or without metastatic lesion resection in patients that meet the following criteria:

- Partial nephron-protective or radical nephrectomy with all surgical excision margins being negative i.e. R0 resection
- If M1 disease this must have been completely resected (i.e. R0 resection) at the time of nephrectomy or within 1 year of nephrectomy
- No more than 12 weeks has elapsed since the date of nephrectomy or metastasectomy
- be at increased risk of recurrence defined as one of the following categories:
    - Intermediate-high risk: pT2 N0 M0 with either Fuhrman grade 4 or sarcomatoid histology or PT3 N0 M0 with any histological grade
    - High risk: pT4 N0 M0 or any pT N1 M0 with any histological grade
    - M1 disease with no evidence of disease after complete resection of both loco-regional disease and all metastatic lesions

(NICE TA830)

## ICD-10 codes

Codes prefixed with C64.

## Regimen details

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 | Pembrolizumab | 400mg every 6 weeks | IV infusion |

## Cycle frequency

42 days.

N.B. NHSE expects the 6 weekly schedule to be used unless there are clear clinical reasons for preferring Pembrolizumab 200mg three weekly.

## Number of cycles

Until unacceptable toxicity, disease recurrence or to a maximum of 1 year (i.e. 9 x 6 weekly cycles).

## Administration

Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes.

Pembrolizumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0µm).

After the infusion the line should be flushed with 30mL sodium chloride 0.9%.

Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) and 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

Nil

## Emetogenicity
This regimen has low emetogenic potential

## Additional supportive medication
Loperamide should be supplied to be used if required.
Antiemetics as per local policy, if required.

## Extravasation
Neutral (Group 1)

## Investigations – pre first cycle

| **Investigation** | **Validity period** (or as per local policy) |
|---|---|
| FBC | 14 days |
| U+E (including creatinine) | 14 days |
| LFT | 14 days |
| Thyroid function | 14 days |
| Glucose | 14 days |
| Calcium | 14 days |
| Cortisol | At consultant discretion |

## Investigations – pre subsequent cycles

| **Investigation** | **Validity period** (or as per local policy) |
|---|---|
| FBC | 7 days |
| U+E (including creatinine) | 7 days |
| LFT | 7 days |
| Thyroid function | 6 weekly |
| 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 |
| Bilirubin | ≤1.5 x ULN |
| ALT/AST | <2.5 x ULN |
| Alkaline Phosphatase | <5 x ULN |

## Dose modifications

- ### Haematological toxicity

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

- **Renal impairment**

The safety and efficacy of pembrolizumab has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment.
Discuss with consultant if CrCl <30mL/min.

- **Hepatic impairment**

The safety and efficacy of pembrolizumab has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

- **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.

| Toxicity | Definition | Action |
|---|---|---|
| Colitis | Grade 1 | Continue and closely monitor |
| | Grade 2-3 | Withhold until symptoms resolve to ≤ grade 1 |
| | Grade 4 or recurrent grade 3 | Permanently discontinue pembrolizumab |
| Pneumonitis | Grade 1 | Continue and closely monitor |
| | Grade 2 | Withhold until symptoms resolve to ≤ grade 1 |
| | Grade 3-4 or recurrent grade 2 | Permanently discontinue pembrolizumab |
| Nephritis | Grade 2 (creatinine 1.5-3 x ULN) | Withhold until symptoms resolve to ≤ grade 1 |
| | Grade 3 (creatinine > 3 x ULN) | Permanently discontinue pembrolizumab |
| Endocrine | Symptomatic hypophysitis | Withhold until symptoms resolve to ≤ grade 1 |
| | Type 1 diabetes with grade > 3 hyperglycaemia (glucose > 13.9 mmol/L) or ketoacidosis | Withhold until ≤ grade 2<br>May consider recommencing after corticosteroid taper or discontinue. |
| | Hyperthyroidism ≥ grade 3 | Withhold until ≤ grade 2<br>May consider recommencing after corticosteroid taper or discontinue. |
| | Hypothyroidism | Continue and manage with replacement therapy |
| Hepatitis | AST/ALT 3-5 x ULN or<br>Bilirubin > 1.5-3 x ULN | Withhold until resolves to ≤ grade 1 |
| | AST/ALT > 5 x ULN or<br>Bilirubin > 3 x ULN | Permanently discontinue pembrolizumab |
| | If liver metastasis with baseline AST/ALT 3-5 x ULN:<br>- If AST/ALT increases ≥ 50% for ≥ 1 week | Permanently discontinue pembrolizumab |
| Infusion-related reactions | Grade 3-4 | Permanently discontinue pembrolizumab |
| Skin reactions | Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) | Withhold until resolves to ≤ grade 1 |
| | Grade 4 or confirmed SJS or TEN | Permanently discontinue |
| Other immune-related adverse reactions | Grade 3 or 4 myocarditis<br>Grade 3 or 4 encephalitis<br>Grade 3 or 4 Guillain-Barre syndrome | Permanently discontinue |

Pembrolizumab 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 prednisolone 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

## 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, pruritus
Fatigue
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Arthralgia

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

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

## Additional comments

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

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## References


- National Institute for Health and Clinical Excellence [TA830] accessed 20 October 2022 via www.nice.org.uk
- Summary of Product Characteristics Pembrolizumab - Keytruda® (MSD) accessed 05 October 2022 via www.medicines.org.uk
- Choueiri, TK. et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med 2021; 385:683-694.

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