

DRUG ADMINISTRATION SCHEDULE

Day	Drug	Dose	Route	Diluent	Rate
Day 1	Pembrolizumab	200mg	IV Infusion	100mL 0.9% Sodium Chloride Or 5% Glucose	Over 30 minutes

CYCLE LENGTH AND NUMBER OF DAYS

Administered every 21 days (3 weeks) for up to 2 years of uninterrupted treatment with no documented disease progression or unacceptable toxicity.

APPROVED INDICATIONS

Pembrolizumab is recommended for use within the Cancer Drugs Fund as an option for

- The treatment of first line treatment of locally advanced or metastatic urothelial cancer in patients who are *ineligible for cisplatin-based chemotherapy* defined as;
 - impaired renal function (EDTA-assessed glomerular filtration rate >30 and <60 mls/min)
 - hearing loss of 25dB or more as assessed by formal audiometry
 - NCI CTCAE grade 2 or worse peripheral neuropathy
 - ECOG PS 2
 - **and**
 - The patient has EITHER not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy for localised urothelial cancer OR, if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy for localised urothelial cancer, has relapsed more than 12 months since completing the platinum-based chemotherapy

Note: Post-marketing data has shown decreased survival for first-line patients with low-levels of PD-L1. It is now a requirement that first-line patients have their tumours tested for PD-L1 and treatment with pembrolizumab only given where they have a PD-L1 with a combined positive score (CPS) ≥ 10

- The treatment of locally advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy where:
 - The patient has either: not received previous adjuvant chemotherapy, neoadjuvant chemotherapy or chemo-radiotherapy, or if previously treated with platinum-based chemotherapy whether as adjuvant chemotherapy or as neoadjuvant chemotherapy or with chemo-radiotherapy, has relapsed ≤ 12 months since completing the platinum-based chemotherapy

EXCLUSION CRITERIA

- PS ≥ 3
- symptomatically active brain metastases or leptomeningeal metastases

CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients e.g. L-histidine, polysorbate 80. Patients with hepatitis B or hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody

PREMEDICATION

None routinely recommended.

Consider premedication with antipyretic (paracetamol) and antihistamine (chlorphenamine) in patients with mild or moderate infusion reactions (close monitoring required.)

RECOMMENDED TAKE HOME MEDICATION

Loperamide 4mg after first loose stool then 2mg after each loose stool thereafter up to a maximum of 16mg in 24 hours.

INVESTIGATIONS / MONITORING REQUIRED

- Pre-treatment: Assessment of renal function, FBC, Cardiac history, FBC, U&E's, glucose, LFT's and tumour markers as appropriate.
- Prior to each cycle: FBC, U&E's, glucose, and LFT's.

ASSESSMENT OF RESPONSE

Metastatic: Tumour size and patient symptomatic response.

Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. SPC recommends continuing treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

REVIEW BY CLINICIAN

To be reviewed either by a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW

Each cycle as applicable according to local protocols.

ADMINISTRATION NOTES

CAUTION

Pembrolizumab administration can result in severe and fatal immune-mediated adverse reactions (irAEs). irAEs may involve gastrointestinal, endocrine, skin, liver, nervous, lung and other organ systems. Unless an alternate aetiology has been identified, signs and symptoms suggestive of irAEs must be considered inflammatory and Immunotherapy related. Early diagnosis and appropriate management are essential to minimise life threatening complications.

Systemic high dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe irAEs

- Risk of infusion related reactions
 - For severe infusion reactions, stop infusion and permanently discontinue pembrolizumab. However, patients with mild or moderate infusion reactions may continue to receive pembrolizumab with close monitoring (premedication with antipyretic and antihistamine may be considered.)
- Administer using a low-protein binding 0.2-5um in-line or add-on filter.
- Consider premedication with antipyretic and antihistamine in patients with mild or moderate infusion reactions (close monitoring required.)
- The use of systemic corticosteroids or immunosuppressants 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.

- All patients must be provided with the Patient Alert Card with each prescription as per the marketing authorisation.
- Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed but solely to allow immune toxicities to settle

EXTRAVASATION See NCA/Local Policy

TOXICITIES (Non-immune related)

- Diarrhoea
- Fatigue
- Rash
- Pruritus
- Nausea & vomiting
- Arthralgia
- Anaemia
- Hyper/hypothyroidism

The majority of adverse reactions reported were of Grade 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions (see non-haematological toxicity section below.)

DOSE MODIFICATION / TREATMENT DELAYS

Haematological Toxicity

Neutrophils (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose
≥ 1.5	And	≥ 100	100% dose
≤ 0.5	Or	≤ 25	Discuss with the Consultant. Dose delays are not recommended, consider discontinuation.

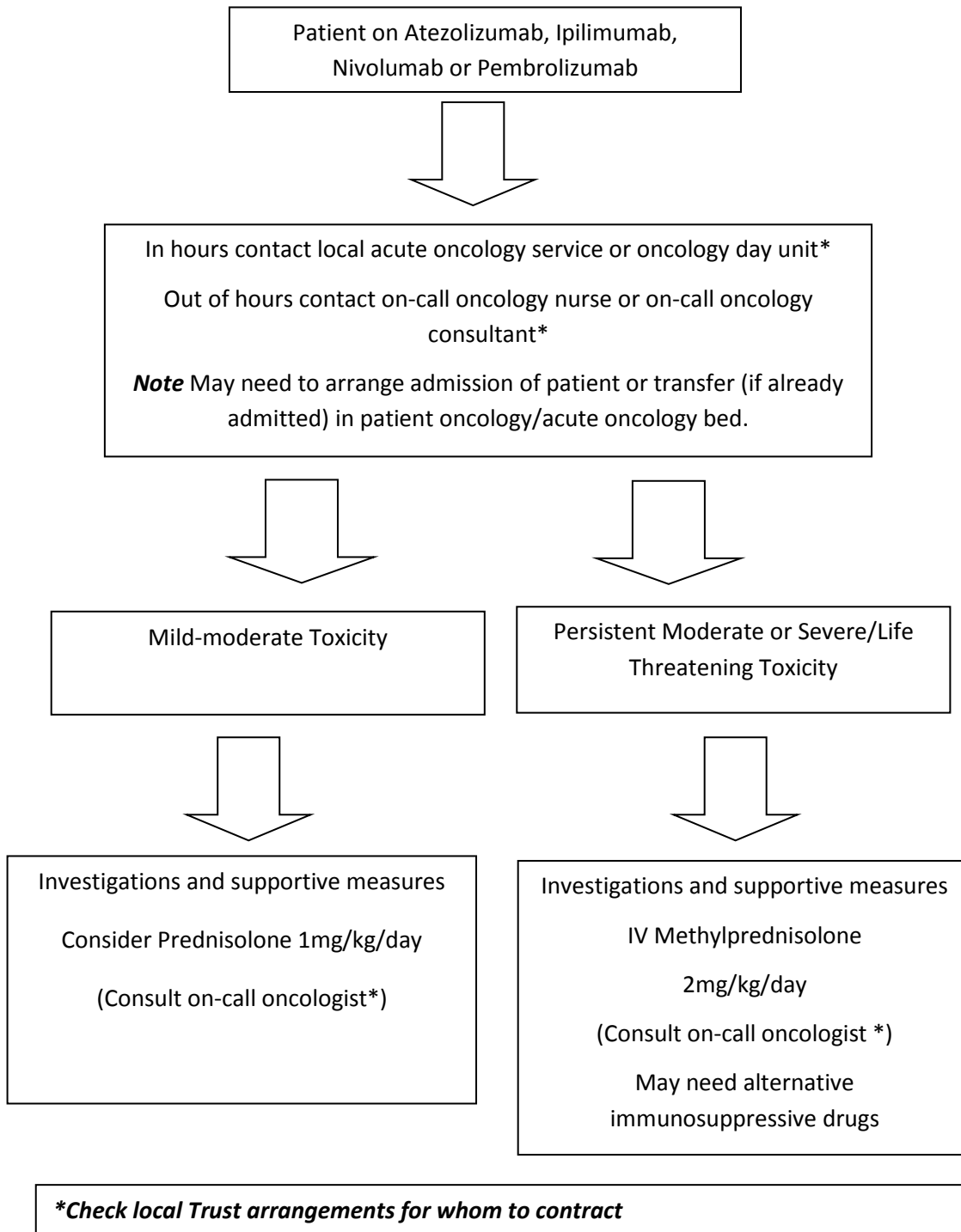
Non-Haematological Toxicity

Immune Related Reactions

For suspected immune related adverse reactions, ensure adequate evaluation to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction:

- Withhold pembrolizumab and administer corticosteroids. Upon improvement to Grade ≤1, corticosteroid taper should be initiated and continued over at least 1 month.
- Consider restarting pembrolizumab within 12 weeks after last dose if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day.
- Pembrolizumab must be permanently discontinued for any Grade 3 immune related adverse reaction that reoccurs a second time, and for any Grade 4 immune related adverse reaction (except for endocrinopathies that are controlled with replacement hormones.)
- Based on limited data from clinical studies in patients whose immune related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

MANAGEMENT OF TOXICITY FLOW DIAGRAM (ADAPTED FROM NCCC POLICY DATED AUG 2015)



Immune Related Pneumonitis

Monitor patients for signs and symptoms of pneumonitis. Confirm suspected pneumonitis with radiographic imaging, and exclude other causes:

- Administer corticosteroids for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper.)
- Withhold pembrolizumab for Grade 2 pneumonitis, and permanently discontinue for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis.

Immune Related Colitis

Monitor patients for signs and symptoms of colitis, and exclude other causes:

- Administer corticosteroids for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisolone followed by a taper.)
- Withhold pembrolizumab for Grade 2 or Grade 3 colitis, and permanently discontinue for Grade 4 colitis.
- In severe cases consider referral to an appropriate medical specialist, i.e. consultant gastroenterologist who will see if patient could benefit from infliximab.

Immune Related Endocrinopathies

Severe endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis and thyroid disorders have been observed with pembrolizumab treatment. Long term hormone replacement therapy may be necessary in cases of immune related endocrinopathies.

Hyperglycaemia

Monitor patients for hyperglycaemia or other signs and symptoms of diabetes (including diabetic ketoacidosis):

- Administer insulin for type 1 diabetes.
- Withhold pembrolizumab in cases of Grade 3 hyperglycaemia until metabolic control is achieved.

Hypophysitis

Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and exclude other causes:

- Administer corticosteroids to treat secondary adrenal insufficiency and any other hormone replacement as clinically indicated.
- Withhold pembrolizumab for symptomatic hypophysitis until event is controlled with hormone replacement.
- Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed.
- Monitor pituitary function and hormone levels to ensure appropriate hormone replacement.

Thyroid disorders

Including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment. Patients must therefore be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders:

- Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.
- Hyperthyroidism may also be managed symptomatically.

- Withhold pembrolizumab for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism.
- For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of pembrolizumab may be considered, after corticosteroid taper, if needed.
- Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

Renal Impairment

No adjustment of the starting dose is needed in patients with mild or moderate renal impairment, but not recommended in patients with severe renal impairment or end stage renal disease.

Hepatic Impairment

No adjustment of the starting dose is needed in patients with mild hepatic impairment, but not recommended in patients with moderate or severe hepatic impairment (bilirubin $>1.5 \times$ ULN, ALT $3 \times$ ULN).

TREATMENT LOCATION

Cancer Centre and Cancer Units*

*Cancer units must have arrangements for monitoring and management of immune related toxicities and access to advices from oncologist experienced in use of immunotherapies.

REFERENCES

1. Summary of Product Characteristics: Pembrolizumab (KEYTRUDA®)
<https://www.medicines.org.uk/emc/medicine/30602> Accessed 29/12/16.
2. Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable. NICE technology appraisal guidance [TA522] Published 13/06/18. Available at: <https://www.nice.org.uk/guidance/ta522> Accessed: 8/8/18.
3. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. NICE technology appraisal guidance [TA519] Published 25/04/18. Available at: <https://www.nice.org.uk/guidance/ta366?unlid=77099842720165191533> Accessed: 01/09/16.
4. Plimack, E.R., Bellmunt, J., Gupta, S., Berger, R., Montgomery, R.B., Heath, K., Juco, J., Emancipator, K., Pathiraja, K., Lunceford, J.K. and Perini, R.F., 2015. Pembrolizumab (MK-3475) for advanced urothelial cancer: Updated results and biomarker analysis from KEYNOTE-012.

Document Control

Document Title:	PEMBROLIZUMAB (KEYTRUDA®) for Urothelial Cancer		
Document No:	CRP17 U023	Current Version:	1.0
Reviewer:	Chris Beck, Cancer Alliance Pharmacist	Date Approved:	04/09/2018
Approved by:	Steve Williamson, Consultant Pharmacist, Northern Cancer Alliance	Due for Review:	04/09/2021
Summary of Changes	1.0	First draft, adapted from lung protocol	