Atezolizumab

Indication
Locally advanced or metastatic urothelial cell cancer for patients who have not received previous chemotherapy where treatment with cisplatin based chemotherapy is unsuitable.

(NICE TA492 – within Cancer Drugs Fund as part of managed access agreement)

ICD-10 codes
Codes pre fixed with C67

Regimen details

Day	Drug	Dose	Route
1	Atezolizumab	1200mg	IV infusion

Cycle frequency
21 days

Number of cycles
Continued until disease progression or unacceptable toxicity.

Administration
Atezolizumab is administered in 250mL sodium chloride 0.9% over 60 minutes. If the initial infusion is well tolerated, subsequent infusions may be administered over 30 minutes.

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For grade 1-2 infusion related reactions, decrease the infusion rate and closely monitor or temporarily interrupt treatment. Premedication with paracetamol and chlorphenamine should be used for further doses and patient should be closely monitored. For grade 3-4 infusion related reactions discontinue treatment.

Pre-medication
Nil required unless infusion related reactions.

Emetogenicity
This regimen has low emetogenic potential.

Additional supportive medication
Nil routinely required.

Extravasation
Atezolizumab is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Thyroid function	14 days
Calcium	14 days
Glucose	14 days
Cortisol	14 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	96 hours
LFT	96 hours
Calcium	As clinically indicated
Thyroid function*	96 hours
Glucose*	96 hours
Cortisol*	96 hours

* every cycle for the first 12 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
Neutrophil count	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
White Cell Count	≥ 2.0 x 10^9/L
Creatinine Clearance (CrCl)	≥ 30mL/min
Bilirubin	< 1.5 x ULN
ALT/AST	< 2.5 x ULN

Dose modifications

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

- **Haematological toxicity**

Discuss with the consultant if:
WBC <2.0 x 10^9/L
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

No modifications required for mild to moderate renal impairment. There are no recommendations for patients with severe renal impairment.

- **Hepatic impairment**

No modifications required for mild hepatic impairment. Atezolizumab has not been studies in moderate or severe hepatic impairment.

- **Other toxicities**

For suspected immune related adverse events, atezolizumab should be withheld and corticosteroids administered. Once symptoms resolved to ≤ Grade 1 the corticosteroid dose should be tapered over 1 month.

Toxicity	Definition	Dose adjustment
Pneumonitis	Grade 2	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 3-4	Permanently discontinue
Hepatitis	Grade 2 Bilirubin 1.5-3 x ULN and/or AST/ALT 3-5 x ULN	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 3-4 Bilirubin > 3 x ULN and/or AST/ALT > 5 x ULN	Permanently discontinue
Colitis	Grade 2-3 diarrhoea or Symptomatic colitis	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 4 diarrhoea or colitis	Permanently discontinue
Hypo or hyperthyroidism	Symptomatic	Hypothyroidism Withhold treatment Treatment may resume once symptoms controlled with thyroid replacement and TSH levels reducing.
		Hyperthyroidism Withhold treatment Treatment may resume once symptoms controlled with anti-thyroid medication and thyroid function is improving.
Adrenal insufficiency	Symptomatic	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
Hypophysitis	Grade 2-3	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids ≤ 10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
	Grade 4	Permanently discontinue
Insulin dependent diabetes melitus	Grade 3-4 hyperglycamia	Withhold treatment Resume once metabolic control achieved with insulin therapy.
Rash	Grade 3	Withhold treatment Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 4	Permanently discontinue
Myasthenic syndrome/ myasthenia gravis/Guillain-Barre	Any grade	Permanently discontinue

Pancreatitis	Grade 2-3 (or Grade 3-4 increase in amylase or lipase)	Withhold treatment Resume once amylase and lipase levels ≤ Grade 1 (within 12 weeks) or where symptoms have resolved and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
	Grade 4 or recurrent pancreatitis	Permanently discontinue

Permanently discontinue treatment in patients with the following symptoms:

- Any grade 4 toxicity, except endocrinopathies that are controlled with replacement hormones.
- Any recurrent Grade 3 toxicity.
- Any treatment related toxicity that does not resolve to ≤ Grade 1 within 12 weeks after onset.
- If a corticosteroid dose ≥ 10mg/day prednisolone (or equivalent) is required for toxicity beyond 12 weeks after onset.

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

- **Serious side effects**

Immune reactions
Interstitial lung disease, pneumonitis
Pancreatitis
Hepatitis
Colitis
Neuropathies
Endocrinopathies

- **Frequently occurring side effects**

Thrombocytopenia
Hypothyroidism, hyperthyroidism
Hypotension
Dyspnoea
Nausea, vomiting
Diarrhoea
Rash
Pruritis
Arthralgia
Fatigue
Infusion related reactions

- **Other side effects**

Decreased appetite
Altered electrolytes
Raised transaminases
Guillain-Barre syndrome

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

No formal drug interaction studies have been carried out with atezolizumab.

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

Additional comments

The prescriber must discuss the risks of treatment with the patient and they will be issued with the Atezolizumab Patient Alert Card and advised to carry the card at all times.

References

- National Institute for Health and Clinical Excellence TA492. Accessed 24 January 2018 via www.nice.org.uk
- Summary of Product Characteristics Atezolizumab (Roche) accessed 24 January 2018 via www.medicines.org.uk
- Balar AV et al, Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017 Jan 7;389(10064):67-76.

Written/reviewed by: Dr M Sephton (Consultant Oncologist, RUH Bath NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology/Haematology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

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