Somerset, Wiltshire, Avon and Gloucestershire Cancer Alliance

Atezolizumab (Urothelial)

Indication

Treatment of locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy.
(NICE TA525)

Treatment of untreated locally advanced or metastatic urothelial carcinoma with PD-L1 expression of 5% or more and where cisplatin-based chemotherapy is unsuitable.
(NICE TA739)

ICD-10 codes

Codes pre fixed with C67

Regimen details

Intravenous

Day	Drug	Dose	Route
1	Atezolizumab	1200mg every 3 weeks *Or* 1680mg every 4 weeks	IV infusion

Subcutaneous

Day	Drug	Dose	Route
1	Atezolizumab	1875mg every 3 weeks	SC injection

Cycle frequency

Intravenous: 21 or 28 days (see above)
Subcutaneous: 21 days

Number of cycles

Untreated - continued until disease progression or unacceptable toxicity
Post-chemotherapy – continued until disease progression or unacceptable toxicity up to a maximum of 2 years.

Administration

Intravenous

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.

Subcutaneous

Remove from refrigerator and allow to reach room temperature prior to administration. Administer via subcutaneous injection into the thigh over approximately 7 minutes. Use of a SC infusion set (e.g. winged/butterfly) is recommended. DO NOT administer the remaining residual hold-up volume in the tubing to the patient. The injection site should be alternated between the right and left thigh only. New injections should be given at least 2.5cm from the old site and never into areas where the skin is red, bruised, tender or hard.

Pre-medication

Nil required unless infusion related reactions with IV preparation

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	7 days
U+E (including creatinine)	7 days
LFT	7 days
Calcium	As clinically indicated
Thyroid function*	7 days
Glucose*	7 days
Cortisol*	7 days

* 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
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:
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 due to limited data.

- **Hepatic impairment**

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

Toxicity	Definition	Dose adjustment
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 mellitus	Grade 3-4 hyperglycamia	Withhold treatment Resume once metabolic control achieved with insulin therapy.
Rash	Grade 3 or suspected Stevens-Johnson syndrome (SJS or toxic epidermal necrolysis (TEN)	Withhold treatment Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 4 or confirmed SJS/TEN	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
Myocarditis/Pericardial disorders	Grade 2 or above	Permanently discontinue
Nephritis	Grade 2 (creatinine 1.5 -3 x baseline or ULN)	Withhold treatment. Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 3 or 4 (creatinine > 3 x baseline or ULN)	Permanently discontinue
Other immune mediated adverse reactions	Grade 2 or 3	Withhold treatment Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 4 or recurrent Grade 3	Permanently discontinue

<u>Permanently discontinue</u> 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
Myocarditis
Nephritis

- **Frequently occurring side effects**

Thrombocytopenia
Hypothyroidism, hyperthyroidism
Hypotension
Dyspnoea
Nausea, vomiting
Diarrhoea
Rash
Pruritis
Arthralgia
Fatigue
Infusion related reactions (IV only)
Injection site reactions (SC only)

- **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 patient will be issued with the Atezolizumab Patient Alert Card and advised to carry the card at all times.

References

- National Institute for Health and Care Excellence TA525. Accessed 12 October 2023 via www.nice.org.uk
- National Institute for Health and Care Excellence TA739. Accessed 12 October 2023 via www.nice.org.uk
- Summary of Product Characteristics Atezolizumab concentrate for IV infusion (Roche) accessed 12 October 2023 via www.medicines.org.uk
- Summary of Product Characteristics Atezolizumab solution for injection (Roche) accessed 12 October 2023 via www.medicines.org.uk
- Powles, T. et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018; 391 (10122):748-757
- 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.
- Burotto, M et al. IMscin001 Part 2: a randomised Phase III, opne-label, multicentre study examining the pharmacokinetics, efficacy, immunogenicity and safety of atezolizumab subcutaneous versus intravenous administration in previously treated locally advanced or metastatic non-small-cell lung cancer and pharmacokinetics comparison with other approved indications. Annals of Oncology 2023; 34(8):693-702

Written/reviewed by: Dr Z Hudson (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

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