Chemotherapy Protocol

UROTHELIAL CANCER

Atezolizumab SC (1875mg – 21 days)

Regimen

- Urothelial cancer – Atezolizumab monotherapy (1st or 2nd line)

Indications

- First line treatment of locally advanced or metastatic urothelial cancer in patients who are ineligible for cisplatin-based chemotherapy and whose tumours have PD-L1 expression of >=5% chemotherapy, until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment, whichever is the sooner (ATE1).

- Second line treatment for locally advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy up to a maximum treatment duration of 2 years of uninterrupted treatment (i.e. a maximum of 35 administrations if given every 3 weeks (ATE3).

All indications require a Blueteq application, see individual forms (ATE1or ATE3) for specific eligibility criteria. Ensure patient meets Blueteq criteria before consenting patient for treatment.

Toxicity

Drug	Adverse Effect
Atezolizumab	Fatigue, rash, pruritis, pneumonitis, colitis, pancreatitis, diarrhoea, diabetes mellitus, adrenal insufficiency, thyroid disorders, nausea, electrolyte disturbances, hepatitis, myasthenic syndrome, Guillain Barre syndrome

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- FBC, LFTs, U&Es and cortisol prior to day one of each cycle

- Thyroid function tests prior to starting treatment and then every 6 weeks or when clinically indicated.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and some drug specific toxicities. Dose adjustments may be necessary for other toxicities as well.

In principle no dose reductions are recommended for atezolizumab. The preference is to delay the dose or discontinue treatment.

Please discuss all treatment delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Consider blood transfusion or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

There are no standard dose adjustments for haematological toxicity with atezolizumab treatment.

Hepatic Impairment

Drug	Bilirubin (µmol/L)		AST/ALT units	Dose
Atezolizumab	1.5-3xULN	OR	3-5xULN	Delay – see notes below
	Greater than 3xULN	OR	Greater than 5xULN	Discontinue – see notes below

For patients with pre-existing mild hepatic impairment no dose adjustment is recommended. Atezolizumab has not been studied in patients with moderate or severe hepatic impairment.

For NCI-CTC grade 2 hepatitis (ALT or AST between 3-5xULN or a bilirubin between 1.5-3xULN) that persists for between 5-7 days then withhold the atezolizumab and consider treatment with a corticosteroid. The corticosteroid may be tapered over at least one month if the LFTs improve. Treatment with atezolizumab may be resumed when the event improves to grade 1 or below within 12 weeks and the corticosteroid dose has been reduced to the equivalent of oral prednisolone 10mg per day or less.

For a grade 3 or above hepatitis (ALT or AST greater than 5xULN or bilirubin greater than 3xULN) permanently discontinue atezolizumab).

Renal Impairment

No dose adjustment is required in patients with pre-existing mild or moderate renal impairment, there is insufficient data to make recommendations for patients with severe renal impairment.

Other

Atezolizumab belongs to the immunotherapy class of cancer treatments. Autoimmune toxicities are most frequently noted and can be life threatening. If autoimmune toxicities occur, delaying treatment should be considered while investigations or treatments are organised. Some, but not all, toxicities mandate cessation of treatment. Please seek guidance from relevant site-specific specialist teams or oncologists / haematologists with experience of prescribing these agents. Clinicians should be aware that the current funding approval precludes further treatment after an interruption of 12 weeks or longer; this situation may change.

Refer to the latest version of the European Society of Medical Oncology guidelines; Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[(2)].

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. Most occur during treatment, however, onset months after the last dose has been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and atezolizumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Atezolizumab should be permanently discontinued for: any NCI-CTC grade 3 or 4 pneumonitis or hepatitis; any other life-threatening NCI-CTC grade 4 reaction (including colitis and renal impairment); any recurrence of a severe or NCI-CTC grade 3 reaction; any persistent NCI-CTC grade 2 or 3 treatment-related adverse reaction that does not recover to grade 1 or resolve within 12 weeks after the last dose.

Immune-related adverse reaction	Severity	Treatment modification
Pneumonitis	Grade 2 pneumonitis	Withhold until symptoms resolve and radiographic abnormalities improve. Consider treatment with oral prednisolone 1-2mg/kg/day or equivalent. Treatment may be resumed if the event improves to grade 0 or grade 1 within 12 weeks, and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day.
	Grade 3 or 4 pneumonitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.
Colitis	Grade 2 or 3 diarrhoea or symptomatic colitis	Withhold the atezolizumab initially. For a grade 2 diarrhoea or colitis, if the symptoms persist for more than 5 days or recur, start treatment with 1-2mg/kg/day oral prednisolone or equivalent. For a grade 3 diarrhoea or colitis treatment with intravenous corticosteroids should be started, this may be converted to oral treatment as symptoms improve. If the symptoms improve to grade 1 or less taper the corticosteroids over one month Treatment may be resumed if the event improves to grade 0 or grade 1 within 12 weeks, and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day
	Grade 4 diarrhoea or colitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (more than 2xULN) or grade 2 or 3 pancreatitis.	Withhold atezolizumab. Treatment with atezolizumab may be resumed if serum amylase and lipase levels improve to grade 0 or grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to 10mg or less oral prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.

Thyroid disorders	Symptomatic	Withhold atezolizumab *Hypothyroidism* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism* Treatment may be resumed when symptoms are controlled by cabimazole or equivalent and thyroid function is improving
Adrenal insufficiency	Symptomatic	Withhold atezolizumab Treatment may be resumed if the symptoms improve to grade 0 or grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10mg or less of oral prednisone per day and patient is stable on replacement therapy
Nephritis	Grade 2	Withhold atezolizumab Start treatment with prednisolone 1-2mg/kg/day or equivalent. Treatment with atezolizumab may be resumed if the symptoms improve to grade 0-1 within 12 weeks and corticosteroids have been reduced to ≤ 10mg prednisolone or equivalent per day.
	Grade 3 or 4	Permanently discontinue atezolizumab
Hypophysitis	Grade 2 or 3	Withhold atezolizumab Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day and patient is stable on replacement therapy.
	Grade 4	Permanently discontinue atezolizumab.

Type I diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose more than 250-500mg/dL or 13.9 mmol/L	Withhold atezolizumab Treatment may be resumed if metabolic control is achieved on insulin replacement therapy
Myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome, meningoencephalitis and facial paresis	Facial paresis Grade 1 or 2	Withhold atezolizumab Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding atezolizumab, permanently discontinue.
	All Grades Myasthenic syndrome/myasthenia gravis, Guillain Barré syndrome and Meningoencephalitis or Facial paresis Grade 3 or 4	Permanently discontinue atezolizumab
Myositis	Grade 2-3	Withhold atezolizumab
	Grade 4 or recurrent grade 3	Permanently discontinue atezolizumab
Infusion related reactions	Grade 1 or 2	Reduce injection rate or pause injection. Treatment may be resumed when the event has resolved.
	Grade 3 or 4	Permanently discontinue atezolizumab
Rash/severe cutaneous reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold atezolizumab Treatment may be resumed when the symptoms improved to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to 10mg or less oral prednisolone or equivalent per day
	Grade 4 rash or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue atezolizumab. Consider treatment with corticosteroids

Regimen

21 day cycle, length of treatment is determined by Blueteq criteria, see indications above. 17 cycles will be set into Aria.

Drug	Dose	Days	Route
Atezolizumab	1875mg	1	Subcutaneous injection

Dose Information

If a planned dose of atezolizumab is missed for reasons other than toxicity, it should be administered as soon as possible. Do not wait until the next planned dose. The schedule of administration must be adjusted to maintain a 21 day period between doses.

Administration Information

Extravasation

- Atezolizumab – neutral

Other

- The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Atezolizumab SC formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.

- Please refer to the toxicity table above for the actions to be taken in relation to infusion related reactions.

Additional Therapy

- No antiemetics are required

- As required for the treatment of infusion related reactions;

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg oral

- Loperamide 4mg oral initially followed by 2mg after each loose stool when required for the relief of diarrhoea (maximum 16mg/24 hours).

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Additional Information

- The use of systemic corticosteroids, before starting treatment with atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids can be used after starting atezolizumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of atezolizumab.

- Patients must be given an atezolizumab Patient Alert Card.

References

1. National Institute for Health and Care Excellence (2021). Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable. NICE technology appraisal guidance 739

2. Haanen J, Carbonnel F, Robert C, Kerr K.M, Peters S, Larkin J, Jordan J on behalf of the ESMO Guidelines Committee. Management of toxicities from immunotherapy. ESMO clinical practice guidelines for diagnosis, treatment and follow up. Ann Oncol 2017; 28 (suppl 4): 119-142.

3. Roche Products Ltd (2023). Tecentriq 1875mg solution for injection Summary of Product Characateristics. Online at https://www.medicines.org.uk/emc/product/15037/smpc last accessed 02/10/2023.

4. National Institute for Health and Care Excellence (2018). Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. NICE technology appraisal guidance 525

REGIMEN SUMMARY

Atezolizumab SC (1875mg 21 days)

Day One

1. Atezolizumab 1875mg subcutaneous injection
   Administration Instructions
   Administer 15 mL of atezolizumab solution for injection subcutaneously 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.

   Ensure the patient has been an atezolizumab patient alert card.

2. Chlorphenamine 10mg intravenous when required for the treatment of infusion related reactions

3. Hydrocortisone sodium succinate 100mg intravenous when required for the treatment of infusion related reactions

4. Paracetamol 1000mg oral when required for the relief of infusion related reactions

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.0	March 2024	None	Eleanor Taylor Oncology Pharmacist	Prof Simon Crabb Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols are only one source of information. They should be read in conjunction with the latest Summary of Product Characteristics and published information.