PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Atezolizumab
Urothelial Carcinoma/Transitional Cell Carcinoma

PROTOCOL REF: MPHAATEZO
(Version No.: 1.4)

Approved for use in:

First Line (PD-L1 ≥ 5%)

- Atezolizumab as 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% or more.
- ECOG performance status (PS) of 0 to 2.

Second Line

- Atezolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults **who have received prior platinum-containing chemotherapy** and fulfils the following criteria:
    - EITHER not received previous adjuvant, neoadjuvant chemotherapy or chemo-radiotherapy (CRT).

    OR

    - If previously treated with platinum-based chemotherapy whether as adjuvant or neoadjuvant chemotherapy or CRT, relapse has occurred within 12 months or less of completing platinum-based chemotherapy.
- ECOG performance status (PS) score of 0 or 1.

******Blueteq registration required for all indications******

Exclusions

- History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, myocarditis, active hepatitis B or C infection
- Active infection requiring systemic treatment
- Less than 4 weeks from major surgery
- History of clinically severe autoimmune disease (can proceed with immunotherapy if well controlled autoimmune disease at the discretion of the clinical team, this needs to be documented on Meditech)
- Patient with active CNS disease (symptomatic despite steroid treatment) or carcinomatosis meningitis

Dosage:

SUBCUTANEOUS ROUTE IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT

Drug	Dosage	Route	Frequency	Duration of Treatment
Atezolizumab	1875mg (Flat dose)	Subcutaneous Injection	3 weekly	1st Line Until progression or unacceptable toxicity 2nd Line Disease progression or unacceptable toxicity or **on completion of 2 years (35 cycles) in total duration,** whichever is first
OR				
Atezolizumab	1680mg (Flat dose)	IV Infusion	4 weekly	1st Line Until progression or unacceptable toxicity 2nd Line

				Disease progression or unacceptable toxicity or **on completion of 2 years (26 cycles) in total duration,** whichever is first
OR				
Atezolizumab	1200mg* (Flat dose)	IV Infusion	3 weekly	1st Line Until progression or unacceptable toxicity 2nd Line Disease progression or unacceptable toxicity or **on completion of 2 years (35 cycles) in total duration,** whichever is first

*Where risk factors (e.g. pre-existing autoimmune disease) for toxicity are present and patient **requires IV treatment** due to intolerance or side-effects with subcutaneous route, the 3 weekly dosing is recommended.*

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). For **grade 1-2 injection site reactions** the following pre-medication to subsequent cycles and administered ahead of **SUBCUTANEOUS DOSE**:

- Paracetamol PO 1g
- Chlorphenamine PO 4mg

Supportive Therapy:

Routine supportive medication not required.

Extravasation risk:

Atezolizumab is a monoclonal antibody- considered to be neutral.

Refer to the CCC policy for the '[Prevention and Management of Extravasation Injuries]'.

Dosing in renal and hepatic impairment (Prior to start of treatment ONLY/Baseline):

Renal	Atezolizumab	GFR ≥ 30ml/min- proceed with treatment GFR < 30ml/min- limited data use with caution

Hepatic	Atezolizumab	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 × ULN and any AST) or Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. * Within normal limits or high Refer to 'Dose Modification and Toxicity' section if LFTs become deranged AFTER starting treatment with immunotherapy

Patient Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last dose of atezolizumab.

Contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis
- **Subcutaneous injection ONLY:** monitor for injection site reaction- pain, swelling and rash.

Interactions:

No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

Please consult SmPC for full information on interactions.

Administration:

<table>
<tr><th>Day</th><th>Drug</th><th>Dose</th><th>Route</th><th>Frequency</th><th>Diluent and rate</th></tr>
<tr><td>1</td><td>Atezolizumab</td><td>1875mg
(flat dose)</td><td>SC</td><td>3 weekly</td><td>Administer over 7 minutes</td></tr>
<tr><td colspan="6">SUBCUTANEOUS ROUTE IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT
Prior to administration, allow the solution to reach room temperature. Administer 15 mL of the Atezolizumab SC injection solution subcutaneously in the thigh in approximately 7 minutes. 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.</td></tr>
<tr><td colspan="6">OR</td></tr>
<tr><td rowspan="2">1</td><td>Sodium chloride 0.9%</td><td>250mL</td><td>IV</td><td>Prior to each Atezolizumab infusion.</td><td>Flush</td></tr>
<tr><td>Atezolizumab</td><td>1680mg
(flat dose)</td><td>IV</td><td>4 weekly</td><td>250mL sodium chloride 0.9%. Infused over 60 minutes for cycle 1 if well tolerated cycle 2 onwards can be administered over 30 minutes in a non-pyrogenic line with a 0.2 micron filter</td></tr>
</table>

OR					
1	Sodium chloride 0.9%	250mL	IV	Prior to each Atezolizumab infusion.	Flush
	Atezolizumab	**1200mg*** (flat dose)	**IV**	3 weekly	250mL sodium chloride 0.9%. Infused over 60 minutes for cycle 1 if well tolerated cycle 2 onwards can be administered over 30 minutes in a non-pyrogenic line with a 0.2 micron filter

First line- until disease progression or unacceptable toxicity

Second line- for a maximum of duration of 2 years of uninterrupted treatment or on loss of clinical benefit or unacceptable toxicity, whichever occurs first (i.e. maximum of 35 administrations every 3 weeks or 26 administrations every 4 weeks).

*Where risk factors (e.g. pre-existing autoimmune disease) for toxicity are present and patient **requires IV treatment** due to intolerance or side-effects with subcutaneous route, the 3 weekly dosing is recommended.*

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). For grade 1-2 injection site reactions the following pre-medication to subsequent cycles and administered ahead of SUBCUTANEOUS DOSE:

- Paracetamol PO 1g
- Chlorphenamine PO 4mg

Please refer to the CCC Hypersensitivity; Management Prevention Policy

Main Toxicities:

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Immune related toxicities	
Immune-Mediated Pneumonitis Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Monitor patients for signs and symptoms and evaluate with radiographic imaging and administer corticosteroids for toxicities of grade 2 or above.
Immune-Mediated Colitis	Monitor patients for signs and symptoms and administer corticosteroids for grade 2 or greater.
Other Immune-Mediated Toxicities: Hepatitis Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia, Guillain-Barré syndrome	Monitor LFTs, biochemistry, cortisol, TFTs and blood glucose, consider corticosteroids for grade 2 or greater.
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Symptomatic management for grade 1 with close monitoring
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Monitor at each cycle and rule out immune-medicated reaction

Injection site reaction	
Injection site pain, erythema, and rash	Symptomatic management for grade 1 with close monitoring. Pre-medication to be added to subsequent cycles.

Investigations and treatment plan:

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x		x		Then every 12 weeks or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (ALT, AST and Bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x	x	Every cycle
Lipid profile (cholesterol)	x				At baseline then if clinically indicated

Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x				At baseline then if clinically indicated
Full set of observations (*BP, heart rate, temperature, respiratory rate and O_2 sats*)		x			At baseline then if clinically indicated
Creatinine Clearance (Cockcroft and Gault)	x				Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
CT scan	x				Every 12 weeks or as clinically indicated
Trop-T, CK, pro-BNP	x				At baseline (refer to 'Pre-assessment Baseline Cardiac Pathway' guidance) and thereafter as clinically indicated (ECG to be reviewed by ANP or ECG clinic or clinical team)
ECG	x				
Weight recorded	x	x	x	x	Every cycle
Height recorded	x				

Pregnancy test if applicable.

Dose Modifications and Toxicity Management:

- Dosing delay or discontinuation may be required based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of doses are contained in dose modifications.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Treatment Threshold

Administer treatment on day 1 if:

Platelets	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤ 1.5 ULN or baseline	<3 x ULN	<3 x ULN	Within range or no change from base line

ULN = upper limit of normal
Platelets must be within normal range prior to Cycle 1.

Toxicity management:

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold treatment. Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

References:

NICE TA525 Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy. Published: 13 June 2018

NICE TA739 Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable Published: 27 October 2021

Tecentriq 1,200 mg concentrate for solution for infusion, Summary of Product Characteristics, Roche products Limited. Available from www.medicines.org.uk/emc/medicine. Last updated 1st September 2023.

Circulation/Dissemination

Date added into Q-Pulse	5th December 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
	1.0	**Anna Burke** **Urology SRG Pharmacist**	New Regimen Protocol V1.0
	1.1	**Rachel Prichard**	**1st line indication added**

		Urology SRG Pharmacist	
	1.2	**Rachel Prichard** **Urology SRG Pharmacist**	**COVID-19 amendment added**
May 2023	1.3	**Hala Ghoz** **Protocols Pharmacist**	**Protocol updated in line with Immunotherapy protocol template**
October 2023	1.4	**Hala Ghoz** **Protocols Pharmacist**	**First line indication for PD-L1 less than 50% removed.** **SC Atezolizumab dosing adding**