PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Atezolizumab
Urothelial Carcinoma/Transitional Cell Carcinoma

PROTOCOL REF: MPHAATEZO
(Version No.: 1.3)

Approved for use in:

This protocol has been temporarily amended - please see the SRG Guidelines during COVID-19 Urology Cancer.

First Line (PD-L1 < 5%)

Interim COVID19 Amendment

Atezolizumab as first line treatment of inoperable locally advanced or metastatic urothelial cancer instead of chemotherapy and whose tumours have PD-L1 expression of less than 5%.

Please NOTE: this is an unlicensed indication. Please refer to the **CCC Unlicensed Medicines Policy** for full details on consenting, prescribing, documentation and supply of unlicensed medicines. As per trust policy please provide the **'Unlicensed Medicines Information'** to patients and carers as appropriate

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.

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, a duration less than or equal to 12 months has elapsed since completing the platinum-based chemotherapy

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

Dosage:

Drug	Dosage	Route	Frequency	Duration of Treatment
Atezolizumab	1200mg (Flat dose)	IV Infusion	3 weekly	**First Line** Until disease progression or unacceptable toxicity **Second Line** Maximum 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)

Exclusions

History of pneumonitis, organ transplantation, HIV infection, active hepatitis B or C infection

Active infection requiring systemic treatment

Less than 4 weeks from major surgery

History of clinically severe autoimmune disease

Supportive Therapy:

Domperidone 10mg oral tablets, up to 3 times a day or as 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

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

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:

Day	Drug	Dose	Route	Diluent and rate
1	Sodium chloride 0.9%	250mL	IV	Flush
1	**Atezolizumab**	**1200mg**	**IV**	250mL sodium chloride 0.9%. Infused over 60 minutes for cycle 1 if well tolerated cycle 2 onwards can be administered over 30minutes in a non-pyrogenic line with a 0.2 micron filter

Repeated every 3 weeks for:
First line- until disease progression or unacceptable toxicity
Second line- and 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)

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.).
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

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
OTR/ Go-ahead	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	x	x	x	Every cycle
Creatinine Clearance (Cockcroft and Gault)	x				Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal and baseline
CT scan	x				Every 12 weeks or as clinically indicated
Trop-T, CK, pro-BNP	x				**At baseline for all Renal and Melanoma and thereafter as clinically indicated** (ECG to be reviewed by 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	Alkaline Phosphatase	TSH and Free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≥ 1.5 ULN or baseline	<3 x ULN	<5 x ULN	<5 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 February 2022.

Circulation/Dissemination

Date added into Q-Pulse	22nd June 2022
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**
	1.3	**Hala Ghoz** **Protocols Pharmacist**	**Protocol updated in line with Immunotherapy protocol template**