PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Atezolizumab NSCLC

PROTOCOL REF: MPHAAATE
(Version No.: 1.4)

Approved for use:

Adjuvant

As adjuvant treatment following complete resection for adult patients with Stage IIB to IIIA or N2 only IIIB non-small cell lung cancer (NSCLC) which satisfies the following criteria:

- No evidence of disease progression (radiologically re-staged- no evidence of residual or metastatic disease) following platinum-based adjuvant chemotherapy.
- PD-L1 expression on ≥ 50% of tumour cells
- Maximum of 4 cycles of adjuvant platinum based chemotherapy commenced within 12 weeks of resection of NSCLC.
- Adjuvant atezoluzimab to start within 12 weeks or less from the start of the last cycle of adjuvant platinum-based chemotherapy.
- ECOG performance status (PS) of 0 or 1.

Palliative

1st Line

As monotherapy for the first line treatment of locally advanced or metastatic NSCLC which has PD-L1 expression in at least 50% of tumour cells or in at least 10% of tumour-infiltrating immune cells which satisfies the following criteria:

- Stage IIIB or IIIC or IV NSCLC or has disease that has recurred after previous potentially curative local management of NSCLC with surgery or chemoradiotherapy or surgery.
- NEGATIVE for EGFR 19 or 21 mutation or an ALK gene fusion (NOT a requirement for squamous histology).
- **Previous SACT for NSCLC PERMITTED if completed** chemotherapy or chemoradiotherapy or checkpoint inhibitor immunotherapy as part of adjuvant/neoadjuvant/maintenance therapy **at least 6 months prior** to the first diagnosis of locally recurrent or metastatic disease.
- The mandatory interval between the last date of administration of any prior adjuvant or neoadjuvant or maintenance immunotherapy and first relapse is **at least 6 months**.
- ECOG performance status (PS) of 0 or 1.

2nd Line

As monotherapy for the treatment of PD-L1 positive or negative locally advanced (stage IIIB or IIIC) or metastatic NSCLC after **at least 2 cycles of platinum-based chemotherapy** for advanced/metastatic disease OR adjuvant therapy/neoadjuvant therapy/chemoradiotherapy that has progressed within 6 months of treatment. Eligibility is subject to the following criteria:

- All appropriate targeted treatments have been tried if the tumour is positive for an actionable genomic change in relation to EGFR or ALK or ROS1 or MET exon 14 or KRAS G12C or RET or BRAF V600 status.
- Prior treatment with checkpoint inhibitor immunotherapy is PERMITTED <u>if discontinued or completed as part of adjuvant/neoadjuvant/maintenance therapy without disease progression AND at least 6 months elapsed between the date of</u>

the last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease.

- ECOG performance status (PS) of 0 or 1.

******Blueteq registration is 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)- treatment at the discretion of the clinical team.
- Carcinomatosis meningitis
- Pregnancy or breast feeding

Dosage:

SUBCUTANEOUS ROUTE IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT

Drug	Dosage	Route	Frequency	Duration of Treatment	
				ADJUVANT	PALLIATIVE
Atezolizumab	1875mg (Flat dose)	Subcutaneous Injection	3 weekly	Disease progression or unacceptable toxicity or **on completion of 1 year in total duration,** whichever is first.	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	Disease progression or unacceptable toxicity or **on completion of 1 year (13 cycles) in total duration,** whichever is first.	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	Disease progression or unacceptable toxicity or **on completion of 1 year in total**	1st Line Until progression or unacceptable toxicity* 2nd Line

				duration, whichever is first.	Disease progression or unacceptable toxicity or **on completion of 2 years (35 cycles) in total duration,** whichever is first

* Note: there is NO stopping rule for atezolizumab in this indication and hence patients continuing to benefit from atezolizumab after 2 years of treatment can continue if the patient and clinician agree. Once atezolizumab is stopped for disease progression or unacceptable toxicity or withdrawal of patient consent, atezolizumab cannot be re-started.

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 treatment 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 interaction

Administration:

Day	Drug	Dose	Route	Frequency	Diluent and rate
1	**Atezolizumab**	**1875mg** (flat dose)	**SC**	3 weekly	Administer over 7 minutes
SUBCUTANEOUS ROUTE IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT 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.					
OR					
1	Sodium chloride 0.9%	250mL	IV	Prior to each Atezolizumab infusion.	Flush
	Atezolizumab	**1680mg** (flat dose)	**IV**	4 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

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

Adjuvant- administered until disease progression or unacceptable toxicity or **on completion of 1 year in total duration of treatment,** whichever is first.

Palliative:

1st line- administered until disease progression or unacceptable toxicity there is NO stopping rule for atezolizumab in this indication and hence patients continuing to benefit from atezolizumab after 2 years of treatment can continue if the patient and clinician agree. Once atezolizumab is stopped for disease progression or unacceptable toxicity or withdrawal of patient consent, atezolizumab cannot be re-started.

2nd line- administered until disease progression or unacceptable toxicity or **on completion of 2 years in total duration of treatment,** 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

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:

Felip, E., Altorki, N., Zhou, C., Csőszi, T., Vynnychenko, I., Goloborodko, O. & IMpower010 Investigators. (2021). Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. *The Lancet*, 398(10308), 1344-1357.

NICE TA (TA823): Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer. Published: 28 September 2022.

NICE TA (TA520): Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. Published: 16 May 2018

NICE TA (TA705): Atezolizumab monotherapy for untreated advanced non-small-cell lung cancer. Published: 02 June 2021

Rittmeyer, A., Barlesi, F., Waterkamp, D., Park, K., Ciardiello, F., Von Pawel, J., Gadgeel, S.M., Hida, T., Kowalski, D.M., Dols, M.C. and Cortinovis, D.L.(2017). Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *The Lancet*, 389(10066), 255-265.

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	2nd February 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
	1.0	**Hala Ghoz** **Lung SRG Pharmacist**	New Regimen Protocol
October 2022	1.1	**Hala Ghoz** **Lung SRG Pharmacist**	**Protocol updated in line with new funding arrangement**
June 2023	1.2	**Hala Ghoz** **Lung SRG Pharmacist**	**Palliative indication added to protocol**
August 2023	1.3	**Hala Ghoz** **Lung SRG Pharmacist**	**TA 705 indication added**
September 2023	1.4	**Hala Ghoz** **Lung SRG Pharmacist**	**Subcutaneous dosing added**