Chemotherapy Protocol

LUNG CANCER– SMALL CELL (SCLC)

ATEZOLIZUMAB-SC-CARBOPLATIN (AUC5)-ETOPOSIDE(IV/PO)

Regimen

- Lung - AtezolizumabSC-Carboplatin (AUC5)-Etoposide(IV/PO)

Indication

- Atezolizumab in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)
- WHO performance status 0 or 1

This indication requires a Blueteq application, see individual form (ATE7) for specific eligibility criteria. Ensure patient meets Blueteq criteria before consenting patient for treatment.

Toxicity

Drug	Adverse Effect
Atezolizumab	Fatigue, rash, pruritis, pneumonitis, colitis, pacreatitis, diarrhoea, diabetes mellitus, adrenal insufficiency, thyroid disorders, nausea, electrolyte disturbances, hepatitis, myasthenic syndrome, Guillain Barre syndrome
Carboplatin	Thrombocytopenia, peripheral neuropathy, nephrotoxicity at high doses, electrolyte disturbances
Etoposide	Hypotension on rapid infusion, alopecia, hyperbilirubinaemia

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

Monitoring

Drugs

- FBC, LFTs (including albumin), U&Es and cortisol prior to day 1 of each cycle
- EDTA or calculated creatinine clearance prior to each cycle
- Thyroid function tests prior to starting atezolizumab treatment and then every 6 weeks or when clinically indicated.

Dose Modifications

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

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Prior to prescribing on day one of cycles 1 – 4 the following criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L
Platelets	equal to or more than $100x10^9$/L

If neutrophils are less than 1.5 or platelets less than 100 delay treatment for 1 week. Repeat FBC and, if within or normal parameters, resume treatment at full dose.
If the counts do not recover within 7 days or repeated delays are required consider reduction of oral etoposide dose to 100mg/m^2 on Day 2 and Day 3.

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

There is little need to adjust the dose of atezolizumab for haematological toxicity.

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 3xULN	Discontinue – see notes below
Carboplatin	N/A		N/A	No dose adjustment needed
Etoposide	26-51	or	60-180	50%
	more than 51	or	more than 180	clinical decision

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 a NCI-CTC grade 2 hepatitis (ALT or AST between 3-5xULN or bilirubin between 1.5-3xULN) that persists for between 5-7 days then withhold the atezolizumab and consider treatment with a corticosteroid. The 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

Drug	Creatinine Clearance (ml/min)	Dose
Atezolizumab	N/A	No dose adjustment needed
Carboplatin*	less than 20	Omit
Etoposide	more than 50	100%
	15-50	75%
	less than 15	50%

* Significant changes in GFR of more than 10% may require dose adjustment.

Other

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.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced to 75% of the original dose or discontinued as appropriate.

Atezolizumab

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[3].

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 prednisolone 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 prednisolone 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 prednisolone 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 carbimazole 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 or equivalent 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 13.9mmol/L)	Withhold atezolizumab Treatment may be resumed if metabolic control is achieved on insulin replacement therapy
Myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome and 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 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	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 10mg or less oral prednisolone or equivalent per day
	Grade 4 rash or confirmed Stevens-Johnson syndrome (SJS) r toxic epidermal necrolysis (TEN)	Permanently discontinue atezolizumab. Consider treatment with corticosteroids

Etoposide

Where significant reductions in albumin levels occur consider reducing the dose of etoposide.

Regimen

A total of 12 cycles will be set in ARIA

Induction - 21 day cycle for 4 cycles

Drug	Dose	Days	Administration
Atezolizumab	1875mg	1	Subcutaneous injection
Carboplatin	AUC 5 (maximum dose)	1	Intravenous infusion in 500ml glucose 5% over 60 minutes
Etoposide	100mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9%
Etoposide	200mg/m^2	2,3	Oral

Followed by:

Maintenance – 21 day cycle until disease progression or unacceptable toxicity

Drug	Dose	Days	Administration
Atezolizumab	1875mg	1	Subcutaneous injection

Dose Information

- The recommended maximum dose when using a calculated creatinine clearance at AUC 5 is 750mg. If you have an obese patient or an individual with a calculated creatinine clearance above 125ml/min please seek advice from the relevant consultant. In ARIA the maximum dose has been set at 790mg to comply with the national dose bands. Please check this maximum dose is suitable for you patient.
- It should be noted that the dose of carboplatin may need to be altered if there is a change (improvement or reduction) in renal function of more than 10% from the previous cycle.
- Carboplatin dose will be dose banded in accordance with the national dose bands (10mg/ml).
- Intravenous etoposide will be dose banded in accordance with the national dose bands (20mg/ml)
- Oral etoposide is available as 50mg and 100mg soft capsules.

Administration Information

Extravasation

- Atezolizumab – neutral
- Carboplatin – irritant
- Etoposide - irritant

Other

- The atezolizumab 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.

Additional Therapy

- Antiemetics (Cycles 1-4 Day 1 only)

  15-30 minutes prior to chemotherapy

  - ondansetron 8mg oral or intravenous

  As take home medication

  - dexamethasone 4mg oral twice a day for 3 days
  - metoclopramide 10mg oral three times a day as required
  - ondansetron 8mg oral twice a day for 3 days

- Growth factor as per local formulary choice (Cycles 1-4 only), for example:

  - filgrastim or bioequivalent 30million units once a day for 5 days starting on day 5 of the cycle subcutaneous
  - lenograstim or bioequivalent 33.6million units once a day for 5 days starting on day 5 of the cycle subcutaneous
  - Pegfilgrastim, lipegfilgrastim or bioequivalent 6mg on the day after SACT administration

- 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 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.

- Oral etoposide capsules should be swallowed whole on an empty stomach or an hour before food.

References

1. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. Horn L, Mansfield AS, Szczęsna A, et al. N Engl J Med 2018; 379:2220-2229

2. National Institute for Health and Care Excellence (2020). Atezolizumab in combination with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer. NICE technology appraisal guidance 638

3. 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.

4. 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 25/03/2024.

REGIMEN SUMMARY

AtezolizumabSC-Carboplatin (AUC5)-Etoposide(IV/PO)

Cycle 1,2,3 and 4 Day 1

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 given an atezolizumab patient alert card.

2. Metoclopramide 10mg oral or intravenous
   Administration Instructions
   Administer 15-30 minutes prior to chemotherapy. This may be given as metoclopramide 10mg IV stat if required.

3. Ondansetron 8mg oral or intravenous
   Administration Instructions
   Administer 15-30 minutes prior to chemotherapy. This may be given as ondansetron 8mg IV stat if required.

4. Warning - Carboplatin Maximum Dose
   Administration Instructions
   The dose of carboplatin is capped at a creatinine clearance of 125ml/min. The internationally recommended maximum dose of carboplatin for AUC 5 is 750mg. The national dose bands do not contain this dose so the cap has been set at 790mg in ARIA. Please check this dose is appropriate for your patient.

5. Carboplatin AUC 5 (maximum dose) intravenous infusion in 500ml glucose 5% over 60 minutes

6. Etoposide 100mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

7. Chlorphenamine 10mg intravenous injection when required for infusion related reactions

8. Hydrocortisone 100mg intravenous injection when required for infusion related reactions

9. Paracetamol 1000mg oral when required for infusion related reactions
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

Take Home Medicines (Day 1 only)

10. Etoposide 200mg/m^2 oral once a day on days 2 and 3

11. Dexamethasone 4mg oral twice a day for 3 days starting the day after chemotherapy

12. Metoclopramide 10mg oral three times a day for three days then 10mg three times a day when required for nausea

13. Ondansetron 8mg oral twice a day for 3 days starting on the evening of day one or treatment
    Administration Instructions
    Start on the evening of day 1 of the treatment cycle

14. Growth Factor as directed

Administration instructions
Growth factor as per local formulary choice. For example;
filgrastim or bioequivalent 30million units once a day for 5 days starting on day 5 of the cycle subcutaneous
lenograstim or bioequivalent 33.6million units once a day for 5 days starting on day 5 of the cycle subcutaneous
Pegfilgrastim or lipegfilgrastim or bioequivalent 6mg on the day after SACT administration

15. Loperamide as directed (cycle 1 only)
    Administration Instructions
    Take 4mg after the first loose stool and then 2mg after each subsequent loose stool to a maximum of 16mg in 24 hours.
    Please supply one original pack size

Cycle 5 onwards

16. 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.

17. Chlorphenamine 10mg intravenous injection when required for infusion related reactions

18. Hydrocortisone 100mg intravenous injection when required for infusion related reactions

19. Paracetamol 1000mg oral when required for infusion related reactions
    Administration Instructions
    Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.0	March 2024	None	Eleanor Taylor Oncology Pharmacist	Judith Cave 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 which occur as a result of following these guidelines.