Atezolizumab, Carboplatin and Etoposide (SCLC)

Indication

First line treatment of extensive-stage small cell lung cancer in adults.

Patients should have performance status of 0-1.

(NICE TA638)

ICD-10 codes

Codes pre fixed with C34

Regimen details

Combination therapy (Cycles 1-4):

Day	Drug	Dose	Route
1	Atezolizumab	1200mg	IV infusion
1	Carboplatin	AUC5*	IV infusion
1	Etoposide	100mg/m²	IV infusion
2 and 3 **or**	Etoposide	100mg/m²	IV infusion
2 and 3	Etoposide	200mg/m²	PO

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) a measured GFR should be performed.
CrCl should be capped at 125mL/min

Subsequent atezolizumab monotherapy (cycle 5 onwards):

Three weekly regimen:

Day	Drug	Dose	Route
1	Atezolizumab	1200mg	IV infusion

Or (if the patient is stable and well):

Four weekly regimen:

Day	Drug	Dose	Route
1	Atezolizumab	1680mg	IV infusion

Cycle frequency

3 weekly as combination treatment then 3 or 4 weekly as monotherapy.

Number of cycles

4 cycles combination treatment, followed by atezolizumab maintenance to continue until disease progression or unacceptable toxicity.

Administration

Atezolizumab is administered in 250mL sodium chloride 0.9% over 60 minutes. If the initial infusion is well tolerated, subsequent infusions may be administered over 30 minutes.

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For grade 1-2 infusion related reactions, decrease the infusion rate and closely monitor or temporarily interrupt treatment. Premedication with paracetamol and chlorphenamine should be used for further doses and patient should be closely monitored. For grade 3-4 infusion related reactions discontinue treatment.

Carboplatin is administered in 500mL 5% glucose over 30 minutes.

IV etoposide is administered in 1000mL sodium chloride 0.9% and infused over a minimum of 1 hour.

Oral etoposide is available as 50mg and 100mg capsules. The dose should be rounded to nearest 50mg and swallowed whole on an empty stomach or an hour before food. In the event that the patient cannot swallow capsules, etoposide injection can be taken orally (diluted with orange juice immediately prior to administration) at a dose of 70% of the usual oral capsule dose on days 2 and 3. (This is an unlicensed use based on medical information from Bristol- Myers Squibb). Note: oral absorption of etoposide is variable.

Pre-medication

Antiemetics as per local guidelines.

Emetogenicity

This regimen has moderate emetic potential (cycles 1-4) and low emetic potential (cycles 5 onwards).

Additional supportive medication

Consider prophylactic ciprofloxacin 250mg BD and fluconazole 50mg OD for 7 days, starting on day 7, for patients with extensive disease, poor performance status or age >70 years during combination treatment.
Nil routinely required from cycle 5 onwards.

Extravasation

Atezolizumab is neutral (Group 1)
Carboplatin and etoposide are irritant (Group 3)

Investigations – pre first cycle

Investigation	**Validity period**
FBC	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Thyroid function	7 days
Calcium	7 days
Glucose	7 days
Cortisol	7 days

Baseline measured GFR if suspected or significant renal dysfunction.

Investigations – pre combination treatment cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFT	7 days
Calcium	As clinically indicated
Thyroid function*	7 days
Glucose*	7 days
Cortisol*	7 days

* every cycle for the first 4 cycles then every other cycle.

Investigations – pre Atezolizumab maintenance cycles

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFT	7 days
Calcium	As clinically indicated
Thyroid function	Every other cycle
Glucose	Every other cycle
Cortisol	Every other cycle

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophil count	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
White Cell Count	>2.0 x 10^9/L
Creatinine Clearance (CrCl)	≥ 50mL/min
Bilirubin	< 1.5 x ULN
ALT/AST	< 3 x ULN
Sodium	≥130 x 10^9/L (if < 130 – discuss with consultant)

Dose modifications

Consider reducing carboplatin dose to AUC 4 for patients with poor performance status.
Dose reductions are not recommended for atezolizumab. Doses should be delayed until an adverse reaction resolves to ≤ grade 1.

- **Haematological toxicity**

Combination treatment:
Defer therapy for 1 week if neutrophils < 1.0 x 10^9/L or platelets < 100 x 10^9/L. If repeat FBC within range continue with treatment.
If significant myelosuppression consider reducing oral etoposide dose to 100mg/m^2 on days 2 and 3. Consider prophylactic GCSF support.

Atezolizumab maintenance:
Discuss with the consultant if:
WBC <2.0 x 10^9/L
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

Atezolizumab: No dose modifications required for mild to moderate renal impairment. The effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.

Etoposide

CrCl (mL/min)	**Etoposide dose**
>50	100%
15-50	75%
<15	50%

Carboplatin:
If the calculated creatinine clearance falls by >10% from previous cycle recalculate dose of carboplatin. If the calculated creatinine clearance appears to improve the dose should not be increased unless a clear cause of renal function improvement is documented (e.g. treatment of urinary tract obstruction). Carboplatin is contraindicated if CrCl <20mL/min.

- **Hepatic impairment**

Atezolizumab: No modifications required for atezolizumab in mild hepatic impairment. Atezolizumab has not been studied in moderate or severe hepatic impairment. See below for management of hepatitis during treatment.

Etoposide: if bilirubin <2.5 x ULN with normal albumin and renal function, no dose reduction indicated. If bilirubin >2.5 x ULN **or** albumin < 35g/L, consider dose reduction to 50% dose and increase if tolerated.

Carboplatin: No dose modification required.

- **Other toxicities**

Any Grade 3-4 toxicity (except mucositis and alopecia) – delay carboplatin & etoposide until ≤ grade 1 toxicity and reduce doses of carboplatin and etoposide to 75%.

For suspected immune related adverse events, atezolizumab should be withheld and corticosteroids administered. Once symptoms resolved to ≤ Grade 1 the corticosteroid dose should be tapered over 1 month.

Toxicity	Definition	Dose adjustment
Pneumonitis	Grade 2	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 3-4	Permanently discontinue
Hepatitis	Grade 2 Bilirubin 1.5-3 x ULN and/or AST/ALT 3-5 x ULN	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 3-4 Bilirubin > 3 x ULN and/or AST/ALT > 5 x ULN	Permanently discontinue
Colitis	Grade 2-3 diarrhoea or Symptomatic colitis	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 4 diarrhoea or colitis	Permanently discontinue
Hypo or hyperthyroidism	Symptomatic	Hypothyroidism Withhold treatment Treatment may resume once symptoms controlled with thyroid replacement and TSH levels reducing.
		Hyperthyroidism Withhold treatment Treatment may resume once symptoms controlled with anti-thyroid medication and thyroid function is improving.

Toxicity	Definition	Dose adjustment
Adrenal insufficiency	Symptomatic	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
Hypophysitis	Grade 2-3	Withhold treatment Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids ≤ 10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
	Grade 4	Permanently discontinue
Insulin dependent diabetes mellitus	Grade 3-4 hyperglycaemia	Withhold treatment Resume once metabolic control achieved with insulin therapy.
Rash	Grade 3	Withhold treatment Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 4	Permanently discontinue
Myasthenic syndrome/ myasthenia gravis/Guillain-Barre	Any grade	Permanently discontinue
Pancreatitis	Grade 2-3 (or Grade 3-4 increase in amylase or lipase)	Withhold treatment Resume once amylase and lipase levels ≤ Grade 1 (within 12 weeks) or where symptoms have resolved and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
	Grade 4 or recurrent pancreatitis	Permanently discontinue

<u>Permanently discontinue</u> atezolizumab in patients with the following symptoms:

- Any grade 4 toxicity, except endocrinopathies that are controlled with replacement hormones.
- Any recurrent Grade 3 toxicity.
- Any treatment related toxicity that does not resolve to ≤ Grade 1 within 12 weeks after onset.
- If a corticosteroid dose ≥ 10mg/day prednisolone (or equivalent) is required for toxicity beyond 12 weeks after onset.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Carboplatin/Etoposide:
Myelosuppression
Neuropathy
Hypersensitivity reactions
Nephrotoxicity

Atezolizumab:
Immune reactions
Interstitial lung disease, pneumonitis
Pancreatitis
Hepatitis
Colitis
Neuropathies
Endocrinopathies

- **Frequently occurring side effects**

Carboplatin/Etoposide:
Myelosuppression
Alopecia
Nausea and vomiting, abdominal pain
Electrolyte disturbances
Abnormal LFTs
Asthenia

Atezolizumab:
Thrombocytopenia
Hypothyroidism, hyperthyroidism
Hypotension
Dyspnoea, cough
Nausea, vomiting
Diarrhoea
Decreased appetite
Headache
Rash, pruritis
Arthralgia
Pyrexia
Fatigue
Infusion related reactions

- **Other side effects**

Carboplatin/Etoposide:
Rash
Flu like illness
Peripheral neuropathy
Visual disturbance

Atezolizumab:
Altered electrolytes
Raised transaminases
Guillain-Barre syndrome

Significant drug interactions – for full details consult product literature/ reference texts

No formal drug interaction studies have been carried out with atezolizumab.

Corticosteroids: the use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab.

Phenylbutazone, sodium salicylate and salicylic acid: can affect protein binding of etoposide.

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Carboplatin only:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use

Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

Patients should be issued with the Atezolizumab Patient Alert Card and advised to carry the card at all times.

References

- National Institute for Health and Care Excellence TA638 accessed 20 September 2022 via www.nice.org.uk
- Summary of Product Characteristics Atezolizumab (Roche) accessed 16 September 2022 via www.medicines.org.uk
- Summary of Product Characteristics Carboplatin (Hospira) accessed 16 September 2022 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Bristol Myers Squibb) accessed 16 September 2022 via www.medicines.org.uk
- Horn L., et al. First-Line Atezolizumab plus Chemotherapy in Extensive Stage Small Cell Lung cancer. 2018. N Engl J Med. 379: 2220-2229
- Krens S D, Lassche, Jansman GFGA, et al**.** Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20:e201-08. Supplementary appendix

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