# Atezolizumab, Carboplatin & Etoposide

## Indication

Small Cell Lung Cancer Extensive stage PS 0-1, no contraindications to immunotherapy, no active untreated brain disease

## Regimen details

Cycles 1-4, given every 21 days

| Day | Drug | Dose | Instructions |
|---|---|---|---|
| 1 | Atezolizumab | 1200mg | 250ml 0.9% sodium chloride over 1 hour IV * |
| 1 | Carboplatin | AUC 5 | 500ml Dextrose 5% 1 hour |
| 1-3 | Etoposide | 100mg/m2 | 1L 0.9% sodium chloride over 1 hour IV** |

*** if cycle 1 infusion tolerated without problems Atezolizumab can be administered over 30 minutes for subsequent cycles**

**** Oral Etoposide can be used on day 2+3 at dose of 200mg/m² (rounded to nearest 50mg)**

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

C5 onwards, given every 28 days

| Day | Drug | Dose | Instructions |
|---|---|---|---|
| 1 | Atezolizumab | 1680mg | 250ml 0.9% sodium chloride over 1 hour IV * |

## Number of cycles

Carboplatin & Etoposide for 4 cycles only, Atezolizumab continued until disease progression or unacceptable toxicity to a maximum of 2 years uninterrupted treatment.

## Administration

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the atezolizumab 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.

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.

## Pre-medication

Anti-emetics

## Emetogenicity

This regimen has moderate emetogenic potential.

## Extravasation

Atezolizumab is neutral , Carboplatin and etoposide are irritant

## Investigations – pre first cycle

| Investigation | Validity period |
|---|---|
| FBC | 14 days |
| U+Es (including creatinine) | 14 days |
| LFTs | 14 days |
| Thyroid function | 14 days |
| Calcium | 14 days |
| Glucose | 14 days |
| Cortisol | 14 days |
| Luteinizing hormone | 14 days |
| Follicle stimulating hormone | 14 days |
| Testosterone | 14 days |

## Investigations – pre subsequent cycles

| Investigation |
|---|
| FBC |
| U+E (including creatinine) |
| LFT |
| Calcium |
| Thyroid function* |
| Glucose* |
| 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 | ≥ 1.5 x $10^9$/L |
| Platelets | ≥ 100 x $10^9$/L |
| Creatinine Clearance (CrCl) | ≥ 30mL/min |
| Bilirubin | < 1.5 x ULN |
| ALT/AST | < 2.5 x ULN |

## Dose modifications

Dose reductions are not recommended with Atezolizumab. Doses should be delayed until an adverse reaction resolves to ≤ grade 1.

- **Haematological toxicity**

  If neutrophils <1.0 defer and consider GCSF prophylaxis and/or dose reduction for carboplatin and etoposide by 20%

  If neuts 1.0-1.5 – discuss with consultant oncologist

- **Renal impairment**

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

No modifications for atezolizumab

- **Hepatic impairment**

| **Bilirubin** (x ULN) | | **AST/ALT** (x ULN) | **Etoposide dose** |
|---|---|---|---|
| <1.5 | and | < 1.5 | 100% |
| 1.5-3.0 | or | 1.5-3.0 | 50% |
| >3.0 | or | > 3.0 | 25% or omit (consultant decision) |

- **Other toxicities**

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.

Please see network Immunotherapy guidelines

Any Grade 2 immune-related event – withhold Atezolizumab, commence Prednisolone 1-2mg/kg (or equivalent) and consider re-starting immunotherapy once symptoms resolved to grade 1 or less on Pred<10mg

**Permanently discontinue treatment 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**

Immune reactions
Interstitial lung disease, pneumonitis
Pancreatitis
Hepatitis
Colitis
Neuropathies
Endocrinopathies
Myelosuppression
Neuropathy
Hypersensitivity reactions
Nephrotoxicity

- **Frequently occurring side effects**

Thrombocytopenia
Hypothyroidism, hyperthyroidism
Hypotension
Dyspnoea
Nausea, vomiting
Diarrhoea
Rash
Pruritis
Arthralgia
Fatigue
Infusion related reactions
Alopecia
Electrolyte disturbances

- **Other side effects**

Decreased appetite
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

The prescriber must discuss the risks of treatment with the patient and they will 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 via www.nice.org.uk
- Summary of Product Characteristics Atezolizumab (Roche) via www.medicines.org.uk
- NEJM 2018; 379:2220-2229, Horn et al.


**THIS PROTOCOL HAS BEEN DIRECTED BY DR BEAUMONT, CLINICIAN FOR LUNG CANCER**
**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**
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