Atezolizumab 1200mg, CARBOplatin AUC 5 and Etoposide 100mg/m^2 Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
First-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).	C34	00689a	Atezolizumab: ODMS 01/03/2022 CARBOplatin: Hospital Etoposide: Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Induction phase: Atezolizumab and CARBOplatin are administered on day 1 and etoposide is administered on days 1, 2 and 3 of a 21 day cycle, for 4 cycles or until disease progression or unacceptable toxicity occurs.

Maintenance phase: The induction phase is followed by a maintenance phase without chemotherapy during which atezolizumab is administered every three weeks. An alternative maintenance administration schedule of 1680mg every 28 days may be considered as described in Regimen 00593 Atezolizumab 1680mg Monotherapy–28 Day.

Treatment with atezolizumab should continue until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment Schedule for Atezolizumab, CARBOplatin and Etoposide (IV)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Atezolizumab[a,b]	1200mg	IV infusion	250ml 0.9% NaCl over 60 mins	Every 21 days
2	1	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 30 mins	Every 21 days for 4 cycles
3	1,2,3	Etoposide	100mg/m^2	IV infusion*	1000ml 0.9% NaCl over 60 mins	Every 21 days for 4 cycles
[a] Initial dose must be given over 60 minutes; subsequent doses may be given over 30 minutes if tolerated.						
[b] If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.						

*See alternate treatment schedule using IV and PO etoposide below.

ALTERNATE TREATMENT SCHEDULE:

Atezolizumab, CARBOplatin and Etoposide (Day 1 IV, Day 2 & 3 oral)

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Induction phase: Atezolizumab and CARBOplatin are administered on day 1 and etoposide is administered as an IV infusion on Day 1 and then administered as PO doses on Days 2 and 3 for 4 cycles or until disease progression or unacceptable toxicity occurs.

Maintenance phase: The induction phase is followed by a maintenance phase without chemotherapy during which atezolizumab is administered every three weeks. An alternative maintenance administration schedule of 1680mg every 28 days may be considered as described in Regimen 00593 Atezolizumab 1680mg Monotherapy–28 Day.

Table 2: Alternate Treatment Schedule for Atezolizumab (IV), CARBOplatin (IV) and Etoposide (IV and PO)

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Atezolizumab[a,b]	1200mg	IV infusion	250ml 0.9% NaCl over 60 mins	Every 21 days
2	1	CARBOplatin	AUC 5	IV Infusion	500ml glucose 5% over 30 mins	Every 21 days for 4 cycles
3	1	Etoposide	100mg/m^2	IV Infusion	1000ml 0.9% NaCl over 60 mins	Every 21 days for 4 cycles
1	2, 3	Etoposide	[c]100mg/m^2 twice daily	PO		Every 21 days for 4 cycles
[a] Initial dose must be given over 60 minutes; subsequent doses may be given over 30 minutes if tolerated.						
[b] If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.						
[c]Etoposide is available in 50mg and 100mg capsules. The capsules should be taken on an empty stomach.						

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- **Estimation of GFR (eGFR)** can be done by using the Wright formula or using the Cockcroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese patients and those with a low serum creatinine, for example due to low body weight or post-operative asthenia, the formulae may not give accurate results and measured GFR is recommended.
  - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available, the use of the adjusted ideal body weight for Cockcroft and Gault may be considered.
  - Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered.
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay*.

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- ≥18 years
- ECOG status 0-1
- No prior systemic treatment for ES-SCLC
- Adequate haematological and organ function

USE WITH CAUTION:

Use with caution in:

- Patients with clinically significant autoimmune disease

EXCLUSIONS:

- Hypersensitivity to atezolizumab, CARBOplatin, etoposide or any of the excipients.
- Symptomatic central nervous system (CNS) metastases
- Any active clinically significant infection requiring therapy
- Pregnancy or lactation
- Symptomatic interstitial lung disease
- Prior treatment with anti–PD-1, or anti–PD-L1 therapeutic antibodies or pathway-targeting agent
- Any medical condition that requires immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisolone/daily (or steroid equivalent, excluding inhaled or topical steroids

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, liver and renal profile
- Glucose
- TFTs
- Virology Screen: Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- Isotope GFR measurement (preferred) or GFR / creatinine clearance estimation

Regular tests:

- FBC, liver, renal and glucose profile prior to each cycle
- TFTs every 3 to 6 weeks

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Atezolizumab:
  - Dose reduction not recommended.
  - Atezolizumab treatment may be interrupted or discontinued due to toxicity. Please refer to Table 3 below for treatment modification.
- CARBOplatin and etoposide:
  - Dose modifications are permitted for CARBOplatin and etoposide to manage haematological toxicities and renal and hepatic impairment. Please refer to Tables 1 and 2 below.

Haematological:

Table 1: Dose modification for CARBOplatin and etoposide for haematological toxicity on Day 1

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥ 1.0	and	≥ 100	100%
0.5 to <1.0	and/or	75 to <100	Delay one week until recovery
<0.5 or neutropenic fever	and/or	<50	Delay and consider dose reduction for etoposide and carboplatin by 25%

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Atezolizumab	Mild/ Moderate	No dose adjustment required	Mild/moderate	No dose adjustment required		
	Severe	Data too limited to draw conclusions	Severe	Has not been studied		
CARBOplatin	See note below*		Probably no dose modification required			
Etoposide	**CrCl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST (Units/L)**	**Dose Etoposide**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent dosing should be based on patient tolerance and clinical effect.					

*Renal Dysfunction and CARBOplatin

- Patients with creatinine clearance values of <60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution
- In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required on each cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to re-measuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 3: Guidelines for withholding or discontinuation of atezolizumab

Immune related adverse reaction	Treatment modification
Pneumonitis Grade 2 Grade 3 or 4	 Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day. Permanently discontinue atezolizumab
Hepatitis Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] or blood bilirubin > 1.5 to 3 x ULN) Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	 Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day. Permanently discontinue atezolizumab
Colitis Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	 Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone equivalent per day. Permanently discontinue atezolizumab
Hypothyroidism or hyperthyroidism 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 anti-thyroid medicinal product and thyroid function is improving.
Adrenal insufficiency Symptomatic	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.

Immune related adverse reaction	Treatment modification
Hypophysitis Grade 2 or 3 Grade 4	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. Permanently discontinue atezolizumab
Type 1 diabetes mellitus Grade 3 or 4 hyperglycaemia (fasting glucose >250 mg/dL or 13.9 mmol/L)	Withhold atezolizumab. Treatment may be resumed when metabolic control is achieved on insulin replacement therapy.
Infusion-related reactions Grade 1 or 2 Grade 3 or 4	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved. Permanently discontinue atezolizumab
Rash/Severe cutaneous adverse reaction Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1] Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	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. Permanently discontinue atezolizumab
Myasthenic syndrome/ myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis All grades	Permanently discontinue atezolizumab
Pancreatitis Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis Grade 4 or any grade of recurrent pancreatitis	Withhold Atezolizumab. Treatment may be resumed when 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 ≤ 10 mg prednisolone or equivalent per day. Permanently discontinue atezolizumab
Myocarditis Grade 2 or above	Permanently discontinue atezolizumab
Nephritis Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN) Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Withhold atezolizumab. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Permanently discontinue atezolizumab
Myositis Grade 2 or 3 Grade 4 or recurrent Grade 3	Withhold atezolizumab Permanently discontinue atezolizumab

Immune related adverse reaction	Treatment modification
Other immune-related adverse reactions	
Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10mg prednisolone or equivalent per day.
Grade 4 or recurrent Grade 3	Permanently discontinue atezolizumab (except endocrinopathies controlled with replacement hormones).
Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).	
[1]Regardless of severity	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Atezolizumab: Minimal **(Refer to local policy)**
CARBOplatin: High **(Refer to local policy)**
Etoposide: Low **(Refer to local policy)**

PREMEDICATIONS: None usually required unless patient has experienced a previous hypersensitivity reaction.

OTHER SUPPORTIVE CARE: Not usually required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

Atezolizumab

- **Immune-mediated adverse reactions:** Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab. For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered. Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones.

- **Infusion related reactions:** These have been observed in clinical trials with atezolizumab. The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion- related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.
- **Immune-related severe cutaneous adverse reactions (SCARs):** Immune-related severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. In case a SCAR is suspected, atezolizumab should be withheld and patients should be referred to a specialist in SCARs for diagnosis and treatment. If SJS or TEN is confirmed, and for any grade 4 rash/SCAR, treatment with atezolizumab should be permanently discontinued. Caution is recommended when considering the use of atezolizumab in patients with previous history of a severe or life-threatening SCAR with other immune-stimulatory cancer medicines.

CARBOplatin and Etoposide

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.
- **Hypersensitivity:** High risk with etoposide and CARBOplatin. Hypersensitivity risk increases with number of cycles of CARBOplatin.

DRUG 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.
- 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.
- Avoid concurrent use of CARBOplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). If necessary perform regular audiometric testing.
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Patient Alert Card (Atezolizumab)
https://www.hpra.ie/img/uploaded/swedocuments/53ca611d-f634-4438-83db-4da11cebd0c6.pdf

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Version	Date	Amendment	Approved By
1	20/01/2022		Prof Maccon Keane
2	08/07/2022	Addition of wording giving option to administer atezolizumab 1680mg every 28 days. Amended CARBOplatin infusion time. Updated wording for CARBOplatin dosing.	Prof Maccon Keane
3	24/03/2023	Reviewed. Updated management of adverse events section. Added alternate treatment schedule.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.