Indication	Atezolizumab, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer. NB: Previous treatment with concurrent chemoradiotherapy for limited stage SCLC is allowed as long as therapy was completed at least 6 months prior to the diagnosis of recurrent and extensive stage disease. The patient has had no prior treatment with anti-PD-L1/PD-1 therapy for small cell lung cancer, unless this was received for this indication via the EAMS scheme or via a Roche (non-EAMS) access program.
Treatment Intent	Palliative
Frequency and number of cycles	**Induction phase:** repeat every 21 days for 4 cycles **Maintenance phase**: 1875mg (SC) repeat every 21 days until disease progression, unacceptable toxicity or patient's choice. Alternative maintenance phase: 1680mg (IV) repeat every 28 days until disease progression, unacceptable toxicity or patient's choice. If this schedule is used, switch Aria regimen to 'MULTI-004 atezolizumab (IV) every 4 weeks' for the maintenance phase. A formal medical review as to whether treatment with atezolizumab in combination with carboplatin plus etoposide should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment. NB patients can be switched between atezolizumab SC and IV during induction (at a dose of 1200mg IV every 3 weeks) if the clinical need arises, if IV is required during maintenance use 28 day IV schedule.

Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.
	• EDTA or estimated CrCl (C&G) prior to cycle 1 must be >/= 30ml/min.
	• **Blood parameters:**
	• Monitor FBC, U&Es, and LFTs at each cycle.
	• If neuts >/=1.5 and PLT >/=100 continue with treatment. If neuts 1.0-1.4 and PLT >/=100 d/w consultant. If neuts <1.0 and/or PLT <100 delay treatment.
	• **ECG** at first cycle. NB: Patients with clinically significant cardiovascular disease were excluded from the IMpower 133 trial. Monitor for signs and symptoms of myocarditis. Carry out further ECGs as clinically indicated.
	• **Thyroid function** must be assessed at baseline then every 6 weeks or as clinically indicated.
	• Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose.
	• The patient has no symptomatically active brain metastases or leptomeningeal metastases.
	• **<u>Renal Impairment</u>**
	  ○ **Atezolizumab:** no dose adjustment is required in patients with mild or moderate renal impairment (30-89ml/min). No recommendation for patients with severe (<30ml/min) renal impairment as data is too limited.
	  ○ **Carboplatin:** If CrCl falls by >25% repeat / do EDTA to dose carboplatin.

- **Etoposide:** If CrCl </= 50ml/min consider dose reduction.

- **Hepatic impairment** (prior to treatment, for immune related hepatitis see below)
  - **Atezolizumab:** no dose adjustment is required for patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 × to 1.5 × ULN and any AST) or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST). No data is available in patients with severe hepatic impairment (bilirubin >3 X ULN and any AST).
  - **Etoposide:** Clinical decision. As a guide, if bilirubin 26-51 or AST 60-180 consider reducing dose by 50%.
- **Dose reductions:**
  - **Carboplatin and etoposide:** d/w consultant if chemotherapy is delayed due to haematological toxicity. Dose reduction should be considered if grade 3 or 4 non-haematological toxicity or repeat appearance of grade 2 (except N&V and alopecia). Delay until resolution of toxicity to </= grade 1
  - **Atezolizumab:** Dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.
  - **Atezolizumab Sub Cutaneous administration and injection-related reactions:**
  - Remove from fridge and allow to reach room temperature before administration.
  - Inject into the subcutaneous tissue of the thigh only, over 7 minutes.
  - Injection site should be alternated between left and right thigh.
  - 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 other medicinal products for subcutaneous administration should preferably be injected at different sites.
  - If a grade 1 or 2 injection-related reaction occurs, the injection should be slowed down or paused and appropriate medical therapies should be administered. Treatment may be resumed once the event has resolved.
  - Permanently discontinue atezolizumab SC in the event of grade 3 or 4 hypersensitivity reaction.
- **Intravenous Infusion-related reactions:**
  - Reduce infusion rate or interrupt treatment if Grade 1 or 2 infusion-related reaction. Atezolizumab may be continued with close monitoring; premedication with antipyretic and antihistamines should be considered.
  - Permanently discontinue in patients with Grade 3 or 4 infusion related reactions.

Adverse reactions:

Immune- related reactions:

- Patients must be advised to contact the oncology team if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment.
- Reactions include myositis, myocarditis, pneumonitis, colitis, hepatitis, pancreatitis, adrenal insufficiency, meningoencephalitis, hyperthyroidism, hypothyroidism, hypophysitis, diabetes, rash, arthralgia, musculoskeletal pain, neuropathies, myasthenic syndrome and Guillain-Barre syndrome. For details on treatment modification for immune related reactions see table 1.
- Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, atezolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, atezolizumab should be permanently discontinued.
- Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some with fatal outcomes, have been observed. Patients should be monitored for clinical signs and symptoms of pericardial disorders.

	○ Atezolizumab should be discontinued in the event of any grade Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis. ○ If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month upon improvement of immune related toxicity to </= grade 1. Treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids (>10mg prednisone) or other immunosuppressive therapy. Prophylactic antibiotics should be used where appropriate to prevent opportunistic infections in patients receiving immunosuppressive therapy. ○ See guidelines for management of immune-related adverse reactions following immunotherapy: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/ • **Driving and machinery:** Atezolizumab can affect the ability to drive and use machines. If patients experience fatigue they should not drive. • **Drug Interactions:** ○ **Atezolizumab:** The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab. ○ Patients should not receive the flu vaccine unless the benefit outweighs the risk and after discussion between consultant and patient. ○ **Etoposide:** Cyclosporin (high doses) increases etoposide plasma levels/toxicity use with caution. ○ **Carboplatin:** Carboplatin: Caution with other nephrotoxic drugs. • **Delayed or missed doses:** • If a planned dose is missed, the next dose should be administered as soon as possible. The administration schedule must be adjusted to maintain a 3-week interval between doses. • Treatment breaks of up to 12 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow any immune toxicities to settle. • The patient should be provided with the appropriate **Tecentriq®** Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment).
References	KMCC protocol LUN-041 v3 CDF v1.210 accessed online 22.04.2022 SPC accessed online 18/09/23

NB For funding information, refer to CDF NICE Drugs Funding List

TABLE 1: Dose modification advice for immune related reactions

Immune related reaction	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold 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
	Grade 3 or 4	Permanently discontinue
Hepatitis in patients without HCC	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 x ULN)	Withhold 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
	Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	Permanently discontinue
Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3x to ≤ 10x ULN ***or*** If AST/ALT is >1 to ≤ 3x ULN at baseline and increases to >5x to ≤10x ULN ***or*** If AST/ALT is > 3x to ≤ 5x ULN at baseline and increases to > 8x to ≤ 10x ULN	Withhold 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
	If AST/ALT increases to >10x ULN ***or*** total bilirubin increases to > 3x ULN	Permanently discontinue
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) ***or*** Symptomatic Colitis	Withhold 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
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold ***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 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 prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	Withhold 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 prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) regardless of severity	Withhold 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 prednisone or equivalent per day
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) regardless of severity	Permanently discontinue
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	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 prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue
Myocarditis	Grade 2 or above	Permanently discontinue
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold 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
Myositis	Grade 2 or 3	Withhold

	Grade 4 or Grade 3 recurrent myositis	Permanently discontinue
Pericardial disorders	Grade 1 pericarditis	Withhold and conduct a detailed cardiac evaluation to determine the etiology and manage appropriately
	Grade 2 or above	Permanently discontinue
Other immune-related reactions	Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.
	Grade 4 or recurrent Grade 3	Permanently discontinue (except endocrinopathies controlled with replacement hormones)

Induction
Repeat every 21 days for 4 cycles

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Dexamethasone	8mg	PO	Stat	
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 minutes	Sodium chloride 0.9% 50ml
	ATEZOLIZUMAB	**1875mg**	SC	7 mins	Inject 15 mL into the subcutaneous tissue of the left or right thigh over 7 minutes. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
	CARBOPLATIN	**AUC 5** **Dose = AUC X (GFR + 25)** **(max 750mg)**	IV	30 minutes	In glucose 5% 500ml
	ETOPOSIDE	**100mg/m²**	IV	I hour	In Sodium Chloride 0.9% 500-1000ml (doses >200mg in 1000ml Sodium chloride 0.9%)

TTO Induction cycles 1-4

TTO	Drug	Dose	Route	Directions
Day 1	**ETOPOSIDE**	**200mg/m² (max 400mg)** (round to the nearest 50 mg)	PO	OD on day **TWO** and **THREE** only. Take an hour before food or on an empty stomach.
	Dexamethasone	6mg	PO	OM for 3 days with or after food
	Metoclopramide	10mg	PO	Up to TDS for 3 days, then 10mg up to 3 times a day when required. Do not take for more than 5 days continuously.
	Ondansetron	8mg	PO	BD for 3 days.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Do not take for longer than 3 days without contacting the oncology team. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified.
	Filgrastim	300 micrograms or consider dose of 480 micrograms if patient > 80kg	S/C	Daily from Day 3 to Day 7

Maintenance Atezolizumab Sub cutaneous cycle 5 onwards
Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		
	ATEZOLIZUMAB	**1875mg**	SC	7 mins	Inject 15 mL into the subcutaneous tissue of the left or right thigh over 7 minutes. Do not inject at other sites of the body. Injection sites should be rotated for successive injections.
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	Up to TDS when required. (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	

Alternative Maintenance Atezolizumab Intravenous Schedule:
Cycle 5 onwards
Repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration Details
1	Metoclopramide	20mg	PO		
	ATEZOLIZUMAB	**1680mg**	IV	1st dose over 60 mins. If tolerated, all subsequent infusions over 30 mins	diluted in 250ml 0.9% sodium chloride
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	up to 3 times a day for 3 days, then 10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	