Indication	Atezolizumab plus bevacizumab, paclitaxel and carboplatin is recommended as an option for metastatic non-squamous non-small-cell lung cancer (NSCLC) in adults: • who have not had systemic therapy for their metastatic NSCLC before and whose PD-L1 tumour proportion score is between 0% and 49% and without EGFR activating mutations/ALK mutation. NB: Either no previous systemic therapy for NSCLC or the patient completed the last treatment with chemotherapy or chemoradiotherapy or checkpoint inhibitor immunotherapy as part of adjuvant/neoadjuvant/maintenance therapy at least 6 months prior to the first diagnosis of locally recurrent or metastatic disease. Or • for patients with EGFR, ALK, ROS1, MET exon 14 skipping alteration, KRAS G12C, RET gene fusion and BRAF mutation positive disease when appropriate targeted therapy has failed. NB: Previous treatment with an anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTL-4) antibody is not allowed unless the patient discontinued or completed checkpoint inhibitor immunotherapy as part of adjuvant/neoadjuvant/maintenance therapy without disease progression and at least 6 months elapsed between the date of the last immunotherapy treatment and the date of first diagnosis of relapse with recurrent or metastatic disease.
Treatment Intent	Palliative
Frequency and number of cycles	Every 21 days For 4 cycles of atezolizumab, bevacizumab, paclitaxel & carboplatin then atezolizumab & bevacizumab only (as maintenance), continuing until progressive disease or unacceptable toxicity or withdrawal of patient consent or a maximum duration of 2 years (35 cycles including the initial 4 induction cycles), whichever occurs first. A formal medical review **MUST** occur by the end of the first 6 weeks of treatment to establish whether treatment should continue. A CT scan should be done at the end of the first 4 cycles to confirm response before starting maintenance therapy. If bevacizumab is permanently discontinued, atezolizumab monotherapy may be continued until loss of clinical benefit or unacceptable toxicity. NB patients can be switched between atezolizumab SC and IV therapy if the clinical need arises.
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. • **Blood parameters:** • Monitor FBC, U&Es, and LFTs at each cycle. • If neuts <1.5 and/or PLT <100 defer treatment by one week and consider dose reduction of paclitaxel and carboplatin on subsequent cycles. • **ECG** at first cycle. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure. • Monitor for signs and symptoms of myocarditis. Carry out ECG 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.
- **Blood pressure:** Monitor blood pressure at each cycle. Pre-existing hypertension should be adequately controlled before starting treatment. Dipstick urine for proteinuria at each cycle. Report to consultant if protein 2+ (equivalent to 1g/l) and/or BP >/= 140/90 respectively. Reference should be made to KMCC guidelines for bevacizumab induced hypertension.
- EDTA should be used to measure GFR prior to cycle 1. C+G to estimate CrCl may only be used before CYCLE 1 when there is a delay in obtaining EDTA result.
- Discuss with consultant if creatinine clearance drops by 25%.
- **Dose reductions**
  - **Paclitaxel:** Dose reduce by 20% in the event of grade ≥ 2 neuropathy and consider delay until recovery to </= grade 1. Consider omitting Paclitaxel in event of recurrent grade >/=3 neuropathy OR recurrent or persistent >/= grade 2 neuropathy following a dose reduction.
  - **Due to increased haematological toxicities, it is recommended that the starting dose of paclitaxel should be 175mg/m² every three weeks in Asian patients.
  - Dose reduction of **carboplatin** and **paclitaxel** should be considered if any other 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.
  - **Bevacizumab:** Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended.
- **Renal**
  - **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.
  - **Bevacizumab:** No dose recommendations.
  - **Carboplatin:** Stop if CrCl<30ml/min.
  - **Paclitaxel:** No dose reduction necessary.
- **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 -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).
  - **Paclitaxel:** If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at full dose. Otherwise consider dose reduction, not recommended in severe hepatic impairment.
  - **Bevacizumab** and **carboplatin:** no dose recommendations
- **SC administration of atezolizumab:**
  - 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.
- **Infusion/injection-related reactions**

  If the infusion/injection related reaction can be attributed to a particular agent, treat as follows:

- **Atezolizumab:** 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.
- **Bevacizumab:** discontinue infusion and treat symptomatically. A systematic premedication is not warranted.
- **Paclitaxel:** Patients developing hypersensitivity reactions may be re-challenged with full dose paclitaxel following prophylactic medication (e.g. famotidine 40mg po given 4 hours prior to treatment plus hydrocortisone 100mg iv and chlorphenamine 10mg iv 30 minutes prior to treatment), then give paclitaxel over 3-6 hours (i.e. starting at over 6 hours and gradually increase rate if possible).

- **Adverse Reactions:**
- **Atezolizumab**

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 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.
- For guidance on managing immune-related adverse reactions, refer to SPC and guidelines available on KMCC website: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/
- Atezolizumab can affect the ability to drive and use machines. If patients experience fatigue they should not drive.

- **Bevacizumab**
  - Use with caution in patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression, after careful consideration of the potential risk-benefit.
  - Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation with bevacizumab. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

	○ Bevacizumab may adversely affect wound healing. Do not give bevacizumab if patient has undergone major surgery within the last 28 days. Treatment should be stopped prior to elective surgery. ○ Patients may be at increased risk for the development of fistulae when treated with bevacizumab. ○ Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with bevacizumab. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. ○ Caution should be exercised when bevacizumab and intravenous bisphosphonates are administered simultaneously or sequentially, as cases of osteonecrosis of the jaw have been reported. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with bevacizumab. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible. ○ Any suspected thrombosis and/or haemorrhage d/w consultant. ○ Patients with a history of arterial thromboembolism, diabetes or >65 years old should be treated with caution. • **<u>Drug interactions</u>:** ○ **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. ○ **Carboplatin:** Caution with other nephrotoxic drugs. ○ **Paclitaxel:** Avoid concomitant use of paclitaxel with CYP2C8 or CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin) and inhibitors (e.g. ketoconazole erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, nelfinavir). ○ Patients should not receive the flu vaccine unless the benefit outweighs the risk and after discussion between consultant and patient. • **<u>Delayed or missed doses:</u>** 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-038 v3 SPC accessed online 15.09.2023 CDF list v1.230 accessed online 22.09.22

NB For funding information, refer to CDF and 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	Metoclopramide	20mg	PO	Stat	
	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.
	BEVACIZUMAB	**15mg/kg**	IV	90min **cycle 1** If tolerated give as below 60min **cycle 2** 30min **cycle 3 onwards**	The final concentration must be between 1.4 and 16.5 mg/ml. In 100ml 0.9% sodium chloride. If the patient >/= 110kg give in total of 250mls sodium chloride 0.9%
	Dexamethasone	16mg*	IV	bolus	30 minutes prior to paclitaxel
	Chlorphenamine	10mg	IV	bolus	
	Ondansetron	< 75yrs 16mg >/=75yrs 8mg	IV	15min	In 50ml sodium chloride 0.9% 30 minutes prior to paclitaxel
	PACLITAXEL	**200mg/m² **(see notes above 175 mg/m² for patients of Asian origin)**	IV	Over 3 hours	Diluted in 500ml sodium chloride 0.9% (non-PVC) Via in-line 0.22micron filter Doses <150mg in 250ml 0.9% sodium chloride
	CARBOPLATIN	**(AUC 6) Dose = AUC X (GFR + 25) (max 700mg)**	IV	30min	500ml glucose 5%
	***From 3rd infusion dexamethasone maybe reduced to 12mg IV**				

Induction continued

TTO	Drug	Dose	Route	Directions
Day 1	Dexamethasone	6mg	PO	OM for 3 days with or after food
	Metoclopramide	10mg	PO	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.
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Do not take for longer than 3 days without contacting the oncology team. Dispense 30 capsules on cycle 1 then only if specified.
	Filgrastim	5mcg/kg	SC	Starting on day 3 for 5 days.

MAINTENANCE

Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO	stat	
	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.
	BEVACIZUMAB	**15mg/kg**	IV	90min **cycle 1** If tolerated give as below 60min **cycle 2** 30min **cycle 3 onwards**	The final concentration must be between 1.4 and 16.5 mg/ml. In 100ml 0.9% sodium chloride. If the patient >/= 110kg give in total of 250mls sodium chloride 0.9%
TTO	Drug	Dose	Route	Directions	
Day 1	Metoclopramide	10mg	PO	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.	