ATEZOLIZUMAB (Tecentriq) BEVACIZUMAB PACLITAXEL CARBOPLATIN

INDICATION (ICD10) C34

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (ATE4) (ATE5)

1. The first line treatment of adult patients with locally advanced or metastatic stage IIIB, IIIC or IV non-squamous non-small cell lung cancer or has disease that has recurred after potentially curative treatment with local management of NSCLC (no symptomatically active brain metastases or leptomeningeal metastases) with surgery/chemoradiotherapy/radiotherapy with a PD-L1 tumour proportion score of 0-49% and without EGFR and ALK mutations. The patient has not received any 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 an anti PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTL-4) antibody completed without disease progression at least 6 months prior to the first diagnosis of locally recurrent or metastatic disease. PS 0 or 1 and is fit for the combination of atezolizumab, bevacizumab, carboplatin (AUC 6) and paclitaxel (200mg/m²). (TA584)
2. The treatment of adult patients with EGFR activating mutation positive or ALK mutation positive or ROS1 mutation positive or MET exon 14 or KRAS G12C or RET or BRAF mutation positive stage IIIB, IIIC or IV or disease that recurred after potentially curative treatment with local management of NSCLC with surgery/chemoradiotherapy/radiotherapy or disease that recurred after potentially curative treatment with local management of NSCLC with surgery/chemoradiotherapy/radiotherapy locally advanced or metastatic non-squamous (No symptomatically active brain metastases or leptomeningeal metastases) non-small cell lung cancer after failure of appropriate targeted TKI therapy. Has not received prior 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 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. Fit for the combination of atezolizumab, bevacizumab, carboplatin (AUC 6mg/ml/min) and paclitaxel (200mg.m²). PS 0 or 1 and is fit for the combination of atezolizumab, bevacizumab, carboplatin (AUC 6) and paclitaxel (200mg/m²). (TA584)

REGIMEN SC

Cycles 1 to 4 (atezolizumab and bevacizumab can be given in any order)

Day 1 ATEZOLIZUMAB 1875mg SC
BEVACIZUMAB 15mg/kg in #ml sodium chloride 0.9% IV infusion
Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
Chlorphenamine 10 mg IV bolus
PACLITAXEL 200*mg/m^2 in #ml sodium chloride 0.9% IV infusion over 3 hours
CARBOPLATIN AUC 6 in #ml glucose 5% IV infusion over 30 minutes
Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC.
(Maximum dose when using CrCl 125+25 x AUC)

Cycles 5 to 35 (atezolizumab and bevacizumab can be given in any order)

Day 1 ATEZOLIZUMAB 1875mg SC
BEVACIZUMAB 15mg/kg in #ml sodium chloride 0.9% IV infusion

diluent volume for dose prescribed as per national standardised product specification
* a lower starting dose of paclitaxel 175mg/m²should be used in patients of Asian origin (SPC).

Atezolizumab 1875mg SC – Administer in the thigh over 7 minutes. Alternate thighs, administer at least 2.5cm from the old site.

REGIMEN IV

Cycles 1 to 4 (atezolizumab and bevacizumab can be given in any order)

Day 1 ATEZOLIZUMAB 1200mg in #ml sodium chloride 0.9% IV infusion
BEVACIZUMAB 15mg/kg in #ml sodium chloride 0.9% IV infusion
Premedication 30 minutes prior to infusion:
Dexamethasone 20 mg IV bolus
Chlorphenamine 10 mg IV bolus
PACLITAXEL 200*mg/m^2 in #ml sodium chloride 0.9% IV infusion over 3 hours
CARBOPLATIN AUC 6 in #ml glucose 5% IV infusion over 30 minutes
Dose calculated by EDTA GFR or calculated CrCl + 25 x AUC.
(Maximum dose when using CrCl 125+25 x AUC)

Cycles 5 to 35 (atezolizumab and bevacizumab can be given in any order)

Day 1 ATEZOLIZUMAB 1200mg in #ml sodium chloride 0.9% IV infusion
BEVACIZUMAB 15mg/kg in #ml sodium chloride 0.9% IV infusion

diluent volume for dose prescribed as per national standardised product specification
* a lower starting dose of paclitaxel 175mg/m²should be used in patients of Asian origin (SPC).

Atezolizumab 1200mg IV – The initial dose should be delivered over 60 minutes.
If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 minutes.
If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Bevacizumab - The initial dose should be administered over 90 minutes, if tolerated well the second infusion may be administered over 60 minutes.
If the 60 minute infusion is well tolerated all subsequent infusions may be administered over 30 minutes.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days paclitaxel and carboplatin for maximum 4 cycles
A formal medical review as to whether treatment with the combination of atezolizumab, bevacizumab, carboplatin and paclitaxel should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment.
Atezolizumab and bevacizumab may continue until disease progression or loss of clinical benefit up to total maximum 35 cycles (maximum 2 years) including the initial 4 induction cycles.

ANTI-EMETICS

Moderate risk day 1 cycles 1 to 4
Low risk day 1 cycles 5 to 35

CONCURRENT MEDICATION REQUIRED

Carboplatin	Anaphylaxis treatment should be prescribed if the patient has had an anaphylactic episode previously. Dexamethasone 20mg IV bolus Chlorphenamine 10mg IV bolus Carboplatin should be given at a slower rate e.g. 2-4 hours.
Paclitaxel	Ensure premedication given before paclitaxel

EXTRAVASATION AND TYPE OF LINE / FILTERS

Atezolizumab IV – neutral
Bevacizumab – neutral
Carboplatin - irritant
Paclitaxel – vesicant

Administer paclitaxel via polyethylene lined administration set with ≤0.22micron filter
Atezolizumab IV use of 0.2-5micron filter is optional
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs, creatinine day 1
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant's discretion.
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
Blood pressure every cycle
Urinalysis for proteinuria every cycle
Baseline weight and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Atezolizumab	Immune mediated pneumonitis Immune mediated hepatitis Immune mediated colitis Immune mediated endocrinopathies
Bevacizumab	Arterial thromboembolism Gastrointestinal perforation Haemorrhage Wound healing complications
Carboplatin	Ototoxicity – monitor Neurotoxicity - monitor
Paclitaxel	(2% risk of severe hypersensitivity) Reactions range from mild hypotension (light-headedness) to full cardiac collapse (anaphylactic shock). Discontinue infusion and resuscitate appropriate to reaction. If reaction is mild and settles promptly (ie within 5-10 minutes), cautiously restart at a slower rate under close supervision. If further reactions occur stop treatment.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Paclitaxel	DOACs to be used with caution, need dose modifications or to be avoided eg apixaban Clopidogrel interacts with paclitaxel Paclitaxel is catalysed, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. inhibitors (e.g. erythromycin, fluoxetine, gemfibrozil) use with caution. inducors (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) use with caution.

DOSE MODIFICATIONS
Non-haematological
Atezolizumab

Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline.

If the drug-related toxicity does not resolve to grade 0-1 within 12 weeks after onset of toxicity, discontinuation is recommended.

Bevacizumab

Hypertension

Baseline blood pressure should be <150/100mmHg.

Diastolic increase >20mmHg above baseline or BP rises to >150/100mmHg	Diastolic increase >20mmHg above baseline or BP rises to >150/100mmHg
Blood pressure >180/110mmHg	It is advised that bevacizumab therapy is withheld until blood pressure controlled.

Proteinuria

Urine dipstick result. 1+ or 2+ on dipstick (0.3–2.9g/L)	Continue with bevacizumab. No additional evaluation required.
3+ on dipstick (3-19g/L)	May have dose of bevacizumab as scheduled, but 24 hour urine to measure 24 hour protein to be done a few days before next cycle due. If 24hr protein result <2g, continue with bevacizumab, with continued proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to <1g/24hr, return to dipstick analysis. If ≥2g, withhold bevacizumab until repeat 24 hour urine collection shows <2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.
4+ on dipstick (≥20g/L)	Withhold bevacizumab. 24 hour urine required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Wound healing
Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. Therapy should also be withheld for at least 28–60 days before elective surgery.

Paclitaxel
If patient complains of tinnitus, tingling of fingers and/or toes or motor weakness discuss with Consultant or Registrar before administration
If grade ≥2 neuropathy, consider giving 75% dose
If grade >3 peripheral neuropathy is >grade 3 omit further paclitaxel

Hepatic impairment
Paclitaxel
In the absence of Gilbert's syndrome:

Transaminase <10xULN and bilirubin ≤1.25xULN	no dose reduction
Transaminase <10xULN and bilirubin 1.26-2xULN	give 77% of original dose
Transaminase <10xULN and bilirubin 2.01-5xULN	give 51% of original dose
Transaminase ≥10xULN or bilirubin >5xULN	contraindicated

Renal impairment
Carboplatin

GFR / calculated CrCl ≤20ml/min or ≤30ml/min with pre-existing severe renal impairment	contraindicated

REFERENCES
1. Socinski, M et al; NEJM 2018; 378: 2288-2301