Lancashire & South Cumbria Cancer Network
Systemic Anticancer Treatment Protocol

Drug regimen

Atezolizumab, Bevacizumab, Paclitaxel and Carboplatin

Indications for use

Locally advanced (stage IIIB or IIIC) or metastatic non-squamous non-small cell lung cancer (NSCLC) either:

- 1st line treatment in patients with PD-L1 tumour proportion score of 0-49% and without EGFR, ALK or ROS1 mutation, or

- Treatment in patients with EGFR, ALK or ROS1 mutation positive NSCLC after failure of appropriate targeted therapy

Patients must be registered on Blueteq. Further detailed eligibility criteria on Blueteq form.

Regimen

DRUG		FLUID	TIME
Immunotherapy & Anti-angiogenic antibody			
Atezolizumab	1200mg	250mls Sodium chloride 0.9%	see below
Bevacizumab	15mg/kg	100mls Sodium chloride 0.9%	see below
Premedication (30 mins pre chemotherapy)			
Chlorphenamine	10mg		IV bolus
Ranitidine	50mg	50mls Sodium chloride 0.9%	Stat
Dexamethasone	20mg	100mls Sodium chloride 0.9%	Stat
Ondansetron	8mg		IV bolus
Chemotherapy regimen			
Paclitaxel	200mg/m²	500mls Sodium chloride 0.9%	3 hours
Carboplatin	AUC 6	500mls Glucose 5%	1 hour

Administration notes:

Atezolizumab – initial dose must be delivered over 60 minutes, if tolerated without any infusion-associated adverse events then subsequent infusions may be delivered over 30 minutes.

Bevacizumab - initial dose must be delivered over 90 minutes, if tolerated without any infusion-associated adverse events then second infusion may be delivered over 60 minutes, if this is well tolerated then subsequent infusions may be delivered over 30 minutes.

Paclitaxel – patients of Asian race/ethnicity will receive a dose of 175mg/m² due to their increased risk of haematological toxicity.

Carboplatin – dose calculated using the Calvert formula:

Total dose (mg) = (target AUC) x (glomerular filtration rate + 25)

The GFR used in the Calvert formula should not exceed 125mL/min and therefore the maximum carboplatin dose for target AUC6 = 890mg; target AUC5 = 790mg; and target AUC4 = 600mg

Cycle should be repeated every 3 weeks for 4 cycles. Thereafter maintenance treatment with Atezolizumab and Bevacizumab every 3 weeks can continue until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent or for a maximum treatment duration of 2 years (or 35 3-weekly cycles), whichever occurs first.

Investigations prior to initiating treatment

FBC, U&Es, LFTs, Bone profile, Glucose, TFTs
Check BP and urine for proteinuria
Weight and vital signs
ECG
Serum samples for HIV, Hep C antibody and HBsAg if risk factors.
Pregnancy test (if applicable)

Cautions

Avoid concomitant use of systemic steroids or immunosuppressants before starting treatment

Investigations and consultations prior to each cycle

ECOG performance status
FBC, U&Es, LFTs,
TFTs every other cycle
Check BP before and after Bevacizumab infusion

Liver function tests may be retrospectively reviewed (i.e. after the chemotherapy treatment) **unless** they are known to be abnormal then they need to be repeated the day before so that the results are available pre-chemotherapy.

Acceptable levels for treatment to proceed

- AST and ALT ≤2.5 X ULN or ≤5 X ULN with liver metastases (see notes below regarding dose adjustments in hepatic impairment)
- Serum total bilirubin ≤1.25 X ULN (see notes below regarding dose adjustments in hepatic impairment)
- Serum creatinine ≤1.5 X ULN (large changes in creatinine may require modification of carboplatin dose, consult with pharmacy)
- Absolute neutrophil count >1.5 $x10^9$/L
- Platelets >100 $x10^9$/L
- Haemoglobin >9 g/dL
- BP < 180/110 mmHg (if BP >150/100 mmHg initiate or increase antihypertensive medication)

Check with consultant prior to any deferrals

Adverse effects

Immune mediated:
Pneumonitis, hepatitis, colitis, endocrinopathy (hypo and hyperthyroidism, adrenal insufficiency, diabetes), meningioencephalitis, neuropathy, pancreatitis

Infusion reactions

Other adverse events:
Alopecia, peripheral neuropathy, nausea/vomiting, fatigue, bone marrow suppression, hypertension, arthralgia, constipation, asthenia, epistaxis, myalgia, proteinuria, rash, stomatitis

Dose modifications

Ateozolizumab - The dose will not be modified.

Important:
For management of toxicities, consult network Immune Related Toxicity Management Guidelines and see table below

Adverse reaction	Severity	Treatment Modification
Pneumonitis	Grade 2	Withhold atezolizumab Start 1-2mg/kg methylprednisolone or equivalent 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 oral prednisone equivalent per day.
	Grade 3 or 4	Permanently discontinue atezolizumab Start 1-2mg/kg methylprednisolone or equivalent

Hepatitis	Grade 2: (ALT or AST >3-5x upper limit of normal [ULN] or blood bilirubin >1.5−3x ULN)	If persists > 5-7 days, withhold atezolizumab Start 1-2mg/kg methylprednisolone or equivalent Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids 1-2 mg/kg have been reduced to ≤ 10 mg oral prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST >5x ULN or blood bilirubin >3x ULN)	Permanently discontinue atezolizumab Start 1-2mg/kg methylprednisolone or equivalent
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥4 stools/day over baseline) or Symptomatic Colitis	Withhold atezolizumab Start 1-2mg/kg methylprednisolone or equivalent 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 oral prednisone equivalent per day
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue atezolizumab Start 1-2mg/kg methylprednisolone or equivalent
Hypothyroidism or hyperthyroidism	Symptomatic	Hypothyroidism: If asymptomatic can receive atezolizumab If symptomatic, withhold treatment and initiate thyroid hormone replacement as needed. Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing Hyperthyroidism: if asymptomatic can receive atezolizumab If symptomatic, withhold treatment and initiate anti hyperthyroid medication as needed. Treatment may be resumed when symptoms are controlled by methimazole or equivalent and thyroid function is improving

Adrenal insufficiency	Symptomatic	Withhold atezolizumab Start 1-2mg/kg methylprednisolone or equivalent Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone or equivalent per day and patient is stable on replacement therapy
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose >250-500 mg/dL)	Withhold atezolizumab Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related reactions	Grade 1	Reduce infusion rate to half Once the event has resolved, wait for 30 min while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to original rate
	Grade 2	Withhold atezolizumab Restart at half of the infusion rate only after the symptoms have resolved
	Grade 3 or 4	Permanently discontinue atezolizumab
Rash	Grade 3	Withhold atezolizumab Start 1-2mg/kg methylprednisolone or equivalent Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg oral prednisone equivalent per day
	Grade 4	Permanently discontinue atezolizumab Start 1-2mg/kg methylprednisolone or equivalent
Myasthenic syndrome / myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue atezolizumab Start 1-2mg/kg methylprednisolone or equivalent
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased	Withhold atezolizumab Start 1-2mg/kg methylprednisolone or equivalent, once symptoms

	(> 2x ULN) or Grade 2 or 3 pancreatitis	resolved follow with 1-2mg/kg oral prednisolone Treatment with atezolizumab 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 oral prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab Start 1-2mg/kg methylprednisolone or equivalent

Bevacizumab - The dose will not be modified.

Event	Action to Be Taken
Hypertension	
Grade 1 (asymptomatic, transient [< 24 hr] blood pressure increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits)	No bevacizumab dose modifications
Grade 2 (recurrent or persistent [> 24 hr] or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits)	Hold bevacizumab. Start antihypertensive therapy. Once blood pressure is < 150/100 mmHg, patient may continue bevacizumab therapy.
Grade 3 Requires more than one antihypertensive drug or more intensive therapy than previously:	If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Haemorrhage	
Grade 1 or 2 non-pulmonary or non-CNS events	No bevacizumab modifications
Grade 3 non-pulmonary or non-brain or non-spinal cord haemorrhage	Hold bevacizumab until all of the following criteria are met: · The bleeding has resolved and haemoglobin is stable. · There is no bleeding diathesis that would increase the risk of therapy. · There is no anatomic or pathologic condition that significantly increases the risk of haemorrhage recurrence. Patients who experience a repeat Grade 3 haemorrhagic event will be discontinued from bevacizumab.
Grade 4 non-pulmonary or non-brain or non-spinal cord haemorrhage	Discontinue bevacizumab.

Haemorrhage (cont.)	
Grade 1 pulmonary or brain or spinal cord haemorrhage	Hold bevacizumab until all of the following criteria are met: · The bleeding has resolved and haemoglobin is stable. · There is no bleeding diathesis that would increase the risk of therapy. · There is no anatomic or pathologic condition that significantly increases the risk of haemorrhage recurrence.
Grade 2, 3, or 4 pulmonary or brain or spinal cord haemorrhage	Discontinue bevacizumab.
Venous thromboembolic event	
Grade 1 or 2	No bevacizumab modifications.
Grade 3 or asymptomatic Grade 4	If the planned duration of full-dose anticoagulation is 〈2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is 〉 2 weeks, bevacizumab may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met: · The patient must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting study treatment. · The patient must not have had a Grade 3 or 4 haemorrhagic event while on anticoagulation.
Symptomatic Grade 4	Discontinue bevacizumab.
Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Congestive heart failure (left ventricular systolic dysfunction)	
Grade 1 or 2	No bevacizumab modifications.
Grade 3	Hold bevacizumab until resolution to Grade ≤1.
Grade 4	Discontinue bevacizumab.
Proteinuria	
Grade 1 (urine dipstick 1+ or urine collection 0.15 to 1.0 g/24 hr)	No bevacizumab modifications
Grade 2 (urine dipstick 2+ to 3 + or urine collection 〉 1.0 to 3.5 g/24 hr)	For 2 + dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose. For 3 + dipstick, obtain 24-hour urine prior to administration of bevacizumab. Hold bevacizumab for proteinuria >2 g/24 hr and resume when proteinuria is ≤ 2 g/24 hr.

Grade 3 (urine dipstick 4+ or urine collection >3.5 g/24 hr)	Hold bevacizumab. Resume when proteinuria is ≤2 g/24 hr.
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab.
GI perforation	
Any grade	Discontinue bevacizumab.
Fistula	
Any grade tracheoesophageal fistula	Discontinue bevacizumab.
Grade 4 fistula (other than tracheoesophageal)	Discontinue bevacizumab.
Bowel obstruction	
Grade 1	Continue for partial obstruction not requiring medical intervention.
Grade ≥ 2	Discontinue bevacizumab.
Wound dehiscence	
Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab.
Reversible posterior leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab.

Paclitaxel and Carboplatin – Dose modification

For neutropenic fever or Grade 4 neutropenia consider GCSF or 25% dose reduction of both Paclitaxel and Carboplatin.

For Grade 3 or 4 gastrointestinal toxicities (diarrhoea, mucositis, vomiting) reduce both Paclitaxel and Carboplatin by 25%.

Paclitaxel dose modification for hepatic toxicity

AST levels		Bilirubin levels	Paclitaxel reduction from starting dose
<10 × ULN	AND	≤1.25 × ULN	No change
<10 × ULN	AND	1.26–2.0 × ULN	25%
<10 × ULN	AND	2.01–5.0 × ULN	50%
>10 × ULN	OR	>5.0 × ULN	Discontinue paclitaxel*

For Grade 2 or worse neuropathy reduce Paclitaxel dose by 25%.

Paclitaxel allergic reaction / hypersensitivity

CAUTION: Patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but the administration of prophylactic medication and intensive monitoring of vital signs is recommended. Patients with severe reactions should not be rechallenged.

· Mild symptoms: Complete paclitaxel infusion with close supervision. No treatment required.

· Moderate symptoms: Stop paclitaxel infusion. Give IV chlorphenamine 10 mg and IV hyrdocortisone 100-200 mg. Resume paclitaxel infusion after recovery of symptoms at a low rate, 20 mL/hour for 15 minutes, then 40 mL/hour for 15 minutes, then if no further symptoms, at full-dose rate until infusion is complete. If symptoms recur, stop paclitaxel infusion. Paclitaxel treatment will be discontinued.

· Severe life-threatening symptoms: Stop paclitaxel infusion. Give IV chlorphenamine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. Paclitaxel treatment will be discontinued.

THIS PROTOCOL HAS BEEN DIRECTED BY DR LAU, CLINICIAN FOR LUNG CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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