Atezolizumab, Bevacizumab, Carboplatin and Paclitaxel

Indication

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 details

DRUG	DOSE	FLUID	RATE
SC Atezolizumab or **IV** Atezolizumab	1875mg 1200mg	 250mL sodium chloride 0.9%	7 minutes See below
Bevacizumab	15mg/kg	100mL sodium chloride 0.9%	See below

Give Pre-medications (see below)

DRUG	DOSE	FLUID	RATE
Paclitaxel	200mg/m^2 *	500mL Sodium Chloride	3 hours
Carboplatin	AUC 5 $^+$	500mL Glucose 5%	30-60 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 frequency

Repeat every 21 days

Number of cycles

Initially 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

Administration

Atezolizumab IV – 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.

Atezolizumab SC - Prior to administration, remove Tecentriq SC formulation from refrigeration and allow the solution to reach room temperature.
Administer solution for injection subcutaneously in the thigh in approximately 7 minutes.

Bevacizumab – check blood pressure before infusion. 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 must be administered via a compatible giving set with a 0.2micron in-line filter
Paclitaxel must be given before carboplatin

Pre-medication

30 mins before **chemotherapy**

Chlorphenamine	10mg		IV bolus
Dexamethasone	20mg	in 100mls Sodium chloride 0.9%	STAT
Ondansetron	8mg		IV Bolus

Emetogenicity

Atezolizumab - minimal
Bevacizumab - Minimal
Carboplatin - Moderate
Paclitaxel - Low

Additional supportive medication

None

Extravasation

Atezolizumab - neutral
Bevacizumab - neutral
Carboplatin - Vesicant
Paclitaxel - Vesicant

Investigations – pre first cycle

Investigation	**Validity period**
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Bone profile	14 days
Glucose	Baseline
TFTs	Baseline
Weight and vital signs	Baseline
BP and urine for proteinuria	Baseline
ECG	Baseline
Serum samples for HIV, Hep C antibody and HBsAg if risk factors	Baseline
Pregnancy test (if applicable)	Baseline
Cortisol	Baseline
LH/FSH	Baseline
Testosterone	Baseline

Pre-existing blood pressure must be controlled before starting treatment
Prior radiotherapy is a risk factor for the development of fistulae
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms

and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension, history of aneurysm, or dissection.

Investigations –pre subsequent cycles

ECOG performance status, FBC, U+E (including creatinine), LFT (including AST)

TFTs every other cycle

Check BP before 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.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Absolute Neutrophil count	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Haemoglobin	>9g/dL
Serum creatinine	≤ 1.5 x ULN (large changes in creatinine may require modification of carboplatin dose, consult with pharmacy)
Bilirubin	≤ 1.25 x ULN (see notes below regarding dose adjustments in hepatic impairment)
AST and ALT	≤2.5 X ULN or ≤5 X ULN with liver metastases (see notes below regarding dose adjustments in hepatic impairment)
BP	< 180/110 mmHg (if BP >150/100 mmHg initiate or increase antihypertensive medication)

Check with consultant prior to any deferrals

Dose modifications

Atezolizumab - The dose will not be modified.

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

Immune-mediated adverse reaction	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	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
	Grade 3 or 4	Permanently discontinue Atezolizumab
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 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
	Grade 3 or 4: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x ULN)	Permanently discontinue Atezolizumab
Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3x to ≤ 10x ULN	Withhold Atezolizumab Treatment may be resumed when the event improves

	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	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 Atezolizumab
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic Colitis	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
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	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 prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	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 prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	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
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected 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 prednisone or equivalent per day
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Permanently discontinue Atezolizumab
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome,	Facial paresis Grade 1 or 2	Withhold Atezolizumab Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding Atezolizumab, permanently discontinue Atezolizumab

Meningoencephalitis and Facial paresis	All Grades Myasthenic syndrome/myasthenia gravis, Guillain Barré syndrome and Meningoencephalitis or Facial paresis Grade 3 or 4	Permanently discontinue Atezolizumab
Myelitis	Grade 2, 3, or 4	Permanently discontinue Atezolizumab
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 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 prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue Atezolizumab
Myocarditis	Grade 2 or above 4	Permanently discontinue Atezolizumab
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 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
	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue Atezolizumab
Myositis	Grade 2 or 3	Withhold Atezolizumab
	Grade 4 or Grade 3 recurrent myositis	Permanently discontinue Atezolizumab
Pericardial disorders	Grade 1 pericarditis	Withhold Tecentriq[2]
	Grade 2 or above	Permanently discontinue Atezolizumab
Other immune-mediated 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 ≤ 10 mg prednisone or equivalent per day
	Grade 4 or recurrent Grade 3	Permanently discontinue Atezolizumab (except endocrinopathies controlled with replacement hormones)
Other adverse reactions	**Severity**	**Treatment modification**
Infusion-related reactions	Grade 1 or 2	Reduce injection rate or pause the injection. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue Atezolizumab

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.
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.

See network policy for hypersensitivity reaction

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Immune reactions
Infertility
Teratogenicity
Hypersensitivity reactions
Pulmonary fibrosis, pneumonitis, interstitial lung disease
Pancreatitis
Hepatitis
Colitis
Endocrinopathies
Nephrotoxicity
Electrolyte disturbances
Arrhythmias
Cardiac failure
Arterial/venous thromboembolism
GI perforation, fistulas
Osteonecrosis of the jaw
Reversible posterior leukoencephalopathy
Wound healing complications

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Myelosuppression
Diarrhoea, constipation
Peripheral neuropathy
Oedema
Phlebitis
Myalgia, arthralgia
Alopecia
Fatigue
Hypertension
Proteinuria
Hyperthyroidism, hypothyroidism

- **Other side effects**

Flu-like symptoms
Taste changes
Headache
Abdominal pain
Deranged liver function
Guillain-Barre syndrome

Significant drug interactions

– for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
Clozapine: increased risk of agranulocytosis

Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity with carboplatin.
Diuretics: increased risk of nephrotoxicity and ototoxicity with carboplatin.
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin.

No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab.

Corticosteroids: 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 immunerelated adverse reactions after starting atezolizumab.

Additional comments

References

- Socinski, M et al; Atezolizumab for First-Line Treatment of Metastatic Non-squamous NSCLC. NEJM 2018; 378: 2288 – 2301
- Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer Technology appraisal guidance [TA584]Published: 05 June 2019.

THIS PROTOCOL HAS BEEN DIRECTED BY DR LAM, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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