Atezolizumab, Bevacizumab, Carboplatin and Paclitaxel

Indication

First line treatment of metastatic non-squamous, non-small-cell lung cancer (NSCLC) in patients whose PD-L1 tumour proportion score is between 1% and 49%.

Treatment of patients with epidermal growth factor receptor (EGFR)-positive or anaplastic lymphoma kinase (ALK) positive NSCLC when targeted therapy has failed. (Tumours with any level of PDL1 expression are eligible)

(NICE TA584)

ICD-10 codes

Codes pre-fixed with C34

Regimen details

Day	Drug	Dose	Route
1	Atezolizumab	1200mg	IV infusion
1	Bevacizumab	15mg/kg	IV infusion
1	Paclitaxel	200mg/m²^	IV infusion
1	Carboplatin	AUC 6*	IV infusion

^Consider starting dose of 175mg/m² for patients of Asian origin (increased risk of haematological toxicity)

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
CrCl should be capped at 125mL/min.

Cycle frequency

21 days

Number of cycles

Carboplatin and paclitaxel 4 cycles.

Atezolizumab and bevacizumab to stop after 2 years of uninterrupted treatment (or 35 x 3 weekly cycles, including the 4 initial induction cycles) or earlier if there is loss of benefit (Atezolizumab) or disease progression (Bevacizumab).

Administration

Atezolizumab is administered in 250mL sodium chloride 0.9% over 60 minutes. If the initial infusion is well tolerated, subsequent infusions may be administered over 30 minutes.

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion-related reactions. For grade 1-2 infusion-related reactions, decrease the infusion rate and closely monitor or temporarily interrupt treatment. Premedication with paracetamol and chlorphenamine should be used for further doses and patient should be closely monitored. For grade 3-4 infusion-related reactions discontinue treatment.
Bevacizumab is administered as an intravenous infusion in sodium chloride 0.9% to a final concentration of between 1.4 and 16.5mg/mL. Doses up to 1650mg are administered in 100mL sodium chloride 0.9%, doses greater than 1650mg are administered in 250mL sodium chloride 0.9%.

Bevacizumab may be administered before or after chemotherapy. The first infusion must be given over 90 minutes. If tolerated, the next infusion can be given over 60 minutes; if this is also tolerated, subsequent infusions can be given over 30 minutes.

Bevacizumab should not be initiated for at least 28 days following major surgery or until the wound is fully healed. For elective surgery, bevacizumab should be withheld for 28-60 days. For minor surgery (including port placement) bevacizumab should be withheld for 7 days following surgery.

Paclitaxel is administered in a 500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 3 hours.
Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

Carboplatin should be administered in 250mL glucose 5% over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of bevacizumab, paclitaxel or carboplatin. Facilities for the treatment of hypotension and bronchospasm **must** be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of bevacizumab, paclitaxel or carboplatin and appropriate therapy should be initiated.

Pre-medication

30 minutes prior to each paclitaxel infusion:

Chlorphenamine 10mg IV slow bolus
Dexamethasone 16-20mg IV slow bolus

Emetogenicity

This regimen has high emetic potential (cycles with chemotherapy) and mild emetic potential (atezolizumab and bevacizumab alone)

Additional supportive medication

H_2 antagonist or proton pump inhibitor if required.
Loperamide if required.
Mouthwashes as per local policy.
Antihypertensives may be required to manage hypertension commonly observed with bevacizumab therapy.

Extravasation

Atezolizumab is neutral (Group 1)
Bevacizumab is neutral (Group 1)
Carboplatin is irritant (Group 3)
Paclitaxel is vesicant (Group 5)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days
Thyroid function	14 days
Glucose	14 days
Cortisol	14 days
Blood pressure (BP)	on day 1
Proteinuria (dipstick)	on day 1

Baseline formal measurement of GFR if suspected or significant renal dysfunction.
Cardiac assessment is also required with ECHO for patients with significant cardiac history or prior chest wall radiation or anthracycline treatment.
Pre-existing hypertension should be adequately controlled before commencing treatment with bevacizumab.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours (7 days during maintenance phase)
U+E (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	7 days
Thyroid function*	7 days
Glucose*	7 days
Cortisol*	7 days
Blood pressure	Before each bevacizumab dose (more frequently if hypertension)
Proteinuria (dipstick)	Before each bevacizumab dose^

* Every cycle for the first 12 weeks, then every other cycle.

^If 3+ on dipstick perform 24 hour urinalysis and delay bevacizumab until <2g/24 hours.

Standard limits for administration to go ahead

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

Investigation	**Limit**
Neutrophils	≥ 1.5 10^9/L
Platelets	≥ 100 x 10^9/L
Bilirubin	< 1 x ULN
AST/ALT	< 2.5 x ULN
Creatinine Clearance (CrCl)	> 30 mL/min (and < 10% change)
Blood pressure	<150/100mmHg

Baseline blood pressure should be < 150/100mmHg. Pre-existing hypertension should be adequately controlled before starting bevacizumab.

Dose modifications

Dose reduction is not recommended for atezolizumab or bevacizumab; doses should be withheld or discontinued.

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Carboplatin dose**	**Paclitaxel dose**
≥ 1.5	and	≥ 100	100%	100%
< 1.5	or	50 - 100	Delay 1 week or until recovery. If longer than 3 weeks then reduce dose to AUC 4.5	Delay 1 week or until recovery. If longer than 3 weeks then reduce dose to 150mg/m^2
< 1.5	and	50 - 100	Delay 1 week or until recovery. Then reduce dose to AUC 4.5	Delay 1 week or until recovery. Then reduce dose to 150mg/m^2
Any		<25 or <50 with bleeding	Delay 1 week or until recovery. Then reduce dose to AUC 4.5	Delay 1 week or until recovery. Then reduce dose to 150mg/m^2
Febrile neutropenia			Delay 1 week or until recovery. Then reduce dose to AUC 4.5	Delay 1 week or until recovery. Then reduce dose to 150mg/m^2

If a second episode of neutropenic fever or thrombocytopenia requiring dose reduction occurs, another 25% dose reduction of carboplatin and paclitaxel is recommended. Chemotherapy should be discontinued if a third episode occurs.

Atezolizumab and Bevacizumab only:
Discuss with the consultant if:
WBC <2.0 x 10^9/L
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

- **Renal impairment**

If calculated CrCl falls by >10% from previous dose, consider dose recalculation.

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	Measure GFR then 100% dose (or consider changing to non-nephrotoxic regimen)
< 20	Contra-indicated

No dose modifications required for paclitaxel.

There is no data regarding administration of bevacizumab in patients with renal impairment and dose modification should not be required.

For atezolizumab no dose modifications required for mild to moderate renal impairment. There are no recommendations for patients with severe renal impairment.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Carboplatin dose**	**Paclitaxel dose**
<1.25 x ULN	and	<5	100%	100%
1.25-2.0	and		100%	75%
2.0-5.0	and		80-100%	50%
> 5.0	or	≥5	Not recommended (consultant decision)	

There is no data regarding administration of bevacizumab in patients with hepatic impairment and dose modification should not be required. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

No modifications of atezolizumab are required for mild hepatic impairment. Atezolizumab has not been studied in moderate or severe hepatic impairment.

- **Other toxicities**

Carboplatin and Paclitaxel

Toxicity	Definition	Carboplatin dose	Paclitaxel dose
Fatigue	Grade 3	100%	1st occurrence – 150mg/m^2, if persistent 90mg/m^2 or omit.
Neuropathy	Grade 2	100%	1st occurrence – 150mg/m^2 for all future cycles, if persistent 100mg/m^2 or omit
	Grade ≥ 3		Withhold until ≤ Grade 1, restart at 100mg/m^2.
Arthralgia/Myalgia	Grade ≥ 2	100%	Consider diclofenac +/- co-codamol or prednisolone 10mg BD for 5 days starting 24 hours post paclitaxel. If persists reduce dose to 135mg/m^2

For all other grade 3 toxicities (except alopecia and nausea and vomiting) withhold until grade ≤ 1 and continue with 75% doses. If further toxicity, consider additional dose reduction, discuss with consultant.

For any grade 4 toxicity (except alopecia and nausea and vomiting) withhold and discuss with consultant.

Bevacizumab

Toxicity	Definition	Dose adjustment
Infusion related reactions	Grade ≤ 2	**90 minute infusion**: premedication prior to next dose and give over 90 minutes (if tolerated may reduce infusion duration for future cycles with premedication) **60 minute infusion**: all subsequent doses should be given over 90 minutes with premedication. **30 minute infusion**: all subsequent doses should be given over 60 minutes with premedication.
	Grade >2	Discontinue bevacizumab
Hypertension	Grade 1 Increase of >20 mmHg (diastolic) or >140/90 mmHg (previously within normal limits) asymptomatic and transient (<24 hours)	Recheck 1 hour later: - if <140/90 mmHg – administer as normal - if 140/90 mmHg - 150/100 mmHg –administer and recheck BP 48 hours later (commence antihypertensives if BP remains >140/90 mmHg). - if >150/100 mmHg – omit and recheck BP 48 hours later (commence antihypertensives if BP remains >140/90 mmHg).
	Grade 2 Recurrent or persistent (> 24 hours) increase by 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits	Withhold bevacizumab. Commence antihypertensive medication. Once BP <140/90 mmHg restart treatment.
	Grade 3 Persistent BP > 140/90mmHg, requiring increase in antihypertensive treatment	Withhold bevacizumab. If hypertension cannot be controlled permanently discontinue treatment.
	Grade 4 Hypertensive crisis	Permanently discontinue bevacizumab.
Proteinuria	1+ or 2+	Continue bevacizumab.

	3+	Continue bevacizumab, with 24 hour urinalysis prior to next cycle, then: - if <2g continue treatment with 24 hour urinalysis prior to each dose. If falls to <1g return to dipstick analysis. - if ≥2g withhold until repeat urinalysis <2g then restart treatment with 24 hour urinalysis prior to each dose.
	4+	Withhold bevacizumab. 24 hour urinalysis. Then treat as above.
	Nephrotic syndrome	Permanently discontinue bevacizumab

Atezolizumab

For suspected immune related adverse events, atezolizumab should be withheld and corticosteroids administered. Once symptoms resolved to ≤ Grade 1 the corticosteroid dose should be tapered over 1 month.

Toxicity	Definition	Dose adjustment
Pneumonitis	Grade 2	Withhold atezolizumab Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 3-4	Permanently discontinue
Hepatitis	Grade 2 Bilirubin 1.5-3 x ULN and/or AST/ALT 3-5 x ULN	Withhold atezolizumab Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 3-4 Bilirubin > 3 x ULN and/or AST/ALT > 5 x ULN	Permanently discontinue atezolizumab
Colitis	Grade 2-3 diarrhoea or Symptomatic colitis	Withhold atezolizumab Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent)
	Grade 4 diarrhoea or colitis	Permanently discontinue atezolizumab
Hypo or hyperthyroidism	Symptomatic	Hypothyroidism Withhold atezolizumab Treatment may resume once symptoms controlled with thyroid replacement and TSH levels reducing.
		Hyperthyroidism Withhold atezolizumab Treatment may resume once symptoms controlled with anti-thyroid medication and thyroid function is improving.
Adrenal insufficiency	Symptomatic	Withhold atezolizumab Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
Hypophysitis	Grade 2-3	Withhold atezolizumab

		Resume once ≤ Grade 1 (within 12 weeks) and when corticosteroids ≤ 10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
	Grade 4	Permanently discontinue
Insulin dependent diabetes mellitus	Grade 3-4 hyperglycaemia	Withhold atezolizumab Resume once metabolic control achieved with insulin therapy.
Rash	Grade 3	Withhold atezolizumab Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 4	Permanently discontinue atezolizumab
Myasthenic syndrome/ myasthenia gravis/Guillain-Barre	Any grade	Permanently discontinue atezolizumab
Pancreatitis	Grade 2-3 (or Grade 3-4 increase in amylase or lipase)	Withhold atezolizumab Resume once amylase and lipase levels ≤ Grade 1 (within 12 weeks) or where symptoms have resolved and when corticosteroids reduced to ≤10mg/day prednisolone (or equivalent) and patient is stable on replacement therapy.
	Grade 4 or recurrent pancreatitis	Permanently discontinue atezolizumab
Myocarditis	Grade 2	Withhold atezolizumab Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 3 and 4	Permanently discontinue atezolizumab
Nephritis	Grade 2 (creatinine >1.5-3 x baseline or ULN)	Withhold atezolizumab Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 3 or 4 (creatinine > 3 x baseline or ULN)	Permanently discontinue atezolizumab
Other immune related adverse events	Grade 2 or 3	Withhold atezolizumab Resume once ≤ Grade 1 and when corticosteroids reduced to ≤ 10mg/day prednisolone (or equivalent)
	Grade 4 or recurrent grade 3	Permanently discontinue atezolizumab

<u>Permanently discontinue</u> treatment in patients with the following symptoms:

- Any grade 4 toxicity, except endocrinopathies that are controlled with replacement hormones.
- Any recurrent Grade 3 toxicity.
- Any treatment related toxicity that does not resolve to ≤ Grade 1 within 12 weeks after onset.
- If a corticosteroid dose ≥ 10mg/day prednisolone (or equivalent) is required for toxicity beyond 12 weeks after onset.

Adverse effects - for full details consult product literature/ reference texts

- **Rare or 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 immune-related adverse reactions after starting atezolizumab.

Additional comments

Bevacizumab is contraindicated in patients who have a history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies.
Bevacizumab should be used with caution in patients with:
• Untreated central nervous system metastases
• Uncontrolled hypertension
• History or risk factors for thromboembolic events
• Significant cardiac risk factors for development of congestive heart failure

The prescriber must discuss the risks of treatment with the patient and they will be issued with the Atezolizumab Patient Alert Card and advised to carry the card at all times.

References

- Summary of Product Characteristics Carboplatin (Hospira) accessed 26 June 2019 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Hospira) accessed 26 June 2019 via www.medicines.org.uk
- Summary of Product Characteristics - Bevacizumab (Roche) accessed 26 June 2019 via www.medicines.org.uk
- Summary of Product Characteristics Atezolizumab (Roche) accessed 26 June 2019 via www.medicines.org.uk
- National Institute for Health and Care Excellence TA584 accessed 26 June 2019 via www.nice.org.uk
- Socinski, M et al; Atezolizumab for First-Line Treatment of Metastatic Non-squamous NSCLC. NEJM 2018; 378: 2288 – 2301
- Reck M et al; Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150) Lancet 2019: 7. 5 387-401.

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