SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

Atezolizumab, Bevacizumab, Paclitaxel and Carboplatin Non-Small Cell Lung Cancer (NSCLC)

PROTOCOL REF: MPHAABPCLU
(Version No: 1.3)

Approved for use in

Stage IIIB, IIIC or IV **non-squamous NSCLC** or disease that recurred after potentially curative treatment with local management of NSCLC with surgery/chemoradiotherapy/radiotherapy has been approved by NICE for the following two indications:

- EGFR, ALK, ROS1, MET exon 14, KRAS G12C, RET or BRAF mutation positive locally advanced or metastatic NSCLC after failure of appropriate targeted therapy.
  OR
- Locally advanced or metastatic non-squamous NSCLC with a PD-L1 tumour proportion score of 0-49% and without EGFR, ALK or ROS1 mutations.

Both indications require the following eligibility criteria:

- Previous systemic therapy for NSCLC PERMITTED provided the last treatment with chemotherapy or chemoradiotherapy or checkpoint inhibitor immunotherapy as part of adjuvant/neoadjuvant/maintenance therapy was completed at least 6 months prior to the first diagnosis of locally recurrent or metastatic disease.
- 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 as part of adjuvant/neoadjuvant/maintenance therapy is PERMITTED provided this was

completed or discontinued WITHOUT disease progression on treatment and at least 6 months elapsed between the date of last immunotherapy treatment to the date of the first diagnosis of relapse with recurrent or metastatic disease.

- ECOG PS 0-1 – it is important to select patients who are predicted to tolerate higher doses of chemotherapy.

BLUETEQ REGISTRATION REQUIRED

Exclusions

- History of pneumonitis, organ transplantation, autoimmune disorders, HIV infection, myocarditis, active hepatitis B or C infection
- Active infection requiring systemic treatment
- Less than 4 weeks from major surgery
- History of clinically severe autoimmune disease (can proceed with immunotherapy if well controlled autoimmune disease at the discretion of the clinical team, this needs to be documented on Meditech).
- Patient with active CNS disease (symptomatic despite steroid treatment)- treatment at the discretion of the clinical team.
- Carcinomatosis meningitis
- Pregnancy or breast feeding

Dosage

SUBCUTANEOUS ADMINISTRATION OF ATEZOLIZUMAB IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT

Cycles 1 to 4- INDUCTION

Drug	Dose	Route	Frequency
Atezolizumab	**1875mg (flat dose)**	SC	Day 1 only Every 3 weeks
OR			

Atezolizumab	**1200mg (flat dose)**	IV infusion	Day 1 only Every 3 weeks
Paclitaxel	*200mg/m²	IV Infusion	Day 1 only Every 3 weeks
Carboplatin	AUC 6		
Bevacizumab	15mg/kg		

*** Lower starting dose of paclitaxel 175mg/m²should be used in patients of Asian origin due to increased incidence of haematological toxicity observed in this patient group in IMpower150 trial.**

As with all taxane and platinum based chemotherapy, patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment. It should be strongly noted that patients who have severe reactions should not be re-challenged.

Cycle 5 onwards- MAINTENANCE Atezolizumab with Bevacizumab

SUBCUTANEOUS ADMINISTRATION OF ATEZOLIZUMAB IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT

Drug	Dosage	Route	Frequency	Duration of Treatment
Atezolizumab	1875mg** (Flat dose)	Subcutaneous Injection	3 weekly	Disease progression or unacceptable toxicity to maximum duration of 2 years*
OR				
Atezolizumab	1200mg (Flat dose)	IV Infusion	3 weekly	Disease progression or unacceptable toxicity to a maximum duration of 2 years*

Bevacizumab	15mg/kg	IV Infusion	3 weekly	Disease progression or unacceptable toxicity to a maximum duration of 2 years*

*Maximum of 35 x 3-weekly cycles of atezolizumab and bevacizumab including the initial 4 induction cycles of treatment.

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). For **grade 1-2 injection site reactions** the following pre-medication to subsequent cycles and administered ahead of **SUBCUTANEOUS DOSE**:

- Paracetamol PO 1g
- Chlorphenamine PO 4mg

Please refer to the CCC Hypersensitivity; Management Prevention Policy.

Carboplatin

Meditech calculates creatinine clearance/GFR using the Wright formula (application for using Wright formula is available on the Remote Citrix Web Portal). Please refer to 'Carboplatin Dosing Calculator' SOP outlining process for checking carboplatin dose ahead of each cycle of treatment.

Creatinine clearance should be capped at 125mL/min for carboplatin

Calvert formula for Carboplatin dosage-:

Carboplatin dose in mg = AUC x (GFR or CrCl + 25)

Bevacizumab

Should be withheld for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

For minor surgery, including port placement, it is recommended that bevacizumab is withheld for 7 days after surgery.

Counselling Points

Women of childbearing potential should use effective contraception throughout treatment and for at least 5 months following the last dose of atezolizumab and 6 months after the last dose of Bevacizumab.

Please contact the triage line if any of the following symptoms occur:

- Easy bruising or bleeding.
- Uncontrolled nausea, vomiting or constipation.
- Severe jaw pain or headache.
- Redness, swelling, pain or sores where the needle was place or along the arm.
- Redness, swelling, pain or sores on your lips, tongue, mouth or throat.
- Skin rash or itching.
- Ringing in your ears or hearing problems.
- Numbness or tingling in feet or hands or painful leg cramps.
- Signs of anaemia such as unusual tiredness, shortness of breath or weakness.
- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain (with or without blood/mucous)

- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitor for signs of infection / sepsis
- Subcutaneous injection ONLY: monitor for injection site reaction- pain, swelling and rash.

Emetogenic risk:

Cycles 1 to 4: Moderately emetogenic.

Cycle 5 onwards: Mildly emetogenic.

Extravasation risk:

Refer to the CCC policy for the '**Prevention and Management of Extravasation Injuries**'.

Carboplatin- IRRITANT

Paclitaxel- VESICANT

Atezolizumab- NEUTRAL

Bevacizumab- NEUTRAL

Supportive Treatments:

Cycles 1 to 4

- Dexamethasone orally 4mg twice daily for 3 days
- Metoclopramide 10mg orally up to 3 times a day as required. Administration for a maximum of 5 consecutive days.
- Ondansetron 8mg twice a day when required for nausea and vomiting.
- Aprepitant 125mg orally 1 hour before treatment on day 1 then 80mg once a day 1 hour before treatment on days 2 and 3 (2nd line anti-emetic).

- Filgrastim to be supplied as primary (≥ 1 risk factor*) or secondary prophylaxis – subcutaneous (SC) injection daily for 7 days starting on day 5, dose as follows:
- Weight < 70kg- Filgrastim 300 micrograms daily SC.
- Weight ≥ 70kg- Filgrastim 480 micrograms daily SC.

*Risk factors for neutropenic sepsis:

- ✓ Prior chemotherapy or radiotherapy
- ✓ Persistent neutropenia
- ✓ Bone marrow involvement by tumour
- ✓ Recent surgery and/or open wounds
- ✓ Liver dysfunction (bilirubin > 43 micromol/dl)
- ✓ Renal dysfunction (creatinine clearance <50ml/min)
- ✓ Age >65 years receiving full chemotherapy dose intensity

Dosing in renal and hepatic impairment:

Renal	Atezolizumab	GFR ≥ 30ml/min- proceed with treatment GFR < 30ml/min- limited data use with caution
	Carboplatin	Patients with creatinine clearance values of less than 60 mL/min are at greater risk of developing myelosuppression. Carboplatin is eliminated primarily in the urine and is nephrotoxic. If there is any significant renal toxicity discuss with consultant before proceeding. Ahead of each cycle of treatment calculate creatinine (CrCl) clearance using the Wright formula (refer to 'Administration' Section)

		Carboplatin is contraindicated if CrCl ≤ 20 ml/min. Do not give carboplatin and discuss with clinical team. <u>Creatinine clearance should be capped at 125mL/min</u>
	Paclitaxel	All grades including patients on haemodialysis - no dose adjustment required.
	Bevacizumab	The kidneys are not a major organ for Bevacizumab metabolism or excretion. Therefore no data regarding renal impairment. Mild to moderate (GFR >15ml/min) - proceed with treatment. Severe (GFR <15ml/min) – refer to clinical team

Hepatic	Atezolizumab	Administered with caution in patients with: Moderate (total bilirubin > 1.5 -3 × ULN and any AST) or Severe (total bilirubin > 3 × ULN and any AST*) hepatic impairment. * Within normal limits or high Refer to 'Dose Modification and Toxicity' section if LFTs become deranged AFTER starting treatment with immunotherapy
	Carboplatin	No need for dose adjustment is required.

<table>
<tr><td></td><td>Paclitaxel</td><td>
<table>
<tr><th>Bilirubin</th><th></th><th>ALT and/or AST</th><th>Dose</th></tr>
<tr><td>≤ 1.25x ULN</td><td>AND</td><td>< 10 x ULN</td><td>100%</td></tr>
<tr><td>1.26 to 2xULN</td><td></td><td></td><td>75%</td></tr>
<tr><td>2.01 to 5xULN</td><td></td><td></td><td>50%</td></tr>
<tr><td>> 5xULN</td><td>OR</td><td>≥10 x ULN</td><td>Discontinue</td></tr>
</table>
</td></tr>
<tr><td></td><td>Bevacizumab</td><td>The liver is not a major organ for Bevacizumab metabolism or excretion. Therefore no data regarding hepatic impairment.</td></tr>
</table>

Interactions

Please consult SmPC for full information on interactions.

Atezolizumab
No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. **Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.** 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-mediated adverse reactions after starting atezolizumab
Bevacizumab
There are no known drug interactions with bevacizumab.

Carboplatin
Concomitant use contraindicated Yellow fever vaccine: risk of generalized disease mortality. Concomitant use not recommended • Live attenuated vaccines (except yellow fever): Risk of systemic, possible fatal disease. This is increased in subjects who are already immunosuppressed by their underlying disease. Use inactivated vaccine where this exist (poliomyelitis). • Phenytoin, fosphenytoin: Risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug), risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin). Concomitant use to take into consideration • Ciclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation. • Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as amino glycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity, particularly in renal failure patients, due to Carboplatin induced changes in renal clearance. • Loop diuretics (e.g. furosemide, indapamide): The concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.

Paclitaxel
Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures. Studies in Kaposi's Sarcoma patients, who were taking multiple concomitant medicinal product, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

Administration

Cycles 1 to 4 every 21 days (INDUCTION)

Pembrolizumab, Paclitaxel, Carboplatin and Bevacizumab

Day	Drug	Dose	Route	Diluent and rate
1	Atezolizumab	1875mg (Flat dose)	SC	Over 7 minutes
1	SUBCUTANEOUS ROUTE IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT Prior to administration, allow the solution to reach room temperature. Administer 15 mL of the Atezolizumab SC injection solution subcutaneously in the thigh in approximately 7 minutes. The injection site should be alternated between the left and right thigh only. 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 course with atezolizumab SC formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.			
	OR			
1	Sodium chloride 0.9%	250ml	IV	Flush
1	Atezolizumab	1200mg (Flat dose)	IV	250mL Sodium Chloride 0.9% over 60 minutes for cycle. If well tolerated cycle 2 onwards can be administered over 30 minutes via a non-pyrogenic line with a 0.2 micron filter.
1	Bevacizumab	15mg/kg	IV	100ml-250ml sodium chloride 0.9% over 90 minutes for cycle 1. If well tolerated reduce to 60 minutes from cycle 2 then cycle 3 onwards can be administered over 30 minutes.
1	Dexamethasone	16.5mg	IV bolus	30 minutes before chemotherapy
1	Ondansetron	16mg	Oral	30 minutes before chemotherapy
1	Chlorphenamine	10mg	IV bolus	30 minutes before chemotherapy
1	Paclitaxel	*200mg/m²	IV	500mL sodium chloride 0.9% over 3 hours using a non-PVC giving set with a 0.22 micron filter

1	Carboplatin	AUC6	IV	500ml 5% Glucose over 30 to 60 minutes

*** Lower starting dose of paclitaxel 175mg/m²should be used in patients of Asian origin due to increased incidence of haematological toxicity observed in this patient group in IMpower150 trial.**

NOTE- Paclitaxel:

- Must be administered using a non-PVC giving set with a 0.22 micron filter prior to carboplatin
- In solution may show haziness which is attributed to the specific paclitaxel formulation**.**
- Avoid excessive shaking, agitation, or vibration of paclitaxel may induce precipitation.

Cycle 5 onwards (Maintenance)

Bevacizumab and Atezolizumab

Day	Drug	Dose	Route	Frequency	Diluent and rate
1	**Atezolizumab**	**1875mg** (flat dose)	**SC**	3 weekly	Administer over 7 minutes
SUBCUTANEOUS ROUTE IS THE PREFERRED ROUTE UNLESS PATIENT INTOLERANT Prior to administration, allow the solution to reach room temperature. Administer 15 mL of the Atezolizumab SC injection solution subcutaneously in the thigh in approximately 7 minutes. The injection site should be alternated between the left and right thigh only. 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 course with atezolizumab SC formulation other medicinal products for subcutaneous administration should preferably be injected at different sites.					
OR					

1	Sodium chloride 0.9%	250mL	IV	Prior to each Atezolizumab infusion.	Flush
	Atezolizumab	**1200mg*** (flat dose)	**IV**	3 weekly	250mL sodium chloride 0.9%. Infused over 60 minutes for cycle 1 if well tolerated cycle 2 onwards can be administered over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
1	**Bevacizumab**	**15mg/kg**	**IV**	3 weekly	100ml-250ml sodium chloride 0.9% over 90 minutes for cycle 1. If well tolerated, cycle 2 onwards can be administered over 30 minutes.

Until progression or unacceptable toxicity to a maximum duration of 2 years (35 x 3-weekly cycles of atezolizumab and bevacizumab including the initial 4 induction cycles of treatment)

Routine prophylaxis against infusion related reactions is not required. However, monitor during the infusion and treatment given if necessary (antihistamines, steroids etc.). For **grade 1-2 injection site reactions** the following pre-medication to subsequent cycles and administered ahead of **SUBCUTANEOUS DOSE**:

- Paracetamol PO 1g
- Chlorphenamine PO 4mg

Please refer to the CCC Hypersensitivity; Management Prevention Policy.

Main Toxicities

For full details on assessment and management of immune-related toxicities refer to CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Atezolizumab	
Immune-Mediated Pneumonitis Pneumonitis occurred in 3% of melanoma patients (including G3 in 0.2%).	Monitor patients for signs and symptoms and evaluate with radiographic imaging and administer corticosteroids for toxicities of grade 2 or above.
Immune-Mediated Colitis	Monitor patients for signs and symptoms and administer corticosteroids for grade 2 or greater.
Other Immune-Mediated Toxicities: Hepatitis Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia, Guillain-Barré syndrome	Monitor LFTs, biochemistry, cortisol, TFTs and blood glucose, consider corticosteroids for grade 2 or greater.
Other non-immune adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Symptomatic management for grade 1 with close monitoring

Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Monitor at each cycle and rule out immune-medicated reaction
Injection site reaction	
Injection site pain, erythema, and rash	Symptomatic management for grade 1 with close monitoring. Pre-medication to be added to subsequent cycles.

Atezolizumab	The most common adverse reactions in combination with bevacizumab, paclitaxel and carboplatin were nausea, diarrhoea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria.
Bevacizumab	The most serious adverse reactions were gastrointestinal perforations, haemorrhage, including pulmonary haemorrhage/haemoptysis, arterial thromboembolism. The most frequently observed adverse reactions across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.
Paclitaxel	Significant hypersensitivity reactions, bone marrow suppression, thrombocytopenia, anaemia, neurotoxicity (mainly peripheral neuropathy), arthralgia or myalgia or injection site reactions. The most common reactions include infection, neurotoxicity, bradycardia, hypotension, diarrhoea, vomiting, nausea and alopecia.

Carboplatin	Significant hypersensitivity reactions, bone marrow suppression, thrombocytopenia, anaemia, neurotoxicity (mainly peripheral neuropathy), ototoxicity, arthralgia or myalgia or injection site reactions. The most common reactions include infection, neurotoxicity, bradycardia, hypotension, diarrhoea, vomiting, nausea and alopecia.

Investigations and treatment plan

If suspicion of endocrinopathies: request TSH, T4, T3, ACTH, cortisol, LH, FSH, testosterone (men) and prolactin (women)

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment	x		x		Then every 12 weeks or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs (ALT, AST and Bilirubin), TFTs, cortisol, blood glucose, LDH, CRP	x	x	x	x	Every cycle
Lipid profile (cholesterol)	x				At baseline then if clinically indicated
Fatigue profile as per Meditech order set: B12, folate, Iron profile, vitamin D, Zinc, Testosterone (men only), ESR	x				At baseline then if clinically indicated

Observations	BP		x	x	x	Required prior to EACH cycle of treatment with **bevacizumab** **Refer to 'Dose Modifications and Toxicity Management' section**
	HR Temperature RR O2 saturations		x			At baseline then if clinically indicated
Creatinine Clearance (Cockcroft and Gault)*		x	x	x	x	<u>Cycles 1 to 4 (INDUCTION)</u> Every cycle <u>Cycle 5 onwards (MAINTENANCE)</u> With every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
Urinalysis			x	x	x	Required prior to EACH cycle of treatment with bevacizumab **If proteinuria detected refer to 'Dose Modifications and Toxicity Management' section**
CT scan		x			x	First response assessment CT scan to be done after 2-3 cycles then every 12 weeks or as clinically indicated
Trop-T, CK, pro-BNP		x				At baseline (refer to 'Pre-assessment Baseline Cardiac
ECG		x				

					Pathway' guidance) and thereafter as clinically indicated (ECG to be reviewed by ANP or ECG clinic or clinical team)
Weight recorded	x	x	x	x	Every cycle
Height recorded	x				

Pregnancy test if applicable.

* Please refer to:

- 'Dosage' section for full details on carboplatin dosing.
- 'Carboplatin Dosing Calculator' SOP outlining process for checking carboplatin dose ahead of each cycle of treatment.

Dose Modifications and Toxicity Management

- Dose modifications due to toxicity are ONLY permitted on chemotherapy agents (paclitaxel and carboplatin).
- Only dosing delay or discontinuation due to toxicity are permitted for atezolizumab based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of atezolizumab are contained in 'Treatment Threshold' section below.

- If either the atezolizumab, bevacizumab or chemotherapy are withheld or discontinued then the other agent(s) can be continued. This decision will be made at the discretion of the clinical team.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Treatment Threshold

Atezolizumab, Paclitaxel, Carboplatin and Bevacizumab (Cycles 1 to 4)
Administer treatment on day 1 if:

<table>
<tr><th>SACT</th><th>Platelets</th><th>Neutrophils</th><th>Serum Creatinine</th><th>Bilirubin</th><th>AST/ ALT</th><th>TSH and Free T4</th></tr>
<tr><td>Atezolizumab</td><td rowspan="3">≥ 100 x 10^9/L (Must be within normal range prior to cycle 1*)</td><td rowspan="3">≥ 1.0 x 10^9/L</td><td>≤1.5 x ULN or baseline</td><td><3 x ULN</td><td><3x ULN</td><td>Within range or no change from base line</td></tr>
<tr><td>Paclitaxel and carboplatin</td><td colspan="3"><u>Refer to ‘Dosing in renal and hepatic impairment’ section for recommended dose modifications for carboplatin, cisplatin and paclitaxel based on individual renal and hepatic function</u></td><td></td></tr>
<tr><td>Bevacizumab</td><td colspan="5"><u>Routine monitoring of FBC is not required. Refer to guidance below on BP and proteinuria monitoring</u></td></tr>
</table>

	and treatment recommendations.	

ULN = upper limit of normal

*****If platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessment and chemotherapy dose reduction

Atezolizumab and Bevacizumab (Cycle 5 onwards)

Administer treatment on day 1 if:

SACT	Platelets	Neutrophils	Serum Creatinine	Bilirubin	AST/ALT	TSH and Free T4
Atezolizumab	≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤ 1.5 x ULN or baseline	<3 x ULN	<3 x ULN	Within range or no change from base line
Bevacizumab	**Routine monitoring of FBC is not required. Refer to guidance below on BP and proteinuria monitoring and treatment recommendations.**					

Non Haematological Immunotherapy Toxicity

Detailed guidelines are provided in the CCC clinical network immunotherapy acute oncology guidelines. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may be required for management of severe immune-related adverse reactions.

Toxicity Grade	Action
Grade 1 Mild	Continue treatment increase monitoring and provide symptomatic treatment.
Grade 2 Moderate	Withhold treatment until resolved to ≤ grade 1. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.
Grade 3 and Grade 4 Severe	Withhold treatment. Treatment will be permanently discontinued for any unresolving grade 3-4, severe or life-threatening adverse reaction at the treating clinician's discretion. Refer to Immuno-Oncology toxicity specific guidance for adverse event management.

Bevacizumab:

Dose reduction NOT permitted. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Hypertension:

Baseline blood pressure should be < 150/100mmHg. Pre-existing hypertension should be adequately controlled (usually by GP) before starting bevacizumab treatment.

If diastolic increase > 20mmHg above baseline or blood pressure rises to >150/100mmHg, antihypertensive therapy may be required. Treatment, and initial monitoring until stabilized, is usually best managed via the patient's GP.

If blood pressure > 180/110mmHg, it is advised that bevacizumab therapy is withheld until blood pressure controlled.

For "white coat syndrome" induced hypertension, please contact patient's GP for monitoring of blood pressure in between cycles.

Proteinuria:

1+ or 2+ on dipstick (0.3 – 2.9g/L)	3+ on dipstick (3 - 19g/L):	4+ on dipstick (≥20g/L)
Continue with bevacizumab. No additional evaluation required	May have dose of bevacizumab as scheduled, but will need 24 hour urine collection to measure protein 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 reintroduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.	**Withhold bevacizumab**. 24 hour urine collection required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Carboplatin

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment, treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible	Interrupt treatment until resolved to at least grade 1, then continue at 75-80% of original dose or with prophylaxis where possible	Discontinue treatment
2nd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose	Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose	
3rd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose	Discontinue treatment	
4th appearance	Discontinue treatment		

Peripheral Neuropathy:

Paclitaxel
CTCAE grade 2 peripheral neuropathy: withhold paclitaxel only until the neuropathy recovers to grade 1 then dose reduce to 75% of the original dose. Where the peripheral neuropathy is ≥ grade 3 omit paclitaxel from subsequent cycles.

References

1. SmPC for Alymsys 25mg/ml concentrate for solution for infusion, Zentiva- accessed via electronic medicines compendium at www.medicines.org.uk/emc/medicine (Last updated 24th October 2023).
2. SmPC for Carboplatin 10 mg/ml Intravenous Infusion, Hospira UK Ltd – accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated June 2020)
3. SmPC for Paclitaxel 6 mg/ml concentrate for solution for infusion, Hospira UK Ltd accessed via electronic medicines compendium at https://www.medicines.org.uk/emc (Last updated 27th April 2020).
4. SmPC for Tecentriq 1,200 mg concentrate for solution for infusion, Roche products Limited- accessed via www.medicines.org.uk/emc/medicine (Last updated 23rd October 2023).
5. SmPC for Tecentriq 1,875 mg concentrate for solution for injection, Roche products Limited- accessed via electronic medicines compendium at www.medicines.org.uk/emc/medicine (Last updated 1st September 2023).

6. Socinski, M.A., Jotte, R.M., Cappuzzo, F., Orlandi, F., Stroyakovskiy, D., Nogami, N., Rodríguez-Abreu, D., Moro-Sibilot, D., Thomas, C.A., Barlesi, F. and Finley, G., 2018. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *New England Journal of Medicine*, *378*(24), pp.2288-2301.
7. Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.
8. NICE TA584: Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. Published: 5th June 2019.

Circulation/Dissemination

Date added into Q-Pulse	5th December 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
April 2021	1.2	Tara Callagy Lung SRG Pharmacist	New regimen protocol

September 2023	1.3	Hala Ghoz Lung SRG Pharmacist	SC atezolizumab administration added