SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

ATEZOLIZUMAB AND BEVACIZUMAB Hepatocellular carcinoma

PROTOCOL REF: MPHAABHCGA
(Version No. 1.1)

Approved for use in:

Required criteria

First-line treatment of locally advanced or metastatic hepatocellular carcinoma (HCC) that is ineligible for or has failed surgical or loco-regional therapies and satisfies the following criteria:

- ECOG (WHO) PS 0-1
- Child-Pugh Class A liver function
- No symptomatically active brain metastases or leptomeningeal metastases

Blueteq registration required (only for patients resident in England): see Blueteq for more detailed eligibility criteria

Treatment breaks of up to 12 weeks beyond the expected cycle length are allowed.

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). Please refer to 'Child-Pugh Grading' section below for further information.

- Patient with active CNS disease (symptomatic despite steroid treatment) or carcinomatosis meningitis
- Pregnancy or breast feeding

Child-Pugh Grading:

Assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

Child-Pugh Class A (mild or no hepatic impairment) = 5-6 points

Child-Pugh Class B (moderate hepatic impairment) = 7-9 points

Child-Pugh Class C (severe hepatic impairment) = 10 or more points

Parameters	1 point	2 points	3 points
Total bilirubin* (µmol/L)	< 34 (<69 for PBC or PSC)	34 – 50 (69 to 170 for PBC or PSC)	> 50 (> 170 for PBC or PSC)
Serum albumin (g/L)	> 35	28 – 35	< 28
Prothrombin time prolongation (s) **OR** **International Normalised Ratio (INR)**	< 4 < 1.7	4 – 6 1.7 – 2.3	> 6 > 2.3
Ascites	None	Mild to Moderate (or diuretic responsive)	Severe (or diuretic refractory)
Hepatic encephalopathy	None	Grade I – II	Grade III – IV

		(or suppressed with medication)	(or refractory to medication)

Please NOTE:-

For patients diagnosed with Primary Biliary cirrhosis (PBC) or Primary Sclerosing Cholangitis (PSC) - consultant decision to determine if patients with these potentially auto-immune liver conditions are suitable for treatment.

**Bilirubin cannot be properly assessed for Child-Pugh Class in patients with Gilbert's syndrome*.

Dosage:

Subcutaneous Atezolizumab (preferred route of administration):

Drug	Dose	Route	Frequency
Atezolizumab	**1875 mg (Flat dose)**	SC injection	Every 3 weeks
Bevacizumab	**15mg/kg**	IV infusion	Every 3 weeks

To be continued until progression or unacceptable toxicity

OR

IV Atezolizumab - ONLY IF the subcutaneous route INTOLERANT:

Drug	Dose	Route	Frequency
Atezolizumab	**1200 mg (Flat dose)**	IV infusion	Every 3 weeks
Bevacizumab	**15mg/kg**	IV infusion	Every 3 weeks

To be continued until progression or unacceptable toxicity

Routine prophylaxis against infusion related reactions is not required.

For SC Atezolizumab - Monitor during SC administration and give hypersensitivity treatment if necessary (antihistamines, steroids etc). For grade 1 to 2 injection site reactions, administer

the following pre-medication prior to subsequent cycles and ahead of SUBCUTANEOUS DOSE:

- Paracetamol PO 1g
- Chlorphenamine PO 4mg

For IV Atezolizumab - Please refer to the CCC Hypersensitivity; Management Prevention Policy, consider increasing the infusion time back up to 60 minutes or 90 minutes, as appropriate.

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.

Ensure that patient is aware to contact the triage team for the following:

- New or worsening cough, chest pain or shortness of breath
- Diarrhoea or severe abdominal pain
- Jaundice, severe nausea or vomiting, or easy bruising or bleeding
- Persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes
- Monitoring for signs of infection / sepsis

Atezolizumab

For SUBCUTANEOUS injection use only – monitor for injection site reactions e.g. pain, swelling, rash, inflammation.

Bevacizumab:

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

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

Pre- and take home medications are not required routinely.

Extravasation risk:

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

Atezolizumab: NEUTRAL

Bevacizumab: NEUTRAL

Dosing in renal and hepatic impairment:

Renal	**Atezolizumab**	GFR ≥ 30ml/min- proceed with treatment GFR < 30ml/min- limited data use with caution
	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
	Bevacizumab	The liver is not a major organ for Bevacizumab metabolism or excretion. Therefore no data regarding hepatic impairment.

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.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and Rate
1	**Atezolizumab**	1875mg (Flat dose)	SC	Over 7 minutes
FOR SUBCUTANEOUS ROUTE OF ADMINISTRATION (PREFERRED ROUTE):				

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%	250 ml	IV	Flush
1	**Atezolizumab**	1200 mg (Flat dose)	IV	250mL Sodium Chloride 0.9%. Infused over 60 minutes for cycle 1 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, cycle 2 onwards can be administered over 30 minutes.

To be continued until progression or unacceptable toxicity

Routine prophylaxis against infusion related reactions is not required.

For SC Atezolizumab - Monitor during SC administration and give hypersensitivity treatment if necessary (antihistamines, steroids etc). For grade 1 to 2 injection site reactions, administer the following pre-medication prior to subsequent cycles and ahead of SUBCUTANEOUS DOSE:

- Paracetamol PO 1g
- Chlorphenamine PO 4mg

For IV Atezolizumab - Please refer to the CCC Hypersensitivity; Management Prevention Policy, consider increasing the infusion time back up to 60 minutes or 90 minutes, as appropriate.

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 (SC administration ONLY) pain, erythema, and rash	Symptomatic management for grade 1 with close monitoring. Pre-medication to be added to subsequent cycles.

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.

Bevacizumab in combination with Atezolizumab

The most frequently observed adverse reactions (all grades) from the clinical trial were hypertension, fatigue, proteinuria, AST/ALT elevations, pruritus/rash, diarrhoea, abdominal pain, decreased appetite, pyrexia, constipation, serum bilirubin increases, nausea, cough, infusion-related reaction (IRR), weight decrease, thrombocytopenia, epistaxis, asthenia, alopecia and palmer-plantar erythrodysesthesia (PPE).

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	Pre Cycle 3	Cycle 3	Cycle 4	Pre Cycle 5	Ongoing
Informed Consent	x							
Clinical Assessment	x			x			x	Every 12 weeks thereafter or as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x		x	x		Every cycle
Immunotherapy bloods as per Meditech order set: FBC, U&E/renal profile, Magnesium, LFTs, TFTs, cortisol, blood glucose, LDH, CRP	x	x	x		x	x		Every cycle
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
Lipid profile (cholesterol)	x							At baseline then if clinically indicated

CrCl (Cockcroft and Gault)		x	x						Every cycle only if baseline CrCL <40ml/min or creatinine increases above 1.5x upper limit of normal or baseline
ECG		x							At baseline (refer to 'Pre-assessment Baseline Cardiac Pathway' guidance) and thereafter as clinically indicated (ECG to be reviewed by ANP or ECG clinic or clinical team)
Trop-T, CK, pro-BNP		x							
Observations	BP		x	x		x	x		Required prior to EACH cycle of treatment with bevacizumab **Refer to 'Dose Modifications and Toxicity**
	HR Temperature RR		x						At baseline then if clinically indicated

	O2 saturations								
Urinalysis			x	x		x	x		Required prior to EACH cycle of treatment with bevacizumab **If proteinuria detected refer to 'Dose Modifications and Toxicity Management' section** If proteinuria detected refer to 'Grading and Management of Toxicity for Bevacizumab' section
CT scan		x				X			Every 12 weeks thereafter or as clinically indicated
Weight recorded		x	x	x		x	x		Every cycle
Height recorded		x							

Pregnancy test if applicable: Women of childbearing potential have to use effective contraception during and for 5 months after treatment.

Serum samples for HIV, Hep C antibody and HBsAg are required if patient has risk factors: patients with these conditions were excluded from clinical trials.

Dose Modifications and Toxicity Management:

- Only dosing delay or discontinuation due to toxicity are permitted for atezolizumab and bevacizumab based on individual safety and tolerability.
- Guidelines for permanent discontinuation or withholding of atezolizumab are contained in 'Treatment Threshold' section below.
- Detailed guidelines for the management of immune-related adverse reactions are provided in the CCC Immuno-Oncology toxicity specific guidance for adverse event management.

Proceed on day 1 if :

Platelets	Neutrophils	Serum Creatinine	TSH and free T4
≥ 75 x 10^9/L	≥ 1.0 x 10^9/L	≤ 1.5 x ULN or baseline	Within range or no change from baseline

LFT Assessment	Management
If AST or ALT is within normal limits at baseline and increases to: >3xULN to ≤10xULN If AST or ALT is >ULN to 3xULN at baseline and increases to: >5xULN to ≤10xULN If AST or ALT is >3xULN to 5xULN at baseline and increases to: >8xULN to ≤10xULN	(1)_Withold Atezolizumab for up to 12 weeks after onset of the event. (2) Monitor LFTs weekly till recovery (guided by clinical judgement). Significant LFT derangement for over a week: (1) Refer to CCC IO-induced hepatitis guidelines (2) Resume Atezolizumab if LFTs revert to baseline or Grade 1 toxicity (i.e. below threshold of significant elevation). (3) Discontinue Atezolizumab if event does not resolve to baseline during 12-week treatment break.

If AST or ALT increases to > 10xULN or total bilirubin increases to > 3xULN	(1) Permanently discontinue Atezolizumab. (2) Refer to CCC IO-induced hepatitis guidelines (3) If no improvement within 48hrs consider additional.immunosuppressive agent to steroids. (4) If events resolve to baseline, taper steroids over a month. (5) Consider referral to Hepatologist for biopsy to ascertain aetiology of hepatic injury.

Inform consultant if there has been a significant increase in liver function test from previous results.

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	Withhold Bevacizumab. 24 hour urine collection required. Follow 24 hour urine monitoring and

	a few days before next cycle due. **<u>If 24hr protein result < 2g</u>** 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. **<u>If 24hr protein result ≥ 2g</u>** Withhold Bevacizumab until repeat 24 hour urine collection shows < 2g protein. Then re-introduce Bevacizumab, with continued proteinuria monitoring via 24 hour urine.	guidance as for 3+ on dipstick.

References:

1. Finn RS., Shukui Q. et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinom. N Engl J Med. 2020 May 14;382(20):1894-1905 (including on-line clinical trial protocol).

2. NICE TA666 (December 2020) – Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma.

3. Krens S D, Lassche, Jansman G F G A, et al. Supplementary Appendix to Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019;20: e201–08.

4. Stockley's Drug Interactions. Ninth Edition. Edited K. Baxter, Pharmaceutical Press, London, 2010.

5. Summary of Product Characteristics, Tecentriq®, Atezolizumab 1200mg concentrate for solution for infusion, Roche Products, www.medicines.org.uk [accessed on 19th May 2019]

6. Summary of Product Characteristics, Avastin®, Bevacizumab concentrate for solution for infusion, Roche Products, www.medicines.org.uk [accessed on 19th May 2019]

7. Summary of Product Characteristics, Tecentriq®, Atezolizumab 1875mg solution for injection, Roche Products Limited, www.medicines.org.uk [accessed on 18th Oct 2023].

Circulation/Dissemination

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

Version History

Version	Author name and designation	Summary of main changes
1.0	**Rob Challoner (Pharmacist)**	
1.1	**Natalie Tan (Pharmacist)**	Addition of new drug formulation Update on toxicity parameters