Atezolizumab, Bevacizumab

Indication:

Advanced or Unresectable Hepatocellular Carcinoma (HCC)

- No previous systemic treatment.
- ECOG PS 0-1.
- Child-Pugh grade A liver impairment.
- No symptomatically active brain metastases or leptomeningeal metastases

Regimen details

Table 1 – Treatment regimen details

DRUG	DOSE	DILUENT	ROUTE	FREQUENCY/DURATION
Atezolizumab	1200mg(flat dose)	250mL Sodium Chloride 0.9%	IV Infusion	1st Dose 60 mins. If tolerated subsequent doses over 30mins.
Bevacizumab	15mg/kg	100mL Sodium Chloride 0.9%	IV Infusion	1st Dose 90 minutes, if tolerated 2nd dose may be delivered over 60mins, if this is well tolerated subsequent doses over 30mins.

Cycle frequency

Every 3 weeks

Number of cycles

To be continued until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent.

Administration

Atezolizumab –

- Initial dose infused of 60 minutes.
- If well tolerated without infusion-associated adverse events then subsequent doses can be administered 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.

Pre-medication

None

Emetogenicity

Minimum Risk (Category D)

Additional supportive medication

None

Extravasation

Atezolizumab	Neutral: Group 1
Bevacizumab	Neutral: Group 1

Investigations – pre first cycle

Table 2 - Standard Investigations prior to first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Bone Profile	14 days
Glucose	14 days
TFT	14 days
ECG	28 day
Serum samples for HIV, Hep C antibody & HBsAg if risk factors	28 days
Pregnancy test (if applicable)	7 days
Blood Pressure	14 days
Urine dipstick for proteinuria	14 days
Cortisol	14 days
Follicle stimulating hormone	14 days
Luteinizing hormone	14 days
Testosterone	14 days

Pre-existing blood pressure must be controlled before starting treatment with Bevacizumab

Prior radiotherapy is a risk factor for the development of fistulae with Bevacizumab

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

FBC, U+E (including creatinine clearance), LFT (including AST) Magnesium, LFTs, TFTs, cortisol, blood glucose, LDH, CRP, blood pressure

Urine dipstick for proteinuria

Standard limits for administration to go ahead

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

Table 3 – Standard test result limits for each administration to go ahead

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 75 x 10^9/L
Creatinine clearance	≥ 30 mL/min
Bilirubin	≤ 3 x ULN
AST	< 3 x ULN
Hb	≥ 95 g/L
Blood pressure	< 140/90 mmHg

Dose modifications

Bevacizumab – The dose will not be modified. Dosing should be interrupted or discontinued as described below:

Table 4 – Management of toxicities associated with Bevacizumab

Toxicity	Grade	Dose adjustment
Infusion related reactions	Grade ≤2	90 minute infusion: continue with dose as normal, but give premedication (paracetamol and chlorphenamine) with the next dose and give over 90 minutes. If well tolerated subsequent infusions can be reduced by 30 minutes as long as use premedication.
		60 minute infusion: all subsequent doses should be given over 90 minutes (with pre-medication)
		30 minute infusion: all subsequent doses should be given over 60 minutes (with pre-medication)
	Grade ≥2	Discontinue permanently
Proteinuria (on dipstick)	<2	Continue with bevacizumab as normal
	≥2+	See algorithm below
	Nephrotic syndrome	Permanently discontinue
Gastro-intestinal perforation or dehiscence		Discontinue permanently
Wound healing complications		Bevacizumab should not be initiated for at least 28 days following surgery or until wound is fully healed Bevacizumab should be withheld for 42 days (6 weeks) prior to elective surgery If would healing complications occur during treatment it should be withheld until the wound is fully healed.
Fistula or intra-abdominal abscess		Discontinue permanently
Venous thromboembolic event	Grade 3 Deep DVT or cardiac thrombosis needing anticoagulation or incidental first PE	Hold bevacizumab for 2 weeks May be resumed after initiation of therapeutic dose anticoagulant
	Grade 4 Embolic event including PE with life-threatening thrombus	Discontinue permanently
Arterial thrombotic event	ANY grade	Permanently discontinue
Haemorrhage	Grade 1 or 2	No modification but institute appropriate treatment
	Grade 3 or 4	Discontinue and institute appropriate treatment

Proteinuria

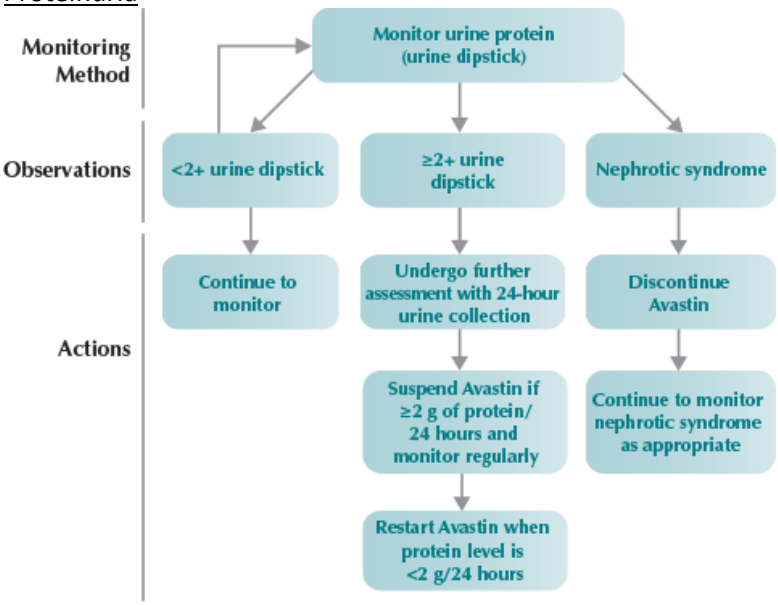

Figure 1- Management of proteinuria

Hypertension

Table 5 – Management of hypertension associated with Bevacizumab treatment

	Definition	Action
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously normal.	Recheck BP 1 hour later If BP <140/90 mmHg: administer as normal If BP 140/90-150/100 mmHg administer but recheck BP 48 hours later If >150/100 mmHg omit bevacizumab and recheck BP 48 hours later If BP after 48 hours still >140/90 mmHg commence antihypertensive therapy
Grade 2	Recurrent or persistent (>24 hour) increase by 20 mmHg (diastolic) or to >140/90 mmHg if previously normal	Anti-hypertensive therapy should be commenced. Once controlled to <140/90 mmHg bevacizumab can be continued
Grade 3	Requiring more than one antihypertensive or more intensive therapy than previously	Withold bevacizumab for persistent hypertension >140/90 mmHg If hypertension cannot be controlled, discontinue permanently
Grade 4	Life threatening (hypertensive crisis)	Medical emergency Permanently discontinue

Atezolizumab – The dose will not be modified.

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

Table 6 – Management of toxicities associated with Atezolizumab

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

Adverse reaction	Severity	Treatment Modification
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

Adverse reaction	Severity	Treatment Modification
	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 (> 2x ULN) or Grade 2 or 3 pancreatitis	Withhold atezolizumab Start 1-2mg/kg methylprednisolone or equivalent, once symptoms 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

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

Atezolizumab:
Immune-Mediated effects (refer to Table 6 – Management of toxicities associated with Atezolizumab):

- Pneumonitis
- Colitis
- Hepatitis
- Hypophysitis
- Nephritis
- Hyperthyroidism or Hypothyroidism
- Adrenal insufficiency
- Infusion-related reactions

Less frequently

- Exfoliative dermatitis
- Uveitis
- Arthritis
- Myostitis
- Pancreatitis
- Myocarditis
- Haemolytic anaemia
- Myasthenic syndrome/ myasthenia gravis
- Guillain-Barré syndrome
- Meningoencephalitis

Non-Immune-Mediated effects

- Fatigue,
- Anaemia
- Cough
- Dyspnoea
- Nausea
- Decreased appetite
- Pruritus
- Rash
- Constipation
- Diarrhoea
- Arthralgia

Bevacizumab (refer to Table 4 – Management of toxicities associated with Bevacizumab):

- Fistulae and gastrointestinal perforations
- Wound healing complications
- Hypertension (see Table 5)
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Proteinuria (see Figure 1)
- Arterial thromboembolism
- Venous thromboembolism
- Haemorrhage (including pulmonary haemorrhage/haemoptysis)
- Aneurysms and artery dissections
- Congestive heart failure (CHF)
- Neutropenia and infections
- Hypersensitivity and infusion reactions
- Fatigue
- Asthenia
- Diarrhoea
- 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
- Palmer-plantar erythrodysesthesia (PPE)

Significant drug interactions – for full details consult product literature/ reference texts

Atezolizumab and Bevacizumab: There are no known drug interactions with atezolizumab bevacizumab. No formal pharmacokinetic drug interaction studies have been conducted with these individual drugs. Since they are cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

References

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THIS PROTOCOL HAS BEEN DIRECTED BY DR FERREIRA, DESIGNATED LEAD CLINICIAN FOR HEPATOCELLULAR CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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