Indication	Atezolizumab, in combination with bevacizumab, is indicated for the treatment of locally advanced or metastatic unresectable hepatocellular carcinoma as first line systemic treatment. NB: the patient has not received previous systemic therapy for his/her hepatocellular carcinoma unless the combination of atezolizumab and bevacizumab has been received via the EAMS scheme.
Treatment Intent	Palliative
Frequency and number of cycles	Every 21 days. Continue until progressive disease or unacceptable toxicity or withdrawal of patient consent, whichever occurs first. Formal medical review to be scheduled to occur at least by the end of the first 6 weeks of treatment.
Monitoring Parameters pre-treatment	• Monitor FBC, U&Es, LFTs and random glucose at each cycle. • Thyroid function and 9am cortisol level must be assessed at baseline then at least 6-8 weeks. • Monitor blood pressure at each cycle. Pre-existing hypertension should be adequately controlled before starting treatment. • ECG at first cycle and then as clinically indicated. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure. • Dipstick urine for proteinurea at each cycle. Report to consultant if protein 2+ (equivalent to 1g/l) and/or BP >/= 140/90 respectively. Reference should be made to KMCN guidelines for bevacizumab induced hypertension. • Monitor for signs and symptoms of myocarditis. • **Renal:** • Atezolizumab: no dose adjustment is required in patients with mild or moderate renal impairment (30-89ml/min). No recommendation for patients with severe (<30ml/min) renal impairment as data is too limited. • Bevacizumab: no dose recommendations. • **Hepatic impairment**: (prior to treatment, for immune related hepatitis see below)- Patient must have Child-Pugh A liver function to be eligible. • Atezolizumab: no dose adjustment is required for patients with mild (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 × to 1.5 × ULN and any AST) or moderate (bilirubin > 1.5 to 3x ULN and any AST) hepatic impairment. No data is available to make a recommendation in patients with severe hepatic impairment. • Bevacizumab: no dose recommendations • **Dose Modification:** • Atezolizumab: dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. • Bevacizumab: Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended. • If either atezolizumab or bevacizumab has to be discontinued on account of toxicity and the patient is otherwise benefitting from therapy, treatment should continue with the remaining agent until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent. • **Infusion-related reactions**: o Atezolizumab: reduce infusion rate or interrupt treatment if Grade 1 or 2 infusion-related reaction. Atezolizumab may be continued with close monitoring; premedication with antipyretic and antihistamines should be considered. Permanently discontinue in patients with Grade 3 or 4 infusion related reactions. o Bevacizumab: If a reaction occurs, the infusion should be discontinued and

appropriate medical therapies should be administered

- **Immune- related reactions:**
  - Reactions include myocarditis,myositis pneumonitis, colitis, hepatitis, pancreatitis, adrenal insufficiency, meningoencephalitis, hyperthyroidism, hypothyroidism, hypophysitis, diabetes, rash, arthralgia, musculoskeletal pain, neuropathies, myasthenic syndrome and Guillain-Barre syndrome.
  - Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any grade 3 nephritis, pneumonitis, or myocarditis (see below for hepatitis) and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones.
  - **Immune related hepatitis:** Cases of immune related hepatitis in patient with HCC, some leading to fatal outcomes have been observed in clinical trials with atezolizumab. Patients should be monitored for signs and symptoms of hepatitis. If AST/ALT is within normal limits at baseline and increases to >3x to </=10x ULN 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 then 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 prednisolone or equivalent per day. If AST/ALT increases to >10x ULN or total bilirubin increases to >3x ULN permanently discontinue atezolizumab.
  - Atezolizumab should be discontinued in the event of any grade Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis
  - If corticosteroids are used to treat an immune related reaction they should be tapered over at least 1 month. Treatment should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids (>10mg prednisolone) or other immunosuppressive therapy. Prophylactic antibiotics should be used where appropriate to prevent opportunistic infections in patients receiving immunosuppressive therapy.
  - See guidelines for management of immune-related adverse reactions following immunotherapy: http://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/sact-pathways-guidelines-for-the-management-of-sact-induced-adverse-reactions-and-nursing/
- **Bevaziumab**
  - Use with caution in patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression, after careful consideration of the potential risk-benefit. No symptomatically active brain metastases or leptomeningeal metastases allowed under BT criteria.
  - Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation with bevacizumab. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. It is recommended an OGD is undertaken in patients at high risk of variceal bleeding and that all sizes of varices be assessed and treated as per local standard of care prior to treatment.
  - Bevacizumab may adversely affect wound healing. Do not give bevacizumab if patient has undergone major surgery within the last 28 days. Treatment should be stopped prior to elective surgery.
  - Patients may be at increased risk for the development of fistulae when treated with bevacizumab.

	○ Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with bevacizumab. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. ○ Caution should be exercised when bevacizumab and intravenous bisphosphonates are administered simultaneously or sequentially, as cases of osteonecrosis of the jaw have been reported. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with bevacizumab. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible. ○ Any suspected thrombosis and/or haemorrhage d/w consultant. ○ Patients with a history of arterial thromboembolism, diabetes or >65 years old should be treated with caution. • **Drug interactions:** ○ The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab. ○ Patients should not receive the flu vaccine unless the benefit outweighs the risk and after discussion between consultant and patient. • **Missed dose:** If a planned dose of treatment is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain a 3-week interval between doses. • Atezolizumab can affect the ability to drive and use machines. If patient experiences fatigue they should not drive. • The patient should be provided with the Tecentriq® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment).
References	UGI-066 v1 SPC accessed on line 19.11.20 Blueteq form accessed online 19.11.20

NB For funding information, refer to CDF and NICE Drugs Funding List

Repeat every 21 days

Day	Drug	Dose	Route	Infusion Time	Administration Details
Day 1	Metoclopramide	20mg	PO		
	Atezolizumab	**1200mg**	IV	1st dose over 60 mins. If tolerated, all subsequent infusions over 30 mins	diluted in 250ml 0.9% sodium chloride
	Bevacizumab	**15mg/kg**	IV	90min **cycle 1** If tolerated give as below 60min **cycle 2** 30min **cycle 3 onwards**	The final concentration must be between 1.4 and 16.5 mg/ml. In 100ml 0.9% sodium chloride. If the patient >/= 110kg give in total of 250mls sodium chloride 0.9%
TTO	Drug	Dose	Route	Directions	
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose) Do not take for more than 5 days continuously.	
	Loperamide	2-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.	