# ATEZOLIZUMAB (Tecentriq) BEVACIZUMAB

**INDICATION (ICD10) C22**

*Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)*

**Atezolizumab in combination with bevacizumab for the first-line systemic treatment of adult patients with locally advanced or metastatic and/or unresectable hepatocellular carcinoma**

2. Fully aware of the management of and the treatment modifications that may be required for immune-related adverse reactions due to anti-PD-L1 treatments including pneumonitis, colitis, nephritis, endocrinopathies and hepatitis.
3. Has a diagnosis of hepatocellular carcinoma and that either the patient has a confirmed histological diagnosis of hepatocellular carcinoma (HCC) or a biopsy is deemed to be very high risk or technically not feasible in the patient and the decision not to biopsy has been made and documented by a specialist HCC multi-disciplinary team meeting and the tumour meets the non-invasive diagnostic criteria of HCC (It is expected will only apply in exceptional circumstances. *EASL-EORTC Clinical Practice Guidelines: Management, Journal of Hepatology 2012 vol 56 p908-943. Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1cm in diameter, a more conservative approach with 2 techniques is recommended in suboptimal settings).
4. Has metastatic or locally advanced disease that is ineligible for or has failed surgical or loco-regional therapies.
5. Has Child-Pugh A liver function.
6. 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.
the patient has not received any previous systemic therapy for his/her hepatocellular carcinoma or the patient has been previously treated with the combination of atezolizumab and bevacizumab and this has been accessed via a previous registration for the EAMS for atezolizumab plus bevaiczumab.
Note: previous systemic treatment with sorafenib or lenvatinib or regorafenib or any immunotherapy or any systemic chemotherapy is not allowed.
7. ECOG performance status score of 0 or 1.
8. Aware of the risk of variceal bleeding due to bevacizumab and will comply with the recommendation that an oesophago-gastro-duodenoscopy (OGD) be considered 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 with atezolizumab and bevacizumab.
9. Treatment with atezolizumab in combination with bevacizumab will continue until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent, whichever occurs first.
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.
10. Has no symptomatically active brain metastases or leptomeningeal metastases.
11. Has not received prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
12. A formal medical review as to how treatment with atezolizumab in combination with bevacizumab is being tolerated and whether treatment with the combination should continue or not will be scheduled to occur at least by the end of the first 6 weeks of treatment.
13. Where a treatment break of more than 12 weeks beyond the expected 3-weekly cycle length is needed, I will complete a treatment break form to restart treatment, including an indication as appropriate if the patient had an extended break because of COVID 19.

14. On discontinuation of the combination of atezolizumab and bevacizumab on account of loss of clinical benefit or treatment intolerance and if the patient is fit for further systemic therapy, the next line of treatment would be a choice of either sorafenib or lenvatinib.
15. Atezolizumab and bevacizumab will otherwise be used as set out in their respective Summary of Product Characteristics (SPCs).

**REGIMEN**
**(atezolizumab and bevacizumab can be given in any order)**

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| Day 1 | ATEZOLIZUMAB | 1200mg in 250ml sodium chloride 0.9% IV infusion |
| | BEVACIZUMAB | 15mg/kg in 100ml sodium chloride 0.9% IV infusion |

Atezolizumab – The initial dose should be delivered over 60 minutes.
If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 minutes.
If the 30 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

Bevacizumab - The initial dose should be administered over 90 minutes, if tolerated well the second infusion may be administered over 60 minutes.
If the 60 minute infusion is well tolerated all subsequent infusions may be administered over 30 minutes.

**CYCLE FREQUENCY AND NUMBER OF CYCLES**
Every 21 days until disease progression

**ANTI-EMETICS**
Low risk day 1

**CONCURRENT MEDICATION REQUIRED**
None required

**EXTRAVASATION AND TYPE OF LINE / FILTERS**
Atezolizumab – neutral
Bevacizumab – neutral

Atezolizumab use of 0.2-5micron filter is optional
Peripheral line

**INVESTIGATIONS**
Blood results required before SACT administration
FBC, U&E and LFTs, creatinine day 1
Neutrophils x $10^9$/L ≥1.5
Platelets x $10^9$/L ≥100
GFR assessed using EDTA result or calculated creatinine clearance at the Consultant's discretion.
Thyroid function baseline, then every cycle
Random cortisol baseline, then every cycle
Random glucose every cycle
Blood pressure every cycle
Urinalysis for proteinuria every cycle
Baseline weight and every cycle

## MAIN TOXICITES AND ADVERSE REACTIONS

| | |
|---|---|
| Atezolizumab | Immune mediated pneumonitis<br>Immune mediated hepatitis<br>Immune mediated colitis<br>Immune mediated endocrinopathies |
| Bevacizumab | Arterial thromboembolism<br>Gastrointestinal perforation<br>Haemorrhage<br>Hypertension<br>Wound healing complications |

## INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
**(not exhaustive list check SPC/BNF/Stockleys)**

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|---|---|
| Bevacizumab | Many interactions check carefully |

## DOSE MODIFICATIONS
### Non-haematological
Atezolizumab
Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline
If the drug-related toxicity does not resolve to Grade 0-1 within 12 weeks after onset of toxicity, discontinuation is recommended.

Bevacizumab
Hypertension
Baseline blood pressure should be <150/100mmHg.

| | |
|---|---|
| Diastolic increase >20mmHg above baseline or BP rises to >150/100mmHg | Diastolic increase >20mmHg above baseline or BP rises to >150/100mmHg |
| Blood pressure >180/110mmHg | It is advised that bevacizumab therapy is withheld until blood pressure controlled. |

Proteinuria
Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that all grade proteinuria may be related to the dose.
Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome.

Wound healing
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.

## REFERENCES
1. Finn, R et al; NEJM 2020; 382: 1894-1905