Chemotherapy Protocol

Hepatocellular Cancer

ATEZOLIZUMAB-BEVACIZUMAB

Regimen

- HCC-Atezolizumab-Bevacizumab

Indication

- Atezolizumab in combination with bevacizumab for the first-line systemic treatment of adult patients with locally advanced or metastatic and/or unresectable hepatocellular carcinoma where the following criteria is met:

  - The patient has a diagnosis of hepatocellular carcinoma and that one of the following applies to the patient:
    1. The patient has a confirmed histological diagnosis of hepatocellular carcinoma (HCC)
    2. A biopsy is deemed to be very high risk or technically not feasible in the patient. The decision to not biopsy has been made and documented by a specialist HCC multi-disciplinary team meeting and the tumour meets the non-invasive diagnostic criteria (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)
  - The patient has metastatic or locally advanced disease that is ineligible or has failed surgical or loco-regional therapies.
  - The patient has Child-Pugh A liver function.
  - 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 (please note previous systemic treatment with sorafenib, Lenvatinib or regorafenib or any immunotherapy or any systemic chemotherapy is not allowed).
  - The patient has an ECOG performance status of 0 or 1.
  - The clinician is 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.
  - Treatment with atezolizumab in combination with bevacizumab will continue until loss of benefit or unacceptable toxicity or withdrawal of patient consent, whichever comes first. If either atezolizumab or bevacizumab has to be discontinued due to toxicity and the patient is otherwise benefitting from treatment, treatment should continue with the remaining agent until loss of clinical benefit or unacceptable toxicity or withdrawal of patient consent.
  - The patient has no symptomatically active brain metastases or leptomeningeal metastases.

- The patient has received no prior treatment with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.
- 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.
- If a treatment break of more than 12 weeks beyond the expected 3 weekly cycle length is needed, a treatment break form to restart treatment should be completed, including an indication as appropriate if the patient had an extended break because of COVID 19.
- Upon 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.
- ECOG performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Atezolizumab	Fatigue, rash, pruritis, pneumonitis, colitis, pancreatitis, diarrhoea, diabetes mellitus, adrenal insufficiency, thyroid disorders, nausea, electrolyte disturbances, hepatitis, myasthenic syndrome, Guillain Barre syndrome
Bevacizumab	Haemorrhage, hypertension, proteinuria, impaired wound healing, gastrointestinal perforations, fistulae, arterial thrombosis, fatigue, diarrhoea, abdominal pain

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to ~~day~~ each cycle
- EDTA or calculated creatinine clearance prior to each cycle
- Blood pressure and dipstick urinalysis for proteinuria prior to treatment with bevacizumab
- Thyroid function tests and random cortisol prior to starting treatment and then every 6 weeks or when clinically indicated.
- Random blood glucose prior to each cycle.
- Prior to starting treatment screening for oesophageal varices should be performed.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

There is little need to adjust the dose of atezolizumab or bevacizumab for haematological toxicity.

Hepatic Impairment

Drug	Bilirubin (µmol/L)		AST/ALT units	Dose
Bevacizumab	N/A		N/A	No information available

Atezolizumab	If AST/ALT within normal limits at baseline, prior to starting treatment and increases to >3x to ≤10xULN Or If AST/ALT is >1 to ≤3 xULN at baseline, prior to starting treatment and increases to >5x to ≤10xULN Or If AST/ALT if >3 to ≤5xULN at baseline, prior to starting treatment and increases to >8 to ≤10xULN	Withhold Atezolizumab. Treatment may be resumed when it improves to grade 0 or grade 1 within 12 weeks and corticosteroids have been reduced to ≤10mg Prednisolone or equivalent per day.
	If AST/ALT increases to >10x ULN Or Total bilirubin increases to >3xULN	Permanently discontinue atezolizumab.

No initial dose adjustment of atezolizumab is required for mild or moderate hepatic impairment. There is only very limited data for HCC patients with Child-Pugh B liver disease and currently no data available for Child-Pugh C liver disease patients.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose
Atezolizumab	N/A	No dose adjustment needed
Bevacizumab	N/A	No information available

* Significant changes in GFR of more than 10% may require dose adjustment.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Atezolizumab

Atezolizumab belongs to the immunotherapy class of cancer treatments. Autoimmune toxicities are most frequently noted and can be life threatening. If autoimmune toxicities occur delaying treatment should be considered while investigations or treatments are organised. Some, but not all, toxicities mandate cessation of treatment. Please seek guidance from relevant site-specific specialist teams or oncologists with experience of prescribing these agents. Clinicians should be aware that the current funding approval precludes further treatment after an interruption of 12 weeks or longer; this situation may change.

Refer to the latest version of the European Society of Medical Oncology guidelines; Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[3].

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. Most occur during treatment, however, onset month's after the last dose has been reported. Unless an alternate aetiology has been identified, diarrhoea, increased stool frequency, bloody stool, LFT elevations, rash and endocrinopathy must be considered inflammatory and atezolizumab-related. Early diagnosis and appropriate management are essential to minimise life-threatening complications.

Atezolizumab should be permanently discontinued for: any NCI-CTC grade 3 or 4 pneumonitis or hepatitis; any other life-threatening NCI-CTC grade 4 reaction (including colitis and renal impairment); any recurrence of a severe or NCI-CTC grade 3 reaction; any persistent NCI-CTC grade 2 or 3 treatment-related adverse reaction that does not recover to grade 1 or resolve within 12 weeks after the last dose.

Immune-related adverse reaction	Severity	Treatment modification
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold until symptoms resolve and radiographic abnormalities improve. Consider treatment with oral prednisolone 1-2mg/kg or equivalent per day Treatment may be resumed if the event improves to grade 0 or grade 1 within 12 weeks, and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day.
	Grade 3 or 4 pneumonitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.
Immune-related colitis	Grade 2 or 3 diarrhoea or symptomatic colitis	Withhold the atezolizumab initially. For a grade 2 diarrhoea or colitis, if the symptoms persist for more than 5 days or recur, start treatment with 1-2mg/kg oral prednisolone or equivalent per day For a grade 3 diarrhoea or colitis treatment with intravenous corticosteroids should be started, this may be converted to oral treatment as symptoms improve. If the symptoms improve to grade 1 or less taper the corticosteroids over one month Treatment may be resumed if the event improves to grade 0 or grade 1 within 12 weeks, and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day
	Grade 4 diarrhoea or colitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.
Immune-related pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (more than 2xULN) or grade 2 or 3 pancreatitis	Withhold atezolizumab Treatment with atezolizumab may be resumed if 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 10mg or less oral

		prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue atezolizumab. Consider treatment with corticosteroids.
Immune-related thyroid disorders	Symptomatic	Withhold atezolizumab *Hypothyroidism* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism* Treatment may be resumed when symptoms are controlled by cabimazole or equivalent and thyroid function is improving
Immune-related adrenal insufficiency	Symptomatic	Withhold atezolizumab Treatment may be resumed if the symptoms improve to grade 0 or grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of 10mg or less of oral prednisone or equivalent per day and patient is stable on replacement therapy
Immune-related diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose more than 250-500mg/dL)	Withhold atezolizumab Treatment may be resumed if metabolic control is achieved on insulin replacement therapy
Immune-related myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome and meningoencephalitis	All grades	Permanently discontinue atezolizumab
Myositis	Grade 2-3	Withhold for a moderate to severe myositis and discontinue
	Grade 3-4	Permanently discontinue

Infusion related reactions	Grade 1	Reduce the infusion rate to half Once the event has resolved, wait for 30minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to original rate. Consider premedication with antihistamine and antipyretic.
	Grade 2	Withhold atezolizumab Restart at half of the infusion rate only after the symptoms have resolved. Consider premedication with antihistamine and antipyretic.
	Grade 3 or 4	Permanently discontinue atezolizumab
Immune-related rash	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold atezolizumab Treatment may be resumed if the rash is resolved and corticosteroids have been reduced to 10mg or less oral prednisone equivalent per day
	Grade 4 rash or confirmed Stevens-Johnsons Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue atezolizumab. Consider treatment with corticosteroids

Bleeding risk

Patients treated with Bevacizumab have an increased risk of haemorrhage. Cases of severe gastrointestinal haemorrhage, including fatal events, have been reported in patients with hepatocellular carcinoma treated with atezolizumab and bevacizumab.

In patients with HCC, screening for and subsequent treatment of oesophageal varices should be performed as per clinical practice prior to starting treatment with the combination of atezolizumab and bevacizumab. Bevacizumab should be permanently discontinued in patients who experience grade 3 or 4 bleeding with the combination treatment.

Bevacizumab

Bevacizumab doses should be omitted and not reduced for adverse reactions. If more than two doses are missed due to adverse events treatment should be stopped. It should be noted that the half-life of bevacizumab is approximately twenty days. Discontinuation of treatment in response to adverse effects is not expected to influence the short-term clinical evolution of the event, symptomatic treatment is often necessary.

Bevacizumab should be stopped if the individual develops;

- Gastrointestinal perforation
- Arterial thromboembolic events
- NCI-CTC grade 3 and above haemorrhagic events (requiring a blood transfusion or a major non-elective intervention)
- NCI-CTC grade 3 and above congestive heart failure or left ventricular function
- NCI-CTC grade 4 fistula

If a NCI-CTC symptomatic grade 4 venous thromboembolic event occurs bevacizumab should be stopped. However, if this is a pulmonary embolism bevacizumab may be re-started once a full recovery has been made and the individual is anti-coagulated with a subcutaneous low molecular weight heparin. An oral anticoagulant must not be used. Hypertension is a common consequence of bevacizumab therapy. For a NCI-CTC grade 1 hypertension no treatment is necessary. NCI-CTC grade 2 hypertension, consider anti-hypertensive therapy. For a NCI-CTC grade 3 and above hypertension that is persistent consider stopping treatment.

Bevacizumab may be continued for a NCI-CTC grade 1 proteinuria or the first occurrence of a grade 2 proteinuria. For the second occurrence of a NCI-CTC grade 2 proteinuria or any NCI-CTC grade 3 proteinuria give the bevacizumab as scheduled. A 24 hour urine collection or UPCR should be conducted at most three days before the next dose. If there is less than 2g protein per 24 hours or a UPCR 0-1 administer the bevacizumab and return to dipstick monitoring. If there is more than 2g protein per 24 hours omit the bevacizumab. Repeat the 24 hour urine collection prior to the next scheduled dose. If this is less than 2g per 24 hours administer the bevacizumab and continue 24 hour urine collection until the protein is 1g per 24 hours or less. 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 (NCI-CTCAE v.3).

Regimen

21 day cycle until disease progression or unmanageable toxicity

Drug	Dose	Days	Administration
Atezolizumab	1200mg	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
Bevacizumab	15mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)

Dose Information

- Bevacizumab will be dose banded in accordance with the national dose bands (bevacizumab).

Administration Information

Extravasation

- Atezolizumab – neutral
- Bevacizumab – neutral

Other

- The first infusion of atezolizumab should be administered over 60 minutes. If this is well tolerated subsequent infusions can be administered over 30minutes.
- The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

Additional Therapy

- As required for the treatment of infusion related reactions;

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg intravenous
  - paracetamol 1000mg oral

Additional Information

- The use of systemic corticosteroids, before starting treatment with atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of the agent. However, systemic corticosteroids can be used after starting atezolizumab to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the efficacy of atezolizumab.
- Patients must be given an atezolizumab Patient Alert Card.

References

1. Zentiva. Alymsys® Summary of product Characteristics. Updated 10/08/2021. Accessed 20/06/2022 via http://www.medicines.org.uk/emc.
2. Roche. Tecentriq® Summary of Product Characteristics. Updated 27/01/2022. Accessed 20/06/2022 via http://www.medicines.org.uk/emc.
3. Finn R S et al. Atezolizumab plus Bevacizumab in unresectable hepatocellular carcinoma. New England Journal of Medicine. 2020 May 4; 382 (20): 1894-1905.
4. Haanen J, Carbonnel F, Robert C, Kerr K.M , Peters S, Larkin J, Jordan J on behalf of the ESMO Guidelines Committee. Management of toxicities from immunotherapy. ESMO clinical practice guidelines for diagnosis, treatment and follow up. Ann Oncol 2017; 28 (suppl 4): 119-142.

REGIMEN SUMMARY

Atezolizumab-Bevacizumab

1. Atezolizumab 1200mg intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes
   Administration Instructions
   The first infusion of atezolizumab should be administered over 60 minutes. If this is well tolerated subsequent infusions can be administered over 30minutes.

   Ensure the patient has been an atezolizumab patient alert card.

2. Bevacizumab 15mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes
   Administration Instructions
   The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes

3. Chlorphenamine 10mg intravenous injection when required for infusion related reactions

4. Hydrocortisone 100mg intravenous injection when required for infusion related reactions

5. Paracetamol 1000mg oral when required for infusion related reactions
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2022		Alexandra Pritchard Pharmacist	Prof Tim Iveson Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.