Atezolizumab and Bevacizumab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Atezolizumab in combination with bevacizumab for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.	C22	00831a	Atezolizumab: ODMS 01/03/2022 (IV) 01/06/2024 (SC) Bevacizumab: N/A

*For post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Atezolizumab (IV or SC) and bevacizumab are administered on day 1 of a 21 day cycle until loss of clinical benefit or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Table 1: Treatment Schedule for Atezolizumab (IV) and Bevacizumab (IV)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Atezolizumab[a, b]	1200mg	IV infusion	250mL NaCl 0.9% over 60 minutes	Every 21 days
2	1	Bevacizumab	15mg/kg	IV infusion	100mL NaCl 0.9% over 90 minutes[c, d]	Every 21 days
[a]Initial dose must be given over 60 minutes; subsequent doses may be given over 30 minutes if tolerated						
[b]If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.						
[c]Flush line with NaCl 0.9% pre and post bevacizumab dose.						
[d]The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion.						

If the first infusion is well tolerated, 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. Alternatively, the unlicensed use of shorter infusion times is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance - Available on the NCCP website [i]. It should not be administered as an intravenous push or bolus.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ALTERNATIVE TREATMENT SCHEDULE:

Table 2: Treatment Schedule for Atezolizumab (SC) and Bevacizumab (IV)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Atezolizumab	1875mg	Subcutaneous*	Over 7 minutes[a]	Every 21 days[b]
2	1	Bevacizumab	15mg/kg	IV infusion	100mL NaCl 0.9% over 90 minutes[c, d]	Every 21 days
[a] Use of a subcutaneous infusion set (e.g. winged/butterfly) is recommended. The remaining residual hold-up volume in the tubing should not be administered to the patient. 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. [b] If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.						
[c]Flush line with NaCl 0.9% pre and post bevacizumab dose.						
[d]The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, 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. Alternatively, the unlicensed use of shorter infusion times is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance -Available on the NCCP website [i] It should not be administered as an intravenous push or bolus.						

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indication as above
- ECOG 0-1
- Child-Pugh score A
- Adequate haematological and organ function

CAUTIONS:

- Patients with clinically significant autoimmune disease
- Previous pelvic radiotherapy
- Pre-existing uncontrolled hypertension
- Clinically significant cardiovascular disease
- Renal disease including proteinuria
- Bleeding/Clotting disorders
- Previous anthracycline exposure
- History of significant venous thromboembolism
- Recent (less than 6 months) arterial thromboembolic events
- Prior radiation to the chest wall or other serious medical illness
- Symptomatic interstitial lung disease
- Moderate or severe ascites
- Symptomatic central nervous system (CNS) metastases
- Immunosuppressive doses of systemic corticosteroids or other immunosuppressive medication(s) (defined as >10mg prednisoLONE/daily (or steroid equivalent, excluding inhaled or topical steroids)
- Any active clinically significant infection requiring therapy
- Surgical procedure or complications that could lead to increased risk of fistulation or perforation
- Underlying condition that could lead to increased risk of fistulation or perforation

EXCLUSIONS:

- Hypersensitivity to atezolizumab, bevacizumab or any of the excipients.
- Prior systemic therapy for advanced or unresectable HCC
- Pregnancy or lactation
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Information regarding prior therapy with an anti PD-1 or anti PD-L1 antibody is Available on the NCCP website

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- TFTs
- Screening for oesophageal varices
- Dipstick urinalysis for protein
- Blood pressure measurement, cardiac assessment including history and physical exam.
- ECHO should be considered in patients who have had chest wall radiation or prior treatment with an anthracycline
- INR if clinically indicated*
  *(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle)

Regular tests:

- FBC, renal and liver profile, blood glucose, dipstick urinalysis for protein prior to each cycle
- TFTs every 6 weeks
- Blood pressure prior to each cycle and post treatment.
- INR if clinically indicated*
  *(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose reduction of atezolizumab or bevacizumab is not recommended.
- Guidelines for withholding of doses or permanent discontinuation are described below in Tables 3, 4, 5 and 6

Table 3: Guidelines for withholding or discontinuation of atezolizumab

Immune related adverse reaction	Treatment modification
Pneumonitis Grade 2 Grade 3 or 4	 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 Permanently discontinue atezolizumab
Hepatitis AST/ALT is within normal limits at baseline and increases to > 3 x to ≤ 10x ULN *or* AST/ALT is > 1 to ≤ 3 x ULN at baseline and increases to > 5x to ≤ 10x ULN *or* AST/ALT is > 3 x to ≤ 5 x ULN at baseline and increases to >8 x to ≤ 10x ULN AST/ALT increases to > 10 x ULN or total bilirubin increases to > 3 x ULN	 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 Permanently discontinue atezolizumab

Immune related adverse reaction	Treatment modification
Colitis Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	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 equivalent per day Permanently discontinue atezolizumab
Hypothyroidism or hyperthyroidism 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 anti-thyroid medicinal product and thyroid function is improving.
Adrenal insufficiency Symptomatic	Withhold atezolizumab. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisolone or equivalent per day and patient is stable on replacement therapy.
Hypophysitis Grade 2 or 3 Grade 4	Withhold atezolizumab. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisoLONE or equivalent per day and patient is stable on replacement therapy. Permanently discontinue atezolizumab
Type 1 diabetes mellitus Grade 3 or 4 hyperglycaemia (fasting glucose >250 mg/dL or 13.9 mmol/L)	Withhold atezolizumab. Treatment may be resumed when metabolic control is achieved on insulin replacement therapy.

Immune related adverse reaction	Treatment modification
Rash/Severe cutaneous adverse reaction Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1] Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Withhold atezolizumab. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisoLONE or equivalent per day Permanently discontinue atezolizumab
Myasthenic syndrome/ **myasthenia gravis, Guillain-Barré syndrome,Meningoencephalitis and Facial paresis** Facial paresis Grade 1 or 2 All grades or Facial paresis Grade 3 or 4	Withhold atezolizumab. Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding atezolizumab, permanently discontinue atezolizumab. Permanently discontinue atezolizumab
Myelitis Grade 2,3 or 4	Permanently discontinue atezolizumab
Pancreatitis Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis Grade 4 or any grade of recurrent pancreatitis	Withhold Atezolizumab. Treatment 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 prednisoLONE or equivalent per day. Permanently discontinue atezolizumab

Immune related adverse reaction	Treatment modification
Myocarditis Grade 2 or above	Permanently discontinue atezolizumab
Nephritis Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN) Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	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 Permanently discontinue atezolizumab
Myositis Grade 2 or 3 Grade 4 or recurrent Grade 3	Withhold atezolizumab Permanently discontinue atezolizumab
Pericardial disorders Grade 1 Grade 2 or above	Withhold atezolizumab[2] Permanently discontinue atezolizumab
Haemophagocytic lymphohistiocytosis Suspected haemophagocytic lymphohistiocytosis[1]	Permanently discontinue atezolizumab
Other immune-related adverse reactions Grade 2 or Grade 3 Grade 4 or recurrent Grade 3	Withhold until adverse reaction recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10mg prednisoLONE or equivalent per day. Permanently discontinue atezolizumab (except endocrinopathies controlled with replacement hormones)

Immune related adverse reaction	Treatment modification
Other adverse reactions **Infusion-related or Subcutaneous-related Reactions** Grade 1 or 2 Grade 3 or 4	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved Permanently discontinue atezolizumab
Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).	
[1]Regardless of severity	
[2] Conduct a detailed cardiac evaluation to determine the etiology and manage appropriately	

Renal and Hepatic Impairment:

Table 4: Dose modification of atezolizumab and bevacizumab in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Atezolizumab	**CrCl (mL/min)**	**Dose**	**Mild**	No dose adjustment is needed
	≥30	No dose adjustment is needed	**Moderate/Severe**	No need for dose adjustment is expected
	<30	No need for dose adjustment is expected		
	Haemodialysis	No need for dose adjustment is expected		
Bevacizumab	Renal impairment: no need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		Hepatic impairment: no need for dose adjustment is expected	
Renal and hepatic dose recommendations from Giraud et al 2023				

Management of adverse events:

Proteinuria:

Table 5: Dose modifications of bevacizumab for proteinuria

Degree of proteinuria	**Action**
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection
24-hour urine total protein (g/24hr)	**Action**
less than or equal to 2	Proceed
greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24hour
greater than 4	Discontinue Therapy

Table 6: Dose modifications of bevacizumab for adverse events

Adverse reactions		Recommended dose modification
Hypertension	Uncontrolled* or symptomatic hypertension on Day 1	Withhold bevacizumab treatment and start antihypertensive therapy or adjust pre-existing medication
	Grade 2-3 hypertension	Initiate antihypertensive therapy and consider interruption of bevacizumab until controlled
	Grade 4 hypertension or persisting grade 3 hypertension	Discontinue bevacizumab
Grade 4 Proteinuria		Discontinue bevacizumab
Tracheoesophageal (TE) fistula or any Grade 4 fistula		Discontinue bevacizumab
Grade 4 Thromboembolic events		Discontinue bevacizumab
Haemorrhagic event ≥ Grade 3		Discontinue bevacizumab
Gastrointestinal Perforation		Discontinue bevacizumab
*Uncontrolled hypertension for initiating bevacizumab is defined as sustained BP>150/100mmHg while receiving anti-hypertensive medication		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting- Available on the NCCP website :

Atezolizumab: Minimal (**Refer to local policy).**
Bevacizumab: Minimal (**Refer to local policy).**

For information:

Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists. Information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Anti-diarrhoeal treatment may be required with bevacizumab **(Refer to local policy).**
- Women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab.

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

Patient Alert Card

https://www.hpra.ie/img/uploaded/swedocuments/b5b77d64-e247-4fd0-bdcb-f5aea32e03a1.pdf

REFERENCES:

1. Finn R, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382:1894-1905. Available at: https://www.nejm.org/doi/10.1056/NEJMoa1915745
2. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
3. Atezolizumab (Tecentriq®) Summary of product characteristics. Last updated 21/05/2024. Accessed August 2024 . Available at: https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf
4. Bevacizumab (Avastin®) Summary of product characteristics. Accessed August 2024. Available at:

https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	19/02/2024		Prof Maccon Keane
2	09/12/2024	Regimen reviewed. Added atezolizumab subcutaneous formulation option (Table 2).Updated PD-L1 information in Exclusion section. Updated cautions section. Update to Table 3 to include hepatitis dose modifications for patients with HCC. Updated Supportive Care section to align with revised Atezolizumab SmPC. Regimen updated in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The rapid infusion is an unlicensed means of administration of bevacizumab for the indication described above, in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy