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 05/03/2024 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 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.

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 90minutes[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 as it should not be mixed with glucose solutions.						
[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 here[i]. It should not be administered as an intravenous push or bolus.						

ELIGIBILITY:

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

CAUTION:

- 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

EXCLUSIONS:

- Hypersensitivity to atezolizumab, bevacizumab or any of the excipients.
- Prior systemic therapy for advanced or unresectable HCC
- Symptomatic central nervous system (CNS) metastases
- Any medical condition that requires 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
- Prior systemic therapy for 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 here

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Glucose
- TFTs
- Virology Screen: Hepatitis B (HBsAg, HBcoreAb) and Hepatitis C
- 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, glucose, dipstick urinalysis for protein prior to each cycle
- TFTs every 3 to 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 1, 2, 3 and 4

Table 1: 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 Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] or blood bilirubin > 1.5 to 3 x ULN) Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 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.
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	Withhold atezolizumab. Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding atezolizumab, permanently discontinue atezolizumab.

Immune related adverse reaction	Treatment modification
All grades or Facial paresis Grade 3 or 4	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
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 prednisone 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)
Other adverse reactions **Infusion-related Reactions** Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved

Immune related adverse reaction	Treatment modification
Grade 3 or 4	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 2: Dose modification of atezolizumab and bevacizumab in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Atezolizumab[1]	**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[1]	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	
[1]Renal and hepatic dose recommendations from Giraud et al				

Management of adverse events:

Proteinuria:

Table 3: 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 4: 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:

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

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE: Anti-diarrhoeal treatment may be required with bevacizumab **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

Atezolizumab

- **Immune-mediated adverse reactions:** Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab. For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered. Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that

recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones.

- **Infusion related reactions:** These have been observed in clinical trials with atezolizumab. The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion- related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.
- **Immune-related severe cutaneous adverse reactions (SCARs):** Immune-related severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients treated with atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. In case a SCAR is suspected, atezolizumab should be withheld and patients should be referred to a specialist in SCARs for diagnosis and treatment. If SJS or TEN is confirmed, and for any grade 4 rash/SCAR, treatment with atezolizumab should be permanently discontinued. Caution is recommended when considering the use of atezolizumab in patients with previous history of a severe or life-threatening SCAR with other immune-stimulatory cancer medicines

Bevacizumab

- **Gastrointestinal perforations:** Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.
- **Wound healing complications:** 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. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for major elective surgery for 28 days and for 7 days for minor surgery or as directed by the prescribing Consultant. Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
- **Hypertension:** An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent.
    - Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician's discretion.
    - Patients should have their blood pressure measured before each dose or more frequently if hypertension develops/worsens.
    - Any patient who develops hypertension (>150/100 mmHg) should be treated with anti-hypertensive medications, or have their pre-existing medications adjusted. Patients developing severe hypertension (>200/110 mm Hg) that is not controlled with medication should have bevacizumab discontinued.
    - It should be permanently discontinued if the patient develops hypertensive crisis or

hypertensive encephalopathy.

- **Posterior Reversible Encephalopathy Syndrome (PRES):** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating therapy in patients previously experiencing PRES is not known.
- **Proteinuria:** Patients with a history of hypertension may be at increased risk for the development of proteinuria.
- **Thromboembolism:** Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolism or age > 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions. Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment. Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.
- **Haemorrhage:** Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage and minor mucocutaneous haemorrhage. Bevacizumab should be used with caution in patients at risk of bleeding.
- **Aneurysms and artery dissections**: 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 or history of aneurysm.

DRUG INTERACTIONS:

- No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.
- The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab.
- Current drug interaction databases should be consulted for more 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. Accessed Jan 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 Jan 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

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