| **Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY** | |
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| **Indication** | Atezolizumab, in combination with bevacizumab, is indicated for the first-line treatment of locally advanced or metastatic unresectable hepatocellular carcinoma.<br><br>NB previous systemic treatment with sorafenib or lenvatinib or regorafenib or any immunotherapy or any systemic chemotherapy is not allowed.<br><br>NB: the patient must have 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. |
| **Treatment Intent** | Palliative |
| **Frequency and number of cycles** | Every 21 days.<br><br>Continue until progressive disease or unacceptable toxicity or withdrawal of patient consent, whichever occurs first.<br>Formal medical review to be scheduled to occur at least by the end of the first 6 weeks of treatment.<br><br>NB patients can be switched between atezolizumab SC and IV therapy if the clinical need arises. |
| **Monitoring Parameters** | • **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.<br>• **Pre-treatment cardiac assessment:**<br>  ○ ECG baseline and as clinically indicated.<br>  ○ Check BNP, and Troponin T prior to treatment.<br>• Monitor FBC, U&Es, LFTs and random glucose at each cycle.<br>• If PLT <75 or neuts <1.0 d/w consultant.<br>• **Thyroid function** must be assessed at baseline then every 6 weeks or as clinically indicated.<br>• Cortisol monitoring should be undertaken in line with ESMO immunotherapy toxicity guidance available on KMCC website (see link below). Cortisol level should not be taken within 24hours of the last steroid dose.<br>• Monitor blood pressure at each cycle. Pre-existing hypertension should be adequately controlled before starting treatment.<br>• Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure.<br>• Monitor for signs and symptoms of myocarditis.<br>• Dipstick urine for proteinuria at each cycle. Report to consultant if protein 2+ (equivalent to 1g/l) and/or BP >/= 140/90 respectively. Reference should be made to KMCC guidelines for bevacizumab induced hypertension. https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/guidelines-for-the-management-of-sact-induced-adverse-reactions/<br>• **Renal Impairment:**<br>  ○ 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.<br>  ○ Bevacizumab: no dose recommendations. |

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| | • **<u>Hepatic impairment</u>**: (prior to treatment, for immune related hepatitis see below)- Patient must have Child-Pugh A liver function to be eligible.<br>o 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.<br>o Bevacizumab: no dose recommendations.<br>• **<u>Dose Modification:</u>**<br>o **Atezolizumab:** dose reductions are not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.<br>o **Bevacizumab:** Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended.<br>o 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.<br>• **<u>SC administration and Injection/Infusion-related reactions</u>**:<br>o **Atezolizumab SC:**<br>o Remove from fridge and allow to reach room temperature before administration.<br>o It is recommended to use a subcutaneous infusion set (e.g. winged/butterfly) containing a 23-25G stainless steel needle for injection with residual hold-up volume NOT exceeding 0.5ml.<br>o Ensure the syringe contains exactly 15ml of the medicinal product solution after priming the line.<br>o DO NOT administer the remaining residual hold-up volume in the tubing to the patient.<br>o Administer immediately to avoid needle clogging.<br>o Inject into the subcutaneous tissue of the thigh only, over 7 minutes.<br>o Do not inject at other sites of the body.<br>o Injection site should be alternated between left and right thigh for successive injections.<br>o 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.<br>o During the treatment other medicinal products for subcutaneous administration should preferably be injected at different sites.<br>o If a grade 1 or 2 injection-related reaction occurs, the injection should be slowed down or paused and appropriate medical therapies should be administered, premedication with antipyretic and antihistamines may be considered. Treatment may be resumed once the event has resolved.<br>o Permanently discontinue atezolizumab SC in the event of grade 3 or 4 hypersensitivity reaction.<br>o **Bevacizumab:** If an infusion reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered.<br>• **<u>Immune- related reactions:</u>**<br>o Patients must be advised to contact the oncology team if they experience any side effect, as some side effects worsen rapidly. Prompt management of side effects can ensure that the patient continues with treatment.<br>o 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. For details on treatment modification for immune related reactions see table 1. |

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| | ○ Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported. For signs or symptoms of SJS or TEN, atezolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, atezolizumab should be permanently discontinued.<br>○ Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some with fatal outcomes, have been observed. Patients should be monitored for clinical signs and symptoms of pericardial disorders.<br>○ Atezolizumab should be discontinued in the event of any grade Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis<br>○ **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.<br>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.<br>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.<br>○ 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.<br>○ For guidance on managing immune-related adverse reactions, refer to SPC and guidelines available on KMCC website: https://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/immunotherapy/<br>• **Bevacizumab**<br>○ 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.<br>○ 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.<br>○ 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.<br>○ Patients may be at increased risk for the development of fistulae when treated with bevacizumab.<br>○ 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.<br>○ 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 |

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| | 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.<br>o Any suspected thrombosis and/or haemorrhage d/w consultant.<br>o Patients with a history of arterial thromboembolism, diabetes or >65 years old should be treated with caution.<br>• **Common drug interactions (for comprehensive list refer to BNF/SPC):**<br>o **Atezolizumab:** 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.<br>o No formal interaction studies have been performed.<br>o **Bevacizumab:** Caution when used with drugs known to cause bleeding, concurrent use may increase risk.<br>• **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.<br>• **Driving & using machinery:** Atezolizumab can affect the ability to drive and use machines. If patient experiences fatigue they should not drive.<br>• The patient should be provided with the appropriate Tecentriq® Patient Alert card with each prescription (to be carried until at least 5 months after the last dose of treatment). |
| **References** | KMCC protocol UGI-066 V4 SPC accessed online 12.11.2025 CDF list accessed online 12.11.25 |

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

| **TABLE 1: Dose modification advice for immune related reactions** | | |
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| **Immune related reaction** | **Severity** | **Treatment modification** |
| **Pneumonitis** | Grade 2 | Withhold<br>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 |
| | Grade 3 or 4 | Permanently discontinue |
| **Hepatitis in patients with HCC** | If AST/ALT is within normal limits at baseline and increases to > 3x to ≤ 10x ULN ***or***<br>If AST/ALT is >1 to ≤ 3x ULN at baseline and increases to >5x to ≤10x ULN ***or***<br>If AST/ALT is > 3x to ≤ 5x ULN at baseline and increases to > 8x to ≤ 10x ULN | Withhold<br><br>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 |
| | If AST/ALT increases to >10x ULN ***or***<br>total bilirubin increases to > 3x ULN | Permanently discontinue |
| **Colitis** | Grade 2 or 3 Diarrhoea<br>(increase of ≥ 4 stools/day over baseline) ***or***<br>Symptomatic Colitis | Withhold<br>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 |
| | Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated) | Permanently discontinue |
| **Hypothyroidism or hyperthyroidism** | Symptomatic | Withhold<br>***Hypothyroidism:***<br>Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing<br>***Hyperthyroidism:***<br>Treatment may be resumed when symptoms are controlled by anti-thyroid medicinal product and thyroid function is improving |
| **Adrenal insufficiency** | Symptomatic | Withhold<br>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 prednisone or equivalent per day and patient is stable on replacement therapy |

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| **Hypophysitis** | Grade 2 or 3 | Withhold<br>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 prednisone or equivalent per day and patient is stable on replacement therapy |
| | Grade 4 | Permanently discontinue |
| **Type 1 diabetes mellitus** | Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L) | Withhold<br><br>Treatment may be resumed when metabolic control is achieved on insulin replacement therapy |
| **Rash/Severe cutaneous adverse reactions** | Grade 3<br>or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) regardless of severity | Withhold<br><br>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 prednisone or equivalent per day |
| | Grade 4<br>or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) regardless of severity | Permanently discontinue |
| **Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, Meningoencephalitis and facial paresis** | Facial paresis Grade 1 or 2 | Withhold<br>Treatment may be resumed if the event fully resolves. If the event does not fully resolve while withholding atezolizumab permanently discontinue. |
| | All Grades Myasthenic syndrome/myasthenia gravis, Guillain Barré syndrome and Meningoencephalitis or Facial paresis Grade 3 or 4 | Permanently discontinue |
| **Myelitis** | Grade 2, 3, or 4 | Permanently discontinue |
| **Pancreatitis** | Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN)<br>or Grade 2 or 3 pancreatitis | Withhold<br>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 prednisone or equivalent per day |
| | Grade 4 or any grade of recurrent pancreatitis | Permanently discontinue |
| **Myocarditis** | Grade 2 or above | Permanently discontinue |
| **Nephritis** | Grade 2:<br>(creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN) | Withhold |

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| | | 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 |
| | Grade 3 or 4:<br>(creatinine level > 3.0 x baseline or > 3.0 x ULN) | Permanently discontinue |
| **Myositis** | Grade 2 or 3 | Withhold |
| | Grade 4 or Grade 3 recurrent myositis | Permanently discontinue |
| **Pericardial disorders** | Grade 1 pericarditis | Withhold and conduct a detailed cardiac evaluation to determine the etiology and manage appropriately |
| | Grade 2 or above | Permanently discontinue |
| **Haemophagocytic lymphohistiocytosis** | Suspected haemophagocytic lymphohistiocytosis[1] | Permanently discontinue |
| **Other immune-related reactions** | Grade 2 or Grade 3 | Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. |
| | Grade 4 or recurrent Grade 3 | Permanently discontinue (except endocrinopathies controlled with replacement hormones) |

**Repeat every 21 days**

| Day | Drug | Dose | Route | Infusion Duration | Administration Details |
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| Day 1 | Metoclopramide | 20mg | PO | | |
| | **ATEZOLIZUMAB** | **1875mg** | SC | 7 mins | Inject 15 mL into the subcutaneous tissue of the left or right thigh over 7 minutes.<br>Do not inject at other sites of the body.<br>Injection sites should be rotated for successive injections. |
| | **BEVACIZUMAB** | **15mg/kg** | IV | 90min **cycle 1**<br>If tolerated give as below<br><br>60min **cycle 2**<br><br>30min **cycle 3 onwards** | The final concentration must be between 1.4 and 16.5 mg/ml.<br>In 100ml 0.9% sodium chloride. If the patient >/= 110kg give in total of 250mls sodium chloride 0.9% |
| TTO | Drug | Dose | Route | Directions | |
| Day 1 | Metoclopramide | 10mg | PO | 10mg up to 3 times a day as required (max. 30mg per day including 20mg pre-chemo dose).<br>Do not take for more than 5 days continuously. | |