Protocol Contains CHECKPOINT INHIBITOR IMMUNOTHERAPY	
Indication	First line treatment of locally advanced or metastatic and/or unresectable hepatocellular carcinoma that is ineligible for or has failed surgical or loco-regional therapies. NB on discontinuation of the combination of durvalumab 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.
Treatment Intent	Palliative
Frequency and number of cycles	**Combination therapy:** Durvalumab in combination with tremelimumab. One single 28 day cycle. **Monotherapy:** Durvalumab Repeat every 28 days Continue until disease progression or unacceptable toxicity or patient choice to stop treatment.

Monitoring Parameters pre-treatment	• **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.
	• **Thyroid function** must be assessed at baseline then every 8 weeks or as indicated based on clinical evaluation.
	• **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.
	• **Pre-treatment cardiac assessment:**
	  ○ **ECG** baseline and as clinically indicated.
	  ○ Check **BNP**, and **Troponin T** prior to treatment.
	• Monitor FBC, U&Es, LFTs, blood pressure and random blood glucose (BM) at each cycle.
	• To be eligible for this treatment the patient must have Child-Pugh A liver function.
	• **Haematological parameters:**
	• Combination: Prior to first cycle neuts >/=1.5 and PLT >/=100.
	• For durvalumab monotherapy, if PLT <75 or neuts <1.0 d/w consultant.
	• **Hepatic impairment:**
	  ○ **Tremelimumab:** No dose adjustment is recommended in mild or moderate hepatic impairment. No data in severe hepatic impairment (bilirubin > 3.0 x ULN and any AST), use with caution after a risk/benefit assessment of each patient. (NB to be eligible to start this treatment the patient must have child-pugh A liver function)
	  ○ **Durvalumab:** No dose adjustment is necessary.
	• **Renal impairment:**
	  ○ **Tremelimumab:** No dose adjustment is necessary in mild or moderate renal impairment. Data too limited in severe impairment (<30ml/min) to make a recommendation, use with caution.
	  ○ **Durvalumab:** No dose adjustment is necessary in mild or moderate renal impairment. No data in severe impairment (<30ml/min).
	• **Dose Modification:**
	  ○ Dose escalation or reduction of durvalumab is not appropriate to manage toxicity or tolerability. Dosing delay or discontinuation may be required based on individual safety and tolerability. See below for guidance on dosing in low body weight patients.
	  ○ **Tremelimumab:** *Patients with a body weight of 40 kg or less must receive weight-based dosing, equivalent to tremelimumab 4 mg/kg until weight is greater than 40 kg.

	○ **Durvalumab:** **Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to durvalumab 20 mg/kg until weight is greater than 30 kg. • **Infusion-related reactions:** Patients should be monitored for signs and symptoms of infusion-related reactions. In the event of grade 3 to 4 infusion-related reactions, discontinue tremelimumab and durvalumab and administer appropriate treatment. In the event of a mild or moderate reaction, interrupt or slow the rate of the infusion. Pre-medication for prophylaxis of subsequent infusion reactions should be considered. • **Management of adverse reactions.** • Tremelimumab and durvalumab: ○ **Immune-related reactions:** Most common reactions are pneumonitis, colitis, nephritis, hepatitis, hyperthyroidism, hypothyroidism, hypophysitis / hypopituitarism, diabetes, immune-related rash. ○ For suspected immune-mediated adverse reactions, based on the severity of the adverse reaction, treatment should be withheld or permanently discontinued (See table 1 for Recommended treatment modifications and management recommendations for immune related reactions). Treatment with corticosteroids or endocrine therapy should be initiated. For events requiring corticosteroid therapy, and upon improvement to </= Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement. ○ After withholding treatment, durvalumab can be resumed within 12 weeks if the adverse reactions improved to </= Grade 1 and the corticosteroid dose has been reduced to </=10 mg prednisone or equivalent per day. ○ Permanently discontinue for recurrent Grade 3 (severe) immune-mediated adverse reactions and for any Grade 4 (life-threatening) immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones. ○ 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/ ○ Non-immune-mediated adverse reactions, withhold treatment for Grade 2 and 3 adverse reactions until </= Grade 1 or baseline. ○ Discontinue in the event of Grade 4 adverse reactions (with the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment). ○ 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. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** • No interaction studies have been performed with either durvalumab or tremelimumab. • The use of systemic corticosteroids or immunosuppressants before starting durvalumab or tremelimumab should be avoided. Systemic corticosteroids or other immunosuppressants can be used after starting treatment to treat immune-related adverse reactions. • Patients treated with tremelimumab must be given the patient alert card (to be carried until at least 5 months after the last dose of treatment) and be informed about the risks which may occur during or after discontinuation of treatment.
References	CDF list accessed online 18.08.2025 SPC accessed online 20.08.2025

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

Table 1 SPC Treatment modifications and management recommendations for immune related reactions

Adverse reactions	Severity[a]	Treatment modification
Immune-mediated pneumonitis/interstitial lung disease	Grade 2	Withhold dose[b]
	Grade 3 or 4	Permanently discontinue
Immune-mediated hepatitis	ALT or AST > 3 - ≤ 5 x ULN or total bilirubin > 1.5 - ≤ 3 x ULN	Withhold dose[b]
	ALT or AST > 5 - ≤ 10 x ULN	Withhold durvalumab and permanently discontinue tremelimumab
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[c]	Permanently discontinue
	ALT or AST > 10 x ULN or total bilirubin > 3 x ULN	
Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values)[d]	ALT or AST > 2.5 - ≤ 5 x BLV and ≤ 20 x ULN	Withhold dose[b]
	ALT or AST > 5 - 7 x BLV and ≤ 20 x ULN or concurrent ALT or AST 2.5 - 5 x BLV and ≤ 20 x ULN and total bilirubin > 1.5 - < 2 x ULN[c]	Withhold durvalumab and permanently discontinue tremelimumab
	ALT or AST > 7 x BLV or > 20 x ULN whichever occurs first or bilirubin > 3 x ULN	Permanently discontinue
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose[b]
	Grade 3 or 4	Permanently discontinue[e]
Intestinal perforation	ANY grade	Permanently discontinue
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable
Immune-mediated hypothyroidism	Grade 2-4	No changes
Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Immune-mediated Type 1 diabetes mellitus	Grade 2-4	No changes
Immune-mediated nephritis	Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline)	Withhold dose[b]
	Grade 3 with serum creatinine > 3 x baseline or > 3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN	Permanently discontinue
Immune-mediated rash or dermatitis (including pemphigoid)	Grade 2 for > 1 week or Grade 3	Withhold dose[b]
	Grade 4	Permanently discontinue
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue
Immune-mediated myositis/polymyositis/rhabdomyolysis	Grade 2 or 3	Withhold dose[b,f]
	Grade 4	Permanently discontinue
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue
Immune-mediated myelitis transverse	Any grade	Permanently discontinue
Immune-mediated meningitis	Grade 2	Withhold dose[b]
	Grade 3 or 4	Permanently discontinue
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue

Immune-mediated Guillain-Barré syndrome	Grade 2-4	Permanently discontinue
Other immune-mediated adverse reactions[g]	Grade 2 or 3	Withhold dose[b]
	Grade 4	Permanently discontinue
Non-immune-mediated adverse reactions	Grade 2 and 3	Withhold dose until ≤ Grade 1 or return to baseline
	Grade 4	Permanently discontinue[h]

a Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BLV: baseline value.
b After withholding, tremelimumab and/or durvalumab can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. Tremelimumab and durvalumab should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable.
c For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.
d If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.
e Permanently discontinue tremelimumab for Grade 3; however, treatment with durvalumab can be resumed once event has resolved.
f Permanently discontinue tremelimumab and durvalumab if the adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.
g Includes immune thrombocytopenia, pancreatitis, cystitis noninfective, immune-mediated arthritis, uveitis and polymyalgia rheumatica.
h With the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue treatment should be based on accompanying clinical signs/symptoms and clinical judgment.

Cycle 1 only: Combination therapy 28 day cycle.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	TREMELIMUMAB	**300mg *(see notes above)**	IV	60 minutes	In 50ml sodium chloride 0.9% (final concentration 0.1 – 10mg/ml) via in-line low-protein binding 0.22micron filter. Do not co-administer other medicinal products through the same infusion line.
	DURVALUMAB	**1500mg **(see notes above)**	IV	60 minutes	In 100ml sodium chloride 0.9% (final concentration 1-15 mg/mL) via in-line low-protein binding 0.22micron filter.
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-treatment dose) Do not take for more than 5 days continuously.	

Cycle 2 onwards: Monotherapy repeat every 28 days.

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Metoclopramide	20mg	PO		stat
	DURVALUMAB	**1500mg **(see notes above)**	IV	60 minutes	In 100ml sodium chloride 0.9% (final concentration 1-15 mg/mL) via in-line low-protein binding 0.22micron filter.
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-treatment dose) Do not take for more than 5 days continuously.	