Durvalumab & Tremelimumab (HCC)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

First-line treatment for advanced or unresectable hepatocellular carcinoma. Eligible patients need to be Child Pugh A and performance status 0 or 1.
(NICE TA 1090)

Response Rates

Phase 3 HIMALAYA trial

- Tremelimumab/Durvalumab (n=393) vs sorafenib (n=389)
- Median overall survival (OS): Tremelimumab/Durvalumab = 16.43 months vs Sorafenib = 13.77 months
- 3 year OS: 30.7% vs 20.2%

Regimen details

Cycle 1

Day	Drug	Dose	Route
1	Tremelimumab	300mg (or 4mg/kg if body weight ≤ 40kg)	IV infusion
1	Durvalumab	1500mg (or 20mg/kg if body weight ≤ 30kg)	IV infusion

Cycle 2 onwards

Day	Drug	Dose	Route
1	Durvalumab	1500mg (or 20mg/kg if body weight ≤ 30kg)	IV infusion

Cycle frequency
28 days

Number of cycles
Until disease progression or unacceptable toxicity.

Pre-medication
Nil

Supportive medication
Loperamide if required.

Emetogenicity
This regimen has low emetogenic potential.

Administration
Tremelimumab should be administered prior to durvalumab, on cycle 1 day 1 only. Tremelimumab is administered over 60 minutes, diluted in sodium chloride 0.9% or glucose 5%, to a final concentration of 0.1-10 mg/mL. Tremelimumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding 0.2 or 0.22 micron filter.

Durvalumab is administered over 60 minutes, diluted in sodium chloride 0.9% or glucose 5%, to a final concentration of 1-15 mg/mL. Durvalumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding 0.2 or 0.22 micron filter.

Patients should be monitored (blood pressure, pulse and temperature) every 30 minutes during the infusion for infusion related reactions. For grade 1-2 infusion related reactions, decrease the infusion rate and closely monitor or temporarily interrupt treatment. Premedication with paracetamol and chlorphenamine should be used for further doses and patient should be closely monitored. For grade 3-4 infusion related reactions permanently discontinue treatment.

Extravasation
Tremelimumab is neutral
Durvalumab is neutral

Mandatory investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFT	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	14 days

Additional investigations advised pre-first cycle

As per IOCN consensus statement, consider the following as part of a baseline cardiac assessment

- ECG
- Troponin
- NT Pro-BNP
- Echocardiogram in high-risk patients (e.g. known CV disease, previous cardiotoxic therapy)

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+E (including creatinine)	7 days
LFT	7 days
Thyroid function	8 weekly
Glucose	7 days
Calcium	As clinically indicated
Cortisol	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance (CrCl)	≥ 30mL/min
Bilirubin	< 1.5 x ULN
ALT/AST	< 2.5 x baseline (and < 20 x ULN)

Dose modifications

Dose reductions are not recommended. Doses should be delayed/omitted until an adverse reaction resolves to ≤ grade 1

Haematological toxicity

Discuss with the consultant if:
Neutrophils <1.0 x 10^9/L
Platelets <75 x 10^9/L

Renal impairment

Tremelimumab & Durvalumab: No dose adjustment is required for mild or moderate renal impairment. There is insufficient data for recommendations to be made regarding dose adjustments in severe renal impairment.
See below for management of immune-mediated nephritis emergent on treatment.

Hepatic impairment

Note: blueteq criteria require patients to have Child Pugh A liver function to commence treatment.
Tremelimumab: No dose adjustment is required for mild or moderate hepatic impairment. There is no data available for use of tremelimumab in severe hepatic impairment.
Durvalumab: No modifications required for mild or moderate hepatic impairment. There is limited data on use of durvalumab in severe hepatic impairment but no need for dose adjustment is expected.
See below for management of immune-mediated hepatitis emergent on treatment. Discuss with consultant if LFTs deranged significantly from baseline, particularly in patients when not abnormal at baseline.

Other toxicities

The table below outlines actions required in terms of withholding or discontinuing treatment for immune-related toxicities. The toxicity should be managed as per local immunotherapy toxicity guidelines.

Toxicity	Definition	Action/Dose adjustment
Immune-mediated pneumonitis /interstitial lung disease	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Immune mediated hepatitis (in HCC)	ALT/AST 2.5 - 5 x baseline and < 20 x ULN **and** bilirubin ≤ 1.5 x ULN	Withhold dose
	ALT/AST 2.5 - 5 x baseline and < 20 x ULN **and** bilirubin 1.5-2 x ULN	Withhold durvalumab and permanently discontinue tremelimumab
	ALT/AST 5-7 x baseline and ≤ 20 x ULN	
	ALT/AST > 7 x baseline value or > 20 x ULN or bilirubin > 3 x ULN	Permanently discontinue
Immune-mediated colitis or diarrhoea	Grade 2	Withhold dose
	Grade 3	Permanently discontinue tremelimumab and durvalumab. Durvalumab may be restarted at consultant discretion.
	Grade 4	Permanently discontinue
Intestinal perforation	Any grade	Permanently discontinue
Immune-mediated hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable
Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Immune-mediated nephritis	Grade 2 (serum creatinine 1.5 - 3 x ULN or baseline)	Withhold dose
	Grade 3 (serum creatinine > 3 x baseline or 3-6 x ULN) or Grade 4 (sereum creatinine > 6 x ULN)	Permanently discontinue
Immune-mediated rash/dermatitis	Grade 2 for > 1 week or Grade 3	Withhold dose
	Grade 4	Permanently discontinue
Immune-mediated myocarditis	Grade 2-4	Permanently discontinue
Immune-mediated myositis / polymyositis / rhabdomyolysis	Grade 2 or 3	Withhold dose, permanently discontinue if does not resolve within 30 days or signs of respiratory insufficiency
	Grade 4	Permanently discontinue
Infusion related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Infection	Grade 3 or 4	Withhold dose until clinically stable
Immune-mediated myasthenia gravis, encephalitis, Guillain-Barre syndrome	Grade 2-4	Permanently discontinue
Immune-mediated myelitis transverse	Any grade	Permanently discontinue
Immune-mediated meningitis	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Pure red cell aplasia (PRCA)	Any grade	Permanently discontinue
Other immune-mediated adverse reactions	Grade 2 or 3	Withhold dose
	Grade 4	Permanently discontinue

Side Effects

HIMALAYA trial:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Anaemia	9.3	2.8
Non-haematological	Diarrhoea	26.5	4.4
	Pruritis	22.9	0
	Rash	22.4	1.5
	Fatigue	17.0	2.1
	Decreased appetite	17.0	1.3
	Pyrexia	12.9	0.3
	Aspartate aminotransferase increased	12.4	5.2
	Nausea	12.1	0
	Hypothyroidism	12.1	0
	Abdominal pain	11.9	1.3
	Insomnia	10.3	0.3
	Asthenia	10.1	1.8
	Alanine aminotransferase increased	9.3	2.6
	Constipation	9.3	0
	Lipase increased	8.8	6.2
	Peripheral oedema	8.5	0.5
	Cough	7.7	0
	Amylase increased	7.5	3.6
	Hypertension	5.9	1.8
	Hyponatraemia	5.4	4.1
	Hyperkalaemia	5.2	1.5
	Blood bilirubin increased	5.2	0.8
	Gamma-glutamyltransferase increased	4.6	2.1
	Hypokalaemia	3.4	1.0
	Palmar-plantar erythrodysesthesia syndrome	0.8	0
	Alopecia	0.5	0

Additional information

The following patients were excluded from clinical studies so tremelimumab/durvalumab should be used with caution in these populations after careful consideration of risk versus benefit.

- Main portal vein thrombosis
- Liver transplant
- Uncontrolled hypertension
- History of or current brain metastases (NB. Blueteq criteria: no active brain or leptomeningeal metastases)
- Spinal cord compression
- Co-infection of viral hepatitis B and C
- Active or prior documented GI bleeding with 12 months
- Ascites requiring non-pharmacological intervention
- Hepatic encephalopathy within 12 months of starting treatment

Significant drug interactions – for full details consult product literature/ reference texts

Corticosteroids: use of systemic corticosteroids at baseline, before starting treatment, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

References

- National Institute for Health and Care Excellence TA1090. Accessed 23rd October 2025 via www.nice.org.uk
- Summary of Product Characteristics Tremelimumab - Imjudo® (Astra Zeneca) accessed 23rd October 2025 via www.medicines.org.uk
- Summary of Product Characteristics Durvalumab - Imfinzi® (Astra Zeneca) accessed 23rd October 2025 via www.medicines.org.uk
- Abou-Alfa, G.K., et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid 2022;1(8)

Version	Issue date	Review date	Revision	Written/Checked/Authorised
1	Nov 2025	Nov 2028	New protocol	Written/reviewed: Dr Z Hudson (Consultant Oncologist, UHBW NHS Trust), Dr L Wade (Consultant Oncologist, UHBW NHS Trust) Checked: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance) Authorised: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)