# DURVALUMAB (Imfinzi) TREMELIMUMAB (Imjudo)

## INDICATION (ICD10) C34

*Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/)* (DUR6)

1. For first-line systemic treatment (no previous systemic therapy with sorafenib or lenvatinib or regorafenib) of adult patients with locally advanced or metastatic and/or unresectable hepatocellular carcinoma with Child-Pugh A liver function. Has no symptomatically active brain metastases or leptomeningeal metastases. PS 0 or 1.

## REGIMEN

Cycle 1 (Administer tremelimumab first)

Day 1 TREMELIMUMAB 300mg* in #ml sodium chloride 0.9% IV infusion over 60 minutes
DURVALUMAB 1500mg** in 250ml sodium chloride 0.9% IV infusion over 60 minutes.

Cycle 2 onwards

Day 1 DURVALUMAB 1500mg** in 250ml sodium chloride 0.9% IV infusion over 60 minutes.

# diluent volume for dose prescribed as per national standardised product specification
* Tremelimumab patients with a body weight of 40kg or less must receive weight-based dosing, equivalent to tremelimumab 4mg/kg until weight is greater than 40kg.
** Durvalumab patients with a body weight of 30kg or less must receive weight-based dosing, equivalent to durvalumab 20mg/kg until weight is greater than 30kg.

## CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days until disease progression

## ANTI-EMETICS

Minimal risk

## CONCURRENT MEDICATION REQUIRED

None required

## EXTRAVASATION AND TYPE OF LINE / FILTERS

Durvalumab – neutral
Tremelimumab – neutral

Durvalumab -administer with low-protein binding 0.2 or 0.22micron in-line filter.
Tremelimumab -administer with low-protein binding 0.2 or 0.22micron in-line filter.

Peripheral line

## INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle
Neutrophils x $10^9$/L ≥1.5
Platelets x $10^9$/L ≥70
Random blood glucose every cycle
Thyroid function baseline and every 1 to 2 cycles
Random cortisol baseline and every 1 to 2 cycles
Baseline weight

## MAIN TOXICITES AND ADVERSE REACTIONS

| | |
|---|---|
| Durvalumab | Immune mediated pneumonitis<br>Immune mediated hepatitis<br>Immune mediated colitis<br>Immune mediated endocrinopathies |
| Tremelimumab | Immune mediated pneumonitis<br>Immune mediated hepatitis<br>Immune mediated colitis<br>Immune mediated endocrinopathies<br>Immune mediated myocarditis<br>Immune mediated nephritis<br>Immune mediated rash |

## INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
**(not exhaustive list check SPC/BNF/Stockleys)**

| | |
|---|---|
| Durvalumab | - |
| Tremelimumab | - |

## DOSE MODIFICATIONS
### Non-haematological
Durvalumab and Tremelimumab

Immune-related adverse reactions - refer to TV immune-oncology agent immune related adverse event clinical guideline.

Immune-mediated adrenal insufficiency, hypophysitis / hypopituitarism

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|---|---|
| Grade 2-4 | Withhold dose until clinically stable |

Immune-mediated Type 1 diabetes mellitus

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|---|---|
| Grade 2-4 | No changes |

Immune-mediated colitis or diarrhoea

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|---|---|
| Grade 2 | Withhold dose.<br>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 ≤10mg prednisone or equivalent per day. Tremelimumab and durvalumab should be permanently discontinued for recurrent grade 3 adverse reactions, as applicable. |
| Grade 3 or 4 | Permanently discontinue tremelimumab for grade 3; however, treatment with durvalumab can be resumed once event has resolved. |

Immune-mediated encephalitis

| | |
|---|---|
| Grade 2-4 | Permanently discontinue |

Immune-mediated Guillain-Barré syndrome

| | |
|---|---|
| Grade 2-4 | Permanently discontinue |

Immune-mediated hepatitis

| | |
|---|---|
| ALT or AST >3-≤5 x ULN or total bilirubin >1.5-≤3xULN | Withhold dose. 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 ≤10mg prednisone or equivalent per day. Tremelimumab and durvalumab should be permanently discontinued for recurrent grade 3 adverse reactions, as applicable. |
| ALT or AST >5-≤10xULN | Withhold durvalumab and permanently discontinue tremelimumab (where appropriate) |
| Concurrent ALT or AST >3xULN and total bilirubin >2xULN | Permanently discontinue |
| ALT or AST >10xULN or total bilirubin >3xULN | |

Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values)

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|---|---|
| ALT or AST >2.5-≤5xBLV and ≤20xULN | Withhold dose. 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 ≤10mg prednisone or equivalent per day. Tremelimumab and durvalumab should be permanently discontinued for recurrent grade 3 adverse reactions, as applicable. |
| ALT or AST >5-7xBLV and ≤20xULN or concurrent ALT or AST 2.5-5xBLV and ≤20xULN and total bilirubin >1.5-<2xULN | Withhold durvalumab and permanently discontinue tremelimumab (where appropriate) |
| ALT or AST >7xBLV or >20xULN whichever occurs first or bilirubin >3xULN | Permanently discontinue |

Immune-mediated hyperthyroidism, thyroiditis

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|---|---|
| Grade 2-4 | Withhold dose until clinically stable |

Immune-mediated hypothyroidism

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|---|---|
| Grade 2-4 | No changes |

Immune-mediated meningitis

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|---|---|
| Grade 2 | Withhold dose.<br>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 ≤10mg prednisone or equivalent per day. Tremelimumab and durvalumab should be permanently discontinued for recurrent grade 3 adverse reactions, as applicable. |
| Grade 3 or 4 | Permanently discontinue |

Immune-mediated myasthenia gravis

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|---|---|
| Grade 2-4 | Permanently discontinue |

Immune-mediated myelitis transverse

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|---|---|
| Any grade | Permanently discontinue |

Immune-mediated myocarditis

| | |
|---|---|
| Grade 2-4 | Permanently discontinue |

Immune-mediated myositis/polymyositis/rhabdomyolysis

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|---|---|
| Grade 2 or 3 | Withhold dose.<br>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. |
| Grade 4 | Permanently discontinue |

Immune-mediated nephritis

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|---|---|
| Grade 2 with serum creatinine >1.5-3x(ULN or baseline) | Withhold dose.<br>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 ≤10mg prednisone or equivalent per day. Tremelimumab and durvalumab should be permanently discontinued for recurrent grade 3 adverse reactions, as applicable. |
| Grade 3 with serum creatinine >3xbaseline or >3-6xULN; grade 4 with serum creatinine >6xULN | Permanently discontinue |

Immune-mediated pneumonitis/interstitial lung disease

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|---|---|
| Grade 2 | Withhold dose |
| Grade 3 or 4 | Permanently discontinue |

Immune-mediated rash or dermatitis (including pemphigoid)

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| Grade 2 for > 1 week or grade 3 | Withhold dose.<br>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 ≤10mg prednisone or equivalent per day. Tremelimumab and durvalumab should be permanently discontinued for recurrent grade 3 adverse reactions, as applicable. |

Infusion-related reactions

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| Grade 1 or 2 | Interrupt or slow the rate of infusion |
| Grade 3 or 4 | Permanently discontinue |

Intestinal perforation

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| ANY grade | Permanently discontinue |

Other immune-mediated adverse reactions

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|---|---|
| Grade 2 or 3 | Withhold dose.<br>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 ≤10mg prednisone or equivalent per day. Tremelimumab and durvalumab should be permanently discontinued for recurrent grade 3 adverse reactions, as applicable. |
| Grade 4 | Permanently discontinue |

Non-immune-mediated adverse reactions

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|---|---|
| Grade 2 and 3 | Withhold dose until ≤grade 1 or return to baseline |
| Grade 4 | Permanently discontinue, 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. |

**Hepatic impairment**

Durvalumab

No dose adjustment is needed for patients with hepatic impairment.

Tremelimumab

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Tremelimumab has not been studied in patients with severe hepatic impairment.

**Renal impairment**

Durvalumab

No dose adjustment is required in mild or moderate renal impairment. There is insufficient data from patients with severe renal impairment (CrCl <30ml/min) for dosing recommendations.

Tremelimumab

No dose adjustment is recommended in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population.

**REFERENCES**

1. CDF
2. SPC