Managing immune-mediated adverse events associated with STRIDE in the HIMALAYA study

This resource is intended for UK healthcare professionals involved in the care of patients with advanced or unresectable hepatocellular carcinoma (HCC) only.

Background

- Immunotherapies, such as immune checkpoint inhibitors, can be associated with immune-mediated adverse events (imAEs) which differ substantially from adverse events (AEs) seen with other anti-cancer therapies and may impact efficacy outcomes.[1,2] Toxicity profiles can vary significantly depending on the therapeutic target[3]
- This material will focus on the imAEs associated with **Single Tremelimumab ▼ Regular Interval Durvalumab (STRIDE)** in advanced or unresectable HCC[4]
- The STRIDE regimen consists of a single priming dose of IMJUDO (tremelimumab) 300 mg IV, an anti-CTLA-4, plus IMFINZI (durvalumab) 1500 mg IV, an anti-PD-L1; followed by IMFINZI 1500 mg IV Q4W[4]
- The randomised, open-label, multicentre, global, Phase III HIMALAYA study evaluated STRIDE vs sorafenib in patients with advanced or unresectable HCC.[4] The primary objective was overall survival for STRIDE versus sorafenib[4]

Licensed therapeutic indications for IMFINZI in combination with IMJUDO in the United Kingdom:

- IMFINZI in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable HCC[5]
- IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable HCC[6]

CLICK HERE for the IMFINZI PI

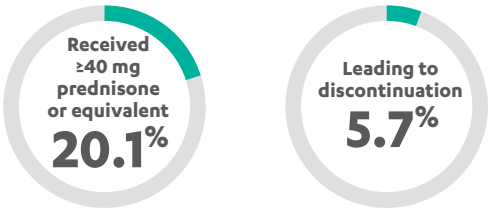
CLICK HERE for the IMJUDO PI

HIMALAYA safety data

STRIDE (n=388)

Any imAEs[4]

imAEs requiring ≥40 mg prednisone or equivalent and imAEs leading to discontinuation[4]



In the sorafenib arm (n=374), any Grade imAEs occurred in 8.0% of patients and 2.4% experienced any Grade 3–4 imAEs. imAEs requiring ≥40 mg prednisone or equivalent was 1.9% and 1.6% led to discontinuation[4]

The most common imAEs were:[4,7]

Thyroid events | **Hepatic events** | **Diarrhoea/colitis** | **Dermatitis/rash**

Dose escalation or reduction is not recommended. Treatment withholding or discontinuation may be required based on individual safety and tolerability[8,9]

imAEs are special warnings for use of IMFINZI and IMJUDO. Please refer to the following sections of the respective SmPCs for full information on the safety profile of IMFINZI in combination with IMJUDO:

- **Section 4.8** (undesirable effects, summary of the safety profile)
- **Sections 4.3** (contraindications), **4.4** (special warnings and precautions for use) and **4.5** (interaction with other medicinal products and other forms of interaction)
- **Section 4.2** (posology and method of administration)

CLICK HERE for the IMFINZI SmPC

CLICK HERE for the IMJUDO SmPC

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to AstraZeneca by visiting https://contactazmedical.astrazeneca.com/ or by calling 0800 783 0033

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information.

AE, adverse event; CTLA-4, cytotoxic T-lymphocyte associated protein 4; HCC, hepatocellular carcinoma; imAE, immune-mediated adverse event; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; PD-L1, programmed death-ligand 1; PI, prescribing information; Q4W, every 4 weeks; SmPC, Summary of Product Characteristics; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

1. Ramos-Casals M, et al. *Nat Rev Dis Primers*. 2020;6(1):38; 2. Lau G, et al. Presented at ASCO 2023; 2–6 June. Chicago, IL. Abstract #4004; 3. Yin Q, et al. *Front Immunol*. 2023;14:1167975; 4. Abou-Alfa GK, et al. NEJM Evid. 2022;1(8):1–12 (including Supplementary Appendix and Protocol); 5. IMFINZI Prescribing Information. United Kingdom; 6. IMJUDO Prescribing Information. United Kingdom; 7. Sangro B, et al. Presented at ILCA 2022; 1–4 September. Madrid, Spain. Abstract #67O; 8. IMFINZI. Summary of product characteristics. Available at: https://www.medicines.org.uk/emc/product/9495/smpc. Accessed March 2025; 9. IMJUDO. Summary of product characteristics. Available at: https://www.medicines.org.uk/emc/product/14841/smpc#gref. Accessed March 2025.

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IMFINZI® durvalumab 50 mg/mL concentrate for solution for infusion

IMJUDO®▼ tremelimumab 20 mg/mL concentrate for solution for infusion

ESMO 2022 guidelines for the most common imAEs observed in the HIMALAYA trial

Most common any Grade imAEs in the STRIDE* arm[1]

imAEs	STRIDE (n=388) Any Grade[1]	ESMO Guidelines[2]
		To access the full ESMO guidelines on the management of toxicities from immunotherapy, please **CLICK HERE** *Please note that this link will direct you to a third-party website not affiliated with AstraZeneca.*
Hypothyroidism	10.1%	For Grade 1–4 hypo- and hyperthyroidism imAEs: Measure baseline endocrine levels of TSH, FT4, T3 (when indicated) TFTs; continue to monitor TFTs during treatment† **Low FT4 with elevated TSH or TSH >10 with normal FT4** Administer thyroxine 0.5–1.5 µg/kg (start low in elderly, if cardiac history)
Hyperthyroidism	4.7%	**Thyrotoxicosis (differential diagnosis thyroiditis, Graves disease)** • Run an additional anti-TSH receptor antibody, anti-TPO antibody, and nuclear medicine thyroid uptake scan • For symptoms, administer propranolol or atenolol • For Graves disease, administer carbimazole • For painful thyroiditis, consider prednisolone 0.5 mg/kg and taper • If unwell, withhold ICI therapy and consider restarting when symptoms are controlled
Diarrhoea/colitis	5.9%	**Grade 1** • For symptoms, manage with low-fibre diet, loperamide, psyllium, and spasmolytic • If failure after 15 days, manage as Grade 2 **Grade 2** • For symptoms, manage with oral CSs 40–60 mg/day • If failure after 5–7 days (depending on endoscopic severity), manage as Grade 3 **Grade 3–4‡** • Administer methylprednisolone 1 mg/kg/day (IV) and assess response at days 3–5 • If there is a response to IV CSs, switch to oral prednisolone 1 mg/kg/day Please consult the full ESMO guidelines for the management of Grade 2–4 response to CSs and Grade 2–4 refractory CSs
Rash	2.3%	**Grade 1** • Apply mild to moderate topical CSs (BID) • For itching, administer oral antihistamines • Apply topical emollient • Advise to avoid sun and skin irritants **Grade 2** • Consider holding ICI therapy • Administer moderate to high potency CSs • Apply topical emollient • If pruritus is present, administer oral AHs • If refractory, initiate prednisone (0.5–1 mg/kg) or equivalent, tapered over >4 weeks • Restart ICI therapy when Grade 1 and prednisone <10 mg/day **Grade 3** • Administer high potency topical CSs • If pruritus is present, administer oral AHs • Apply topical emollient • If refractory, initiate prednisone (0.5–1 mg/kg) or equivalent, tapered over >4 weeks • Restart ICI therapy when Grade 1 and prednisone <10 mg/day **Grade 4** • Admit to hospital • Rule out systemic complications • Initiate IV (methyl)prednisone (1–2 mg/kg) or equivalent tapered over >4 weeks once reaction is controlled • Consider additional therapies such as infliximab or tocilizumab if refractory to CSs
Hepatitis	2.3%	**Grade 1** • ALT or AST >ULN to 3x ULN **Grade 2** • ALT or AST 3–5 x ULN • Avoid hepatotoxic drugs • If rising ALT and/or AST when re-checked, start CSs 0.5–1.0 mg/kg/day • Upon improvement, resume ICI therapy after tapering CSs to <10 mg/day • If no improvement (despite steroid use), increase dose of CSs to 1–2 mg/kg/day and discontinue ICI therapy **Grade 3** • ALT or AST 5–20x ULN • If ALT and/or AST <400 U/l with normal bilirubin, INR and albumin administer CSs 1–2 mg/kg/day • If ALT and/or AST >400 U/l or raised bilirubin/INR/low albumin, administer methylprednisolone 2 mg/kg (IV) **Grade 4** • ALT or AST >20x ULN • Administer methylprednisolone 2 mg/kg (IV)

KEY: Continue ICI therapy · Withhold ICI therapy · Discontinue ICI therapy

This document provides an overview on the management of imAEs; as imAEs are special warnings for use of IMFINZI and IMJUDO, please consult the IMFINZI and IMJUDO SmPCs for full guidance.[3,4] Please refer to the SmPCs of each individual product for further information[2]

The IMJUDO patient alert card is available to patients and carers to help them understand the risk of imAEs CLICK HERE

CLICK HERE to discover more on the IMFINZI resource hub

*Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.[1] †Monitoring of patients varies between treatment with anti-CTLA-4 (including combination with anti-PD-1) and anti-PD-(L)1 ICIs.[2] ‡The IMFINZI and IMJUDO SmPCs state to permanently discontinue treatment for Grade 3–4 immune-mediated diarrhoea or colitis.[3,4]

AH, antihistamine; ALT, alanine transaminase; AST, aspartate aminotransferase; BID, twice a day; CTLA-4, cytotoxic T-lymphocyte associated protein 4; CS, corticosteroid; ESMO, European Society for Medical Oncology; FT4, free thyroxines; ICI, immune checkpoint inhibitor; INR international normalised ratio of prothrombin time; imAE, immune-mediated adverse event; IV, intravenous; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q4W, every 4 weeks; T3, triiodothyronine; TFT, thyroid function test; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; SmPC, Summary of Product Characteristics; STRIDE, Single Tremelimumab Regular Interval Durvalumab; ULN, upper limit normal.

1. Sangro B, et al. Presented at ILCA 2022; 1–4 September. Madrid, Spain. Abstract #67O; 2. Haanen J, et al. *Ann Oncol*. 2022;33(12):1217–1238; 3. IMFINZI. Summary of product characteristics. Available at: https://www.medicines.org.uk/emc/product/9495/smpc. Accessed March 2025; 4. IMJUDO. Summary of product characteristics. Available at: https://www.medicines.org.uk/emc/product/14841/smpc#gref. Accessed March 2025.

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