Tremelimumab (Imjudo®) in combination with durvalumab for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC)

General information [1]

Drug description	Indication
Tremelimumab (Imjudo®) is a monoclonal antibody. It binds to CTLA-4, which is primarily expressed on the surface of activated T lymphocytes, and thus enhances T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced anti-tumour activity.	Tremelimumab (Imjudo®) in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable HCC.

Current treatment

- **NICE** recommends the following treatment options for advanced (stage B not eligible for locoregional therapy or stage C) HCC [2]:
  - Lenvatinib is recommended as an option for untreated, advanced, unresectable HCC in adults.
  - Sorafenib is recommended as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment.
- Systemic therapies for advanced HCC according to **ESMO** [3]:
  - Chemotherapy has not been shown to improve survival in randomised trials and is not recommended as a standard of care (II, C).
  - Targeted first-line therapies:
    - Sorafenib is the standard of care for patients with advanced HCC and those with intermediate-stage (BCLC B) disease not eligible for, or progressing despite, locoregional therapies. It is recommended in patients with well-preserved liver function and ECOG PS 0–2 (I, A).
    - Lenvatinib showed non-inferiority efficacy compared with sorafenib and can be considered in patients with advanced HCC without main portal vein invasion and with ECOG PS 0–1 as a front-line systemic treatment, pending EMA approval (I, A).

Regulatory status

EMA

Tremelimumab (Imjudo®) [1, 6]

Approval status for this indication: On 15 December 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Imjudo®.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 20/02/2023

The full indication is:

- Imjudo® in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable HCC.

Other indications: none

- ✓ Medicine is under additional monitoring

Durvalumab (Imfinzi®) [7]

Approval status for this indication: On 15 December 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Imfinzi®.

The CHMP adopted a new indication as follows:

FDA [4, 5]

Tremelimumab (Imjudo®)

Approval status for this indication: On 21 October 2022, the FDA approved tremelimumab (Imjudo®) in combination with durvalumab for adult patients with unresectable HCC.

- ✓ Tremelimumab was granted orphan drug designation.

- **Other indications**: Imjudo ® is indicated in combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumour aberrations [8].

Durvalumab (Imfinzi®)

Approval status for this indication: Imfinzi® is indicated in combination with tremelimumab-actl, for the treatment of adult patients with unresectable hepatocellular carcinoma.

Other indications: Imfinzi® is indicated:

- for the treatment of adult patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- in combination with tremelimumab-actl and platinum-based chemotherapy, for the treatment of adult patients with metastatic NSCLC with no sensitizing EGFR mutations or ALK genomic tumour aberrations.

- ❖ Imfinzi® in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable HCC.

Other indications:

- ❖ Imfinzi® as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
- ❖ Imfinzi® in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR-mutations or ALK-positive mutations.
- ❖ Imfinzi® in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer.
- ❖ Imfinzi® in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer.

✓ **Medicine is under additional monitoring**

Costs

15 ml Imjudo® concentrate for solution for infusion 20 mg/ ml = € 22,020.00 (ex-factory price)
10 ml Imfinzi® concentrate for solution for infusion 50mg/ml = € 3,088.00 (ex-factory price) [9]

Warnings and precautions [5, 8]

- ❖ **Immune-mediated adverse reactions**
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis with renal dysfunction and immune-mediated pancreatitis.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose.
  - Withhold or permanently discontinue based on severity and type of reaction.
- ❖ **Infusion-related reactions**
  - Interrupt, slow the rate of infusion, or permanently discontinue treatment based on the severity of the reaction.
- ❖ Complications of Allogeneic HSCT (durvalumab only):
  - Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- ❖ **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and use of effective contraception.

Study characteristics [10-13]

Trial name	*n*	Intervention (I)	Intervention2 (I2)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
HIMALAYA NCT03298451	1,171	STRIDE: tremelimumab (300 mg, one dose) + durvalumab	durvalumab (1500 mg every 4 weeks)	sorafenib (400 mg twice daily)	OS for STRIDE versus sorafenib	**ongoing**[2], global, open-label, phase 3 trial,	-	AstraZeneca	[12]

[2] The HIMALAYA trial is currently ongoing; estimated study completion date is 08/2024.

	(1:1:1)[1]	(1500 mg every 4 weeks)							

Efficacy (I vs. I2 vs. C)	**Safety** (I vs. I2 vs. C vs. T75+D[3])
Median follow-up durations at data cut-off: 33.18 vs. 32.56 vs. 32.23 months **<u>Superiority analysis for STRIDE vs. sorafenib (I vs. C):</u>** Patients who had died at data cut-off: 66.7% vs. 75.3%; HR 0.78; 96.02% CI, 0.65-0.93; p=0.0035 Median OS for STRIDE: 16.43 months (95% CI, 14.16-19.58) vs. 13.77 months (95% CI, 12.25-16.13) Survival rates at 18 months: 48.7% (95% CI, 43.6-53.5) vs. 41.5% (95% CI, 36.5-46.4) Survival rates at 24 months: 40.5% (95% CI, 35.6-45.3) vs. 32.6% (95% CI, 27.9-37.4) Survival rates at 36 months: 30.7% (95% CI, 25.8-35.7) vs. 20.2% (95% CI, 15.8-25.1) **<u>Non-inferiority analysis for durvalumab vs. sorafenib (I2 vs. C):</u>** Patients who had died at data cut-off: 72.0% vs. 75.3%; overall survival HR 0.86; 95.67% CI, 0.73-1.03; the non-inferiority margin was an upper bound of the 95.67% CI for this of 1.08. **<u>Additional analyses:</u>** HR for STRIDE vs. sorafenib: 0.87 (95% CI, 0.68-1.11) up to 9 months and 0.70 (95% CI, 0.56-0.89) after 9 months HR for durvalumab versus sorafenib: 0.98 (95% CI, 0.77-1.24) up to 9 months and 0.77 (95%CI, 0.61-0.97) after 9 months **<u>Secondary efficacy endpoints:</u>** Patients who had progresses or died: 85.2% vs. 88.7% vs. 84.1% HR for PFS were 0.90 (95% CI, 0.77-1.05) for STRIDE vs. sorafenib and 1.02 (95% CI, 0.88-1.19) for durvalumab vs. sorafenib Patients remaining progression free at data cut-off: 12.5% vs. 8.2% vs. 4.9% Median time to progression: 5.4 months (95% CI, 3.8-5.6) vs. 3.8 months (95% CI, 3.7-5.4) vs. 5.6 months (95% CI, 5.1-5.8) Confirmed objective response rates per investigator assessment: 20.1% vs. 17.0% vs. 5.1% Confirmed complete responses: 3.1% vs. 1.5% vs. 0% Median duration of response: 22.3 months vs. 16.8 months vs. 18.4 months Patients remaining in response at 12 months: 65.8% vs. 57.8% vs. 63.2%	**Treatment-emergent AEs:** Any AE: 97.4% vs. 88.9% vs. 95.5% vs. 95.4% Any serious AEs: 40.5% vs. 29.6% vs. 29.7% vs. 34.2% Grade 3 or 4 AEs: 50.5% vs. 37.1% vs. 52.4% vs. 39.5% AEs leading to discontinuation: 13.7% vs. 8.2% vs. 16.8% vs. 15.1% AEs with outcome of death: 7.7% vs. 6.7% vs. 7.2% vs. 7.9% **Treatment-related AEs:** Any AEs: 75.8% vs. 52.1% vs. 84.8% vs. 69.7 Any serious AEs: 17.5% vs. 8.2% vs. 9.4% vs. 18.4% Grade 3 or 4 AEs: 25.8% vs.12.9% vs. 36.9% vs. 21.1% AEs leading to discontinuation: 8.2% vs.4.1% vs. 11.0% vs. 8.6% Leading to dose delay: 21.4% vs. 13.9% vs. 38.5% vs. 27.6% Leading to death: 2.3% vs. 0 vs. 0.8% vs.1.3% Grade 3 or 4 hepatic SMQ: 5.9 vs. 5.2 vs. 4.5 vs. 9.9 **Immune-mediated adverse events:** Any immune-mediated AEs: 35.8% vs. 16.5% vs. 8.0% vs. 34.9% Any grade 3 or 4 immune-mediated AEs: 12.6% vs. 6.4% vs. 2.4% vs. 12.5% Any serious immune-mediated AEs: 10.6% vs. 5.2% vs. 1.1% vs. 11.2% Any immune-mediated adverse event leading to death: 1.5 vs. 0 vs. 0 vs. 0 **Treatment-related immune-mediated AEs:** Any immune-mediated AEs: 34.5% vs. 14.9% vs. 5.6% vs. 32.2% Any grade 3 or 4 immune-mediated AEs: 12.6% vs. 6.2% vs. 2.4% vs. 11.8% Any serious immune-mediated AEs: 10.6% vs. 4.9% vs. 1.1% vs. 10.5% Any immune-mediated adverse event leading to death: 1.5% vs. 0 vs. 0 vs. 0

[1] Originally, there were 4 treatment groups with patients randomly assigned 1:1:1:1 to receive the following: 300 mg of tremelimumab for one dose plus 1500 mg of durvalumab every 4 weeks (a regimen termed STRIDE), 1500 mg of durvalumab every 4 weeks, 75 mg of Tremelimumab every 4 weeks for four doses plus 1500 mg of durvalumab every 4 weeks (a regimen termed T751D), or 400 mg of sorafenib twice daily. Data from a preplanned analysis of the supportive phase 2 Study 22 demonstrated that, although all regimens had acceptable side effects and manageable safety profiles, T751D did not meaningfully differentiate from durvalumab monotherapy in terms of efficacy [6]. Thus, enrolment to T751D in HIMALAYA was closed and the protocol was amended to randomly assign patients 1:1:1 to receive STRIDE, durvalumab, or sorafenib.

[3] T75+D=75 mg of tremelimumab every 4 weeks for four doses plus 1500 mg of durvalumab every 4 weeks.

	Immune-mediated events leading to treatment with high-dose Glucocorticoids: Any immune-mediated AEs: 20.1% vs. 9.5% vs. 1.9% vs. 19.1% **Immune-mediated events leading to discontinuation:** Any immune-mediated adverse event: 5.7% vs. 2.6% vs. 1.6% vs. 5.3% **Grade 3 or 4 treatment-related haemorrhage events:** 0.5% vs. 0% vs. 1.1% vs. 2%

Patient-reported outcomes [14]

- The EORTC 30-item QoL questionnaire and the EORTC 18-item HCC QoL questionnaire were used to assess disease-related symptoms, PF and GHS/QoL.
- TTD, defined as time from randomisation to first clinically meaningful deterioration (worsening ≥10 points) confirmed at a subsequent visit or death, was assessed in pts with baseline scores ≤90 for symptoms or ≥10 for PF and GHS/QoL.
- Across treatment arms, compliance rates for PROs were >77% at baseline and >70% overall. Baseline scores were comparable across treatment arms.
- TTD in fatigue, appetite loss, abdominal pain, PF, and GHS/QoL were significantly longer for both STRIDE and durvalumab vs. sorafenib.
- TTD in nausea and abdominal swelling were significantly longer for STRIDE vs. sorafenib.
- Median time to deterioration of patient-reported global health status or QoL: 7.5 months vs. 7.4 months vs. 5.7 months; HR 0.76 (95% CI, 0.61–0.96).

ESMO-MCBS version 1.1 [15]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	>12 months ≤24 months	Median OS: + 2.66 months 3-year survival: +10.5%	0.78 (0.65-0.93)	Increase in 3 year survival alone ≥10%	4	-	Improvement	+1	5
Adapted	NC	2a	>12 months ≤24 months	Median OS: + 2.66 months 3-year survival: +10.5%	0.78 (0.65-0.93)	Increase in 3 year survival alone ≥10%	4	+10.8% treatment-emergent SAEs	Improvement	-1/+1	4

Risk of bias (RCT) [16]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	unclear	no, open-label	unclear[4]	yes[5]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CTLA-4=cytotoxic T-lymphocyte-associated Protein 4, ECOG PS=Eastern Cooperative Oncology Group performance status, EGFR= epidermal growth factor receptor, EMA=European Medicines Agency, EORTC=European Organisation for Research and Treatment of Cancer, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GHS= Global Health Status, HCC=hepatocellular carcinoma, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, n=number of patients, NSCLC=non-small cell lung cancer, OS=overall survival, PE=primary endpoint, PF=physical functioning, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SMQ=Standardized MedDRA Queries, ST=standard treatment, TTD=Time to deterioration

[4] The HIMALAYA trial is currently ongoing.
[5] AstraZeneca sponsored the trial, provided the trial drugs, and collaborated with the steering committee on the trial design, collection, analysis, and interpretation of the data. All drafts of the manuscript were prepared by the authors, with editorial assistance funded by the sponsor.

References:

1. European Medicines Agency (EMA). Medicines. Imjudo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/imjudo].
2. National Institute for Health Research (NIHR). Durvalumab in combination with tremelimumab for unresectable hepatocellular carcinoma – first line. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/20506-TSID_10254-Durvalumab-in-Combination-with-Tremelimumab-for-Hepatocellular-Carcinoma-V1.0-OCT2019.-NON_CONF.pdf].
3. Vogel A, Cervantes A, Chau I, et al., on behalf of the ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 29 (Supplement 4): iv238–iv255, 2018.
4. U.S. Food and Drug Administration (FDA). FDA approves tremelimumab in combination with durvalumab for unresectable hepatocellular carcinoma. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-unresectable-hepatocellular-carcinoma].
5. U.S. Food and Drug Administration (FDA). Imfinzi. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761069s033lbl.pdf].
6. European Medicines Agency (EMA). Medicines. EPAR. Imjudo. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/imjudo].
7. European Medicines Agency (EMA). Imfinzi: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf].
8. U.S. Food and Drug Administration (FDA). Imjudo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761270s000lbl.pdf].
9. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
10. Protocol for: Ghassan K. Abou-Alfa, George Lau, Masatoshi Kudo, et al. Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid. DOI: 10.1056/ EVIDoa2100070.
11. Supplement to: Ghassan K. Abou-Alfa, George Lau, Masatoshi Kudo, et al. Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid. DOI: 10.1056/ EVIDoa2100070.
12. Abou-Alfa GK, Lau G, Kudo M, et al., for the HIMALAYA Investigators. Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. Published June 6, 2022 NEJM Evid 2022;1 (8).
13. U.S. National Library of Medicine, ClinicalTrials.gov. Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma (HIMALAYA). [Available from: https://www.clinicaltrials.gov/ct2/show/NCT03298451].
14. Sangro B, et al. Patient-reported outcomes from the phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Journal of Clinical Oncology 40, no 16_suppl (June 01, 2022) 4074-4074 Abstract.
15. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
16. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].