Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy for the first-line treatment of metastatic non-small cell lung cancer (NSCLC)

General information [1]

Drug description	Indication
Tremelimumab is a monoclonal antibody. It binds to CTLA-4, which is primarily expressed on the surface of T lymphocytes, and thus enhances T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced anti-tumour activity.	Tremelimumab AstraZeneca in combination with durvalumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic non-small cell lung cancer (NSCLC) with no sensitising epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) positive mutations.

Current treatment [2]

- The main treatments available for NSCLC include surgery, chemotherapy, radiotherapy, chemoradiotherapy and symptoms control treatment. The treatment given depends on the cancer stage and how well the treatment works.
- The aim of treatment for stage 4 (metastatic) NSCLC is to control the cancer for as long as possible and to treat symptoms. Treatment for stage 4 NSCLC includes:
  - Chemotherapy: It should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Patients who are unable to tolerate a platinum drug can be offered a single agent chemotherapy with a third generation drug. For example, NICE recommends first line treatment with pembrolizumab for PD-L1+ NSCLC with no EGFR- or ALK-positive mutations.
  - Radiotherapy.
  - Symptom control treatment.

Regulatory status

EMA [1, 3]

Tremelimumab AstraZeneca

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

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 20/02/2023 [6]

The full indication is:

- Tremelimumab AstraZeneca in combination with durvalumab 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.

Other indications: none

- ✓ Medicine is under additional monitoring

Durvalumab (Imfinzi®)

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:

- Imfinzi® in combination with tremelimumab and platinum-based chemotherapy for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations.

FDA [4, 5]

Tremelimumab (Imjudo®)

Approval status for this indication: On 10 November 2022, the FDA approved tremelimumab (Imjudo®, AstraZeneca Pharmaceuticals) in combination with durvalumab (Imfinzi®) and platinum-based chemotherapy for adult patients with metastatic NSCLC with no sensitising EGFR mutation or ALK genomic tumour aberrations.

Other indications: Imjudo® is indicated:

- in combination with durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma.

Durvalumab (Imfinzi®)

Imfinzi® is indicated [7]:

- 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 etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer.
- in combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic biliary tract cancer.
- in combination with tremelimumab-actl, for the treatment of adult patients with 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 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.
- ❖ Imfinzi® in combination with tremelimumab is indicated for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

✓ Medicine is under additional monitoring

Costs

Currently, there is no cost information available for Tremelimumab AstraZeneca®.
Imfinzi® concentrate for solution for infusion 50 mg/10ml = € 3,088.00 (ex-factory price) [8].

Warnings and precautions [7, 9]

- ❖ **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.
- ❖ **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and use of effective contraception.
- ❖ **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.

Study characteristics [10-13]

Trial name	*n*	Intervention (T+D+CT)	Intervention (D+CT)	Comparator (CT)	PE	Characteristics	Biomarker	Funding	Publication(s)
POSEIDON NCT03164616	1,013 (1:1:1)	tremelimumab 75 mg + durvalumab 1,500 mg and chemotherapy for up to 4	durvalumab 1,500 mg + chemotherapy for up to four 21-day cycles, followed by	chemotherapy for up to six 21-day cycles	PFS (by BICR per RECIST v1.1) and OS for D+CT vs. CT[1]	**ongoing**[2], global, randomised, open-label phase 3 study	EGFR/ALK	AstraZeneca	POSEIDON trial [12]

[1] Key alpha-controlled secondary end points were PFS and OS for T+D+CT vs. CT.
[2] The POSEIDON trial is currently ongoing; estimated study completion date is 05/2025.

		21-day cycles, followed by durvalumab 1,500 mg once every 4 weeks until PD with 1 additional tremelimumab dose after chemotherapy at week 16/cycle 6 (fifth dose)	durvalumab 1,500 mg once every 4 weeks until PD						

Efficacy	Safety
Data cutoff was 24 July 2019 for PFS and other RECIST-related endpoints, and 12 March 2021, for OS, safety, and all other data. As of these dates, the median follow-up in censored patients was 10.3 months for PFS and 34.9 months for OS. **PFS/OS with D+CT vs. CT** **PFS**: significantly improved; HR 0.74; 95% CI, 0.62-0.89; p=0.0009 **Median PFS**: 5.5 (95% CI, 4.7-6.5) vs. 4.8 (95% CI, 4.6-5.8) **12-month PFS rates**: 24.4% vs. 13.1% **OS**: Trend for improvement, but not statistically significant; HR 0.86; 95% CI, 0.72-1.02; p=0.0758 **Median OS**: 13.3 (95% CI,11.4-14.7) vs. 11.7 (95% CI, 10.5-13.1) **24-month OS rates**: 29.6% vs. 22.1% **PFS/OS with T+D+CT vs. CT (**PFS was formally assessed as the primary PFS endpoint for D+CT vs. CT had been met. As this key secondary endpoint was also met, the comparison of OS for T+D+CT vs. CT was also formally assessed) **PFS**: statistically significant improvement; HR 0.72; 95% CI, 0.60-0.86; p=0.0003 **OS:** statistically significant improvement; HR 0.77; 95% CI, 0.65-0.92; p=0.0030 **Median PFS**: 6.2 months (95% CI, 5.0-6.5) vs. 4.8 months (95% CI, 4.6-5.8) **12-month PFS rates**: 26.6% vs. 13.1% **Median OS**: 14.0 months (95% CI, 11.7-16.1) vs. 11.7 months (95% CI, 10.5-13.1) **24-month OS rates**: 32.9% vs. 22.1% **ORR and DoR** (T+D+CT vs. D+CT vs. CT) **Unconfirmed ORR**: 46.3% (OR v CT, 1.72; 95% CI, 1.26-2.37) vs. 48.5% (OR v CT, 1.90; 95%CI, 1.38-2.62) vs. 33.4% **Confirmed ORR** in post hoc analysis: 38.8% (OR v CT, 2.00; 95% CI, 1.43-2.81) vs. 41.5% (OR v CT, 2.26; 95% CI, 1.61-3.19) vs. 24.4% **Median DoR among patients with a confirmed response**: 9.5 months (95% CI, 7.2-not estimable) vs. 7.0 months (95% CI, 5.7-9.9) vs. 5.1 months (95% CI, 4.4-6.0)	**Any-grade TREAEs**: 92.7% vs. 88.6% vs. 89.5% **TRAEs with maximum grade 3/4 severity**: 51.8% vs. 44.6% vs. 44.4% **Serious TRAEs:** 27.6% vs. 19.5% vs. 17.7% **Treatment-related deaths**: 3.3% vs. 2.1% vs. 2.4% **TRAEs leading to treatment discontinuation**: 15.5% vs. 14.1% vs. 9.9% **Immune-mediated AEs:** 33.6% vs. 19.2% vs. 5.1% **Immune-mediated AEs with maximum grade 3/4**: 10.0% vs. 6.9% vs. 1.5% **Serious immune-mediated AEs:** 9.7% vs. 6.0% vs. 1.2% **Immune-mediated AEs leading to treatment discontinuation**: 5.8% vs. 4.2% vs. 0.6% **Immune-mediated AEs leading to death**: 0.6% vs. 0.3% vs. 0%

Patient-reported outcomes [14]

- GHS/QoL, functioning and symptoms were assessed as a secondary endpoint using EORTC QLQ-C30/LC13.
- TTD was assessed using a stratified log-rank test with a Cox proportional-hazards model, with medians estimated by the Kaplan-Meier method, and improvement rates by logistic regression.

- ❖ Compliance was ≥60% for C30 and LC13 up to 88 weeks, 64 weeks and 24 weeks for the T+ D + CT, D + CT and CT arms, respectively.
- ❖ Baseline GHS/QoL, functioning and symptom scores were generally similar across treatment arms.
- ❖ HRs indicated longer TTD with T + D + CT and D + CT vs. CT across nearly all PROs, including prespecified symptoms/domains of interest (with exception of appetite loss for D + CT vs CT).
- ❖ Improvement rates in PROs, including prespecified symptoms/domains of interest, were greater for T + D + CT and D + CT vs CT alone.
- ❖ Median GHS/QoL (C30) T + D + CT vs. CT: 8.3 vs. 5.6; HR 0.79 (95% CI; 0.64-0.96)
- ❖ Median GHS/QoL (C30) D + CT vs. CT: 7.8 vs 5.6; HR 0.78 (95% CI; 0.63-0.96)

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	Median OS: +2.3 months 2-year survival gain 10.8%	0.77 (0.65-0.92)	Increase in 2-year survival ≥10%	4	-	Improvements	+1	5
Adapted	NC	2a	≤12 months	Median OS: +2.3 months 2-year survival gain 10.8%	0.77 (0.65-0.92)	Increase in 2-year survival ≥10%	4	-	Improvements	-	4

Risk of bias [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	yes	no, open-label	unclear[3]	yes[4]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, BICR=blinded independent central review, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CT=chemotherapy, CTLA-4=cytotoxic T-lymphocyte-associated antigen 4, D=durvalumab, DoR=duration of response, 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, HR=hazard ratio, I=intervention, HSCT=hematopoietic stem cell transplantation, Int.=intention, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health Care excellence, NSCLC=non small cell lung cancer, ORR=objective response rate, OS=overall survival, PD-L1=programmed cell death-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PROs=patient-reported outcomes, QLQ-LC13=QLQ-LC13 13-item Lung Cancer QoL Questionnaire; QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment, T=Tremelimumab, TRAE=treatment-related adverse event, TTD=Time to deterioration

References:

1. European Medicines Agency (EMA). Medicines. Tremelimumab AstraZeneca. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/tremelimumab-astrazeneca].
2. National Institute for Health Research (NIHR). Durvalumab in combination with tremelimumab and standard of care chemotherapy for EGFR negative, ALK negative metastatic NSCLC– first line. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/19355-Durvalumab-Tremelimumab-Chem-for-NSCLC-V1.0-MAY2018-NON-CONF.pdf].
3. European Medicines Agency (EMA). Medicines. Imfinzi. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/imfinzi-1].

[3] The POSEISON trial is currently ongoing; final analysis data not (yet) available.
[4] Industry-funded.

4. U.S. Food and Drug Administration (FDA). Imjudo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761270s000lbl.pdf].
5. U.S. Food and Drug Administration (FDA). FDA approves tremelimumab in combination with durvalumab and platinum-based chemotherapy for metastatic non-small cell lung cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-and-platinum-based-chemotherapy-metastatic-non].
6. European Medicines Agency (EMA). Medicines. EPAR. Tremelimumab AstraZeneca. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tremelimumab-astrazeneca].
7. U.S. Food and Drug Administration (FDA). Imfinzi. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761069s033lbl.pdf].
8. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
9. US FDA. Durvalumab. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761069s033lbl.pdf].
10. Johnson ML, Cho BC, Luft A, et al. Supplement to: Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study. 2022.
11. Johnson ML, Cho BC, Luft A, et al. Protocol to: Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study. 2022.
12. Johnson ML, Cho BC, Luft A, et al., for the POSEIDON investigators. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study. Journal of Clinical Oncology (2023) 41(6):1213-1227 [Available from: https://ascopubs.org/doi/full/10.1200/JCO.22.00975].
13. U.S. National Library of Medicine, ClinicalTrials.gov. Study of Durvalumab + Tremelimumab With Chemotherapy or Durvalumab With Chemotherapy or Chemotherapy Alone for Patients With Lung Cancer (POSEIDON). [Available from: https://clinicaltrials.gov/ct2/show/NCT03164616].
14. Garon EB, et al. Patient-reported outcomes (PROs) with 1L durvalumab (D), with or without tremelimumab (T), plus chemotherapy (CT) in metastatic (m) NSCLC: Results from POSEIDON. Annals of Oncology (2022) 33 (suppl_2): S27-S70 101016/annonc/annonc856 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].