Durvalumab (Imfinzi®) in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of extensive-stage small cell lung cancer (ES-SCLC)

General information

Drug description [1]	Indication [2]
Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80.	Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with ES-SCLC.

Current treatment [3]

As first-line treatment for ES-SCLC, NICE recommends to:

- ❖ offer platinum-based combination chemotherapy to patients if they are fit enough
- ❖ assess the patient's condition before each cycle of chemotherapy and offer up to a maximum of six cycles, depending on response and toxicity
- ❖ consider thoracic radiotherapy after chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax.

Regulatory status

EMA [2, 4]

Approval status for this indication: On 23 July 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Imfinzi®. The CHMP adopted an extension to the existing indication as follows:

Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with ES-SCLC.

Other indications:
Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy.

✓ **Medicine under additional monitoring**

FDA [5, 6]

Approval status for this indication: On 27 March 2020, the FDA approved durvalumab in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with ES-SCLC.

Other indications:
Durvalumab is indicated:

- ❖ for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (accelerated approval)
- ❖ for the treatment of adult patients with unresectable, stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Costs

Imfinzi® concentrate for solution for infusion 50 mg/ml, 10 ml vial = **€ 3,088.00** (ex-factory price) [7]
CASPIAN trial patients received durvalumab at a dose of 1500 mg every 3 weeks [1] → € 9,264.00/dose (trial patients received a median number of 7 durvalumab doses)

Study characteristics[1] [1]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CASPIAN trial NCT03043872	805	durvalumab (1,500 mg every 3 weeks, up to 4 cycles, followed by maintenance durvalumab 1,500 mg every 4 weeks) + platinum–etoposide	durvalumab plus tremelimumab plus platinum–etoposide or platinum–etoposide alone (1:1:1 ratio)	OS in the ITT population	randomised, open-label, sponsor-blind, international, phase 3 trial	-	AstraZeneca	Link

Efficacy
(durvalumab plus platinum–etoposide vs. platinum–etoposide)

OS: statistically significantly longer in the durvalumab plus platinum–etoposide group than the platinum–etoposide group, with an HR of 0.73 (95% CI, 0.59–0.91; p=0.0047).
Median OS: 13.0 months (95% CI, 11.5–14.8) vs. 10.3 months (9.3–11.2) with platinum– etoposide
Post-hoc **12-month OS rates**: 54% (47.4–59.5) versus 40% (33.7–45.8)

Safety
(durvalumab plus platinum–etoposide vs. platinum–etoposide)

Grade ≥3 AEs: n=163/265 (62%) vs. 166/266 (62%)
Any grade SAEs: n=82/265 (31%) vs. n=96/266 (36%)
Grade 3 or 4 SAEs: n=57/265 (22%) vs. n=70/266 (26%)
imAEs: n=52/265 (20%) vs. n=7/266 (3%); most of these events were grade 1 or 2

[1] Interim analysis data; reported were results for the durvalumab plus platinum– etoposide group versus the platinum–etoposide group. Safety was assessed in all patients who received at least one dose of their assigned study treatment.

Prespecified **18-month OS rates** were 34% (26.9–41.0) versus 25% (18.4–31.6) **PFS**: HR of 0.78 (95% CI, 0.65–0.94) **Median PFS:** 5.1 months (95% CI 4.7–6.2) vs. 5.4 months (4.8–6.2) **6-month PFS rates**: 45% (39.3–51.3) versus 46% (39.3–51.7) **12-month PFS rates**: 18% (13.1–22.5) versus 5% (2.4–8.0). **Unconfirmed objective response**: 79% vs. 70% (OR 1.64, 95% CI, 1.11–2.44). **Confirmed objective response** (analysed post hoc): 68% vs. 58% (OR 1.56, 1.10–2.22) **Confirmed complete response**: 2% vs. 1% **Median duration of (confirmed) response**: 5.1 months in both groups **QoL**: NR	**Grade 3 or 4 imAEs:** n=12/265 (5%) vs. n=1/266 (<1%) **Deaths due to imAEs:** n=1/265 (<1%) vs. n=1/266 (<1%) **Deaths**[2]**:** n=13/265 (5%) vs. 15/266 (6%) **Discontinuation**[3]**:** n=25/265 (9%) vs. n=25/266 (9%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤ 12 m	OS: +2.7 m	0.73 (0.59–0.91)	HR ≤0.65 AND Gain ≥2.0, <3 m	3	x	NA	x	3
Adapted	NC	2a	≤ 12 m	OS: +2.7 m	0.73 (0.59–0.91)	HR >0.65-0.70 AND Gain ≥1.5 m	2	x	NA	x	2

Risk of bias (study level)

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	no	no (open-label)	unclear[4]	yes[5]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ES-SCLC=extensive-stage small cell lung 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, HR=hazard ratio, I=intervention, imAEs=immune-mediated adverse events, Int.=intention, m=months, n=number, NA=not available, NICE=National Institute for Health and Care Excellence, NSCLC=non-small cell lung cancer, MG=median gain, n=number of patients, NR=not reported, OR=odds ratio, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

1. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019; 394: 1929–39 Published Online October 4, 2019.
2. European Medicines Agency (EMA). Medicines. Imfinzi [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/imfinzi.
3. National Institute for Health Research (NIHR). Durvalumab with or without tremelimumab in addition to platinum based chemotherapy for extensive-stage disease small-cell lung cancer [Available from: http://www.io.nihr.ac.uk/wp-content/uploads/2019/05/26898-Durvalumab-Tremelimumab-for-SCLC-V1.0-MAR19-NONCONF.pdf.
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5. U.S. Food and Drug Administration (FDA). FDA approves durvalumab for extensive-stage small cell lung cancer [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-extensive-stage-small-cell-lung-cancer.
6. U.S. Food and Drug Administration (FDA). Drugs@FDA. Imfinzi. Label information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761069s020lbl.pdf.

[2] death due to AE(s)
[3] discontinuation due to AE(s)
[4] Presented data is interim analysis data; the CASPIAN trial is ongoing until March 2021
[5] Industry-funded; the sponsor participated in study design, data collection, data analysis, data interpretation, and writing of the report.

7. Apotheker-Verlag Ö. Warenverzeichnis Online [Available from: https://warenverzeichnis.apoverlag.at/.