Cemiplimab (Libtayo®) as monotherapy for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells)

General information

Drug description [1]	Indication [2]
Cemiplimab is a programmed cell death 1 inhibitor.	Cemiplimab as monotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have: ❖ locally advanced NSCLC who are not candidates for definitive chemoradiation, or ❖ metastatic NSCLC.

Current treatment [3]

❖ Patients with a PD-L1 mutation in ≥ 50% tumours, and no gene mutation or fusion protein, NICE recommends the first-line treatment of immunotherapy, pembrolizumab alone or in combination with pemetrexed and platinum chemotherapy.

Regulatory status

EMA [2]

Approval status for this indication: On 20 May 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Libtayo®.

<u>The CHMP adopted new indications as follows:</u>

❖ Libtayo® as monotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:
- locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- metastatic NSCLC.

Other indications: Libtayo® is indicated

❖ as monotherapy for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation.

❖ as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

✓ **Medicine under additional monitoring**

✓ **Medicine received a conditional marketing authorisation**[1]

FDA [4, 5]

Approval status for this indication: On 22 February 2021, the FDA approved cemiplimab-rwlc (Libtayo®) for the first-line treatment of patients with advanced NSCLC (locally advanced who are not candidates for surgical resection or definitive chemoradiation or metastatic) whose tumours have high PD-L1 expression (TPS > 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations.

✓ This application was granted priority review.

Other indications: Libtayo® is indicated:

❖ for the treatment of patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation.

❖ for the treatment of patients with laBCC previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

❖ for the treatment of patients with mBCC previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate (accelerated approval).

Costs

Libtayo® concentrate for solution for infusion 350 mg/7ml = **€ 5,653.00** (ex-factory price) [6]

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

Warnings and precautions [4]

- **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 and renal dysfunction, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue Libtayo® based on the severity of the reaction.
- **Infusion-Related Reactions:**
  - Interrupt, slow the rate of infusion, or permanently discontinue based on the severity of the reaction.
- **Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT):**
  - 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 [1, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
EMPOWER-Lung 1, Study 1624. NCT03088540	710	cemiplimab 350 mg every 3 weeks	platinum-doublet chemotherapy	OS + PFS	multicentre, open-label, global, randomised, controlled phase 3 trial	PD-L1	Regeneron Pharmaceuticals and Sanofi.	[1]

Efficacy (I vs. C)

PD-L1 of at least 50% population (n=563)

Overall median duration of follow-up: 10.8 months (IQR 7.6-15.8) vs. 10.9 months (IQR 7.8-15.6)
Median OS: not reached (95% CI 17.9–not evaluable) vs. 14.2 months (11.2–17.5); HR 0.57; 95% CI 0.42–0.77; p=0.0002
Estimated probability of OS from baseline through 24 months: 50% (36–63) and 27% (14–43)
Median PFS: 8.2 months (95% CI 6.1–8.8) vs. 5.7 months (4.5–6.2) ; HR 0.54; 95% CI 0.43-0.68; p<0.0001
Estimated probability of PFS from baseline through 12 months: 41% (34–48) and 7% (4–12)
OS and PFS benefits with cemiplimab were evident in all **subgroups** examined, except for OS in female patients (n=84)
IRC-assessed objective response in: 39% (95% CI 34–45) vs. 20% (16–26)
Median duration of response: 16.7 months (95% CI 12.5–22.8) vs. 6.0 months (4.3–6.5)

ITT-population (n=710[2])

Overall median duration of follow-up: 13.1 months (IQR 8.6–20.2) and 13.1 months (IQR 8.7–20.1)
Median OS: 22.1 months (95% CI 17.7–not evaluable) vs. 14.3 months (11.7–19.2); HR 0.68; 95% CI 0.53–0.87; p=0.0022
OS rate at 12 months: 70% vs. 56%
Median PFS: 6.2 months (4.5–8.3) vs. 5.6 months (4.5–6.1); HR 0.59; CI 95% 0.49–0.72; p<0.0001
ORR (95% CI): 36.5% (31.5-41.8) vs. 20.6% (16.5-25.2)
Complete response rate: 3.1% vs. 0.8%
Partial response rate: 33.4% vs. 19.8%

Safety (I vs. C)

Grade 3-4 TEAEs: n=98/355 (28%) vs. n=135/342 (39%)
Serious TEAEs: n=100/355 (28%) vs. 94/342 (27%)
Discontinuation due to TEAEs: n=23/355 (6%) vs. n=14/342 (4%)
TEAEs leading to death: n=34/355 (10%) vs. n=31/342 (9%)
TRAEs: n=204/355 (57%) vs. n=303/342 (89%)
Grade 3-4 TRAEs: n=41/355 (12%) vs. n=127/342 (37%)
Serious TEAEs considered treatment-related: n=38/355 (11%) vs. n=53/342 (15%)
Events leading to death that were considered related to treatment: n=9/355 (3%) vs. n=7 (2%)

[2] Consisting of n=563 patients from the aforementioned PD-L1 of at least 50% population, and also the 56 patients who were definitively PD-L1<50% based on validated retest and the 91 patients for whom PD-L1 expression could not be established because validated retest could not be performed.

Median DOR: 21.0 months vs. 6.0 months
Patients with observed DOR ≥ 6 months: 69% vs. 41%

Additional sensitivity analysis requested by the FDA for a patient population excluding those with known PD-L1 expression <50% (n=654[3])
HRs for OS: 0.65 (95% CI 0.50–0.85)
HR for PFS: 0.58 (95% CI 0.47–0.70)

HRQoL in the ITT population:

- Early and sustained clinically meaningful **improvements in HRQoL** were observed with cemiplimab but not with chemotherapy.

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +7.8 months[4]	0.68 (0.53–0.87)	HR≤0.65 AND gain ≥3 months	4	-	-	-	4
Adapted	NC	2a	≤ 12 months	OS: +7.8[4] months	0.68 (0.53–0.87)	HR>0.65-0.70 AND gain ≥1.5 months	2	-25% Grade 3-4 TRAEs	-	+1	3

Risk of bias (study level) [11]

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[5]	yes[6,7]	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, DOR=duration of response, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HHI=hedgehog pathway inhibitor, HR=hazard ratio, HRQoL=health-related quality of life, HSCT=hematopoietic stem cell transplantation, I=intervention, Int.=intention, IQR=interquartile range, IRC=independent review committee, ITT=intention-to-treat, laBCC=locally advanced basal cell carcinoma, laCSCC=locally advanced cutaneous squamous cell carcinoma, mBCC=metastatic basal cell carcinoma, mCSCC=metastatic cutaneous squamous cell carcinoma, MG=median gain, n=number of patients, NICE=National Institute of Health and 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, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, TPS=tumour proportion score

[3] Including 563 patients in the PD-L1 of at least 50% population and 91 patients for whom PD-L1 expression could not be determined because validated retest could not be done.
[4] Median OS results of the ITT-population were graded.
[5] Second interim analysis data reported; EMPOWER-Lung 1 is ongoing until 11/2022.
[6] Data were collected by investigators, analysed by statisticians employed by the funders, and interpreted by the authors, including employees of the funders. The first draft ofthe manuscript was prepared by a medical writer (funded by the funders) and was based on the authors' comments on the manuscript outline; also prepared by the medical writer. Thereafter, the first draft was critically reviewed and revised by the authors, including employees of the funders.
[7] There were several protocol changes throughout the duration of the study. Major amendments included changing OS from being a secondary endpoint to a primary endpoint, the inclusion of an additional four timepoints for the interim analyses, and an update to the target enrolment from 300 to 700 patients to accommodate the expected weaker effect of PFS because of emerging data from other studies of anti-PD-1s in a similar setting.

References:

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