Cemiplimab (Libtayo®) in combination with platinum-based chemotherapy for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

General information

Drug description [1]	Indication [2]
Cemiplimab (Libtayo®) is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands PD-L1 and PD-L2.	Cemiplimab (Libtayo®) in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have: ❖ locally advanced NSCLC who are not candidates for definitive chemoradiation, or ❖ metastatic NSCLC.

Incidence

In Austria, in 2020, the age-standardised incidence rate[1] for trachea, bronchia and lung carcinoma was 52.9/100,000 persons, 67.4/100,000 men and 41.1/100,000 women. In 2020, 2,788 men and 2,011 women were newly diagnosed with cancer of the trachea, bronchia and lung [3].

Lung carcinoma is the third most common malignant tumour in women and the second in men in German-speaking countries. The median age of onset is between 68 and 70 years [4].

In Europe, the crude rate[2] for lung cancer is 63.8/100,000 persons [5].

Current treatment [4]

- ❖ Treatment options for lung cancer include surgery, radiation, and systemic therapy, often combined as a multimodality approach.
- ❖ Patients with NSCLC are eligible for curative therapy in early stages and some advanced stages.
- ❖ For most stage IIIB/C and IV patients, therapy is not curative.
- ❖ In recent years, integrating immune checkpoint and kinase inhibitors in conjunction with predictive biomarkers has significantly improved the prognosis of many patients. In addition, cytostatics, angiogenesis inhibitors, local endoscopic and percutaneous interventional therapies, and supportive care are available.
- ❖ **First-line therapy for NSCLC without activating EGFR-, ROS1-, or ALK aberrations**

  In patients without genetic aberrations for whom targeted drugs are approved, the following recommendations apply:
  - **Expression of the immune marker PD-L1 on >50% of tumour cells:**
    - Monotherapy with the anti-PD1 antibody pembrolizumab vs. platinum-containing chemotherapy resulted in prolonged OS (HR, 0.62; 26.3 vs. 13.4 months), prolonged PFS (HR 0.50; median 4.3 months), and reduced rates of SAEs. The results of the KEYNOTE-042 trial support these data. Data from a direct comparison of pembrolizumab monotherapy vs. pembrolizumab + combination chemotherapy are unavailable.
    - Monotherapy with the anti-PDL1 antibody atezolizumab was tested in patients with PD-L1 on ≥50% of tumour cells or a rate of PD-L1 positive tumour-infiltrating immune cells (IC) of ≥10%. Compared with platinum-containing chemotherapy, atezolizumab prolonged OS (HR 0.59; 20.2 vs. 13.1 months), and PFS (HR 0.63; median 3.1 months), and reduced the rate of SAEs (52.5 vs. 30.1%).
    - Monotherapy with cemiplimab resulted in prolongation of OS (HR 0.57; median NR vs. 14 months), prolongation of PFS (HR 0.63; median plus 2.5 months), and in the overall study, a reduction in the rate of SAEs (28 vs. 39%) in patients with PD-L1 expression >50% vs. platinum-containing chemotherapy.
    - Combining an immune checkpoint inhibitor with chemotherapy is a potential alternative, especially in patients needing treatment due to distressing symptoms, high tumour burden and/or rapid tumour growth. A meta-analysis by the FDA showed no significant differences in OS between monotherapy and combination therapy but a slight numerical advantage in favour of immuno-chemotherapy and a significant advantage in PFS. In patients >75 years, there is evidence of an advantage in favour of immuno-monotherapy. In addition, there appears

1 European Standard Population 2013

2 For a specific tumour in a given population, crude rates are calculated simply by dividing the number of new cancers or cancer deaths observed during a given time period by the corresponding number of individuals in the population at risk. For cancer, the result is commonly expressed as an annual rate per 100 000 individuals at risk.

to be an impact of gender on the efficacy of immune checkpoint inhibitor monotherapy vs. ICI + chemotherapy. Women appear to consistently benefit less than men from ICI monotherapy, as do non-smokers. These observations require confirmation to guide treatment decisions.

- **Independent of PD-L1 expression on tumour cells or tumour-infiltrating immune cells**:
  - In non-squamous cell carcinoma, the combination of pembrolizumab with chemotherapy (platinum/pemetrexed) vs. chemotherapy resulted in prolonged OS (HR 0.56; median 11.3 months) and prolonged PFS (HR 0.48; median 3.9 months). The relative gain by pembrolizumab increases with the degree of PD-L1 expression but is also significant in terms of OS (HR 0.52) in the group of PD-L1 negative patients. In the subgroup of TTF1-negative patients, the use of other cytostatic agents instead of pemetrexed should be considered.
  - In squamous cell carcinoma, the combination of pembrolizumab with chemotherapy (platinum/(nab)paclitaxel) vs. chemotherapy was shown to prolong OS (HR 0.63; median 4.6 months) and PFS (HR 0.56; median 1.6 months). Thereby, no significant benefit was seen for the subgroup of patients with PD-L1 expression <1% in the final survival analysis of the KEYNOTE-407 trial.
  - In non-squamous cell carcinoma, the combination of atezolizumab with carboplatin/paclitaxel/bevacizumab (BCP) versus BCP resulted in prolonged OS (HR 0.78; median 5.5 months) and PFS (HR 0.62; median 1.5 months). The need for bevacizumab in this combination is unclear. This combination is the only approved combination therapy with immune checkpoint inhibitors for patients with EGFR and ALK alterations. There is no approval in Switzerland. However, this combination should only be used in this indication if the options for targeted therapy have been exhausted. One group of patients who may particularly benefit from atezolizumab-BCP therapy versus BCP are patients with liver metastases.
  - In non-squamous cell carcinoma, the combination of atezolizumab with carboplatin / nab-paclitaxel also resulted in prolonged OS (HR 0.79; median 4.7 months) and PFS (HR 0.64; median 1.5 months).
  - In squamous or non-squamous cell carcinoma, regardless of PD-L1 expression, the combination of nivolumab/ipilimumab in combination with chemotherapy for 2 cycles and continuation of immune combination therapy vs. conventional chemotherapy for 4 cycles resulted in significant prolongation of OS (HR 0.66; median 15.6 vs. 10.9 months). Side effects of immuno-combination therapy are higher than with immuno-monotherapy or combination of immunotherapy with chemotherapy and mainly involve liver, skin, and endocrine toxicities. In the study, patients with low PD-L1 expression and squamous histology benefited particularly well. A direct comparison of dual immune checkpoint inhibitor chemotherapy vs. single immune checkpoint inhibitor chemotherapy is unavailable.
- When chemotherapy alone is chosen, combining chemotherapy with two cytostatic agents is more effective than monotherapy regarding remission rate, PFS, and OS. Combinations are burdened with higher therapy-associated toxicity. Most experience is with platinum-containing combinations. Previous studies have shown that significantly higher remission rates are achieved with cisplatin than with carboplatin; however, these differences are not evident in combinations with third-generation drugs. In terms of OS, the two platinum derivatives are equieffective. The choice is mainly based on the individual expected toxicity. Non-platinum combinations have lower remission rates than platinum-containing combinations.
- In patients with non-squamous cell carcinoma, the combination of bevacizumab with carboplatin/paclitaxel, cisplatin/gemcitabine, or another platinum-containing two-drug combination increased remission rates and prolonged PFS compared with chemotherapy alone but also increased the rate of side effects. The paclitaxel/carboplatin/bevacizumab combination also increased OS.
- In stable disease, first-line platinum-containing therapy should be stopped after 4 cycles. If there is a response, combination therapies should be stopped after 4-6 cycles.
- If the disease is at least stable, therapy with single agents can be continued in terms of maintenance therapy. In some randomized trials, survival was significantly prolonged compared to controls. Current options are:
  - Pemetrexed for non-squamous cell carcinoma.
  - Pembrolizumab - monotherapy (for TPS >50%) every 3 or every 6 weeks in continuation of the induction immuno-monotherapy; in the pivotal trial, pembrolizumab was given for up to 35 cycles.
  - Pembrolizumab + pemetrexed every 3 or every 6 weeks following combination immunochemotherapy; in the pivotal study, pembrolizumab was given for up to 35 cycles.
  - Nivolumab + ipilimumab following induction with combination immunotherapy and chemotherapy; in the pivotal trial, nivolumab + ipilimumab was given for 2 years.
- An alternative to maintenance chemotherapy is the initiation of second-line therapy at progression. Close monitoring, e.g., at 6-8 week intervals, is necessary to diagnose progression early. However, in this concept, only about 60% of patients receiving first-line therapy are treated with second-line therapy.

Regulatory status

EMA [2]	FDA [6, 7]
Approval status for this indication: On 23 February 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Libtayo®. The CHMP adopted a new indication as follows:	**Approval status for this indication**: On 8 November 2022, the FDA approved cemiplimab-rwlc (Libtayo®) in combination with platinum-based chemotherapy for the first-line treatment of adult patients with NSCLC with no EGFR, ALK or ROS1 aberrations and is: ❖ locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or ❖ metastatic. **Other indications**: Libtayo® is indicated:

- ❖ Libtayo® in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of 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 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).
- ❖ as monotherapy 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.
- ❖ as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

✓ **Medicine under additional monitoring**

- ❖ 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 HHI or for whom a HHI is not appropriate.
- ❖ for the treatment of patients with mBCC previously treated with a HHI or for whom a HHI is not appropriate.
- ❖ as single agent for the first-line treatment of adult patients with NSCLC whose tumours have high PD-L1 expression (TPS ≥ 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations, and is:
  - locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
  - metastatic.

Manufacturer

Regeneron Pharmaceuticals Inc. and Sanofi are the manufacturers of Libtayo®.

Costs

Libtayo® concentrate for solution for infusion 350 mg/7 ml = € 5,653.00 (ex-factory price) [8].

Warnings and precautions [7]

- ❖ **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 infusion rate, 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 [9, 10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
EMPOWER-Lung 3 (part 2[3]), Study 16113 NCT03409614	466 (2:1)	**cemiplimab 350 mg** every 3 weeks for up to 108 weeks in combination with **4 cycles of platinum-doublet chemotherapy** (followed by pemetrexed maintenance as indicated)	**placebo** every 3 weeks for up to 108 weeks in combination with **4 cycles of platinum-doublet chemotherapy** (followed by pemetrexed maintenance as indicated)	OS	16.3 months (IQR, 13.9–19.1) vs. 16.7 months (IQR, 14.2–19.0); **early stopping**[4]	**ongoing**[5], double-blind, placebo-controlled, phase 3 study	PD-1	Regeneron Pharmaceuticals and Sanofi	EMPOWER-Lung 3 trial [9]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline
❖ Patients ≥18 years of age (≥20 years of age for Japanese patients) ❖ An archival or on-study-obtained formalin-fixed, paraffin-embedded tumour tissue sample; ❖ At least 1 radiographically measurable lesion per RECIST 1.1 ❖ Histologically or cytologically confirmed squamous or non-squamous stage IIIB/C (if deemed not candidates for treatment with definitive chemoradiation) or stage IV NSCLC; ECOG PS ≤1 ❖ Anticipated life expectancy of at least 3 months ❖ Adequate organ and bone marrow function ❖ Willingness and ability to comply with clinic visits and study-related procedures ❖ Provided signed informed consent ❖ Ability to understand and complete study-related questionnaires	❖ Active or untreated brain metastases or spinal cord compression ❖ Tumours positive for EGFR mutations/ALK translocations/ ROS1 fusions ❖ Encephalitis, meningitis or uncontrolled seizures in the year before enrolment ❖ History of interstitial lung disease or of active, non-infectious pneumonitis within the last 5 years ❖ Evidence of substantial autoimmune disease ❖ Corticosteroid therapy within 14 days of randomisation ❖ Another malignancy ❖ Active hepatitis B or C ❖ Prior anti–PD-1/PD-L1 therapy ❖ Treatment-related immune-mediated AEs from immune-modulatory agents ❖ Receipt of an investigational drug or device within 30 days of enrolment ❖ receipt of a live vaccine within 30 days of planned start of study drug	❖ Median age: 63 years in both groups ❖ Men: 83.9% ❖ Squamous histology: 42.9% of patients ❖ ECOG PS1: 84.3% ❖ Locally advanced disease: 14.8% ❖ Previous cancer-related radiotherapy: 10.9%

[3] Part one is considered a separate study evaluating cemiplimab plus abbreviated chemotherapy and ipilimumab or cemiplimab plus chemotherapy compared to platinum-doublet chemotherapy alone in patients with aNSCLC whose tumours express PD-L1 in <50% of tumour cells (part one is ongoing, and – according to the authors - results will be reported separately).
[4] EMPOWER-Lung 3 part two was stopped early per recommendation of the IDMC, based on meeting preset OS efficacy criteria, resulting in a primary analysis in which cemiplimab plus chemotherapy showed superior efficacy vs. placebo plus chemotherapy in first-line treatment of NSCLC as measured by OS (PE) and PFS and ORR (key secondary endpoints).
[5] EMPOWER-Lung 3 trial is ongoing until 07/2023.

	❖ major surgery or substantial traumatic injury within 4 weeks before the first dose ❖ documented allergic or acute hypersensitivity reaction attributed to antibody treatments ❖ known psychiatric or substance abuse disorder ❖ pregnant or breastfeeding women	

Efficacy (I vs. C)

Data cutoff 14 June 2021; median duration of follow-up was 16.3 months vs. 16.7 months:

Median OS: 21.9 months (95% CI, 15.5–NE) vs. 13.0 months (95% CI, 11.9–16.1); HR = 0.71; 95% CI, 0.53–0.93; p=0.014

Estimated proportion of patients who were alive at 12 months: 65.7% (95% CI, 59.9–70.9) vs. 56.1% (95% CI, 47.5–63.8)

Median OS in the squamous histology subgroup: 21.9 months (95% CI, 15.6–NE) vs. 13.8 months (95% CI, 9.3–18.0); HR = 0.56 (95% CI, 0.37–0.84)

Median OS in the non-squamous histology subgroup[6]: 15.8 months (95% CI, 13.7–NE) vs. 13.0 months (95% CI, 10.0–NE); HR = 0.79; (95% CI, 0.54–1.14)

Median PFS: 8.2 months (95% CI, 6.4–9.3) vs. 5.0 months (95% CI, 4.3–6.2); HR = 0.56; 95% CI, 0.44–0.70; p<0.0001

Estimated proportion of patients who were alive and had no disease progression at 12 months: 38.1% (95% CI, 32.4–43.8) vs. 16.4% (95% CI, 10.5–23.4)

ORR per independent central review: 43.3% (95% CI, 37.7–49.0) vs. 22.7% (95% CI, 16.4–30.2)

CR: 2.6% vs. 0

PR: 40.7% vs. 22.7%

DOR: 15.6 months (95% CI, 12.4–NE) vs. 7.3 months (95% CI, 4.3–12.6)

Pharmacokinetics and immunogenicity

- Cemiplimab concentrations in serum in patients from the cemiplimab plus chemotherapy arm were similar, irrespective of tumour histology type and baseline PD-L1 expression level, and in agreement with those reported for cemiplimab monotherapy.
- At steady state (week 24; n = 177), mean C_{max} (s.d.) was 129 (46.9) mg L, and mean C_{trough} (s.d.) was 48.6 (25.0) mg L.
- Immunogenicity was low, with treatment-emergent anti-drug antibodies (ADAs) in 3.5% (7/200) of patients who received cemiplimab plus chemotherapy at low titer (<1,000) and negative in the neutralising ADA assay; this did not affect cemiplimab concentrations in serum.

Safety (I vs. C)

Data cutoff 14 June 2021 (I vs. C):

Any grade TEAEs: 95.8% vs. 94.1%

TEAEs grade ≥3: 43.6% vs. 31.4%

TEAEs that led to treatment discontinuation: 5.1% vs. 2.6%

TEAEs of any grade that led to death: 6.1% vs. 7.8%

TRAEs: 88.1% vs. 84.3%

AEs in I:

Sponsor-identified irAEs: 18.9%

Sponsor-identified irAEs with grade ≥3: 2.9% of patients

Discontinuation due to an irAE: 1.0%

Death due to immune-mediated pneumonitis: 0.3%

Patient-reported outcomes

- A significant improvement in the secondary endpoints of overall change from baseline in global health status (GHS)/QoL on the EORTC QLQ-C30 questionnaire was observed in the cemiplimab plus chemotherapy arm (least squares mean change: 1.69; 95% CI, 0.20–3.19) compared to a non-significant overall change in the placebo plus chemotherapy arm (1.08; 95% CI, –1.34 to 3.51).
- The overall difference between treatment groups was insignificant (0.61; 95% CI, –2.23-3.45; p= 0.673). Compared to placebo plus chemotherapy, cemiplimab plus chemotherapy treatment resulted in a trend toward a delay in the onset of definitive clinically meaningful deterioration according to the GHS/QoL scale (HR = 0.78; 95% CI, 0.51–1.19; p= 0.248).
- There was also a significant overall improvement from baseline in pain symptoms (EORTC QLQ-C30) with cemiplimab plus chemotherapy (–4.52; 95% CI, –6.32 - –2.73) compared to a non-significant overall change with placebo plus chemotherapy (0.46; 95% CI, –2.42 - 3.34).
- Significant overall difference between treatment groups favoured the cemiplimab plus chemotherapy arm (–4.98; 95% CI, –8.36 - –1.60; p=0.004). Compared to placebo plus chemotherapy, cemiplimab plus chemotherapy treatment significantly delayed the onset of definitive clinically meaningful deterioration according to the pain symptoms scale (HR = 0.39; 95% CI, 0.26–0.60; p<0.0001).

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

[6] Of note, due to the capping applied to the enrolment of patients with squamous histology, follow-up was shorter in the non-squamous subset (14.7 months; IQR, 12.5–17.9) vs. the squamous subset (18.2 months; IQR, 15.9–20.2).

Original	NC	2a	>12 months ≤24 months	OS: + 8.9 months	0.71 (0.53–0.93)	HR ≤0.70 AND gain ≥5 months	4	-	Improved[7]	+1	5
Adapted	NC	2a	>12 months ≤24 months	OS: + 8.9 months	0.71 (0.53–0.93)	HR >0.70-0.75 AND gain ≥1.5 months	2	-	improved	+1	3

Risk of bias (RCT) [12]

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	yes	no[8] (high risk)	yes[9] (high risk)	high

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
NCT03409614/ EMPOWER-Lung 3	Please see above.	07/2023
NCT03409614	A two-part randomised, phase 3 study of combinations of cemiplimab and platinum-based doublet chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC.	07/2023
NCT03088540	Global, randomised, phase 3, open-label study of REGN2810 (anti-PD 1 antibody) vs. platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic PD L1+ NSCLC.	04/2024
NCT05344209/ LUNGVAC	A randomised phase II, open-label, multi-centre study investigating efficacy and safety of anti-PD-1/PD-L1 treatment (either pembrolizumab, atezolizumab or cemiplimab) +/- UV1 vaccination in patients with NSCLC.	07/2027

Available assessments

- NIHR assessed "Cemiplimab in combination with chemotherapy for advanced or metastatic non-small cell lung cancer – first-line" in March 2021 [14].
- Another assessment, evaluating the efficacy of cemiplimab in patients with NSCLC has been conducted by the G-BA/IQWiG (October 2021) [15].
- CADTH published a clinical and pharmacoeconomic report in August 2022 [16].
- Currently, there is no assessment available from NICE and ICER.

Other aspects and conclusions

- The EMA and the FDA approved Libtayo® for the assessed indication.
- In EMPOWER-Lung 3, a phase 3 trial evaluating cemiplimab plus platinum-doublet chemotherapy as first-line treatment for NSCLC patients with at least 1 radiographically measurable lesion per RECIST 1.1 were included. This involves a histologically or cytologically confirmed squamous or non-squamous stage IIIB/C (if deemed not candidates for treatment with definitive chemoradiation) or stage IV NSCLC and an ECOG PS ≤1. The study has a wide range of exclusion criteria.
- The primary endpoint of EMPOWER-Lung 3 was OS: median OS 21.9 months (95% CI, 15.5–NE) vs. 13.0 months (95% CI, 11.9–16.1); HR = 0.71; 95% CI, 0.53–0.93; p=0.014.
- The EMPOWER-Lung 3 trial **was stopped early** due to a highly significant survival improvement noted at the protocol-specified interim analysis. This decision was based on a recommendation from an IDMC [17].
- Assessment of patient-reported outcomes showed a significant improvement in the secondary endpoint of overall change from baseline in GHS/QoL in patients receiving cemiplimab.

[7] A significant improvement in the secondary endpoints of overall change from baseline in GHS/QoL on the EORTC QLQ-C30 questionnaire; significant overall improvement from baseline in pain symptoms; significant overall difference between treatment groups favoured the cemiplimab plus chemotherapy arm; cemiplimab plus chemotherapy treatment resulted in a significant delay in the onset of definitive clinically meaningful deterioration according to pain symptoms scale.

[8] The trial was stopped early.

[9] This study was funded by Regeneron Pharmaceuticals and Sanofi. Medical writing support was funded by Regeneron Pharmaceuticals, according to Good Publication Practice guidelines. The sponsor was involved in the study design and in the collection, analysis and interpretation of data as well as data checking of information provided in the manuscript.

- ❖ The original and adapted ESMO-MCBS were applied, resulting in a final adjusted magnitude of clinical benefit grade 5 and 3, respectively.
- ❖ Although the second part of the study was conducted in a double-blind design, the risk of bias of the EMPOWER-Lung 3 trial was considered high due to the industry-funded background and the early stopping of the trial.
- ❖ 3 RCTs evaluating the efficacy and safety of cemiplimab in NSCLC, will provide more data in the near future. Of note, the median age of onset of lung cancer is between 68 and 70 years. The median age of EMPOWER-Lung 3 patients was 63 years in both treatment groups; 84.3% of patients had an ECOG PS of 1, indicating that the trial population was younger and had a better performance status than the average lung cancer patient.

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Abbreviations: AE=adverse event, ADA= anti-drug antibodies, AJ=adjustment, ALK=anaplastic lymphoma kinase, aNSCLC=advanced non-small cell lung cancer, BCP=carboplatin/paclitaxel/bevacizumab, C=comparator, CADDTH=Canada´s Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, DOR=duration of response, ECOG PS= Eastern Cooperative Oncology Group performance status, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, EORTC-QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, GHS=global health status, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, ICER=Institute for Clinical and Economic Review, IDMC=independent data monitoring committee, Int.=intention, IQR=interquartile range, IQWIQ=Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, irAEs=immune-related adverse events, 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 for Health and Care Excellence, NIHR=National Institute for Health Research, NSCLC=non-small cell lung cancer, OS=overall survival, PD-1=anti-programmed cell death-1, PD-L1=PD-ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, RCT=randomized controlled trial, RECIST=Response Evaluation Criteria in Solid Tumors, ROS1= ROS proto-oncogene 1, SAE=serious adverse event, ST=standard treatment, TEAEs=treatment-emergent adverse events, TRAES=treatment-related adverse events, TTF1=thyroid transcription factor 1

References:

1. European Medicines Agency (EMA). Libtayo: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/libtayo-epar-product-information_en.pdf].
2. European Medicines Agency (EMA). Medicines. Libtayo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/libtayo-1].
3. Statistik Austria. Ausgewählte Krebslokalisationen nach Inzidenz (Neuerkrankungen pro Jahr), Österreich ab 1983. [Available from: https://www.statistik.at/statistiken/bevoelkerung-und-soziales/gesundheit/krebserkrankungen].
4. DGHO, Onkopedia. Onkopedia Guidelines. Lung cancer. [Available from: https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/lung-cancer-non-small-lung-cancer-nsclc/@@guideline/html/index.html#ID0E1QBG].
5. International Agency for Research on Cancer. Cancer Today. [Available from: https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=908&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=0&include_nmsc_other=1#collapse-group-0-4].
6. U.S. Food and Drug Administration (FDA). FDA approves cemiplimab-rwlc in combination with platinum-based chemotherapy for non-small cell lung cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-cemiplimab-rwlc-combination-platinum-based-chemotherapy-non-small-cell-lung-cancer].
7. U.S. Food and Drug Administration (FDA). Libtayo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761097s014lbl.pdf].
8. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
9. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. Nature Medicine VOL 28 November 2022, 2374–2380.
10. U.S. National Library of Medicine, ClinicalTrials.gov. Combinations of Cemiplimab (Anti-PD-1 Antibody) and Platinum-based Doublet Chemotherapy in Patients With Lung Cancer. [Available from: https://clinicaltrials.gov/ct2/show/NCT03409614].
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.

12. 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].
13. U.S. National Library of Medicine, ClinicalTrials.gov. [Available from: https://clinicaltrials.gov/ct2/home].
14. National Institute for Health Research (NIHR). Cemiplimab in combination with chemotherapy for advanced or metastatic non-small cell lung cancer – first-line. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/24085-Cemiplimab-Chemotherapy-for-NSCLC-v1.0-MAR2021-NON-CONF.pdf].
15. IQWIQ. Cemiplimab (nicht kleinzelliges Lungenkarzinom). [Available from: https://www.g-ba.de/downloads/92-975-4970/2021-08-01_Nutzenbewertung-IQWiG_Cemiplimab_D-705.pdf].
16. Canada´s Drug and Health Technology Agency. CADTH Reimbursement Review. Cemiplimab (Libtayo). [Available from: https://www.cadth.ca/sites/default/files/DRR/2022/PC0262-Libtayo-combined.pdf].
17. Cancernetwork, Virgil H. Phase 3 Clinical Trial of First-Line Cemiplimab Combo in NSCLC Stopped Early Due to Significantly Improved Survival. [Available from: https://www.cancernetwork.com/view/phase-3-clinical-trial-of-first-line-cemiplimab-combo-in-nsclc-stopped-early-due-to-significantly-improved-survival].