Cemiplimab (Libtayo®) as monotherapy for the treatment of recurrent or metastatic cervical cancer

General information

Drug description [1]	Indication [2]
Cemiplimab (Libtayo®) is a fully human programmed cell death 1 (PD-1)–blocking antibody.	Cemiplimab (Libtayo®) as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

Current treatment [3]

- ❖ According to the current NICE treatment pathway for women with recurrent and stage 4B cervical cancer, topotecan with cisplatin is recommended as a treatment option only if they have not previously received cisplatin.
- ❖ Women who have previously received cisplatin and are currently being treated with topotecan in combination with cisplatin, for recurrent and stage 4B cervical cancer, should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

Regulatory status

EMA [2]

Approval status for this indication: On 13 October 2022, 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:

- ❖ Libtayo® as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

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 non-small cell lung cancer (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.

✓ **Medicine under additional monitoring**

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

FDA [4, 5]

Approval status for this indication: not approved

On 28 January 2022, Regeneron Pharmaceuticals, Inc. and Sanofi announced the **voluntary withdrawal** of the supplemental Biologics License Application for Libtayo® as a second-line treatment for patients with advanced cervical cancer. The decision was made after the companies and the FDA were not able to align on certain post-marketing studies. Discussions with regulatory authorities outside of the U.S. are ongoing.

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 HHI 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 (indication approved under accelerated approval based on tumour response rate and durability of response).
- ❖ 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.
- ❖ 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.

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.

Posology [7]

- **PD-L1 testing** for patients with NSCLC
  - For treatment with cemiplimab as monotherapy, patients should be selected based on PD-L1 tumour expression using a validated test.

Special warnings and precautions for use [7]

- **Traceability**
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- **Immune-mediated adverse reactions**
  - Severe and fatal immune-mediated adverse reactions have been observed with cemiplimab. These immune-mediated reactions may involve any organ system. Immune-mediated reactions can manifest at any time during treatment with cemiplimab; however, immune-mediated adverse reactions can occur after discontinuation of cemiplimab. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously, such as myositis and myocarditis or myasthenia gravis, in patients treated with cemiplimab or other PD-1/PD-L1 inhibitors.
  - Monitor patients for signs and symptoms of immune-mediated adverse reactions. Immune-mediated adverse reactions should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected immune-mediated adverse reactions, patients should be evaluated to confirm an immune-mediated adverse reaction and to exclude other possible causes, including infection. Depending upon the severity of the adverse reaction, cemiplimab should be withheld or permanently discontinued.
  - **Immune-mediated pneumonitis,** defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab. Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-mediated pneumonitis should be ruled out. Patients with suspected pneumonitis should be evaluated with radiographic imaging as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids.
  - **Immune-mediated diarrhoea or colitis,** defined as requiring use of corticosteroids with no clear alternate aetiology, has been observed in patients receiving cemiplimab. Patients should be monitored for signs and symptoms of diarrhoea or colitis and managed with cemiplimab treatment modifications, anti-diarrhoeal agents, and corticosteroids.
  - **Immune-mediated hepatitis,** defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab. Patients should be monitored for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids.
  - **Immune-mediated endocrinopathies,** defined as treatment-emergent endocrinopathies with no clear alternate aetiology, have been observed in patients receiving cemiplimab.
- **Thyroid disorders (hypothyroidism/hyperthyroidism/thyroiditis)**
  - Immune-mediated thyroid disorders have been observed in patients receiving cemiplimab. Thyroiditis can present with or without an alteration in thyroid function tests. Hypothyroidism can follow hyperthyroidism. Thyroid disorders can occur at any time during the treatment. Patients should be monitored for changes in thyroid function at the start of treatment and periodically during the treatment as indicated based on clinical evaluation. Patients should be managed with hormone replacement therapy (if indicated) and cemiplimab treatment modifications. Hyperthyroidism should be managed according to standard medical practice.
- **Hypophysitis**
  - Immune-mediated hypophysitis has been observed in patients receiving cemiplimab. Patients should be monitored for signs and symptoms of hypophysitis and managed with cemiplimab treatment modifications, corticosteroids and hormone replacement, as clinically indicated.
- **Adrenal insufficiency**
  - Adrenal insufficiency has been observed in patients receiving cemiplimab. Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment and managed with cemiplimab treatment modifications, corticosteroids and hormone replacement, as clinically indicated.
- **Type 1 diabetes mellitus**
  - Immune-mediated type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed in patients receiving cemiplimab. Patients should be monitored for hyperglycaemia and signs and symptoms of diabetes as indicated based on clinical evaluation and managed with oral anti-hyperglycaemics or insulin and cemiplimab treatment modifications.
- **Immune-mediated skin adverse reactions**
  - Immune-mediated skin adverse reactions, defined as requiring use of systemic corticosteroids with no clear alternate aetiology, including severe cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (some cases with fatal outcome), and other skin reactions such as rash, erythema multiforme, pemphigoid, have been reported in association with cemiplimab treatment.
  - Patients should be monitored for evidence of suspected severe skin reactions and exclude other causes. Patients should be managed with cemiplimab treatment modifications and corticosteroids. For symptoms or signs of SJS or TEN, refer the patient for specialised care for assessment and treatment and manage patient with treatment modifications. Cases of SJS, fatal TEN and stomatitis occurred following 1 dose of cemiplimab in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkin

Lymphoma, and who had recent exposure to sulfa containing antibiotics. Patients should be managed with cemiplimab treatment modifications and corticosteroids as described (please see product information).

- **Immune-mediated nephritis,** defined as requiring use of corticosteroids with no clear alternate aetiology, including a fatal case, has been observed in patients receiving cemiplimab. Monitor patients for changes in renal function. Patients should be managed with cemiplimab treatment modifications and corticosteroids.
- **Other fatal and life-threatening immune-mediated adverse reactions** have been observed in patients receiving cemiplimab including paraneoplastic encephalomyelitis, meningitis myositis and myocarditis. Non-infective cystitis has been reported with other PD-1/PD-L1 inhibitors. Evaluate suspected immune-mediated adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed with cemiplimab treatment modifications and corticosteroids as clinically indicated. Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with cemiplimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with cemiplimab versus the risk of possible organ rejection should be considered in these patients. Cases of graft-versus-host disease have been reported in the post-marketing setting in patients treated with other PD-1/PD-L1 inhibitors in association with allogeneic hematopoietic stem cell transplant.
- **Infusion-related reactions**
  - Cemiplimab can cause severe or life-threatening infusion-related reactions. Patients should be monitored for signs and symptoms of infusion-related reactions and managed with cemiplimab treatment modifications and corticosteroids. Cemiplimab should be interrupted or the rate of infusion slowed for mild or moderate infusion-related reactions. The infusion should be stopped and cemiplimab should be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions.
- **Patients excluded from clinical studies**
  - Patients that had active infections, were immunocompromised, had a history of autoimmune diseases, ECOG PS ≥2 or a history of interstitial lung disease were not included. For a full list of patients excluded from clinical studies, please see product information.
  - In the absence of data, cemiplimab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

Study characteristics [1, 8-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
EMPOWER Cervical 1/ GOG-3016/ ENGOT-cx9/ Study 1676 NCT03257267	608 (1:1)	cemiplimab 350 mg IV every 21 days for up to 96 weeks [2]	chemotherapy[3]	OS	**ongoing**[4], open-label, randomised, multi-center, phase 3 trial	PD-1	Regeneron Pharmaceuticals and Sanofi	[1]

Efficacy (I vs. C)	**Safety** (I vs. C)
Reported data are based on a data cut-off date of 4 January 2021: **Median duration of follow-up from randomisation to the data cut-off was 18.2 months** (range, 6.0-38.2) for all patients. At the second planned interim analysis (median follow-up of 16.8 months in the population with squamous-cell carcinoma), the trial was stopped on the basis of prespecified criteria for efficacy in the population with squamous-cell carcinoma. **Median OS In the overall population**: 12.0 months (CI, 10.3-13.5) vs. 8.5 months (95% CI, 7.5-9.6); HR 0.69; 95% CI, 0.56-0.84; two-sided p<0.001	**AEs (regardless of attribution):** 88.3% vs. 91.4% **AEs of grade ≥3:** 45.0% vs. 53.4% **AEs leading to trial treatment discontinuation:** 8.7% vs. 5.2% **AEs (regardless of attribution) leading to death:** 1.7% vs. 0.7%[5] **Immune-related AEs:** 15.7% vs. 0.7%

[2] With an option for repeat treatment for patients who completed 16 treatment cycles and then had progressive disease in the post-treatment follow-up period. Patients receiving cemiplimab who had an unconventional response consistent with pseudo-progression were allowed to be treated beyond progression, provided the ECOG performance-status score did not increase, rapid disease progression did not occur, and severe adverse events warranting cemiplimab discontinuation were not encountered.

[3] Control therapy was determined before randomisation by the investigator from protocol-specified options reflecting the availability of drugs in different regions of the world. Antifolate therapy consisted of pemetrexed (500 mg/m^2 of body-surface area administered IV every 21 days), with vitamin B12 and folate support given as needed. Topoisomerase I inhibitors included topotecan (1 mg/m^2 administered IV daily for 5 days) or irinotecan (100 mg/m^2 administered IV weekly for 4 weeks). The nucleoside analogue gemcitabine (1000 mg/m^2 administered IV on days 1 and 8 every 21 days) and the vinca alkaloid vinorelbine (30 mg/m^2 administered IV on days 1 and 8 every 21 days) were also available. Control therapy was discontinued at the onset of disease progression or development of unacceptable toxic effects, with stopping rules for adverse events outlined in the protocol and no crossover allowed.

[4] The EMPOWER Cervical 1 trial is currently ongoing; estimated study completion date is 07/2023.

[5] None of the AEs leading to death were considered by the treating investigator to be related to cemiplimab.

Median overall survival in the chemotherapy group (assessment according to the type of chemotherapy chosen by the investigator) in the overall population: 6.5 months (95% CI, 4.4-8.8) with topotecan; 11.8 months (95% CI, 6.9-14.9) with irinotecan
Median OS In the population with squamous cell carcinoma: 11.1 months (95% CI, 9.2-13.4) vs. 8.8 months (95% CI, 7.6-9.8); HR 0.73; 95% CI, 0.58-0.91; two-sided p=0.006
Median OS in the population with adenocarcinoma or adenosquamous carcinoma: 13.3 months (95% CI, 9.6-17.6) vs. 7.0 months (95% CI, 5.1-9.7); HR 0.56; 95% CI, 0.36-0.85
Median PFS in the overall population: 2.8 months (95% CI, 2.6-3.9) vs. 2.9 months (95% CI, 2.7-3.4); HR for disease progression or death 0.75; 95% CI, 0.63-0.89; two-sided p<0.001
Median PFS in the population with squamous-cell carcinoma: 2.8 months (95% CI, 2.6-4.0) vs. 2.9 months (95% CI, 2.7-3.9); HR 0.71; 95% CI, 0.58-0.86; two-sided p<0.001
Median PFS in the subgroup analysis of the population with adenocarcinoma or adenosquamous carcinoma: 2.7 months (95% CI, 2.3-4.0) vs. 2.8 months (95% CI, 2.0-3.2); HR 0.91; 95% CI, 0.62-1.34
Patients with an objective response in the overall population: 16.4% (95% CI, 12.5-21.1) vs. 6.3% (95% CI, 3.8-9.6); two-sided p<0.001
Kaplan–Meier estimate of the median duration of response in the overall patient population: 16.4 months (95% CI, 12.4-not reached) vs. 6.9 months (95% CI, 5.1-7.7)
Objective response in the population with squamous-cell carcinoma: 17.6% (95% CI, 13.0-23.0) vs. 6.7% (95% CI, 3.9-10.7); two-sided p<0.001
Objective response in the population with adenocarcinoma or adenosquamous carcinoma: 12% (95% CI, 6-23) vs. 4% (95% CI, 1-13)

PD-L1 Expression

- Of the 608 patients who underwent randomisation, 254 had baseline tumour samples that could be evaluated for PD-L1 expression: 126 in the cemiplimab group and 128 in the chemotherapy group.
- This subpopulation of patients had clinical outcomes similar to those observed in the overall population.
- Among patients with a baseline sample that could be evaluated, PD-L1 expression of 1% or greater was more common among the patients with squamous-cell carcinoma (70.7%) than among those with adenocarcinoma or adenosquamous carcinoma (32.6%).
- Among the patients with PD-L1 expression of 1% or greater, median OS was 13.9 months (95% CI, 9.6-not reached) with cemiplimab vs. 9.3 months (95% CI, 7.0-11.4); HR for death 0.70; 95% CI, 0.46-1.05).
- Among the patients with PD-L1 expression of less than 1%, median OS was 7.7 months (95% CI, 4.3-12.3) vs. 6.7 months (95% CI, 3.9-9.5) with chemotherapy; HR 0.98; 95% CI, 0.59-1.62.
- Objective responses to cemiplimab were observed in 15 of 82 patients with PD-L1 expression of 1% or greater (18%; 95% CI, 11-28) and in 5 of 44 patients with PD-L1 expression of less than 1% (11%; 95% CI, 4-25).

Quality of life [1]

- The percentage of patients who completed the QLQ-C30 global health status and QoL scale was greater than 95% at baseline and remained high during the entire treatment period in both treatment groups, at approximately 90% among those expected to complete the questionnaire (i.e., those who were alive and still receiving trial treatment).
- In the overall population, the estimated least-squares mean difference between cemiplimab and chemotherapy from baseline through cycle 8 in the global health status and QoL score was 7.8 points (95% CI, 3.3-12.3).
- The within-group overall least-squares mean change from baseline QoL score was 1.0 (95% CI, –2.0-4.0) in the cemiplimab group and –6.8 (95% CI, –11.0 to –2.6) in the chemotherapy group.

ESMO-MCBS version 1.1 [11]

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

Original	NC	2A	≤12 months	OS: + 3.5 months	0.69 (0.56-0.84)	HR ≤0.65 AND gain ≥3 months	4	-	improved	+1	5
Adapted	NC	2A	≤12 months	OS: + 3.5 months	0.69 (0.56-0.84)	HR >0.65-0.70 AND gain ≥1.5 months	2	-	-	-	2

Risk of bias [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	-	no, open-label	unclear[6]	yes[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, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, ECOG=Eastern Cooperative Oncology Group, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HHI=hedgehog pathway inhibitor, HR=hazard ratio, I=intervention, Int.=intention, 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, NSCLC=non-small cell lung cancer. OS=overall survival, PD-1= programmed cell death 1, 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, SJS= Stevens-Johnson syndrome, ST=standard treatment, TEN=toxic epidermal necrolysis

References:

1. Tewari K, Monk B, Vergote I, et al., for the Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cx9. Survival with Cemiplimab in Recurrent Cervical Cancer. N Engl J Med 2022;386:544-55. [Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2112187].
2. European Medicines Agency (EMA). Medicines. Libtayo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/libtayo-0].
3. National Institute for Health and Research (NIHR). Cemiplimab for recurrent, persistent or metastatic cervical cancer – second line. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/20479-TSID_10120-Cemiplimab-for-Cervical-Cancer-v1.0-DEC2020-NON-CONF.pdf].
4. Regeneron. Regeneron and Sanofi provide regulatory update on Libtayo® (cemiplimab-rwlc) in advanced cervical cancer. [Available from: https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-regulatory-update-libtayor].
5. U.S. Food and Drug Administration (FDA). Libtayo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761097s014lbl.pdf].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. 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].
8. Supplement to: Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022;386:544-55.
9. Protocol for: Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022;386:544-55.
10. U.S. National Library of Medicine, ClinicalTrials.gov. Study of Cemiplimab in Adults With Cervical Cancer.
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].

[6] The EMPOWER-Cervical 1 trial is currently ongoing.
[7] Industry-funded; the sponsors provided cemiplimab free of charge in accordance with European Network for Gynecological Oncological Trial groups– Gynecologic Oncology Group model C.