Cemiplimab (Libtayo®) as monotherapy for the treatment of locally advanced or metastatic basal cell carcinoma (laBCC or mBCC)

General information

Drug description [1]	Indication [2]
Cemiplimab is an anti-programmed cell death-1 monoclonal antibody.	Cemiplimab (Libtayo®) as monotherapy is indicated for the treatment of adult patients with laBCC or mBCC who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

Current treatment [3]

<u>According to the National Cancer Institute, treatment options for mBCC or locally advanced disease untreatable by local modalities include the following:</u>

- ❖ HHI:
  - Vismodegib
  - Sonidegib

  BCCs frequently exhibit constitutive activation of the Hedgehog/PTCH1 signalling pathway. Vismodegib and sonidegib, two inhibitors of Smoothened, a transmembrane protein involved in the Hedgehog pathway, are approved for the treatment of adults with metastatic BCC, patients with locally advanced BCC that has recurred after surgery, and patients who are not candidates for surgery or radiation therapy.
- ❖ Chemotherapy:
  - No standard chemotherapy regimens exist, and there are only anecdotal reports in the literature.
- ❖ Because there is no curative therapy for mBCC of the skin, clinical trials are appropriate.

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 a new indication as follows:</u>

- ❖ Libtayo® as monotherapy is indicated for the treatment of adult patients with laBCC or mBCC who have progressed on or are intolerant to a HHI.

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 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: On 9 February 2021, the FDA granted regular approval to cemiplimab-rwlc (Libtayo®) for patients with laBCC previously treated with an HHI or for whom an HHI is not appropriate and granted accelerated approval to cemiplimab-rwlc for patients with mBCC previously treated with an HHI or for whom an HHI is not appropriate.

- ✓ The **mBCC indication** is approved under **accelerated approval** based on tumour response rate and durability of response. Continued approval for mBCC may be contingent upon verification and description of clinical benefit.

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 first-line treatment of 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:
  - o locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
  - o metastatic.

[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

Costs

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

Study 1620: patients received cemiplimab at a dose of 350 mg IV every 3 weeks for up to 93 weeks until disease progression, unacceptable toxicity, or completion of planned treatment. Median duration of exposure was 42 weeks (range: 2.1 weeks to 94 weeks) [5], resulting in 14 doses of 350 mg IV per patient, on average, at approximately 79,140.00 euros.

Warnings and precautions [5]

- **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, 5, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
Study 1620 NCT03132636	112[2]/132[3]	Cemiplimab 350 mg IV every 3 weeks for up to 93 weeks until disease progression, unacceptable toxicity, or completion of planned treatment.	-	ORR per ICR	open-label, multi-centre, non-randomised, phase 2 study	-	Regeneron Pharmaceuticals	[1] (Abstract/Interim analysis of the mBCC cohort)

Efficacy (n=112)[4]	**Safety** (n=132)
<u>mBCC (n=28)</u> **Median duration of follow-up**: 9.5 months **Median time to response for the responding patients**: 3.2 months (range 2.1-10.5 months)	**Serious adverse reactions**: 32% **Fatal adverse reactions:** 1.5% **Permanent discontinuation due to an adverse reaction**: 13%

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.

[2] A total of 112 patients with advanced BCC were included in the efficacy analysis of Study 1620. Of these, 25% had mBCC and 75% had laBCC.

[3] The safety of Libtayo® was evaluated in 132 patients with advanced BCC (mBCC: n=48, laBCC: n=84)

[4] Interim efficacy analysis data

Confirmed ORR: 21% (95% CI: 8-41) **Complete response**: 0 **Partial response**: 21% **Median DOR**: NR (range: 9-23.0+ months) Patients with observed **DOR ≥6 months**: 100% **Median Kaplan-Meier estimation of PFS:** 8.3 months **Median Kaplan-Meier estimation of OS:** 25.7 months **Disease control rate:** 67.9% (95% CI: 47.6-84.1) **laBCC (n=84)** **Median duration of follow-up:** 15.1 months **Median time to response for the responding patients**: 4.2 months (range 2.1-13.4 months) **Confirmed ORR:** 29% (95% CI: 19-40) **Complete response**: 6% **Partial response**: 23% **Median DOR:** NR (range: 2.1 .21.4+ months) Patients with observed **DOR ≥6 months**: 79.2%	**Treatment-emergent adverse events leading to death:** 3.6% (considered unrelated to study treatment)

ESMO-MCBS version 1.1 [8]

The ESMO-MCBS is not applicable since the reported endpoints were not scorable.

Risk of bias (study level) [9]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
Not appropriate, single-arm study	Not appropriate, single-arm study	No, open-label	yes[5]	yes[6]	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=endothelial 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, HSCT=hematopoietic stem cell transplantation I=intervention, ICR=independent central review, Int.=intention, IV=intravenous, 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, NSCLC=non small cell lung cancer, NR=not reached, ORR=objective response rate, OS=overall survival, PD-L1=programmed cell death-ligand1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TPS=tumour proportion score

[5] Currently only interim analysis data available. Study 1620 is ongoing until 05/2022.
[6] Industry-funded.

References:

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