REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Libtayo

350 mg concentrate for solution for infusion x 1 vial

Cemiplimab

Therapeutic indication(s)	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.
Start/end date of procedure	30.03.2020 – 30.12.2020
Final decision	Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act for payment by the National Health Insurance Fund (NHIF) outside of the value of rendered medical services.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Libtayo

Health problem

Skin malignancies (skin cancers) comprise the majority of all cancers and include many subtypes, including melanoma and non-melanoma (NMSC) skin cancers. Non-melanoma skin cancer, the most common group of cancers, is further divided into several categories, including basal cell carcinoma (BCC), squamous cell carcinoma (CSCC) and other rare subtypes. CSCC is ranked as the second most common subtype, representing approximately 20% of NMSC.

CSCC is less common than BCC, but is more likely to be invasive. Tumors can also grow into deeper layers of the skin and spread to other parts of the body. Advanced CSCC includes metastatic disease and locally advanced disease that is not amenable to curative surgery or curative radiation therapy. There are currently no approved systemic therapies for advanced CSCC.

Changes in patients' appearance can have long-term effects, including decreased self-confidence, low self-esteem, difficulties in social interactions, and social withdrawal.

Libtayo (cemiplimab) is a human, immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death receptor-1 (PD-1), blocks its binding to PD-L1 and PD-L2 ligands, and potentiates T-cell responses, including anti-tumor responses. Libtayo is the first systemic therapy and the first PD-1 inhibitor approved for patients with advanced CSCC that demonstrates high levels of objective response, clinically significant response duration, improved quality of life, and improved survival. Libtayo has demonstrated high therapeutic efficacy, significant and sustained reduction in tumor mass, and survival benefits in a small population of patients with advanced disease. The medicinal product leads to a clinically significant reduction in pain as well as to an improvement or stabilization of the health-related quality of life. Libtayo demonstrates an acceptable safety profile.

Epidemiological data

The incidence of malignant skin tumors is one of the highest in the world and in Bulgaria. According to the National Cancer Registry (NRR), 12.8% of all malignancies are malignant tumors of the skin. About 20% of them are squamous cell carcinomas. The proportion of patients with cSCC who develop advanced disease is about 5%.

Efficacy data

The therapeutic efficacy and safety profile of cemiplimab, which is indicated as monotherapy for the treatment of adult patients with metastatic or locally advanced squamous cell

carcinoma of the skin, who are not candidates for radical surgery or radical radiotherapy, was evaluated based on the results of two clinical trials:

Clinical study R2810 ONC-1423, evaluating the efficacy of cemiplimab as monotherapy or in combination in extended cohorts, involving patients with advanced malignancies, as well as the safety, tolerability and dose-limiting toxicity of cemiplimab.

The Kaplan-Meier analysis of PFS shows that the proportion of patients without PFS or occurrence of death was higher in patients with locally advanced CSCC (90.0%) than in those with metastatic CSCC (56.3%). The probability of no event occurring from baseline to month 16 was higher in the population with locally advanced CSCC (88.9%) than in metastatic CSCC (52.6%).

The proportion of patients with no registered death was higher in numerical terms in the population with locally advanced CSCC (90.0% vs. 75.0%). Patients with locally advanced CSCC were more likely to have no event from baseline to month 16 than patients with metastatic CSCC (90% vs. 66.8%).

EMPOWER-CSCC 1 clinical trial, evaluating the clinical benefit of cemiplimab monotherapy in patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or unresectable advanced CSCC, as measured by the total response rate (ORR).

Cemiplimab demonstrated efficacy independent of tumor PD-L1 expression. In patients with advanced CSCC and PD-L1 < 1%, ORR is 40.9%. In patients with advanced CSCC and PD-L1 ≥ 1% ORR was 54.7%. In patients with metastatic CSCC the ORR was 60% in patients with PD-L1 <1% and 56.3% in PD-L1 ≥ 1%. In patients with locally advanced CSCC, the ORR was 35.3% in patients with PD-L1 < 11% and 54.1% in PD-L1 ≥ 1%.

Due to a lack of direct comparisons of cemiplimab with other therapies, an indirect comparison was performed. The analysis showed that cemiplimab administration resulted in better survival (OS) compared to other advanced CSCC therapies. The results for the objective response are mixed, showing that cemiplimab is at least comparable to existing therapies.

Patient-reported data
A clinically significant improvement in the mean EORTC QLQ-C30 pain score was observed. There was also improvement in the scores for general health (GHS), emotional functioning, social functioning, insomnia, loss of appetite and constipation; however, the threshold for clinically significant change has not been reached. Quality of life has been improved or preserved in most cemiplimab-treated patients.

Safety data

Adverse reactions observed in ≥10% of patients in both studies are related to:

- Disorders of the skin and subcutaneous tissue - rash, pruritus
- Gastrointestinal disorders - diarrhea, nausea, constipation
- General disorders and administration site conditions - fatigue, musculoskeletal and connective tissue disorders (musculoskeletal pain), metabolic and eating disorders (decreased appetite).

Data on comparators

Cisplatin, cyclophosphamide, fluorouracil, paclitaxel were selected as comparators.

Pharmacoeconomic indicators

Published health technology assessments of governmental institutions intended for the health care systems of other countries

Three assessments were provided, performed by the following governmental institutions: NICE, IQWiG, TLV.

- NICE recommends cemiplimab for use as an option for the treatment of locally advanced or metastatic cutaneous squamous cell carcinoma in adults who are not candidates for radical surgery or radical radiation therapy, until disease progression or up to 24 months (whichever comes first). Recommended only if the terms of the cemiplimab access agreement are met.
- The evaluation, carried out by IQWiG does not provide evidence of added benefits.
- TLV - No recommendation is presented

Applied analysis

A cost-benefit pharmacoeconomic analysis was employed to evaluate the cost effectiveness of cemiplimab in the treatment of patients with metastatic or locally advanced squamous cell carcinoma of the skin, who were not candidates for radical surgery or radical radiotherapy. The measures of the result are the quality adjusted life years (QALY) and life-years gained (LYG). The perspective is that of the paying institution NHIF, with only the direct costs being calculated. The time horizon is lifelong. Costs and benefits are discounted with an annual discount factor of 3.5%. As a comparator, chemotherapy was selected: cisplatin + 5-fluorouracil, paclitaxel + cisplatin, cisplatin + cyclophosphamide, which reflects the clinical practice in Bulgaria and the guidelines of ESMO, ASCO, NCCN. A survival model was used, and the health benefits and costs of cemiplimab and alternatives were modeled.

The applied analysis shows that cemiplimab therapy is associated with additional expenditure and with addition of years of life and QALY compared to chemotherapy regimens. From the point of view of the healthcare system in Bulgaria, Libtayo therapy is not cost-effective in comparison with chemotherapy. The applied sensitivity analysis confirms the conclusions made.

Costs of the assessed health technology

Costs have been calculated for drug therapy with Libtayo and alternatives, for follow-up treatment after progression, for medical services, for control of adverse events, for outpatient monitoring/dispensarisation, for excisional procedures, for palliative care in the terminal stage.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the paying institution for a 5-year time horizon. The target population includes adult patients with metastatic or locally advanced squamous cell carcinoma of the skin who are not candidates for radical surgery or radical radiotherapy. The results show that the use of Libtayo as a therapeutic alternative is associated with the generation of additional expenditure over the entire time horizon, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Libtayo is the first systemic therapy and the first PD-1 inhibitor approved for patients with advanced CSCC that demonstrates high levels of objective response, clinically significant response duration, improved quality of life, and improved survival. Libtayo has demonstrated high therapeutic efficacy, significant and sustained reduction in tumor mass, and survival benefits in the small population of patients with advanced disease. The use of the medicinal product results in a clinically significant reduction of pain as well as to an improvement or stabilization of the health-related quality of life. Libtayo demonstrates an acceptable safety profile. In the therapeutic algorithm, Libtayo is a cost-inefficient alternative, as the incremental ratio falls above the break-even point. The use of the medicinal product Libtayo is expected to generate additional cost for the paying institution, without taking into account risk-sharing agreements and patient access schemes.