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

HEALTH TECHNOLOGY ASSESSMENT

Keytruda
25 mg/ml – 4 ml concentrate for solution for infusion x 1
Pembrolizumab

Therapeutic indication(s)	As monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.
Start/end date of procedure	13.05.2020 – 05.11.2020
Final decision	To add a therapeutic indication in Annex 2 of the Positive Drug List (PDL) for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the cost of the rendered medical services. Restriction: as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 20.

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

Health problem

Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease characterized by complex clinical and pathological manifestations. The disease accounts for approximately 90% of all head and neck cancers. Males are affected more often than females, with a ratio of 2:1 to 4:1 in different regions of the world.

Head and neck cancer includes a number of tumors that originate in the upper gasrointestinal tract mucosa: carcinoma of the oral cavity, carcinoma of the oropharynx, carcinoma of the hypopharynx, carcinoma of the larynx.

Tumors originate from epithelial cells of the mucous surface layer of the oral cavity, oropharynx, larynx or hypopharynx. In recent decades it has been established that human papillomavirus (HPV) and Epstein Barr virus (EBV) are linked to the development of squamous cell carcinoma of the oropharynx and nasopharynx, respectively. Oropharyngeal SCC (OPSCC) can be divided into HPV-negative (HPV-ve) and HPV-positive (HPV+ve).

The early symptoms of HNSCC are generally nonspecific; they are also frequently seen in inflammatory diseases. Patients with head and neck cancer report significant and persistent problems: physical (radionecrosis, mucositis, loss of taste, dysphagia, weight loss), functional (pain, difficulty swallowing, voice disorder and poor dental condition) and psychosocial problems (depression, disfigurement, social isolation). In patients with HNSCC, impaired functions such as breathing, speech, eating, and potential disfigurement adversely affect social and emotional functioning.

Data show that PD-L1 may be one of the main immunosuppressive drivers in many types of malignancies. Prevention of the binding of PD-L1 to PD-1 and B7.1 can enhance antitumor T-cell activity and T-cell preparation, leading to the destruction of T-cell mediated tumors.

When HNSCC is diagnosed at an early stage, the prognosis is better and there are more treatment options, while in the late stages, maintaining the function and integrity of the organs is impossible. Most patients with HNSCC have a locally advanced disease with a high risk of recurrence, and approximately 10% of patients with HNSCC have metastatic disease. Despite advances in surgery and radiation therapy, the five-year survival of patients with HNSCC at all stages (except EBV associated with nasopharyngeal cancer) remains 40-50% for HPV-negative tumors caused by traditional carcinogens. The overall survival (OS) in patients with recurrent/metastatic (R/M) disease is 10-13 months.

Keytruda (pembrolizumab) demonstrated a clinically meaningful and sustained response in patients with R/M HNSCC with disease progression during or after platinum-containing chemotherapy. The efficacy of pembrolizumab has also been demonstrated in patients who have progressed after treatment with cetuximab and platinum-containing therapy.

Epidemiological data

Head and neck cancer is the seventh most common type of cancer in the world, with an incidence of over 700,000 cases per year and a 5-year global prevalence of over 1.8 million. Approximately 90% of all head and neck cancers are squamous cell carcinoma (HNSCC), most of which originate in the epithelium of the oral mucosa, larynx, oropharynx and hypopharynx.

Based on GLOBOCAN, 2018 data, Europe has the second highest regional incidence rate of 10.8 cases per 100,000 population and a population of 146,711 HNSCC patients. 25% of patients were diagnosed at stage IV C.

Efficacy data

In order to assess the therapeutic efficacy and safety profile of pembrolizumab indicated as monotherapy or in combination with chemotherapy (CT) for the treatment of recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) in adults, the results of the clinical study KEYNOTE-048 – a randomized, open-label, phase 3 study have been analyzed.

In the PD-L1 CPS≥1 population, pembrolizumab as a monotherapy resulted in significantly improved OS as compared with EXTREME. Pembrolizumab has long-term survival benefits. No ORR benefit was observed with pembrolizumab monotherapy, but the response to treatment was more sustained than with EXTREME. In the CPS≥20 population, pembrolizumab monotherapy significantly improved OS compared with EXTREME. Pembrolizumab treatment is associated with long-term survival benefits. In the CPS≥1 to CPS<20 population, OS outcomes show a tendency to improve with pembrolizumab monotherapy compared to EXTREME. No ORR benefit was observed with pembrolizumab monotherapy, but the response to treatment was more sustained than with EXTREME.

Pembrolizumab + chemotherapy vs EXTREME

In the ITT population, pembrolizumab + CT significantly improved OS compared to EXTREME. Pembrolizumab therapy is beneficial in terms of long-term survival. ORR with pembrolizumab + CT is comparable to that with EXTREME and treatment responses are more sustained compared with EXTREME. In the PD-L1 CPS ≥1 population, pembrolizumab + chemotherapy significantly improved OS compared with EXTREME. ORR with pembrolizumab + chemotherapy is comparable to EXTREME, the response to treatment is

more sustained than with EXTREME. In the CPS≥20 population, pembrolizumab + chemotherapy significantly improved OS compared with EXTREME. ORR is comparable in pembrolizumab + chemotherapy compared to EXTREME, the response to treatment is more sustained than with EXTREME. Treatment with pembrolizumab + chemotherapy resulted in a clinically significant improvement in OS compared with EXTREME in the CPS≥1 to CPS <20 population. ORR with pembrolizumab + chemotherapy is comparable to that with EXTREME, the response to treatment is more sustained compared with EXTREME.

Safety data

Pembrolizumab is most frequently associated with immune-related adverse reactions. The most common adverse reactions after the administration of pembrolizumab are fatigue (32%), nausea (20%) and diarrhea (20%).

In the population of patients with NSCLC or HNSCC the most frequent side effects are anemia (50%), nausea (50%), fatigue (37%), constipation (35%), diarrhea (30%), neutropenia (30%), decreased appetite (28%) and vomiting (25%). Grade 3-5 adverse events were 67% in patients with NSCLC in combination therapy with pembrolizumab and 66% in chemotherapy alone, and in patients with HNSCC they are 85% in combination therapy with pembrolizumab and 84% in chemotherapy.

Data on comparators

In HNSCC, the following first-line chemotherapy for recurrent or metastatic disease is employed:

- Cisplatin in combination with Fluorouracil, Cetuximab, Docetaxel and Gemcitabine;
- Fluorouracil in combination with Cisplatin, Cetuximab and Vincristine;
- Cetuximab in combination with Cisplatin, Fluorouracil and as maintenance therapy after CT;
- Docetaxel as well as Docetaxel + Cisplatin. Docetaxel is also used in combination with Gemcitabine + Cisplatin;
- Carboplatin is used in combination with Paclitaxel + Carboplatin + Fluorouracil.

Pharmacoeconomic indicators

Publicly available assessments of the health technology by government institutions intended for another national health care system

Pembrolizumab has received a positive assessment by IQWiG, Germany as a therapy for adult patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).

Applied analysis

A pharmacoeconomic analysis of the cost-benefit type has been applied. The health benefits for patients in the applied model were measured as life years gained (LYG) and quality adjusted life years (QALY). The analysis was conducted from the payer's, the NHIF perspective. The time horizon is 20 years. Health benefits and costs are discounted at an annual discount rate of 3.5%. A partitioned survival model is applied that includes three health conditions - no progression, progression and death. Cetuximab was chosen as a comparator. Pembrolizumab demonstrates therapeutic superiority, expressed in more years of life gained. The results of the cost-benefit analysis did not identify pembrolizumab as a cost-effective therapy compared to the alternative.

Subgroup analyses

Not applicable.

Cost of the assessed health technology

Direct medical costs are included - for medication with alternatives, for administration, for ADR management.

Budget impact analysis

The analysis of the budget impact was conducted from public payer's, the NHIF point of view. The time horizon is 5 years. The expected number of patients for the first year is 18 and for the fifth year it is 20. The reimbursement of the health technology will lead to additional cost for the NHIF in the first year, which will increase every year, not taking into account risk-sharing agreements and patient access schemes.

Conclusion

Pembrolizumab represents a new approach in the treatment of patients with head and neck squamous cell carcinoma. Pembrolizumab has shown clinically meaningful effect in patients with substantial prior therapy for head and neck squamous cell carcinoma, regardless of the HPV status. In addition, compared to standard therapy, pembrolizumab offers a clinically meaningful benefit to survival. The therapy is not cost-effective compared to the alternative cetuximab and the reimbursement of the health technology is expected to result in additional cost for the NHIF, without taking into account risk-sharing agreements and patient access schemes.