



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

INN Pembrolizumab

Therapeutic indication	Monotherapy for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and in who have undergone complete resection.
Start/end date of procedure	04.08.2022 – 22.12.2022
Final decision	Addition of a new therapeutic indication to Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act, and reimbursement by the NHIF beyond the value of the provided medical services.



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

Health problem

Melanoma is a form of skin cancer that affects melanocytes found in the epidermis. Melanocytes produce melanin, which gives skin its color and protects the deeper layers of the skin from the harmful effects of the sun. Melanocytes are present in the stratum basale of the epidermis. Malignant melanoma is a neoplasm of melanocytes. Melanoma develops when melanocytes undergo malignant transformation due to inherited or acquired mutations from exposure to ultraviolet rays. During this process, melanocytes begin to divide uncontrollably, become aggressive, and rapidly spread to different parts of the body. Metastasized melanomas, in turn, affect not only the skin but also spread through the blood or lymphatic system to other organs and bones.

There are three types of skin cancer: squamous cell carcinoma, basal cell carcinoma, and melanoma. Melanoma is the rarest form, accounting for only 1% of all skin cancer cases, but despite this, it is the most aggressive, fastest-progressing, and deadliest form of skin cancer.

Melanomas have two phases of growth: horizontal and vertical. During the horizontal growth phase, malignant cells grow along the epidermis. Over time, most melanomas progress to the vertical growth phase, where malignant cells invade the dermis and develop the ability to metastasize. Melanomas are usually red-brown to blue-black asymmetrical tumors. They may also have white areas and, rarely, a complete absence of melanin (amelanotic melanomas). Variations in size, elevation, depth (of invasion), color, and secondary changes, such as erosions or ulcerations, make the clinical picture extremely diverse and sometimes associated with diagnostic difficulties.

Despite the advances made in the treatment of advanced melanoma, there is still an unmet medical need in the treatment of earlier stages of the disease. The use of Keytruda (pembrolizumab) as monotherapy is indicated for adjuvant treatment of adults and adolescents over 12 years of age with stage IIB, IIC, or III melanoma, and in those who have undergone complete resection, is associated with longer recurrence-free survival, lower mortality rates, and a safe clinical profile.

Keytruda (pembrolizumab) is a humanized monoclonal antibody that binds to the programmed cell death receptor-1 (PD-1) and blocks its interaction with the PD-L1 and PD-L2 ligands. The PD-1 receptor is a negative regulator of T-cell activity involved in controlling the T-cell immune response. Pembrolizumab enhances T-cell responses, including antitumor responses, by blocking the binding of PD-1 to PD-L1 and PD-L2, which are expressed by antigen-presenting cells and may be expressed by tumor or other cells in the tumor microenvironment.



Epidemiological Data

As of 2020, according to GLOBOCAN data, melanoma is the 16th most common types of cancer in Bulgaria, with a total of 627 diagnosed cases (1.7% of all malignant diseases in the country). As a result of the disease, 213 deaths (1.1% of all deaths from malignant diseases) were reported for the year. The total number of diagnosed cases over a 5-year period is 1,954.

Efficacy data

Therapeutic efficacy and safety profile of pembrolizumab were analyzed in one clinical trial. The clinical trial **KEYNOTE-716** is a randomized, two-part, double-blind, placebo-controlled, multicenter phase III trial of anti-PD-1 therapy (pembrolizumab) versus placebo for patients with resected stage IIB/IIC melanoma. Participants were randomized to receive pembrolizumab or placebo. The trial consists of two parts:

- **Part 1:** Eligible patients were randomly assigned in a 1:1 ratio to receive adjuvant therapy with pembrolizumab for adults (aged ≥ 18 years) at a dose of 200 mg intravenously (IV) every 3 weeks or a pediatric dose (aged ≥ 12 to < 18 years) at a dose of 2 mg/kg IV up to a maximum of 200 mg every 3 weeks, or a placebo with saline intravenously every 3 weeks. The treatment lasts up to 17 cycles (each cycle = 21 days);
- **Part 2:** An open-label crossover/re-treatment phase of the trial, where eligible patients with disease recurrence can receive additional pembrolizumab treatment if they meet the eligibility criteria.

Participants will receive up to 17 cycles (up to ~ 1 year) of pembrolizumab for local/distant recurrence after disease resection or up to 35 cycles (up to ~ 2 years) of pembrolizumab for unresectable disease recurrence.

Participants with distant metastases who have undergone complete resection will receive 17 cycles (up to ~ 1 year) of pembrolizumab, but under certain circumstances may receive up to 35 cycles (up to ~ 2 years) of pembrolizumab. Recurrence-free survival (RFS) is the only efficacy endpoint considered in the analysis.

The trial results, with a median follow-up of 14.4 months, show that pembrolizumab significantly prolongs RFS compared to placebo. The 12-month RFS rate is 90.5% versus 83.1%.

Safety data

The most common adverse drug reactions are immune-mediated and occurred in 36.2% in the pembrolizumab arm and 8.4% in the placebo arm, most commonly hypothyroidism (15.7% vs. 3.5%) and hyperthyroidism (10.4% vs. 0.6%). Most of them are of 1-2 degrees of weight.



Data on comparators

Currently, an alternative to pembrolizumab is routine monitoring the patients.

Pharmacoeconomic indicators

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

A positive evaluation by NICE has been published for pembrolizumab in adults and adolescents over 12 years of age with stage IIB and IIC melanoma who have undergone complete resection.

Applied analysis

A cost-effectiveness analysis (CEA) was applied, where the final result in terms of health benefits is presented as life years gained (LYG), and it was further refined with a cost-utility analysis (CUA), where the final result in terms of health benefits is presented as quality-adjusted life years (QALY). Routine surveillance was chosen as the comparative alternative. The analysis perspective is that of the paying institution – the National Health Insurance Fund (NHIF). The selected time horizon in the model is lifetime. The analysis is based on a Markov model.

According to the conditionally accepted threshold for favorable cost-effectiveness, pembrolizumab therapy is determined to be a cost-effective therapeutic approach for the evaluated health outcomes (LYG and QALY).

Costs for the assessed health technology

The model includes only direct medical costs: costs for the evaluated health technology (pembrolizumab), application costs, outpatient follow-up/dispensary costs, subsequent treatment costs, and palliative care costs.

Subgroup analysis

No subgroup analyses were presented.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the paying public institution – the NHIF. The time horizon of the analysis is 5 years. The estimated number of adult patients with stage IIB and IIC melanoma suitable for treatment with Keytruda in the first year is 21, and in the fifth year – 44. For the pediatric population, the expected number of patients in the first year is one, and in the fifth year – two.

The budget impact analysis includes two scenarios – "World without the new health technology" and "World with the new health technology." The "World without the new health technology"



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scenario includes the current therapeutic practice – routine surveillance, while the "World with the new health technology" scenario reflects the market impact after the introduction of pembrolizumab.

The expected total annual budget impact of Keytruda for the treatment of patients with stage IIB and IIC melanoma who have undergone complete resection equals the additional costs for the NHIF in a "world with Keytruda" over a five-year period, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Malignant melanoma is the rarest and most aggressive form of skin cancer with increasing annual incidence of morbidity and mortality. It most often affects young and middle-aged women, but the risk of developing the disease is high in all age groups. In the cited data from the Keynote 716 clinical trial, the use of Keytruda in the earlier stages after a complete resection had been performed, is associated with a longer recurrence-free life expectancy, a lower mortality rate and a safe and modifiable toxicological profile.

Lack of therapeutic option in early IIB and stage IIC malignant melanoma, as well as positive clinical trial data confirm the role of Keytruda as a new standard of adjuvant therapy in II and III stage malignant melanoma after complete resection. In the budget impact analysis an increase in the costs of the NHIF is expected.