



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	Keytruda in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent or metastatic cervical carcinoma in adults whose tumors express PD-L1 with CPS $\geq$ 1.
Start-end of the procedure	16.09.2022 – 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.



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



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

Health problem

Cervical carcinoma is a gynecological malignancy that arises from the cells of the cervix and affects relatively younger women. The most common types of cervical cancer are squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. Cervical carcinoma is the eighth most common cancer worldwide and the leading cause of cancer-related death in many countries around the world.

Infection with the human papillomavirus (HPV) is the main risk factor for the occurrence of cervical carcinoma, and it is estimated that over 90% of all cases are caused by HPV. Approximately two-thirds of cervical cancer cases are due to infection caused by HPV types 16 and 18. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 are high-risk for cervical carcinoma.

Women with early-stage cervical carcinoma or precancerous lesions usually have no symptoms. Symptoms often occur after the tumor grows larger and grows into the surrounding tissue. Then the most common symptoms are: abnormal vaginal bleeding, for example, bleeding after vaginal sex, bleeding after the onset of menopause, bleeding and spotting between periods, or a longer or heavier period than usual. Bleeding after vaginal douching may also occur, unusual vaginal discharge — it may be bloody or occur between periods or after menopause, pain during intercourse, pain in the pelvic area. Signs and symptoms in more advanced disease: swelling of the legs, problems with urination or defecation, blood in the urine.

There is a high unmet need in the treatment of cervical carcinoma, as there are very few targeted therapies and most patients with cervical carcinoma receive only first-line treatment.

Keytruda (pembrolizumab) addresses this medical need. It is a humanized monoclonal antibody that binds to programmed cell death receptor-1 (PD-1) and blocks its interaction with PD-L1 and PD-L2 ligands. The PD-1 receptor is a negative regulator of T-cell activity involved in the control of the T-cell immune response. KEYTRUDA potentiates 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. The antiangiogenic effect of lenvatinib (an inhibitor of a number of tyrosine kinases) in combination with the immunostimulatory effect of pembrolizumab (anti-PD-1) results in a tumor microenvironment with higher T-cell activation to overcome primary and acquired resistance to immunotherapy and may improve tumor responses compared to either therapy given alone. In preclinical mouse models, PD-1 plus TKI inhibitors demonstrated enhanced antitumor activity compared to either agent alone.



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



Epidemiological data

In Bulgaria, 3.10 million women (≥ 15 years of age) are at risk of developing cervical cancer. The frequency of the disease in Bulgaria is above the average norm for Eastern Europe and the world. According to GLOBOCAN data (2020), cervical carcinoma is the 10th most common cancer in Bulgaria.

Efficacy data

The therapeutic efficacy and safety profile of pembrolizumab was analyzed in one clinical trial:

Clinical trial KEYNOTE-826 is a phase III, randomized, multicenter, double-blind, placebo-controlled trial evaluating the use of pembrolizumab in combination with platinum-based chemotherapy (with or without bevacizumab) compared with placebo in combination with platinum-based chemotherapy (with or without bevacizumab) for the treatment of 1L patients with persistent, recurrent or metastatic cervical cancer. After a screening period of 28 days, eligible patients were stratified by metastatic stage (FIGO 2009, stage IVB) at initial diagnosis (yes or no), investigator decision to use bevacizumab (yes or no), and PD-L1 status by CPS (CPS < 1 vs. CPS 1 to < 10 vs. CPS ≥ 10). Finally, they were randomized 1:1 to receive pembrolizumab in combination with paclitaxel/cisplatin or paclitaxel/carboplatin with or without bevacizumab or placebo in combination with paclitaxel/cisplatin or paclitaxel/carboplatin with or without bevacizumab. All treatments under investigation were to be administered on day 1 of each 3-week treatment cycle. Primary endpoints were progression-free survival (PFS) by (Response Evaluation Criteria in Solid Tumors) RECIST v1.1, assessed by the investigator and overall survival (OS). Secondary endpoints - investigator-assessed RECIST v1.1 overall response rate (ORR), investigator-assessed RECIST v1.1 duration of response (DOR), 12-month RECIST progression-free survival (PFS-12) v1.1 investigator-assessed RECIST 1.1 PFS assessed by blinded independent central review (BICR), safety and tolerability, health-related quality of life (HRQoL).

Trial results show that in patients with PD-L1 CPS ≥ 1 tumors, treatment with pembrolizumab + chemotherapy $\pm$ bevacizumab provided a statistically significant improvement in PFS, OS compared to treatment with placebo + chemotherapy $\pm$ bevacizumab. The proportion of patients with PD-L1 CPS ≥ 1 tumors who had an improved ORR was higher in the pembrolizumab + chemotherapy $\pm$ bevacizumab arm compared to the placebo + chemotherapy $\pm$ bevacizumab arm. In responders with PD-L1 CPS ≥ 1 tumors, treatment with pembrolizumab + chemotherapy $\pm$ bevacizumab provided a more durable response compared to treatment with placebo + chemotherapy $\pm$ bevacizumab. Similarly, in patients with PD-L1 CPS ≥ 10 .

Safety data

Pembrolizumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolve after initiation of appropriate treatment or



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



discontinuation of pembrolizumab. With pembrolizumab in combination with chemotherapy, the most common side effects were anemia (55%), nausea (54%), fatigue (38%), neutropenia (36%), constipation (35%), alopecia (35%), diarrhea (34%), vomiting (28%) and decreased appetite (27%).

Data on comparators

The selection of comparative alternatives to Keytruda is based on data from real clinical practice. The regimens projected to change in market share are cisplatin + paclitaxel + bevacizumab and carboplatin + paclitaxel + bevacizumab. Due to the absence of a recommendation for platinum combination with paclitaxel without bevacizumab, combination chemotherapy without bevacizumab was not considered as an alternative.

Pharmacoeconomic indicators

Applied analysis

Cost-effectiveness pharmacoeconomic analysis (CEA) was applied, in which the final result in terms of health benefits is presented in the form of life years gained (LYG) and cost-utility analysis (CUA), in which the final outcome in terms of health benefits is expressed as a quality-adjusted life years (QALY) gained. As comparative alternatives, paclitaxel + cisplatin (Pac + Cis), paclitaxel + carboplatin (Pac + Carbo), paclitaxel + cisplatin + bevacizumab (Pac + Cis + Bev), paclitaxel + carboplatin + bevacizumab (Pac + Carbo + Bev) were selected. Combinations of Pac + Cis and Pac + Carbo, and Pac + Cis + Bev and Pac + Carbo + Bev, were defined as clinically equivalent. The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF). The time horizon is assumed to be for life (50 years). Health benefits and costs are discounted with an annual discount factor of 3.5%. A semi-Markov model was used in the analysis - three health states were included: "no progression", "progression" and an absorbing health state - "death".

The conducted analysis shows that the applicant health technology is not cost-effective from the point of view of the paying institution, as ICER/LYG and ICER/QALY are above the established profitability threshold of 3xGDP/capita. Although the new technology is associated with higher costs, it is also associated with significantly higher health benefits for patients, measured in life-years gained and quality-of-life data, which meets the requirements for costly therapies in the context of unmet medical needs.

Costs for the assessed health technology

Only direct medical costs are included in the model - treatment costs with Keytruda / pembrolizumab, treatment costs with comparator alternatives, treatment costs with different therapeutic combinations, treatment costs with different therapeutic combinations - alternatives, costs of follow-up treatment for a duration of 20 weeks, administration costs of the therapeutic



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



combinations with pembrolizumab and/or bevacizumab, administration costs of chemotherapy combination regimens, administration costs of regimens containing carboplatin or cisplatin - follow-up treatment and adverse event control costs.

Subgroup analysis

Not attached.

Budget impact analysis

The analysis of the budget impact was carried out from the point of view of the paying public institution - NHIF. The time horizon of the budget impact analysis is 5 years. The expected number of patients treated with Keytruda + platinum + paclitaxel ± bevacizumab in the first year is 22, and in the fifth year - 57. The analysis considers two hypotheses - "A world with the new health technology Keytruda" for the treatment of adult patients with persistent, recurrent or metastatic cervical carcinoma, whose tumors express PD-L1 with $CPS \geq 1$ and "World without the new health technology" - when Keytruda is not included in the PDL with the corresponding therapeutic indication and will not be reimbursed by the public fund.

If the health technology Keytruda / pembrolizumab is reimbursed, the budgetary impact forecasts an increase in NHIF costs over a period of five years, not taking into account risk-sharing agreements and patient access schemes.

Conclusion

Cervical cancer is a rare gynecological malignancy that arises from the cells of the cervix and affects relatively younger women compared to other common cancers. Cervical cancer is the eighth most common cancer worldwide and the leading cause of cancer death in many countries around the world. There is a need for better cervical cancer treatment targeting disease burden. Effective chemotherapy or chemoradiotherapy regimens in cervical cancer are associated with cumulative or irreversible toxicity, which limits the application of subsequent therapies and proves to impact the quality of life of patients. Pembrolizumab in combination with chemotherapy with or without bevacizumab is characterized by durable efficacy and a favorable safety profile when administered to treat patients with recurrent or metastatic cervical cancer.

The addition of Keytruda to the PDL with the new therapeutic indication (treatment of persistent, recurrent or metastatic cervical carcinoma in adults whose tumors express PD-L1 with $CPS \geq 1$ with pembrolizumab in combination with chemotherapy with or without bevacizumab) will inevitably increase the budgetary costs of the NHIF. From a pharmacoeconomic point of view, the treatment with Keytruda is located above the conditionally accepted favorable threshold of 3 times GDP per capita, which in Bulgaria is adopted as a criterion for cost-effectiveness/usefulness of health technology. The target population has a limited number of therapeutic choices to increase survival and quality of life, suggesting additional benefit from the reimbursement of the health technology.