



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 as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment after surgery is indicated for the treatment of adults with locally advanced or early-stage triple-negative breast cancer at high risk of recurrence.
Start-end of the procedure	24.06.2022 – 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

Breast cancer is the most commonly diagnosed cancer and causes the most deaths among women from malignancies worldwide. Triple-negative breast cancer (TNBC) is characterized by a lack of expression of the estrogen and progesterone hormone receptors, as well as a lack of overexpression or amplification of the human epidermal growth factor receptor 2 (HER2 protein/NEU gene). Triple-negative breast cancer accounts for 10-15% of the newly diagnosed cases of breast cancer. TNBC is a heterogeneous and aggressive disease with a poor prognosis. It is characterized by rapid progression and lower overall survival (OS) of patients compared to other subtypes of breast cancer. Median time to death is shorter in TNBC (4.2 years vs. 6.0 years). Patients have a higher risk of local or distant recurrence.

Breast cancer, especially in the early stages, is often asymptomatic and is usually diagnosed after an abnormal mammogram or physical examination. However, when symptomatic, signs and symptoms may include, but are not limited to: a lump in the breast, a lump or lump in the armpit, a change in the shape, size, or texture of the breast, and a change in the nipple (e.g., retraction or discharge of secretion). Breast cancer patients have a poorer health-related quality of life, and are more likely to experience fatigue, sexual dysfunction, infertility, stress and mental disorders than the general population.

Most of the neoadjuvant and adjuvant therapy options recommended for TNBC patients lead to initial improvement and delay in TNBC progression. However, despite initial positive results, increased toxicity, lack of improved OS, and deteriorated quality of life were observed. Therapy is needed to provide a balance between the treatment benefits and the side effects that accompany it.

Pembrolizumab is a humanized monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2 ligands. Pembrolizumab 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. In addition, data from clinical trials show that pembrolizumab is a well-tolerated therapy with a good safety profile. Pembrolizumab is indicated in combination with chemotherapy as neoadjuvant treatment and then continued as monotherapy for adjuvant treatment after surgery in patients with locally advanced or early stage triple-negative breast cancer at high risk of recurrence.

Efficacy data

The therapeutic efficacy and safety profile of pembrolizumab was analyzed in two clinical trials.



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Clinical trial KEYNOTE-522 is a phase III randomized controlled trial of pembrolizumab plus chemotherapy as neoadjuvant treatment followed by pembrolizumab monotherapy as adjuvant treatment in patients with locally advanced TNBC. The trial enrolled 1,174 patients with previously untreated stage II or III TNBC and were randomized 2:1 to neoadjuvant therapy with four cycles of pembrolizumab 200 mg Q3W plus chemotherapy (paclitaxel and carboplatin) or placebo Q3W plus chemotherapy (paclitaxel and carboplatin). Both groups then received an additional four cycles of pembrolizumab or placebo. Both groups received doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide. Primary endpoints were pathologic complete response (pCR) rate using the ypT0/Tis ypN0 definition and event-free survival (EFS). Secondary endpoints were pCR rate using alternative definitions, EFS in PD-L1-positive patients, and overall survival (OS).

Clinical trial KEYNOTE-243 (I SPY 2) is a phase II, multicenter, adaptively randomized, open-label neoadjuvant trial with multiple concurrent experimental arms. This trial is expected to end in December 2030. Approximately 4,000 participants are enrolled in the trial. Patients with invasive breast cancer (≥ 2.5 cm upon examination) were assigned paclitaxel 80 mg/m² once weekly for 12 weeks (control) with or without experimental agent (pembrolizumab 200 mg every 3 weeks for 4 doses), followed by AC for 4 doses. Adaptive randomization was based on the Bayesian probability of each arm being superior to the control group. The primary endpoint was pCR, defined as no residual invasive cancer in the breast or lymph nodes (ypT0/e ypN0). Secondary endpoints – research biomarkers, EFS, OS, safety and MRI volume.

Results from **KEYNOTE-522** reported that pembrolizumab plus chemotherapy/pembrolizumab showed a higher pCR rate compared to placebo plus chemotherapy/placebo at interim analysis 4 (IA4) in all randomized patients. Statistically significant and clinically meaningful improvement in EFS compared to placebo plus chemotherapy/placebo is revealed - the 24-month and 36-month EFS rates in the pembrolizumab plus chemotherapy/pembrolizumab group were 87.8% and 84.5%, respectively, compared to 81.0%. Improvements in OS favoring pembrolizumab plus chemotherapy/pembrolizumab compared with placebo plus chemotherapy/placebo were also reported.

Results from **KEYNOTE-243** reported that Pembrolizumab achieved the prespecified completion threshold ($\geq 85\%$ predicted probability of success in a phase III trial) for all three types studied (all HER2-, HR+/HER2-, TNBC). The calculated pCR rates for ERBB2-negative, HR-positive/ERBB2-negative, and TNBC in the pembrolizumab arm were 44%, 30%, and 60%, respectively, compared with 17%, 13%, and 22% in the control populations.

Safety data

Immune-related side effects are most often manifested - endocrinopathies, with thyroid gland dysfunction being the most common (hypothyroidism and hyperthyroidism). Most of these, including severe reactions, resolve after initiation of appropriate treatment or discontinuation of pembrolizumab. The most commonly reported adverse events (incidence $\geq 30\%$) in the pembrolizumab plus chemotherapy arm during the combined neoadjuvant and adjuvant phases



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were nausea, alopecia, anemia, neutropenia, fatigue, constipation, diarrhea, vomiting, and ALT elevation.

Data on comparators

The selected comparative alternatives in the neoadjuvant phase are paclitaxel + carboplatin and cyclophosphamide + epirubicin/doxorubicin, in accordance with the Pharmacotherapeutic Guideline for Medical Oncology and the medicinal products available in Bulgaria and included in the Positive Drug List (PDL) and reimbursed by the National Health Insurance Fund (NHIF).

Based on the data on applied chemotherapeutic regimens, the selected alternatives in the adjuvant line are paclitaxel, carboplatin, cyclophosphamide, doxorubicin and epirubicin.

Pharmacoeconomic indicators

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

TLV (Sweden) issued a positive reimbursement opinion for pembrolizumab in combination with chemotherapy as neoadjuvant treatment and then continued monotherapy for the treatment of adult patients with locally advanced or early stage triple-negative breast cancer at high risk of recurrence.

Applied analysis

The cost-effectiveness pharmacoeconomic analysis (CEA) was applied, in which the final result in terms of health benefits was presented in the form of a life years gained (LYG) and was upgraded with the cost-utility analysis (CUA) where the final outcome in terms of health benefits is presented in the form of quality-adjusted life years (QALY) gained. The model compared the assessed health technology pembrolizumab to the following chemotherapy regimen: 4 cycles of paclitaxel (80mg/m² once weekly) + carboplatin (AUC 5 once every 3 weeks or AUC 1.5 once weekly for the first 12 weeks) followed by 4 cycles of doxorubicin (60mg/m²) or epirubicin (90mg/m²) + cyclophosphamide (600mg/m² once every 3 weeks for the following 12 weeks). The perspective of the analysis is that of the paying institution - the National Health Insurance Fund (NHIF). A 51-year time horizon is used, which is suitable for the purposes of the model and justified considering the expected life expectancy. Health benefits and costs are discounted with an annual discount factor of 3.5%. A standard cohort Markov model with 4 health states was developed.

The results of the analysis show that the ICER values per QALY unit of the assessed health technology exceed the cost-effectiveness threshold of 3 times GDP per capita, but the ICER per LYG unit is located below the cost-effectiveness threshold. On the other hand, the technology demonstrates significant patient benefits with more QALYs and LYGs gained.



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Costs for the assessed health technology

Only direct medical costs were included in the model – treatment costs with pembrolizumab in combination with chemotherapy during the neoadjuvant phase, treatment costs with pembrolizumab in the adjuvant phase, treatment costs with chemotherapy in the neoadjuvant phase, follow-up treatment costs after progression, cost for application of the assessed technology and comparative therapies, costs of outpatient procedure, costs of surgical intervention and costs of ADR control.

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 analysis is 5 years. The expected number of patients treated with Keytruda for the two treatment arms (neoadjuvant and adjuvant therapy) in the first year is 112 and in the fifth year – 108. Two scenarios are presented: a world with Keytruda and a world without Keytruda. The model is structured in two variants - variant 1 at dose intensity =100% and variant 2 at dose intensity <100%.

Both budget impact options show that reimbursing the assessed indication of Keytruda leads to increased costs to the NHIF over a five-year period, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Breast cancer is the most commonly diagnosed cancer and causes the most deaths from malignancies among women worldwide. Pembrolizumab is the first and only anti-PD-1/PD-L1 therapy for early TNBC. Pembrolizumab plus chemotherapy/pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in EFS compared with placebo plus chemotherapy/placebo, as well as a significant improvement in pCR compared with placebo plus chemotherapy. An improvement was also seen in the overall survival (OS) compared with placebo plus chemotherapy. Reimbursing Keytruda for TNBC offers patients an additional alternative and is expected to increase NHIF expenditure for all budget impact scenarios.