



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(s)	In combination with chemotherapy for the treatment of locally recurrent unresectable or metastatic triple-negative breast carcinoma in adults, whose tumors express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease.
Start/end date of procedure	12.08.2022 – 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

Breast cancer is the most common oncological disease among women and the second leading cause of cancer-related death among women worldwide. Triple-negative breast cancer (TNBC) is a basal-like breast cancer characterized by the lack of expression of HER2, PR, and ER. TNBC accounts for 15% of all breast cancer types and is typically diagnosed in women under 50 years of age. TNBC is an aggressive cancer, with a high tendency to metastasize and a higher risk of recurrence compared to other breast cancer subtypes.

In the early stages, TNBC is often asymptomatic and is usually diagnosed after an abnormal mammogram or through a physical exam. However, in more advanced stages (stage III-IV) of the disease, the signs and symptoms include a lump in the breast, a lump or swelling in the armpit, a change in the shape, size, or structure of the breast, and changes in the nipple (e.g., retraction or discharge).

Treatment of TNBC can be categorized into therapy for early-stage and advanced/metastatic stages of the disease. Before the introduction of targeted therapies, chemotherapy was the only standard therapeutic option for treating metastatic TNBC. Pembrolizumab meets the unmet medical need and is approved for use in combination with one of three chemotherapy regimens (nab-paclitaxel, paclitaxel, or gemcitabine + carboplatin) in patients with previously untreated, unresectable locally advanced, or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10).

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 the control of T-cell immune responses. 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

According to GLOBOCAN data for 2020, breast cancer is the third most common and deadliest oncological disease in Bulgaria. The number of newly diagnosed cases of the disease in 2020 was 4,061, representing 11.1% of all cancer cases in the country. The number of deaths for the same year was 1,533 people (7.9% of the total number of all cancer-related deaths in Bulgaria).



Efficacy data

Therapeutic efficacy and safety profile of pembrolizumab in combination with chemotherapy was analyzed in one clinical trial.

The **KEYNOTE-355** clinical trial is a randomized, controlled phase III trial of pembrolizumab plus chemotherapy in patients with previously untreated locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC). The trial included 847 patients. Patients received pembrolizumab (or placebo [normal saline]) 200 mg IV infusion on day 1 of every 3-week cycle, plus paclitaxel 90 mg/m² or nab-paclitaxel 100 mg/m² on days 1, 8, and 15 of every 28-day cycle, or gemcitabine/carboplatin 1000 mg/m² on days 1 and 8 of every 3-week cycle.

The trial was conducted in two parts:

- Part 1 was an open-label phase to assess any unacceptable toxicity in 35 patients. Patients were assigned to each treatment group (pembrolizumab plus paclitaxel, pembrolizumab plus nab-paclitaxel, or pembrolizumab plus gemcitabine/carboplatin) by randomizing at least 10 patients per group.
- Part 2 was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of pembrolizumab on the background of chemotherapy in 847 patients. Each patient was randomized to receive pembrolizumab plus chemotherapy or placebo plus chemotherapy in a 2:1 ratio.

Primary endpoints were progression-free survival (PFS) and overall survival (OS) for all patients and those with PD-L1-positive tumors.

Secondary endpoints included overall response rate (ORR), duration of response (DOR), and disease control rate (DCR) for all patients and those with PD-L1-positive tumors.

Trial results showed:

- For PD-L1 CPS ≥ 10 tumors, pembrolizumab plus chemotherapy versus placebo plus chemotherapy:
 - Median OS: 23.0 months vs. 16.1 months (HR for OS of 0.73 represents a 27% reduction in the risk of death for the pembrolizumab plus chemotherapy group compared to the placebo plus chemotherapy group).
 - Median PFS: 9.7 months vs. 5.6 months (HR for PFS represents a 34% reduction in the risk of disease progression or death for the pembrolizumab plus chemotherapy group compared to the placebo plus chemotherapy group).
 - Improved ORR compared to placebo + chemotherapy with a clinically significant difference in ORR of 12.1%, median DOR: 12.1 months vs. 7.3 months.



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- For PD-L1 CPS ≥ 1 tumors, pembrolizumab plus chemotherapy versus placebo plus chemotherapy:
 - Median OS: 17.6 months vs. 16.0 months (HR for OS favored pembrolizumab plus chemotherapy, but the p-value did not cross the predefined boundary for efficacy, so the criterion for success for the primary OS hypothesis was not met).
 - Median PFS: 7.6 months vs. 5.6 months (HR for PFS represents a 25% reduction in the risk of disease progression or death for the pembrolizumab plus chemotherapy group compared to the placebo plus chemotherapy group).
 - Improved ORR compared to placebo + chemotherapy with a difference in ORR of 6.1%, median DOR: 10.1 months vs. 6.8 months.

Safety data

The most common adverse reactions 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 choice of comparative alternatives is tailored to the main clinical trial KEYNOTE-355 comparing therapy with pembrolizumab + chemotherapy versus chemotherapy alone (including gemcitabine + carboplatin therapies, paclitaxel and nab-paclitaxel at the choice of the treating person), as well as with the guidelines for the treatment of triple-negative carcinoma, published in the Pharmacotherapeutic Guideline (PTG) on medical oncology.

Pharmacoeconomic indicators

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

Three opinions from other national institutions have been published: NICE (UK), HAS (France), and IQWiG (Germany).

1. **NICE (UK):** Recommends pembrolizumab plus chemotherapy as a treatment option for locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) in adults who have not received prior chemotherapy for metastatic disease. It is recommended only if tumors express PD-L1 with a combined positive score (CPS) ≥ 10 and immune cell staining (IC) $< 1\%$, and if the company provides pembrolizumab under a commercial agreement.



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2. **HAS (France):** Recommends including KEYTRUDA (pembrolizumab) in the list of drugs approved for hospital use for the following indication: in combination with chemotherapy for the treatment of locally recurrent unresectable or metastatic TNBC in adults whose tumors express PD-L1 with CPS ≥ 10 and who have not received prior chemotherapy for a metastatic disease.
3. **IQWiG (Germany):** Considers that there is evidence of a non-quantifiable added benefit in treatment with pembrolizumab plus chemotherapy.

Applied analysis

A cost-effectiveness analysis (CEA) was conducted, presenting health benefits in terms of life years gained (LYG) and cost-utility analysis (CUA) presenting health benefits as quality-adjusted life years (QALY). The comparative alternatives selected were:

- Pembrolizumab + chemotherapy (weighted average distribution of regimens) vs. chemotherapy (weighted average distribution of regimens).
- Pembrolizumab + taxanes vs. taxanes.
- Pembrolizumab + gemcitabine + carboplatin vs. gemcitabine + carboplatin.
- Pembrolizumab + nab-paclitaxel vs. nab-paclitaxel.
- Pembrolizumab + paclitaxel vs. paclitaxel.

The primary analysis compares pembrolizumab + chemotherapy (combination of regimens) to chemotherapy (combination of regimens) alone. The perspective of the analysis is that of the payer, the National Health Insurance Fund (NHIF). The model's time horizon is 20 years, with health benefits and costs discounted at an annual rate of 3.5%. A partitioned survival model (PSM) was used, consisting of three mutually exclusive health states: progression-free (PF), progressive disease (PD), and death.

Main analysis results: The therapy with pembrolizumab + chemotherapy showed higher treatment costs compared to chemotherapy alone, but also higher health benefits in terms of more life years and more quality-adjusted life years. The cost-utility analysis places the ICER (incremental cost-effectiveness ratio) of pembrolizumab + chemotherapy above the threshold for favorable cost-effectiveness compared to chemotherapy alone. The additional analysis showed higher treatment costs for pembrolizumab + chemotherapy compared to carboplatin and docetaxel, with correspondingly higher health benefits.

Costs for the assessed health technology

The model included only direct medical costs: costs for treatment with pembrolizumab + chemotherapy, costs for treatment with alternatives, costs for subsequent treatment, application costs, outpatient monitoring/dispensary costs, palliative care costs, and costs for managing adverse events.

Subgroup analysis

A subgroup analysis was conducted comparing:



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- Pembrolizumab + taxanes vs. taxanes.
- Pembrolizumab + gemcitabine + carboplatin vs. gemcitabine + carboplatin.
- Pembrolizumab + nab-paclitaxel vs. nab-paclitaxel.
- Pembrolizumab + paclitaxel vs. paclitaxel.

The subgroup analysis results corresponded with the main analysis, with ICER values above the threshold for favorable cost-effectiveness.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the payer, NHIF, over a 5-year time horizon. The expected number of adult patients with locally recurrent unresectable or metastatic TNBC treated with Keytruda + chemotherapy is forecasted to increase from one in the first year to 13 in the fifth year. Costs are calculated in two scenarios:

- **Scenario 1:** A world where Keytruda (INN pembrolizumab) is introduced and reimbursed by NHIF.
- **Scenario 2:** A world where Keytruda is not introduced and reimbursed by NHIF.

The budget impact analysis for both scenarios predicts an increase in NHIF expenditures over five years, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Triple negative breast cancer is an extremely aggressive disease with few therapeutic options. The application of immunotherapy in combination with chemotherapy definitely gives better chances of a longer life in the patients. Pembrolizumab is approved for use in combination with any of the three chemotherapy regimens (nab-paclitaxel, paclitaxel or gemcitabine + carboplatin) at patients with previously untreated unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10). Although the combined treatment regimen pembrolizumab + chemotherapy versus chemotherapy alone of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumors express PD-L1 with CPS ≥ 10 results in added costs of first-line treatment, it also results in improved patient survival, accompanied by approximately twice as long time spent in a progression-free state and improved quality of life.