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

HEALTH TECHNOLOGY ASSESSMENT

Keytruda
50 mg powder for concentrate for solution for infusion x 1
25 mg/ml – 4 ml concentrate for solution for infusion x 1
pembrolizumab

Therapeutic indication(s)	As monotherapy, indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
Start/end date of procedure	02.07.2019 – 16.12.2019
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 value of the rendered medical services, with 100% level of payment.

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

Health problem

Melanoma is an aggressive malignant disease with high growth potential and a tendency to metastasize. Considered as the main risk factors for its development are heredity, prolonged exposure to sunlight, exposure to artificial ultraviolet light, fair skin. Cutaneous melanoma accounts for less than 5% of all skin cancers, but causes 90% of all skin cancer-related deaths. Over 95% of melanoma develops in the skin, but can also affect the eyes (uveal melanoma), the lining of the sinuses, the nasal cavity, the oral cavity (mucosal melanoma).

Individuals with stage III melanoma, who have undergone complete resection are still at high risk of disease recurrence, while the 5-year survival without recurrence is 28 to 44%. About 50% to 55% is the estimated five-year survival at stage III of the disease. This puts this particular patient population at risk. During the last year it has been shown that the adjuvant administration of pembrolizumab in patients at this stage, who have undergone radical resection and lymph node dissection, significantly reduces the risk of recurrence or distant spread of the disease.

Epidemiological data

In 5% - 9% of melanoma cases, patients are diagnosed with regional disease, while 4% -5% of newly diagnosed patients have 13 distant metastases. In patients with melanoma without stage III metastases, who have undergone surgical resection, the rate of appearance is reported to be 51.0% and the recurrence rate is 90%.

According to the Bulgarian National Cancer Registry, the standardized incidence of cutaneous melanoma in Bulgaria is lower than the European average (11.5/100 000 men and 11.3/100 000 women).

The main treatment of operable melanoma is surgical removal with extensive excision. Since the mid 1990s, the standard in the treatment of melanoma has been the collection of biopsy material from sentinel lymph nodes to determine stage and prognosis. In patients with lymph node metastases, complete removal is recommended. Adjuvant systemic therapy is indicated in patients at high risk of recurrence (stage IIB or more advanced), based on primary tumor density, ulceration, frequency of mitosis, and degree of lymph node involvement.

Efficacy data

Data have been presented from the main clinical trial KEYNOTE-054, assessing the efficacy of adjuvant therapy with pembrolizumab in stage III melanoma, and a meta-analysis with RFS

(recurrence free survival) values, presented as network diagram, from therapies versus observation.

The primary endpoint of the drug registration study is recurrence-free survival (RFS) in the general intention-to-treat population (ITT) and in the subgroup of patients who were positive for tumor PD-L1 expression. Secondary endpoints are: distant metastasis-free survival (DMFFS), overall survival (OS), safety assessment, and assessment of the health-related quality of life (HRQoL).

As at the date of completion of the interim analysis data collection, the median of RFS follow-up was 15.1 months and the number of RFS events was 351 (34.4%). Recurrence-free survival was significantly longer in the pembrolizumab group compared to the placebo group (relapse or death risk ratio 0.57; 98.4% CI, 0.43 to 0.74; Figure 1).

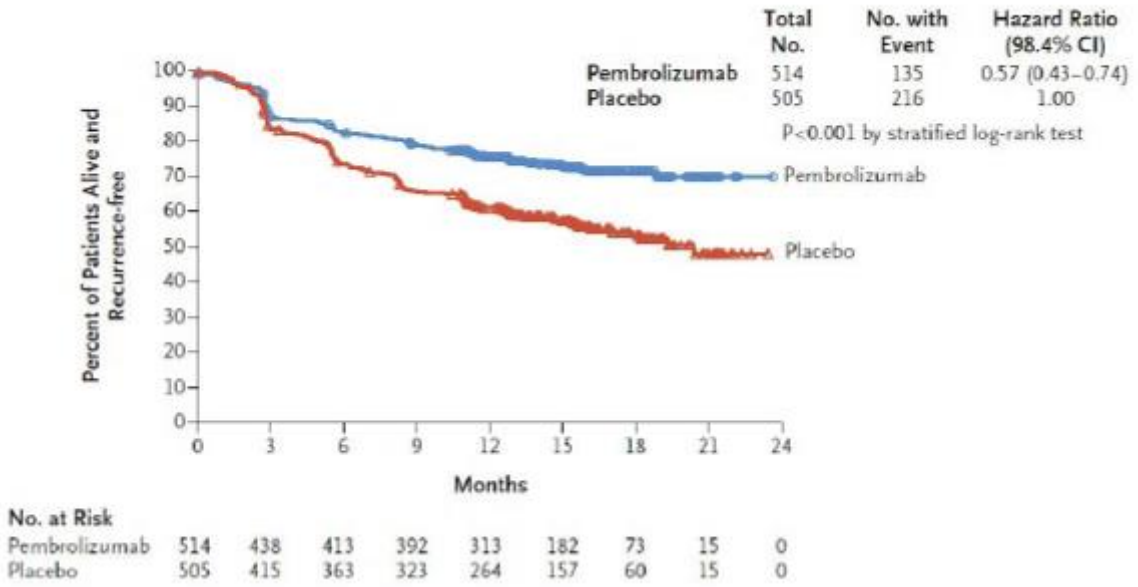

Figure 1. Recurrence-free survival in the general population (ITT)

RFS according to tumor PD-L1 expression

In the subgroup of 853 patients, positive for tumor PD-L1 expression (melanoma score ≥ 2), the 12-month recurrence-free survival rate was 77.1% (95% CI, 72.7 to 80.9) in the pembrolizumab group and 62.6% (95% Cl, 57.7 to 67.0) in the placebo group. Recurrence-free survival was significantly longer in the pembrolizumab group compared to the placebo group (relapse or death risk ratio 0.54; 95% CI, 0.42 to 0.69; $p < 0.001$).

The beneficial effect of pembrolizumab treatment is similar in patients with stage IIIA, IIIB or IIIC disease; the 12-month recurrence-free survival rate for patients with stage IIIB or IIIC treated with pembrolizumab was 72.2% (95% CI, 67.7 to 76.2). In addition, after a repeated analysis, this time against *AJCC criteria, 8th edition*, recurrence-free survival improved in all substages.

Also, the benefits of pembrolizumab treatment are similar in patients whose lymph nodes have micro- or macro-metastases; the benefit of pembrolizumab treatment is greater in patients with ulcerated melanoma, although without a statistically significant difference compared to those with non-ulcerated melanoma. BRAF status, gender, and baseline body mass index did not significantly affect the difference in RFS between pembrolizumab and placebo groups.

Analysis of data reported by patients

The chief goal of quality of life assessment (HRQoL) is to determine the effect of adjuvant immunotherapy compared to placebo. The results confirmed that pembrolizumab preserved HRQOL compared with placebo, when administered as adjuvant therapy to patients with resection of high-risk stage III melanoma.

Safety data

The most common adverse reactions (ADR) to pembrolizumab are pneumonitis, anemia, thrombocytopenia, hypothyroidism, decreased appetite, insomnia, headache, dyspnoea, cough, colitis, abdominal pain, nephritis, rash, pruritus, musculoskeletal pain. In the KEYNOTE 054 clinical trial, the most frequently reported ADR in decreasing frequency (frequency ≥ 15%) are as follows:

- For the pembrolizumab group: fatigue, diarrhea, pruritus, headache, nausea and arthralgia
- For the placebo group: fatigue, diarrhea, headache, weight gain and hypertension

ADR were comparable between the two groups except for the higher rate of hypothyroidism, hyperthyroidism and pruritus in the pembrolizumab group. In both treatment groups, most ADR were grade 1 or 2 in severity.

The most frequently reported serious ADR in both groups was basal cell carcinoma (3.3% in the pembrolizumab arm and 5.0% in the placebo group).

Patients in the pembrolizumab group experienced more ADR of special interest than patients in the placebo group (34.0% vs. 7.6%, respectively). Most of the ADR of special interest are grade 1 or 2 in severity and can be managed by interruption of treatment, discontinuation of

treatment and/or corticosteroid therapy. The most frequently reported ADR of special interest in the pembrolizumab group were hypothyroidism, hyperthyroidism, pneumonitis, colitis, and thyroiditis.

Data on comparators

In line with the most recently published guidelines for the treatment of melanoma, the present assessment considers routine monitoring of patients as a comparative alternative to Keytruda (pembrolizumab) for the specified indication.

Advantages of the new health technology are mainly directed at patients with engaged lymph nodes, as they are at the highest risk of recurrence and metastasis and the lowest survival rate of all patients with resectable melanoma. Standard adjuvant interferon therapy (IFN) has led to little improvement in relapse-free survival and overall survival, while being associated with fatigue and a risk of life-threatening neuropsychiatric disorders. Newer adjuvant therapies, such as ipilimumab and dabrafenib + trametinib also pose safety concerns (severe and prolonged ADR such as colitis and endocrinopathy with ipilimumab, pyrexia, fatigue and nausea with dabrafenib + trametinib combination therapy).

In the EU, the standard treatment for stage III melanoma is observation or IFN in patients who can tolerate IFN treatment.

Pharmacoeconomic indicators

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

A health technology assessment was performed by NICE, the UK. NICE recommends pembrolizumab as a possible adjuvant therapy in adults with stage III melanoma and lymph node involvement, in whom complete resection has been performed; it is included in the treatment algorithm.

Applied analysis

A pharmacoeconomic cost-benefit analysis with a QALY outcome measure, calculated on a utility basis, and LYG was applied. The perspective of the analysis is of the National Health Insurance Fund (NHIF), the lifelong time horizon is consistent with the development of the disease, costs and outcome level of discounting is 3.5%. Routine monitoring (placebo) was selected as a comparative alternative. To model the development of the disease, a Markov model was applied with a transition between 4 health conditions: no recurrence (RF), locoregional recurrence (LR), distant metastases (DM) and death. The cycle duration is

1 week. Probabilistic and deterministic sensitivity analyses were applied to assess uncertainty. Administration of pembrolizumab as adjuvant therapy resulted in 8.28 years (LYs) spent in a relapse-free state compared to 4.04 LYs in routine follow-up. Pembrolizumab is expected to lead to a significant improvement in the quality of life and survival of patients with stage III melanoma compared to routine monitoring - 8.00 QALYs versus 5.05 QALYs; 9.98 LYs versus 6.46 LYs. The ICER of the compared approaches in the target group of patients (adjuvant therapy with pembrolizumab versus routine monitoring) is below the break-even point. Pembrolizumab, administered as adjuvant therapy is a cost-effective approach, compared to routine monitoring of patients with stage III melanoma after complete resection of the affected lymph nodes. A one-way sensitivity analysis revealed that pembrolizumab remained a cost-effective alternative.
A subgroup analysis is not applicable.

Costs for the assessed health technology
The following types of costs have been calculated:

1. For adjuvant therapy with pembrolizumab
2. For subsequent treatment in case of recurrent and metastatic disease
3. For administration of medicines
4. For monitoring and follow-up, for medical services (MRI, hospitalization, PKK, palliative care, CT, etc.), with the frequency of use of these services presented, depending on the patient's condition: no relapse, with locoregional recurrence, with distant metastases.

Budget impact analysis
The analysis of the budget impact was conducted from the NHIF, the paying public institution’s perspective. The time horizon is 5 years. The estimated number of patients, diagnosed with stage III melanoma (ICD C43) and lymph node involvement, who have undergone complete resection and falling within the scope of treatment with Keytruda, for the next 5 years is 13 patients in the first year through 27 in the fifth year.

Sensitivity analysis was performed to test uncertain parameters. The inclusion in the Positive Drug List (PDL) of the following indication of the medicinal product Keytruda: monotherapy for adjuvant treatment of adults with stage III melanoma and lymph node involvement in whom a complete resection was performed, will lead to an increase in NHIF costs every following year, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The administration of Keytruda at a dose of 200 mg every three weeks as adjuvant monotherapy in patients with complete stage III resection of melanoma is based on its clinical efficacy and safety. The results of the main clinical study (KEYNOTE 054) show a statistically and clinically significant improvement in relapse-free survival, irrespective of disease substage, PD-L1 tumor expression status, and BRAF mutation status. The results reported by the patients confirmed that pembrolizumab preserved the health-related quality of life, compared to placebo. The safety profile of pembrolizumab adjuvant monotherapy is consistent with the established safety profile of pembrolizumab.

Keytruda is a cost-effective therapy compared to routine monitoring, with ICERs below the break-even point. The use of the medicinal product Keytruda is expected to generate costs for the paying institution, increasing every following year within the 5-year time horizon of the budget impact analysis, given the expected increase in the number of patients.