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**

Pembrolizumab

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| **Therapeutic indication(s)** | Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. |
| **Start/end date of procedure** | 24.04.2020 – 11.11.2020 |
| **Final decision** | Rejects inclusion of a new 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 cost of rendered medical services. |

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

## Health problem

Urothelial carcinoma (UC) is a malignant disease originating from the transitional cell epithelium of the superficial layer of the organs of the urinary system - renal pelvis, ureters, bladder and urethra. Approximately 90% of urothelial carcinomas are bladder carcinomas, most frequently affecting men between the ages of 60 and 80.

Bladder cancer (BC) is the most common malignancy of the urinary system. The types of bladder cancer are transitional cell carcinoma, squamous cell carcinoma (SCC), adenocarcinoma (AC) and sarcoma.

About 5% of all newly diagnosed patients with bladder cancer are in the metastatic stage, about half have relapsed after a definitive cystectomy. Local recurrences are about 10 to 30%, while distant metastasis is significantly more common, with the affected organs usually being the lungs, bones, liver, and abdominal lymph nodes.

Risk factors for bladder UC are variable (external exposures) and/or invariable (genetic predispositions). The main variable risk factor is smoking. Leading invariable risk factors are age and gender - older people and males have a higher risk of developing UC.

Clinically, malignant neoplasms of the bladder are generally characterized by the appearance of hematuria, which is found in 80%-90% of patients. Other possible symptoms include frequent urination or ineffective urge to urinate. Dysuria occurs in 20%-30% of patients with bladder cancer.

Epidemiological data

Urothelial carcinoma of the bladder ranks seventh as a cancer in men and 17th in women worldwide. Approximately 11% of patients with bladder cancer are diagnosed with advanced disease (stages III or IV).

*Epidemiological data for Bulgaria*

Based on data of GLOBOCAN 2018, the approximate age-standardized incidence of UC in Bulgaria in 2018 is 12.1 per 100,000 population, for both sexes, all age groups. An approximate 5-year number of cases of UC in Bulgaria in 2018 is 35.3 per 100,000, for both sexes, all age groups. The approximate age-standardized mortality rate for UC in Bulgaria in 2018 is 3.8 per 100,000 population, for both sexes, all age groups.

## Efficacy data

The therapeutic efficacy and safety profile of pembrolizumab as first-line treatment were analyzed in a KEYNOTE-052 clinical trial, evaluating the efficacy and safety of pembrolizumab in patients with locally advanced or metastatic urothelial carcinoma.

Outcomes in terms of tumor response are: ORR: 24.1%, of which patients with complete response: 4.6%; partial response - 19.5%; stable disease - 22.7%. At a later end date, the ORR is similar. The mean OS was 10.9 months, the 6-month OS was 67.4% and the 12-month OS was 41.2%. As of the date of analysis, 67.0% of patients in the overall population had disease progression; the median PFS was 2.1 months, 6-month PFS was 30.0%, and 12-month PFS was 18.6%.

*Analysis of patient-reported data*
When analyzing the EORTC QLQ-C30 results in the PRO full analysis set (FAS) population, the majority of patients had an improvement of at least 10 points (31%) or a stable quality of life (QoL) (42%) in the 9th week. In patients who remain on treatment, QoL is improved (relative to baseline) through 27th week. EQ-5D VAS and EQ-5D results remain stable over time.

## Safety data

96% of patients have one or more adverse events (AE), and 61.9% have AE that is considered treatment-related. Grade 3 to 5 AE were observed in 54% of patients; in 15.7% they were reported as treatment-related. Serious AE were reported in 41.4% of patients, in 9.7% they were treatment-related. The discontinuation rate due to treatment-related AE was 11.1%. These results indicate that pembrolizumab is better tolerated than the current treatment used in these patients.

The most frequently reported AE are fatigue (31.1%), decreased appetite (21.6%) and constipation (21.1%). Less frequently patients reported itching - 18.9%, diarrhea - 18.6%, nausea - 18.4%, anemia - 16.5%, cough - 13.8%, shortness of breath - 10.5%.

## Data on comparators

According to international and national consensuses for the treatment of UC, comparators of Keytruda (pembrolizumab) included in this analysis are (first line therapy):
1. gemcitabine + carboplatin;
2. gemcitabine monotherapy
3. atezolizumab

## Pharmacoeconomic indicators

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

NICE recommends reimbursement of pembrolizumab, but under certain conditions. The agencies of Scotland and Canada do not recommend reimbursement. IQWiG of Germany consider that there are no confirmed additional benefits.

**Applied analysis**

Two pharmacoeconomic analyzes have been applied - cost-effectiveness and cost-utility, evaluating the cost effectiveness of the health technology as first line therapy. The health benefits for patients in the applied model were measured as years of life gained (LYG) and quality adjusted life years (QALY). The perspective of the analysis is of the paying institution – the NHIF. The time horizon for first-line therapy is 20 years, and for second-line therapy is 35 years. A 3.5% discount of costs and health benefits is applied. Comparators to first-line therapy are gemcitabine monotherapy, gemcitabine + carboplatin and atezolizumab. The analysis uses a pre-set threshold of favorable cost-effectiveness (3 times GDP per capita). The results show that pembrolizumab is defined as a cost-effective treatment option compared to comparators. Pembrolizumab therapy showed a higher cost of treatment than gemcitabine monotherapy and carboplatin + gemcitabine and a higher value of acquired health benefits expressed in more years of life and more quality adjusted life years. Pembrolizumab is the dominant therapeutic choice over atezolizumab because it has a lower cost with higher health benefits.

**Costs of the assessed health technology**

Direct medical costs are included in the model.

**Subgroup analyzes**

The analysis evaluates two patient populations:

1. patients whose tumors express PD-L1 with CPS≥10 and have not been treated or do not qualify for cisplatin-based chemotherapy;
2. patients who have not been treated or do not qualify for cisplatin-based chemotherapy - overall population.

**Budget impact analysis**

The analysis of the budget impact was conducted from the point of view of the paying public institution – the NHIF. The time horizon is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 19 in the first year, reaching 33 in the fifth year. The reimbursement of the health technology by the NHIF will lead to increased costs, without taking into account risk-sharing agreements and patient access schemes.

## Conclusion

Pembrolizumab is a new approach to the treatment of patients with advanced or locally advanced urothelial carcinoma. Pembrolizumab improves or maintains quality of life (QoL) and is well tolerated. The budget impact analysis shows that treatment of patients with locally advanced or metastatic urothelial carcinoma with Keytruda is expected to increase treatment costs.