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
Pembrolizumab

Therapeutic indication(s)	In combination with axitinib, indicated for the first-line treatment of advanced renal cell carcinoma in adults.
Start/end date of procedure	29.05.2020 – 11.11.2020
Final decision	Rejects inclusion of a new therapeutic indication in Annex 2 of the Positive Drug List (PDL) for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the cost of the rendered medical services.

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

Health problem

Renal cell carcinoma (RCC) is a rare tumor, with a frequency of 2%-3% of all malignancies in adults. Predominantly affected are people around the age of 65, but it is also diagnosed at a much earlier age. At the time of diagnosis, about 20%-30% of patients are in a metastatic stage. RCC accounts for approximately 90% of the renal oncological diseases.

RCC may remain asymptomatic for most of the natural course of the disease. The classic triad of hematuria, pain and palpable tumor mass in the lumbar region is not infrequent (10%) and is indicative of advanced disease. Between 25% and 35% of patients are asymptomatic, and RCC is detected by random ultrasound or radiological examination.

RCC is a tumor with frequently occuring paraneoplastic syndromes, including hypercalcaemia, erythrocytosis and nonmetastatic hepatic dysfunction syndrome (Stauffer syndrome). The release of cytokines from the tumor (e.g. interleukin (IL) -6, erythropoietin, nitric oxide) is the cause of the paraneoplastic conditions.

Immunotherapy has been a major focus of research in the development of new therapies for the treatment of malignancies in recent years. By blocking specific biochemical pathways, immunotherapy aims to stimulate antitumor immunity and elicit a lasting response.

Keytruda (pembrolizumab) is a potent PD-1 receptor immunotherapy, which in combination with axitinib is indicated for first-line treatment of advanced renal cell carcinoma in adults.

Epidemiological data

RCC is a malignant disease with a significant impact on public health. It ranks tenth in the incidence of all malignancies in males (2.7%). RCC is about 50% more common in males than in females.

According to GLOBOCAN, the standardized incidence of RCC in 2018 for Bulgaria is 6.4 (per 100,000 population, for both sexes, all age groups).

The approximate 5-year prevalence of RCC in 2018 for Bulgaria is 16.1 (per 100,000 population, for both sexes, all age groups).

Efficacy data

The therapeutic efficacy and safety profile of pembrolizumab were investigated in two clinical studies:

Clinical study KEYNOTE-035 investigated the safety, pharmacokinetics and pharmacodynamics of pembrolizumab in combination with axitinib in patients with advanced RCC. In the primary analysis with a follow-up of 20.4 months, a total of 73% of patients had an objective response. The median of objective response rate (DOR) was 18.6 months and the median PFS was 20.9 months. The median OS was not reached by the end date for analysis. The response to pembrolizumab + axitinib was sustained with an improvement in the median DOR and median progression-free survival (PFS) as compared to the primary analysis. The median overall survival (OS) was not reached.

Clinical study KEYNOTE-426 investigated the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib in adult patients with locally advanced or metastatic RCC. Pembrolizumab + axitinib caused a significant improvement in the median PFS compared to sunitinib (15.1 months versus 11.1 months). At 6, 12, and 18 months, the incidence of PFS was higher with pembrolizumab + axitinib than with sunitinib. The combination shows an advantage in terms of objective response rate (ORR), PFS, OS. The improvement in PFS and ORR with pembrolizumab + axitinib compared to sunitinib was sustained in most of the subgroups analyzed, regardless of PD-L1 status, risk category, and geographic region. Pembrolizumab + axitinib caused a significant improvement in the median PFS compared to sunitinib. More patients in the pembrolizumab + axitinib group achieved an objective response (59.3%) compared to those in the sunitinib group. Higher DCR was observed in the pembrolizumab + axitinib group compared to the sunitinib group. As of the end date for analysis, the median DOR for patients in the pembrolizumab + axitinib group was not reached, while that in the sunitinib group was 15.2 months.

Safety data

Pembrolizumab is most frequently associated with immune-related adverse reactions. Most of them, including severe reactions, resolve after appropriate treatment or discontinuation of pembrolizumab.

The safety of pembrolizumab in combination with axitinib was investigated in a clinical study of 429 patients with advanced RCC who received 200 mg pembrolizumab every 3 weeks and 5 mg axitinib twice daily. In this patient population, the most common adverse reactions were diarrhea (54%), hypertension (45%), fatigue (38%), hypothyroidism (35%), decreased appetite (30%), palmar-plantar erythrodysaesthesia syndrome (28%), nausea (28%), elevated ALT (27%), elevated AST (26%), dysphonia (25%), cough (21%), and constipation (21%). The incidence of grade 3-5 adverse reactions was 76% with pembrolizumab combination therapy and 71% with sunitinib alone.

Data on comparators

The available therapeutic alternatives in Bulgaria are sunitinib and pazopanib.

Pharmacoeconomic indicators

Publicly available assessments of the health technology by government institutions intended for another national health care system

NICE does not recommend the combination of pembrolizumab + axitinib for first-line treatment of advanced RCC. iQWIG, Germany has stated that there are data suggesting significant health benefits of the combination. In Canada, the health technology is recommended as a first-line therapeutic option in patients with advanced RCC.

Applied analysis

A pharmacoeconomic cost-benefit analysis has been applied. The outcome measure is quality adjusted life years. The perspective of the analysis is that of the paying institution – the NHIF. The time horizon in the cost-benefit analysis is lifelong. Cost and benefit discounting with an annual discount factor of 3.5% is applied. A survival model was used. The model consists of three mutually exclusive health conditions: stable disease without progression/disease with response to treatment, disease progression (progressive disease) and death.

The comparators are sunitinib and pazopanib. According to the applied methodology, the therapy with pembrolizumab/axitinib is accompanied by additional cost, with added quality adjusted life years, compared to alternative therapies. The results indicate that pembrolizumab therapy is not a cost-effective option for patients with untreated advanced renal cell carcinoma.

Analysis of subgroups

Not attached.

Costs of the assessed health technology

Direct medical costs are included in the model.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the public payer - the NHIF. The time horizon is 5 years. The expected number of patients in the first year is 30, and in the fifth it reaches 45. The use of pembrolizumab/axitinib as a therapeutic alternative is accompanied by additional cost for the NHIF throughout the time horizon of the analysis, not taking into account risk sharing agreements and patient access schemes.

Conclusion

Renal cell carcinoma (RCC) is a rare tumor with a frequency between 2%-3% of all malignancies in adults. It represents a serious therapeutic problem for the multidisciplinary team responsible for its treatment. The combination of pembrolizumab/axitinib in the therapeutic algorithm for patients with advanced RCC is not a cost-effective alternative. The budget impact analysis shows that, as first-line treatment of advanced RCC, pembrolizumab in combination with axitinib is expected to lead to increased cost for the NHIF.