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)	In combination with carboplatin and either paclitaxel or nab-paclitaxel (nanoparticle albumin-bound paclitaxel), is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma (NSCLC) in adults.
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

Lung cancer is the most common cause of death from cancer both worldwide and in Bulgaria. According to its histological classification, lung cancer is generally divided into non-small cell lung cancer (NSCLC) - 85% of cases, and small cell lung cancer (SCLC). NSCLC is frequently diagnosed at an advanced stage, with a 5-year survival as a result of chemotherapy being about 5% for stage IV. NSCLC is histologically divided into several subtypes, the most common being adenocarcinoma (40%) and large cell carcinoma (10% to 15%), together representing non-squamous and squamous cell carcinoma (25% to 30%). These, as well as other rarer types of NSCLC, may exist in atypical histological variants and mixed combinations of cell types, with approximately 10% of NSCLC comprising two or more histological subtypes.

Patients at a locally advanced stage - IIIB, IIIC, as well as in metastatic stage IV, are eligible only for palliative antitumor drug treatment, the main objective of which is to prolong the overall survival with a good quality of life. In the locally advanced stage, the standard practice is the combined radiation-chemotherapy (or sequential in case the combined is impossible to administer), and in the recent year and a half the benefit of subsequent immunotherapy in patients with PDL > 1% has been established. In patients with metastatic disease, the only treatment option is systemic therapy, and until a few years ago the main option was cytostatic therapy.

Non-squamous and squamous NSCLC have distinctive genomic profiles. Non-squamous cell carcinomas are often characterized by the presence of various mutations or genomic translocations (presence of EGFR mutations, ALK gene rearrangements, ROS 1 mutations, etc. - 25% in total), while squamous cell carcinomas are characterized by increased tumor mutation burden (TMB) and less frequently have mutational changes.

Epidemiological data

NSCLC is a socially important disease. Disease symptoms - fatigue, loss of appetite, shortness of breath and pain exert a significant negative effect on patients' quality of life. Moreover, the severe mental distress seriously affects the emotional state of patients and their families. Lung cancer quickly develops drug resistance, leading to deterioration of symptoms and low survival. The poor prognosis and the expected increase in morbidity determine the social and economic burden of the disease.

According to GLOBOCAN data, the newly diagnosed cases of lung cancer in 2018 were 4250 (3360 men and 890 women). According to data for 2015 of the National Cancer Registry, lung cancer is the most common type of cancer in men in Bulgaria (18.5%). Of all malignancies, lung cancer is the most frequent cause of death in men - 26.1% of cancer deaths are due to lung cancer. In women, lung cancer is the sixth most common cancer (5.4% or 800 new cases); it is the third most common cause of death from cancer with a rate of 9.8%. The newly diagnosed individuals with III-IV stage lung cancer are about 64%.

Squamous cell NSCLC represents 27.6% of all cases of NSCLC or about 23% of all cases of lung cancer. It commonly develops in the central bronchus, with common genetic changes being an increased expression of the oncogenes EGFR (60-85%) and CD44 (48%), amplification of the oncogene PI3CA (33-36%), mutations in the tumor-suppressing gene p53 (60-70%), as well as loss of expression of tumor-suppressing genes such as p16 (60-75%), PTEN (70%) and FUS1 (81%) (68). Subtypes of squamous cell carcinoma of NSCLC are keratinizing, non-keratinizing, and basaloid squamous cell carcinoma. The most common risk factor for its occurrence is smoking, with both the years of smoking and the number of cigarettes per day being important. Passive smoking also has been shown to be associated with a statistically significant risk of developing squamous cell NSCLC.

Currently, a confirmed squamous cell metastatic lung cancer entails the option of two main types of drug therapy, depending on PD-L1 expression. When it is above 50% and there are no any contraindications to the use of immunotherapy, the standard practice is to start immunotherapy with pembrolizumab 200 mg every three weeks. When PD-L1 expression is below 50%, the only option for patients is to receive platinum-based chemotherapy (cisplatin/carboplatin) in combination with a second- or third-generation cytotoxic agent. In the event of progression during the first-line cytostatic therapy and PD-L1 > 1% (and with no first-line immunotherapy), a treatment option is pembrolizumab 200 mg every three weeks until disease progression or occurrence of toxicity. In PD-L1 < 1% and again with no first-line immunotherapy treatment, a treatment option is atezolizumab 1200 mg every three weeks until emergence of toxicity or disease progression. When the first line option had been immunotherapy, the only option for the second and subsequent line of drug treatment is chemotherapy - docetaxel 80 mg/m2 q3w, (+/- ramucirumab) with a rate of objective tumor response rarely exceeding 10%.

Keytruda in combination with carboplatin and paclitaxel/nab-paclitaxel is indicated as first-line treatment of adult patients with squamous NSCLC, who have not been exposed to metastatic NSCLC therapy, regardless of the level of PD-L1 in tumor cells.

Efficacy data

The efficacy of pembrolizumab in combination with carboplatin-paclitaxel/nab-paclitaxel for first-line treatment of metastatic squamous NSCLC in adults whose tumors don't have EGFR or ALK positive mutations, was analyzed, based on the results of one clinical study and one network meta-analysis:

Clinical study KEYNOTE-407 (NCT02775435) to assess the efficacy and safety of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab in untreated patients with metastatic squamous NSCLC.

The KEYNOTE-407 clinical trial is a randomized, phase III, multicenter, international trial. Patients were randomized 1:1 to receive one of the following treatment regimens until disease progression:

- Pembrolizumab 200 mg (day 1) + carboplatin AUC 6 mg/mL/ min (day 1) + paclitaxel 200 mg/m² (day 1) or nab-paclitaxel 100 mg/m² (days 1, 8 and 15) Q3W for four cycles followed by pembrolizumab 200 mg (day 1) Q3W for up to 35 cycles.
- Placebo + carboplatin AUC 6 mg/mL/min (day 1) + paclitaxel 200 mg/m² (day 1) or nab-paclitaxel 100 mg/m² (days 1, 8 and 15) Q3W for four cycles followed by placebo (day 1) Q3W for up to 35 cycles.

Patients were stratified according to chemotherapy regimen (paclitaxel versus nab-paclitaxel), PD-L1 status (TPS ≥ 1% versus <1%), and geographic region (East Asia versus the rest of the world).

The primary endpoints of the study were progression free survival and overall survival (PFS, OS), secondary endpoints - objective tumor response (ORR), duration of response (DOR) and safety. Patients were evenly divided into two cohorts – with respect to gender, age, smoking, general condition and others. The mean OS was 15.9 months in the pembrolizumab + chemotherapy (HT) arm and 11.3 months in the control arm. OS was statistically significantly improved in the pembrolizumab + HT arm compared to the control arm (HR, 0.64). In addition, the OS results were in favor of pembrolizumab + HT relative to the control arm in all subgroups - age, sex, general condition, smoking, geographic area, PD-L1 expression, and taxane type.

With regard to PD-L1 status in particular, the OS benefit of adding pembrolizumab to HT was observed in all subgroups:

- TPS <1%: HR, 0.61– 15.9 versus 10.2 months
- TPS 1% -49%: HR, 0.57 - 14 months compared to 11.6 months
- TPS ≥ 50%: HR, 0.64 - 11.3 months versus 7.4 months

The median PFS was 6.4 months in the pembrolizumab + HT arm and 4.8 months in the control arm (HR, 0.56). Here again, the benefits of combination therapy apply to all groups and independent of PD-L1 expression.
Regarding the secondary endpoints of the study, ORR was 57.9% in the pembrolizumab + HT arm and 38.4% in the control arm. The median time to response was 1.4 months in both groups. The best overall response rate was lower in the pembrolizumab + HT arm compared to the control arm (6.1% vs. 13.9%). Disease control was 86% for immunochemotherapy compared to 75.4%. The BICR – based DOR median was 7.7 months in the pembrolizumab + HT arm and 4.8 months in the control arm.

The systematic literature review (SLR) covers randomized controlled trials (RCT) with pembrolizumab as monotherapy and in combination with chemotherapy, versus comparison arms for first-line treatment of EGFR and ALK negative NSCLC. 119 publications for 68 clinical trials have been identified. Five studies examined regimens featuring pembrolizumab: KEYNOTE-024, KEYNOTE-021G, KEYNOTE-189, KEYNOTE-042, and KEYNOTE-407. The median age of the patients included in the studies was 54 to 77 years. In all but two studies, > 50% of patients were male. ECOG functional status 0 or 1 was most commonly reported. Fifteen studies have been conducted in East Asian countries. A total of 65 studies provided data for OS and 60 studies for PFS. In these studies, the median OS ranged from 5.9 to 30.0 months. The median PFS ranged from 2.7 to 24.0 months.

The results of the systematic literature review also show a benefit in terms of overall survival for the immuno-chemotherapy combination. Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin is statistically superior to platinum + nab-paclitaxel + atezolizumab [HR: 0.64] and platinum + gemcitabine or paclitaxel [HR: 0.67]. NMA based on constant HR shows that pembrolizumab-based regimens have a higher OS compared to platinum + gemcitabine or paclitaxel/nab-paclitaxel in the PD-L1 subgroup ≥ 1%. Pembrolizumab monotherapy had a higher OS than platinum + gemcitabine or paclitaxel/nab-paclitaxel and platinum + gemcitabine + necitumumab in the PD-L1 subgroup ≥ 50%. In the same subgroup (PD-L1 ≥ 50%) pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin did not lead to a statistically significant improvement in OS compared to other interventions. The results observed in the PD-L1 1-49% subgroup show that pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin have a better OS than platinum + gemcitabine or paclitaxel/nab-paclitaxel. No statistically significant differences were observed in the PD-L1 1-49% subgroup with pembrolizumab monotherapy compared to other interventions. Less statistically significant results and higher HR were observed in the PD-L1 subgroups < 1% and < 50% with pembrolizumab + paclitaxel /nab-paclitaxel + carboplatin. HR in most platinum + gemcitabine or paclitaxel/nab-paclitaxel interventions did not change statistically significantly over time. HR with platinum + paclitaxel + necitumumab decreased over time in all PD-L1 – related subgroups. In patients

with PD-L1 expression, HR in pembrolizumab monotherapy versus platinum + gemcitabine or paclitaxel/nab-paclitaxel also decreased over time. The same conclusions were made for progression-free survival - pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin had a statistically significantly higher PFS compared to all comparative interventions in the network, except for platinum + nab-paclitaxel + atezolizumab [HR: 0.79].

Safety data

Pembrolizumab is most frequently associated with immune-related adverse reactions. The majority of these, including severe reactions, subside after appropriate treatment or on discontinuing pembrolizumab.

The most serious adverse drug reactions (ADR) are immune-related and severe infusion-related reactions.

The most common ADR to pembrolizumab are pneumonitis, anemia, thrombocytopenia, hypothyroidism, decreased appetite, insomnia, headache, dyspnoea, cough, colitis, abdominal pain, nephritis, rash, pruritus, musculoskeletal pain.

For the KEYNOTE-407 study, the mean duration of exposure was longer in the pembrolizumab + HT arm than in the control arm (6.3 versus 4.7 months). Adverse events, regardless of treatment regimen, were observed in 98.2% of patients in the pembrolizumab + HT group and 97.9% of patients in the control group. Adverse events resulted in death in 8.3% in the pembrolizumab + HT group and 6.4% in the control group. The most frequent adverse events in both groups were anemia, alopecia and neutropenia.

The risks posed by the most frequently reported ADR (frequency ≥ 10% in each group) were comparable between the two groups. Pneumonitis and autoimmune hepatitis are grade 3-5 ADR, with a greater risk in the pembrolizumab + HT arm than in the control arm.
Immunomediated adverse events and infusion reactions occurred in 28.8% of patients in the pembrolizumab + HT group and 8.6% of patients in the control group; events were grade ≥ 3 in 10.8% and 3.2% of patients, respectively.

Data on comparators

The present assessment considers the platinum couple carboplatin/paclitaxel in patients as a comparative alternative to Keytruda (pembrolizumab) with the same couple for the examined indication.

Pharmacoeconomic indicators

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

There are no published health technology assessments from the UK, France, Germany and/or Sweden. The NICE (UK) opinion refers to the approval of the use of Keytruda in combination with carboplatin + paclitaxel/nab-paclitaxel for the treatment of patients with metastatic squamous non-small cell lung cancer.

Applied analysis

A cost-benefit pharmacoeconomic analysis has been applied to assess the value effectiveness of pembrolizumab used in combination with carboplatin + paclitaxel/nab-paclitaxel for the first-line treatment of adult patients with metastatic squamous non-small cell lung cancer. Chemotherapy (combination of carboplatin + paclitaxel/nab-paclitaxel) has been selected as a comparative alternative. Outcome measures: QALY, calculated on the basis of utility, and LYG. The perspective of the analysis is of the National Health Insurance Fund (NHIF) for a time horizon of 10 years, in line with development of the disease. The costs and results level of discounting is 3.5%.

To model the development of the disease, a cohort model of survival was applied, consisting of 3 health conditions: no progression, progression and death. The value effectiveness of pembrolizumab + carboplatin + paclitaxel versus chemotherapy in the target patient population was assessed. Probabilistic and deterministic sensitivity analysis were applied to assess uncertainty.

Pembrolizumab + chemotherapy is expected to lead to improved quality of life and higher QALY. The value of ICER, when comparing the pembrolizumab + chemotherapy combination therapy to chemotherapy, is above the break-even point and the therapy is not cost-effective. The applied sensitivity analysis confirms the conclusions made about the value ineffectiveness of the treatment. The one-way sensitivity analysis found that the health benefits of pembrolizumab + chemotherapy had the greatest impact on ICER.

Subgroup analysis has not been applied.

Costs for the assessed health technology

The following types of costs have been calculated:

1. For pembrolizumab + chemotherapy (CARBOPLATIN + PACLITAXEL)
2. For chemotherapy (CARBOPLATIN + PACLITAXEL)
3. For administration of medicines
4. For subsequent treatment after initial therapy

5. For palliative care and ADR

Budget impact analysis

The analysis of the budget impact was conducted from the perspective of the paying public institution – the NHIF, with a time horizon of 5 years. The number of patients eligible for treatment with Keytruda in the first year was projected to be 130, increasing to 155 in the fifth year. The budget impact analysis includes only costs for the acquisition of medicines and costs applicable to outpatient procedure no. 6 in the amount of BGN 150 per month.

Sensitivity analysis was performed to test the uncertain parameters in the budget impact analysis using a tornado diagram. The cost of Keytruda + chemotherapy and the number of patients have the greatest impact on the budget.

The inclusion of Keytruda + chemotherapy in the PDL will lead to additional costs for the NHIF, increasing over a period of 5 years, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The outcomes of the principal study, assessing the effectiveness and safety, show a clear and sustained clinical benefit with first-line treatment with Keytruda (pembrolizumab) in combination with chemotherapy with carboplatin and paclitaxel or nab-paclitaxel compared with chemotherapy. The benefit comprises improved overall survival (OS) and progression-free survival (PFS), independent of PD-L1 expression. In addition, the safety profile of the combination of Keytruda (pembrolizumab), carboplatin and paclitaxel/nab-paclitaxel is consistent with the profile of pembrolizumab as monotherapy or chemotherapy with carboplatin and paclitaxel/nab-paclitaxel. Keytruda is not a cost-effective therapy compared to chemotherapy alone. The administration of the medicinal product Keytruda is expected to generate additional costs for the paying institution, which will increase every following year within the 5-year time horizon of the budget impact analysis, given the expected increase in the number of patients. The current first-line therapy for metastatic squamous NSCLC without positive EGFR and ALK mutations in Bulgaria is platinum-based chemotherapy in combination with third-generation cytostatics. Based on the demonstrated high efficacy and controllable safety profile, Keytruda in combination with carboplatin and paclitaxel/nab-paclitaxel provides new treatment options for patients with metastatic squamous NSCLC, irrespective of PD-L1 expression status.