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

HEALTH TECHNOLOGY ASSESSMENT

Tecentriq

1200 mg – 20 ml concentrate for solution for infusion x 1 vial

atezolizumab

Therapeutic indication(s)	In combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC), who have not received prior treatment and have PD-Ll expression between 1% and 49%, or liver metastases. In patients with EGFR mutant or ALK-positive NSCLC, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.
Start/end date of procedure	15.05.2019 - 23.12.2019
Final decision	To add a 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 National Health Insurance Fund (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 Tecentriq

Health problem

Lung cancer is the most common cancer worldwide. It is classified according to its histology, the two main forms being non-small cell lung cancer (NSCLC) and small cell lung cancer. The more common type, which accounts for about 85% of all lung cancer cases, is NSCLC, with majority of patients with NSCLC being diagnosed with advanced disease. Lung cancer remains the leading cause of cancer-related death worldwide. The majority of patients are diagnosed with an already advanced disease when the 5-year survival rate is low, especially in patients with multiple metastases (5-year survival about 5% for stage IV). According to International Classification of Diseases (ICD) 10, the code for lung cancer is C34 Malignant neoplasm of the bronchi and lungs.

Early-stage lung cancer is usually asymptomatic, with relatively few disease-related symptoms affecting the HRQoL (health-related quality of life), hence the majority of diagnosed patients already have locally advanced or metastatic disease. The diagnosis requires a complete medical history of the patient, including smoking status, comorbidities, weight loss, functional status (PS), and physical examination. Visual examination of trachea and the major airways may be performed, as well as tissue biopsy for samples from the lungs and mediastinal lymph nodes to allow for more accurate diagnosis, as well as histological and biomarker analyses. Clinical guidelines recommend chest X-ray and computed tomography (CT) scans to determine the location, size, spread of the tumor, and lymph node involvement. Fluorodeoxyglucose (FDG) positron emission tomography (PET), magnetic resonance imaging or radionuclide bone scans may be recommended to detect extrathoracic lesions in patients with advanced or metastatic disease. Molecular testing for EGFR mutations, ROS1 mutations, and ALK rearrangements is recommended in all patients with advanced non-squamous NSCLC to determine appropriate treatment.

Approximately 30% of patients with advanced lung cancer have symptoms associated with the primary tumor (cough, dyspnea, chest pain, and hemoptysis). 35% have non-specific systemic symptoms suggestive of metastases, including anorexia, weight loss and fatigue, and another 35% have symptoms specific to metastatic sites. According to studies, a large proportion of patients with stage IIIB/IV NSCLC report fatigue (100%), anorexia (97%), dyspnoea (95%), cough (93%), pain (92%) and haemoptysis (63%).), with fatigue, cough, anorexia and dyspnoea being the most severe symptoms.

Tecentriq (atezolizumab) is the first approved inhibitor to target the PD-L1 ligand. The medicinal product in combination with bevacizumab, paclitaxel and carboplatin is indicated

as a first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer. The use of atezolizumab in combination resulted in a significant increase in life expectancy compared to bevacizumab and chemotherapy (paclitaxel and carboplatin). The alternative combination of pembrolizumab with chemotherapy is also associated with more health benefits than chemotherapy alone.

Tecentriq in combination with bevacizumab, paclitaxel and carboplatin is included in the following guidelines:

- Recommendations of the European Society of Medical Oncology (ESMO), 2018
- National Comprehensive Cancer Network (NCCN) Recommendations, 2019 v.4
- National medical standards for systemic drug therapy, assessment of therapeutic effect and follow-up of malignant solid tumors in adults. National Consensus Decision of the Bulgarian Cancer Scientific Society (BCSS), 2019
- Pharmacotherapeutic guide on medical oncology, published on the official website of the National Council for Prices and Reimbursement of Medicinal Products (NCPRMP)

Tecentriq in combination with bevacizumab, paclitaxel and carboplatin is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq in combination with bevacizumab, paclitaxel and carboplatin is indicated only after failure of appropriate targeted therapies. The proposed health technology is approved for treatment in patients regardless of PD-L1 status and does not require a diagnostic test.

The health technology combines several therapeutic approaches with established effectiveness in the treatment of non-squamous NSCLC:

- The use of paclitaxel and carboplatin physically destroys cancer cells and facilitates exposure to tumor antigens that activate the immune system.
- Bevacizumab helps the activation of T lymphocytes, restores tumor vasculature and has a beneficial effect on the immunosuppressive tumor microenvironment.
- Atezolizumab restores the effective antitumor response by blocking the interaction between PD-1 and PD-L1 and helping the activation of T lymphocytes in the lymph nodes.

The health technology improves overall survival (OS) and progression-free survival (PFS) in patients with metastatic non-squamous NSCLC.

Epidemiological data

In 2018, according to GLOBOCAN, 2 093 876 cases of lung cancer were diagnosed worldwide (11.6% of newly diagnosed cancers), the number of deaths was 1 761 007 (18.4% of cancer deaths). In Europe, the number of newly diagnosed cases in 2018 is 470 039 (22.4% of newly diagnosed cancers), while the number of deaths is 387 913 (22% of all cancer deaths).

According to the National Cancer Registry, in Bulgaria lung cancer holds the first place among malignant diseases in men with 18.5% and 5.4% in women respectively. More than half of the cases have been diagnosed in advanced stage III or IV. Lung cancer occurs mainly in elderly patients.

The incidence of lung cancer in men is 85.5 per 100 000 and in women 21.7 per 100 000.

Efficacy data

A randomized 1:1:1 three-arm, multicenter, open-label, phase III study, assessing the efficacy and safety of atezolizumab in combination with carboplatin + paclitaxel with or without bevacizumab was performed compared to bevacizumab + carboplatin + paclitaxel in non-treated patients with (metastatic) non-squamous NSCLC in stage IV. The duration of the study was 2 years and 9 months.

Study name: IMpower150 (ClinicalTrials.gov number, NCT02366143)

Clinical study	Country(s)	Participants	Type of study, duration	Intervention	Comparative alternatives	Results
IIpower150	Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, France, Germany, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands,	1202 Men or women > 18 years Men 59.9% Age 62.8 years Liver metastases in the beginning - 13.5% Ethnicity - Hispanic or Latin 9.6%,	Randomized 1: 1: 1 three-arm, multicenter, open-label, phase III study assessing the efficacy and safety of atezolizumab in combination with carboplatin +	Atezo + Bev + CP	Atezo + Bev + CP vs Atezo + CP vs Bev + CP	PFS: 11.3 for ABCP versus 6.8 months for BCP OS: 19.2 for ABCP versus 14.7 months for BCP Disease progression or death (as of 15.07.2017):

	Peru, Portugal, Russia, Singapore, Slovakia, Spain, Switzerland, Taiwan, Ukraine, USA	other - 85.2%, not reported 4.2%, unknown 1.1% Race - white 82.2%, Asian 12.5% Weight 72.4 kg Initial ECOG: 0 - 43.3%; 1 - 56.7%	paclitaxel with or without bevacizumab, compared with bevacizumab + carboplatin + paclitaxel in untreated patients non-squamous NSCLC in stage IV Duration: 03.2015 - 01.2018 (2 years and 9 months)			62.6% for ABCP compared to 79.8% for BCP Mortality (as of Jan. 22, 2018): 49.9% for ABCP compared to 58.5% for BCP PFS at 6 months: 71.7 for ABCP versus 57.0 months for BCP PFS at 12 months: 46.0 for ABCP versus 18.0 months for BCP ORR: 63.5% for ABCP versus 48.0% for BCP

According to the final data analysis, the combination of atezolizumab with carboplatin + paclitaxel and bevacizumab demonstrated a statistically significant improvement in progression-free survival (PFS) compared to the control arm group of 8.3 months (7.7, 9.8) versus 6.8 months (6.0, 7.1) (stratified HR 95% CI: 0.59 (0.50, 0.70) $p < 0.0001$). In the group of patients with EGFR mutant/ALK+, progression-free survival was also in favor of the group treated with atezolizumab + carboplatin + paclitaxel + bevacizumab versus control arm: 10.0 months (7.9, 15.2) versus 6.1 months (5.6, 8.4) (non-stratified HR 95% CI: 0.552 (0.35, 0.87).

Overall survival analysis also demonstrated a convincing benefit for patients treated with atezolizumab + bevacizumab + carboplatin + paclitaxel: in the group of patients without EGFR mutant/ALK+ (ITT WT), the overall survival was 19.2 (17.0, 23.8) months in the experimental arm, compared to 14.7 (13.3, 16.9) in the control arm (stratified HR 95% CI: 0.78 (0.64, 0.96), p 0.0164). In patients with EGFR mutant/ALK+, median overall survival in atezolizumab + bevacizumab + carboplatin + paclitaxel arm was not achieved and for the control arm it was 17.5 months (95% CI: [10.4, NE]), HR 0.54 (95% CI) : [0.29, 1.03]).

In the ITT-WT population, the proportion of patients with a confirmed objective response (full response [CR] or partial response [PR]) was higher in the atezolizumab + bevacizumab + carboplatin + paclitaxel group (55.3%; 95% CI: [50.0, 60.6]].) compared to the bevacizumab + carboplatin + paclitaxel group (40.4%; 95% CI: [35.0, 45.9]; odds ratio [OR]: 1.83; 95% CI: [1.35, 2.49]). More patients in the atezolizumab + bevacizumab + carboplatin + paclitaxel group compared to the bevacizumab + carboplatin + paclitaxel group achieved CR (2.5% vs. 0.6%) or PR (52.8% vs. 39.8%). More patients in the bevacizumab + carboplatin + paclitaxel group compared to the atezolizumab + bevacizumab + carboplatin + paclitaxel group had the best response/stable disease (SD; 40.1% vs. 28.9%) or PD (10.2% vs. 5,9%). The results in the ITT population are similar to those observed in the ITT-WT population.

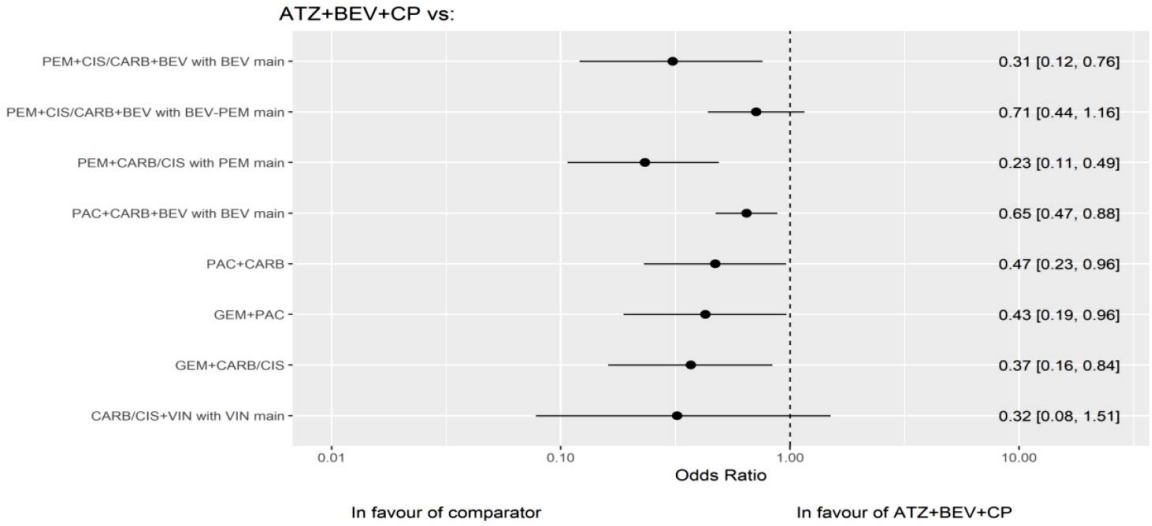
In the ITT-WT population, treatment with atezolizumab + bevacizumab + carboplatin + paclitaxel resulted in a prolonged duration of response (DOR) compared to bevacizumab + carboplatin + paclitaxel. Among patients with a confirmed response, the median DOR was greater in the atezolizumab + bevacizumab + carboplatin + paclitaxel group (11.5 months) than in the bevacizumab + carboplatin + paclitaxel group (6.4 months). The stratified HR was 0.45 (95% CI: [0.34, 0.59]). It should be noted that at the time of data collection, 39.1% of patients in the atezolizumab + bevacizumab + carboplatin + paclitaxel arm had a response to treatment compared with 13.4% in the bevacizumab + carboplatin + paclitaxel arm.

The majority of patients in the atezolizumab + bevacizumab + carboplatin + paclitaxel arm had a confirmed objective response in the ITT-WT population (full response [CR] or partial response [PR]) (55.3%; 95% CI: [50.0, 60.6]) compared to the bevacizumab + carboplatin + paclitaxel group (40.4%; 95% CI: [35.0, 45.9]; odds ratio [OR]: 1.83; 95% CI: [1.35, 2.49]). The treatment with the proposed health technology was also characterized by a significantly longer median duration of response compared to the control arm (11.5 versus 6.4 months, respectively) in the ITT-WT population. The results were similar in all treated patients (ITT population). With the proposed health technology, the expected survival is higher than with most comparators (extrapolation over a period of 60 months). The combination was well

tolerated by the patients and no clinically significant deterioration in their quality of life was observed, compared to the control arm.

Safety data

The results of a network meta-analysis show that the probability of treatment discontinuation due to ADR with the proposed health technology is lower compared to other technologies:



Atezolizumab in combination with chemotherapy with or without bevacizumab is well tolerated and has a safety profile corresponding to each individual medicinal product. The results for the proportion of patients with at least one ADR (regardless of grade) are consistent with the first interim analysis and were similar between the groups (bevacizumab + carboplatin + paclitaxel: 99.0%; atezolizumab + bevacizumab + carboplatin + paclitaxel: 98.2 atezolizumab + carboplatin + paclitaxel: 97.8%). Grade 3-4 ADR are comparable between groups (bevacizumab + carboplatin + paclitaxel: 58.4%; atezolizumab + bevacizumab + carboplatin + paclitaxel: 63.6%; atezolizumab + carboplatin + paclitaxel: 57.5%). Treatment-related grade 3-4 ADR are more frequent in the atezolizumab + bevacizumab + carboplatin + paclitaxel group (56.7%) compared to the bevacizumab + carboplatin + paclitaxel group (48.5%) and the atezolizumab + carboplatin + paclitaxel (43.0%). The proportion of patients with ADR considered as treatment-related by the investigator is comparable between the groups (bevacizumab + carboplatin + paclitaxel: 95.7%; atezolizumab + bevacizumab + carboplatin + paclitaxel: 94.1%; atezolizumab + carboplatin + paclitaxel: 94,3%). The incidence of adverse drug events of special interest (AESI) for atezolizumab in the second intermediate analysis is consistent with the first intermediate analysis as well as with the known safety profile of atezolizumab. The majority of atezolizumab AESI are mild or moderate in severity. The incidence of bevacizumab ADR of particular interest is consistent

with that reported during the first interim analysis, as well as with the known safety profile of bevacizumab.

Data on comparators

The alternatives that could be partially or completely displaced with the introduction of the new technology are:

- Bevacizumab + Paclitaxel + platinum-based therapy
- Pemetrexed + platinum-based therapy with maintenance treatment with Pemetrexed
- Pemetrexed + platinum-based therapy
- Gemcitabine + platinum-based therapy
- Vinorelbine + platinum-based therapy
- Paclitaxel + platinum-based therapy
- Pembrolizumab + Pemetrexed + platinum-based therapy

Atezolizumab is currently reimbursed by the NHIF as monotherapy in adult patients with locally advanced or metastatic NSCLC following prior chemotherapy, as well as for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC).

Pharmacoeconomic indicators

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

Decisions by the state institutions of UK and Germany have been presented. The assessment by NICE (UK) is positive with certain recommendations, and the assessment of IQWiG (Germany) is not positive in terms of added benefits.

Applied analysis

A cost-utility (CUA) method with long-term measuring of therapeutic outcomes (LYG) and quality-adjusted life years (QALY) was used. Analysis perspective is on the part of the paying institution, the NHIF. Costs and outcomes have been discounted with 3.5% per year. Analysis was applied for a period of 20 years, which is too long given the expected development of the disease. A partitioned survival model is applied to assess the value effectiveness of atezolizumab + bevacizumab + carboplatin + paclitaxel against therapeutic alternatives. After predicting survival, a Markov model of 3 conditions - no progression, progression and death, respectively, was constructed. Data on long-term survival (OS), duration of progression-free survival (PFS) and time to discontinuation (TTD) were modelled. Comparative alternatives

were selected from a network meta-analysis (NMA) in the treatment of patients with NSCLC, who have non-squamous cellular histology of the tumor.

A subgroup analysis of three subgroups of patients who, according to clinical trials, have the greatest benefit of treatment with atezolizumab and bevacizumab has been presented:

- patients with EGFR mutant or ALK-positive non-squamous NSCLC, only after failure of appropriate targeted therapies (EGFR/ALK + subgroup of patients),
- patients with non-squamous NSCLC who have not been treated before and with PD-L1 expression between 1% and 49% (subgroup of patients with low levels of PD-L1 expression or without PD-L1 expression) (PD-L1 0-49%)),
- patients with non-squamous NSCLC who have not been treated so far and who have liver metastases (subgroup of patients with liver metastases).

ICER was calculated in each group of patients comparing atezolizumab + bevacizumab + carboplatin + paclitaxel therapy and associated alternatives.

In EGFR/ALK+ subgroup of patients, therapy with atezolizumab + bevacizumab + carboplatin + paclitaxel was compared to platinum-based therapy and to pembrolizumab + platinum-based therapy + maintenance treatment with pembrolizumab.

In the subgroup of patients with low levels of PD-L1 expression or without PD-L1 expression (PD-L1 0-49%), therapy with atezolizumab + bevacizumab + carboplatin + paclitaxel was compared to bevacizumab + carboplatin + paclitaxel; versus pembrolizumab + platinum-based therapy, and versus pembrolizumab + platinum-based therapy + maintenance treatment with pembrolizumab.

In the subgroup of patients with liver metastases, therapy with atezolizumab + bevacizumab + carboplatin + paclitaxel was compared to bevacizumab + carboplatin + paclitaxel.

In the EGFR/ALK+ subgroup of patients, ICER values are the lowest, respectively treatment is the most cost-effective.

In the three examined subgroups of patients, when compared with the available therapeutic alternatives, the combination therapy with atezolizumab + bevacizumab + carboplatin + paclitaxel achieved a higher value of acquired health benefits and a higher direct cost per patient. Atezolizumab + bevacizumab + carboplatin + paclitaxel demonstrates therapeutic superiority, expressed by more years of life gained and QALY. There is an unmet need for the use of immunotherapies for treatment in these subgroups of patients, in whom the combination atezolizumab + bevacizumab + carboplatin + paclitaxel demonstrates clinically significant benefits in terms of OS and PFS.

Sensitivity analysis of all subgroups of patients (deterministic and probabilistic) was performed, which shows that various factors influence the incremental ratio, such as costs, health benefits and health care. The sensitivity analysis confirms the results of the main analysis.

Costs for the assessed health technology

The costs included are: for drug therapy with atezolizumab in combination with bevacizumab, paclitaxel and carboplatin; for drug therapy with alternatives; administration costs; costs of disease monitoring and follow-up, palliative care and side effects.

Budget Impact Assessment

Two budget impact analyses were presented, for EGFR/ALK+ liver metastases, and in patients with PD-L1 expression of 1-49% respectively. All available alternatives have been presented and the number of all suitable patients has been distributed among them.

The analysis of the budget impact was conducted from the perspective of the National Health Insurance Fund with a time horizon of 5 years. The target population is 56 patients in the first year thrpugh 105 patients in the fifth year.

The introduction of the new technology leads to savings for the NHIF within the 5-year period compared to the main therapeutic alternative - combination therapy with pembrolizumab, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Lung cancer is the most common cancer, with the majority of cases being diagnosed at an advanced stage, characterized by a low 5-year survival. As the disease progresses, patients encounter difficulties performing daily activities and become dependent on the help of relatives. Health technology *Tecentriq (atezolizumab), in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq in combination with bevacizumab, paclitaxel and carboplatin is indicated only after failure of appropriate targeted therapies.*

The health technology combines several therapeutic approaches with established effectiveness in the treatment of non-squamous NSCLC and has established clinical efficacy and safety:

- administration of paclitaxel and carboplatin physically destroys cancer cells and facilitates exposure to tumor antigens that activate the immune system.

- Bevacizumab helps the activation of T lymphocytes, restores tumor vasculature and has a beneficial effect on the immunosuppressive tumor microenvironment.
- Immunotherapy with atezolizumab restores the effective antitumor response by blocking the interaction between PD-1 and PD-L1 and helping the activation of T lymphocytes in the lymph nodes. The combination has established clinical efficacy and safety.

Treatment with the health technology improves mean overall survival (OS) by 4.9 months and progression-free survival (PFS) by 1.6 months, compared to standard treatment with bevacizumab + carboplatin + paclitaxel in the ITT population.

Tecentriq in combination with carboplatin, paclitaxel and bevacizumab significantly improves overall survival compared to bevacizumab + chemotherapy. In the three studied subgroups of patients, compared to the available therapeutic alternatives, the combination therapy with atezolizumab + bevacizumab + carboplatin + paclitaxel achieved a higher value of acquired health benefits at a higher direct cost per patient. The introduction of the new technology is associated with lower costs for the NHIF within the 5-year period compared to the main therapeutic alternative - combination therapy with pembrolizumab.