



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



HEALTH TECHNOLOGY ASSESSMENT

Tecentriq

1200 mg concentrate for solution for infusion x 1 vial

Atezolizumab

Therapeutic indication(s)	Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.
Start/end date of procedure	17.07.2020 – 27.11.2020
Final decision	Addition of 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 Tecentriq

Health problem

Lung cancer is the most common cancer worldwide. It is classified according to the histological picture, with the two main forms being non-small cell (NSCLC) and small cell lung cancer (SCLC). Despite advances in the early identification of NSCLC, the majority of patients are diagnosed with advanced disease with a low 5-year survival rate, especially in patients with multiple metastases (5-year survival <5% for stage IV).

Approximately 30% of patients with advanced lung cancer have symptoms associated with the primary tumor, about 35% have nonspecific systemic symptoms suggestive of metastasis, and another 35% have symptoms specific to the location of metastases. Pain, fatigue, dyspnea, and cough are the most common and clinically significant disease-related symptoms observed in patients with NSCLC, with a significant prognostic value for the health-related quality of life (HRQoL). Despite treatment, most symptoms associated with the disease increase in frequency and intensity as the disease progresses, most notably chest pain, back pain, and dyspnea.

Survival rate in patients with NSCLC vary according to the characteristics of the disease, but is generally low. 5-year survival rates decreased from approximately 70% to 90% in patients with stage I NSCLC to 50% -60% in stage II and are less than 15% in patients with locally advanced NSCLC (stage IIIA: 36%; stage IIIB: 26%; stage IIIC: 13%). Patients with metastatic stage IV of NSCLC have a very low 5-year survival rate (10% for stage IVA and less than 1% for stage IVB).

For patients with tumors without EGFR mutations or ALK translocations, as well as patients without high expression of PD-L1, the standard care is platinum-based chemotherapy in combination with agents such as taxanes (paclitaxel, docetaxel), vinorelbine, gemcitabine and pemetrexed, or platinum-based chemotherapy with or without bevacizumab (including in patients following one or more TKI lines). In the second and subsequent treatment lines for NSCLC, anti-PD-1 and anti-PD-L1 antibodies showed superiority over docetaxel as monotherapy.

The evaluated indication is the treatment of adult patients with metastatic NSCLC - first line of treatment, where atezolizumab is administered in combination with nab-paclitaxel and carboplatin in adult patients with metastatic non-squamous NSCLC who do not have an EGFR mutant or ALK-positive NSCLC.



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



Epidemiological data

According to GLOBOCAN data for 2018, 2,093,876 cases of lung cancer have been diagnosed worldwide (11.6% of newly diagnosed cancers), the number of deaths is 1,761,007 (18.4% of deaths from cancer).

Epidemiological data for Bulgaria

Lung cancer is the number one malignant disease in men in Bulgaria, accounting for 18.5% of all malignancies. The data for Bulgaria show that those diagnosed with stage III-IV are about 52%, of which about 40% are with NSCLC.

Efficacy data

The IMpower130 clinical study has been analyzed, an open-label, randomized, phase III study to evaluate the efficacy and safety of atezolizumab in combination with nab-paclitaxel and carboplatin in previously untreated with chemotherapy patients with metastatic non-squamous NSCLC. Patients with EGFR mutations or ALK rearrangements should have been pre-treated with tyrosine kinase inhibitors.

The primary efficacy endpoints were progression-free survival (PFS) according to RECIST (Response Evaluation Criteria in Solid Tumors) v1.1 and overall survival (OS) in ITT-WT (intention-to-treat population - patients with a wild-type genotype, patients without EGFR or ALK alterations) population. Major secondary endpoints were progression-free survival (PFS) and overall survival (OS) in other populations, objective response rate (ORR), and duration of response (DOR).

IMpower130 showed statistically and clinically significant improvement in overall survival and significant improvement in progression-free survival with atezolizumab plus chemotherapy versus chemotherapy as first-line treatment of patients with stage IV non-squamous non-small cell lung cancer and without ALK or EGFR mutations. The median OS is 4.2 months longer with atezolizumab + CnP; the mean OS was 18.1 months in the atezolizumab + CnP arm versus 13.9 months in the CnP arm. The mean duration of PFS was longer in the atezolizumab + CnP arm (7.0 months) than in the CnP arm (5.6 months).

PFS benefit was observed in atezolizumab + CnP in all analyzed subgroups, except in patients with liver metastases and in patients with EGFR mutations or ALK translocations.

Sustained OS benefit has been observed in subgroups defined by key initial clinical factors, except in patients with liver metastases and in patients with EGFR mutations or ALK translocations.



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



The study supports the benefit of atezolizumab in combination with platinum-based chemotherapy as a first-line treatment for metastatic non-small cell lung cancer.

Safety data

The safety of atezolizumab in combination with other medicinal products has been evaluated in 3,878 patients with various tumor types. The most common adverse reactions ($\geq 20\%$) were anemia (40.3%), neutropenia (39.4%), nausea (37.3%), fatigue (34.4%), alopecia (29.6%), thrombocytopenia (28.9%), diarrhea (28.1%), rash (27.7%), constipation (27.2%), peripheral neuropathy (25.7%) and decreased appetite (25.5%).

Data on comparators

The main comparator is platinum-based therapy with bevacizumab and pemetrexed. Pembrolizumab in combination with carboplatin and nab-paclitaxel (nanoparticle albumin-bound paclitaxel) is also an option.

Pharmacoeconomic indicators

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

IQWiG has issued a positive assessment, referring to added benefit.

Applied analysis

A cost-benefit analysis was employed for comparative assessment the health technology atezolizumab in combination with nab-paclitaxel and carboplatin. Also presented is additional cost-effectiveness analysis, which estimates the cost of life year gained (ICER/LYG). Measures of health benefits for patients in the applied model are gained years of life (LYG) and quality adjusted life years (QALY). The perspective of the analysis is that of the paying institution - NHIF. The time horizon is lifelong (30 years), and the duration of the cycle in the model is one week. Health benefits and costs are discounted at an annual discount rate of 3.5%. For the purposes of the analysis, a partitioned survival model, also known as the area under the curve (AUC), was used to evaluate the cost-effectiveness of atezolizumab + CnP over therapeutic alternatives. Three states are included in the model - "no progression", "post progression" and "death". The model includes 8 comparative alternatives - Carboplatin + paclitaxel + bevacizumab + maintenance therapy with bevacizumab; Cisplatin/carboplatin + bevacizumab + pemetrexed + maintenance therapy with bevacizumab + pemetrexed; Cisplatin/carboplatin + pemetrexed + maintenance therapy with pemetrexed; Cisplatin/carboplatin + pemetrexed; Carboplatin + paclitaxel; Cisplatin/carboplatin + gemcitabine; Cisplatin + vinorelbine; Nab-paclitaxel + carboplatin + maintenance therapy with pemetrexed.



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



The results of the analysis define the evaluated therapeutic combination (atezolizumab + CnP) as a recommended first choice for the treatment of patients with NSCLC versus platinum-based therapy with bevacizumab and pemetrexed. The Atezolizumab combination dominates with a lower final cost and higher value of health benefits. The savings generated by atezolizumab are in the health state of progression and associated follow-up treatment. The therapeutic combination of Atezolizumab + CnP compared to platinum-based therapy and maintenance treatment with pemetrexed is not a cost-effective therapy. The use of atezolizumab in combination with platinum and nab-paclitaxel dominates the triple combination of carboplatin, paclitaxel and bevacizumab. Atezolizumab + CnP incurs additional costs compared to carboplatin + paclitaxel, with an incremental ratio above the break-even point. Atezolizumab + CnP is not effective versus platinum-based gemcitabine or platinum-based vinorelbine.

Sensitivity analyses confirm the conclusions made.

Costs of the assessed health technology

There have been calculated the following costs: medication cost, medical services – medication administration, ADR management and outpatient monitoring, medication cost for subsequent treatment.

Analysis of subgroups

No subgroup analysis was performed.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the paying institution – the NHIF. The time horizon in the budget impact analysis is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 60 in the first year, reaching 288 in the fifth year. The reimbursement of the health technology by the NHIF leads to a reduction in the cost for the paying institution compared to the higher-cost alternatives, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Lung cancer is one of the most common and malignant cancers worldwide. The addition of atezolizumab to carboplatin and nab-paclitaxel in the first-line treatment of patients with metastatic, non-squamous NSCLC without EGFR mutations or ALK translocations showed clinically meaningful and statistically significant improvements in OS and PFS. The assessed health technology atezolizumab (Tecentriq) in combination with carboplatin and nab-paclitaxel leads to cost savings for the paying institution for a period of five years, while prolonging the life of patients and improving its quality.