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 carboplatin and etoposide, indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
Start/end date of procedure	13.09.2019 – 20.12.2019
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.

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 and with the highest mortality oncological disease in the world. Depending on its histology, lung cancer is classified as non-small cell (NSCLC) and small cell (SCLC). NSCLC is the more common form, comprising about 85% of all cases of lung cancer. SCLC accounts for approximately 15% of lung cancer cases and, unlike NSCLC, is characterized by extreme aggression, poor differentiation, high initial chemo- and radiation sensitivity, and early metastasizing.

According to the VALG system (Veterans Administration Lung Group), which has been used since 1950, depending on the stage of the disease, SCLC is classified as SCLC with limited stage disease (LS) or extensive stage disease (ES). ES-SCLC includes malignant pleural and pericardial effusions, contralateral hilar or supraclavicular lymph node involvement, and metastases that cannot be covered by a single radiological field during treatment.

SCLC is associated with a number of severe symptoms. The most common and persistent symptom is cough, which occurs in about 75% of patients. Other symptoms are dyspnoea (~ 60%), chest pain (~ 50%) and hemoptysis (~ 35%). Fatigue, weight loss, and anorexia due to systemic disease have been reported in many patients. Esophageal and mediastinal involvement is common in patients with invasive or advanced disease. Distress associated with the onset of lung cancer symptoms (both SCLC and NSCLC) is greatest compared to other cancers. Symptoms can interfere with normal daily activities and affect patients' emotional and social well-being.

Epidemiological data

NSCLC represents ~ 85% of all lung cancer cases, while SCLC is ~ 15%. In 2015, 260,000 new cases of SCLC were registered worldwide and over 11,000 in Europe.

According to GLOBOCAN data from 2018, the number of newly diagnosed cases of lung cancer in Bulgaria is 4,250 (12% of all cases of cancer), of which 3,360 cases (17%) in men and 890 (5.7%) in women. The number of deaths in 2018 amounted to 3,867 (20.2% of all deaths from cancer).

According to data from the National Cancer Registry from 2013 (2015 edition), out of 4160 cases of lung cancer, 463 are those with small cell lung cancer, or 11.13%.

In clinical practice, a combination of the two classification systems is used to determine the stage of the disease. The choice of classification system is important in determining treatment and prognosis.

Table 1. Classification of LS-SCLC and ES-SCLC

Classification system	LS - SCLC	ES - SCLC
VALG	• Confined to a single radiation port • Ipsilateral mediastinal or supraclavicular lymph nodes • Confined to the ipsilateral mediastinum	• Not confined to a single radiation port • Metastatic disease • Contralateral mediastinal or supraclavicular lymph nodes • Malignant pleural or pericardial effusion
LASLC	• Confined to a single radiation port • Ipsilateral mediastinal or supraclavicular lymph nodes • Contralateral mediastinal or supraclavicular lymph nodes • Ipsilateral pleural effusion (benign or malignant)	• Not confined to a single radiation port • Metastatic disease

ES - extensive stage; LS - limited stage; SCLC - small cell lung cancer; VALG - Veterans Administration Lung Cancer Study Group

The majority of SCLC patients are diagnosed with ES-SCLC and their prognosis is unfavorable: the median overall survival is ~ 10 months. Currently, the standard first-line treatment for patients with ES-SCLC is platinum-based chemotherapy in combination with etoposide, a topoisomerase II inhibitor.

In SCLC, the frequency of mutations is high, suggesting that these tumors may be immunogenic and respond to immune checkpoint inhibitors. The addition of immunotherapy to chemotherapy may increase the antitumor immune response and improve the results achieved with chemotherapy alone. Immunotherapeutic agents offer an alternative treatment approach that may improve the prognosis in patients with ES-SCLC.

Tecentriq (atezolizumab) is the first approved checkpoint inhibitor targeting ligand 1 of the programmed cell death receptor (PD-L1). For the first time in two decades, the addition of Tecentriq (atezolizumab) to the current first-line treatment standard for patients with ES-SCLC (carboplatin and etoposide) demonstrated statistically and clinically significant improvements in survival, quality of life, and reduced risk of death.

Tecentriq (atezolizumab) health technology, in combination with carboplatin and etoposide, indicated for the first-line treatment of adult patients with advanced stage small cell lung cancer, is included in the NCCN treatment guidelines and in the Pharmacotherapeutic guide on medical oncology, adopted by Ordinance №11/17.10.2019

Efficacy data

Clinical study IMpower133 (GO30081, NCT02763579)
Study design - a multicenter, randomized, phase I/III, double-blind, placebo-controlled study.

As of the time of the primary survival follow-up analysis (median 13.9 months), Atezo + CE demonstrated a statistically and clinically significant improvement in OS and a statistically significant improvement in the investigator-assessed PFS compared to PBO + CE. The results for OS and PFS in most of the subgroups are consistent with the results of the ITT population. ORR and median DOR are similar between the arms. More patients in the Atezo + CE arm than in the PBO + CE arm responded to treatment during CCOD (April 24, 2018).

In an explorative OS analysis with a longer follow-up (median 22.9 months), the median OS for both arms was unchanged compared to the primary intermediate OS analysis with HR = 0.76 (95% CI: 0.60, 0.95).

Updated 12-month OS rates (51.9% in the treatment arm and 39.0% in the control arm) remained unchanged compared to the primary intermediate OS analysis. Updated 18-month OS rates were 34.0% in the treatment arm and 21.0% in the control arm.

In most of the analyzed subgroups the risk of death is numerically lower with Atezo + CE compared to PBO + CE. This is consistent with the benefit observed in the ITT population. No difference in OS benefit was observed between patients with treated brain metastases. However, no conclusion can be drawn due to the small number of patients with asymptomatic, treated brain metastases and the exploratory nature of the analysis.

Impower 133 clinical trial evaluated disease-related symptoms reported by patients and the impact of treatment on functioning and health-related quality of life (measured by EORTC QLQ-LC13 and EORTC QLQ-LC30).

Safety data

The safety profile of atezolizumab in combination with carboplatin + etoposide in ES-SCLC patients who have not received chemotherapy, is consistent with the profile of the individual therapy components and is comparable to PBO + CE. In summary:

- The incidence of grade 3-4 ADR was comparable between the arms (Atezolizumab + CE: 67.2% versus PBO + CE: 63.8%), with no significant differences between the arms in terms of type and frequency of events.
- The proportion of patients with severe ADR was comparable between the arms (Atezolizumab + CE: 37.4% versus PBO + CE: 34.7%), with no significant differences between the arms in terms of type and frequency of events.
- The incidence of grade 5 ADR was lower in the Atezolizumab + CE arm (2.0%) compared to the PBO + CE arm (5.6%).
- The proportion of patients with ADR leading to treatment discontinuation was higher in the Atezolizumab + CE (11.1%) arm than in PBO + CE (3.1%) arm. Infusion-related reaction was the only ADR leading to discontinuation of treatment, with a ≥ 2% difference in frequency between the arms (2.5% versus 0 [PBO + CE]).
- The proportion of patients with ADR leading to modification/discontinuation of treatment was higher in the Atezolizumab + CE arm (69.7%) than in the PBO + CE arm (60.7%).
- ADR with special interest were observed in more patients in the Atezolizumab + CE arm (39.9%) compared to the PBO + CE arm (24.5%), most of which were mild or moderate in severity. The difference in frequency was mainly due to the higher number of cases of hypothyroidism in Atezolizumab + CE arm (12.6% vs. 0.5% [PBO + CE]).
- A higher proportion of Atezolizumab + CE patients reported a clinically relevant increase in creatinine (4.1% vs. 0.5%); all events are grade 1-2.

Data on comparators

In the analysis, the cisplatin (carboplatin) + etoposide combination was selected as comparative alternative.

Pharmacoeconomic indicators

Applied analysis

A cost-utility analysis (CUA) was employed to evaluate the health technology of atezolizumab in combination with carboplatin and etoposide. The health benefits for patients in the applied model were measured as life-year gained (LYG) and quality-adjusted life years (QALY). In the principle case, the proximity to death approach was used in the model (four *time before death* intervals were included), the categories were further stratified according to whether or not the patients received treatment. The health benefit values used in the model are based on the EQ-5D data from the IMpower133 study. The model uses the perspective of the payer, the National Health Insurance Fund (NHIF). The selected time horizon is lifelong (20

years). Health benefits and costs have been discounted at an annual discount factor of 3.5%. The baseline scenario presents a comparison of atezolizumab in combination with carboplatin and etoposide versus carboplatin + etoposide (the main alternative in the IMpower 133 study), and a comparison to cisplatin + etoposide is included as an additional scenario. The analysis uses a survival model that divides overall survival (OS) into progression-free survival (PFS) and post-progression survival. The model included all grade 3 to 5 ADR or serious ADR from the IMpower 133 study that were identified by the investigator as treatment-related.

The results of the cost-benefit analysis have been presented as ICER (incremental cost-effectiveness ratio) of the evaluated health technology of atezolizumab in combination with carboplatin and etoposide, compared to alternatives. Atezolizumab therapy in combination with carboplatin and etoposide demonstrates a higher value of acquired health benefits at a higher direct cost per patient compared to carboplatin + etoposide and cisplatin + etoposide, exceeding 3 times GDP per capita and is value efficient. Atezolizumab + carboplatin + etoposide demonstrated therapeutic superiority in terms of more years of life gained than etoposide in combination with platinum-based therapies, as demonstrated by the results of IMpower 133 and MMA studies. The performed probabilistic (PSA) and one-way sensitivity analysis (DSA) confirm the results of the basic analysis.

The inclusion of atezolizumab in the treatment algorithm meets the unmet need for new therapies with innovative mechanisms of action and non-overlapping toxicity that can be combined with already approved therapies and thus prolong the response to treatment and significantly improve overall survival. For the first time in more than 20 years, a new first-line treatment regimen is improving the OS while maintaining quality of life (QoL) in the global ES-SCLC population. Based on the breakthrough in the treatment of these patients with unmet needs, the EMA granted an additional year patent for Atezolizumab as a medicinal product with significant clinical benefits for patients.
No subgroup analysis was performed.

Costs for the assessed health technology
Included in the model are costs for drug therapy with atezolizumab in combination with carboplatin and etoposide, for drug therapy with alternatives (carboplatin + etoposide and cisplatin + etoposide), for medication administration and palliative care, for management of adverse drug reactions.
Costs in the event of disease progression and for disease follow-up have not been included in the analysis, as the model assumes a similar annual cost for disease follow-up and control for different therapeutic alternatives.

Budget impact analysis

The budget impact analysis is conducted from the perspective of the payer - the NHIF. The time horizon is 5 years. The estimated number of first-line SCLC patients eligible for treatment with the health technology and alternatives is 60 in the first year, increasing to 115 in the fifth year. Patients on Atezolizumab in combination with carboplatin and etoposide remained on treatment until the mean duration of 6 months within the set time horizon, while those on treatment with carboplatin + etoposide remained on treatment until the mean duration of 3 months. The introduction of the new therapy leads to an increase in the costs of the National Health Insurance Fund, risk-sharing agreements and patient access schemes are not being taken into account.

The sensitivity analysis performed using a tornado diagram shows that the budget impact is largely determined by the cost of therapy with Tecentriq (atezolizumab) in combination with carboplatin + etoposide and the number of patients over a 5-year period.

Conclusion

The efficacy and safety outcomes of the Impower 133 clinical trial provide significant evidence of a favorable benefit/risk profile when atezolizumab is used in combination with carboplatin and etoposide as a first-line treatment in patients with ES-SCLC. The addition of atezolizumab to carboplatin and etoposide demonstrated a statistically and clinically significant improvement in OS, a statistically significant improvement in PFS, and an acceptable safety profile that is consistent with the known safety profile of the individual components, as well as comparable to PBO + CE.

Following the reimbursement of the health technology Tecentriq in combination with carboplatin and etoposide, the cost of extending the first-line treatment of adult patients with advanced stage SCLC increases for the paying institution, associated with more years of life gained and higher QALY. Tecentriq (atezolizumab), combined with chemotherapy, meets the unmet need for new therapies with innovative mechanisms of action and non-overlapping toxicity, which could be combined with already approved therapies and thus prolong the response to treatment and significantly improve overall survival.