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

HEALTH TECHNOLOGY ASSESSMENT

Tecentriq

840 mg concentrate for solution for infusion x 1 vial

Atezolizumab

Therapeutic indication(s)	Tecentriq in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.
Start/end date of procedure	11.10.2019 - 22.12.2020
Final decision	Rejects inclusion of a new 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 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

Breast cancer is the most frequently diagnosed cancer and causes the majority of death cases in women with malignancies globally. Triple-negative breast cancer (TNBC) is characterized by a lack of expression of the hormone receptors for estrogen (ER) and progesterone (PR), as well as a lack of overexpression or amplification of the human epidermal growth factor 2 receptor (HER2 protein/NEU gene). TNBC represents 15% of the newly diagnosed cases of breast cancer. TNBC is an aggressive disease with a poor prognosis. It is characterized by rapid progression and lower overall survival (OS) compared to other subtypes of breast cancer. The median survival in patients with metastatic TNBC (mTNBC) is approximately 13 to 18 months.

TNBC affects all aspects of the lives of patients and their families, negatively affects work capacity, social life, daily activities, physical functioning and mental state.

Epidemiological data

Nearly 24% of all cancers in women are due to breast cancer. It is believed that in 2018 there were approximately 2.1 million cases. The incidence in Western Europe and North America in 2018 is 94.9 and 84.8 per 100,000 people, respectively, the mortality is 15.5 and 12.6 per 100,000 people.

In Bulgaria in 2018, 4016 cases of breast cancer were diagnosed. Annually, in Bulgaria there are approximately 1387 deaths caused by breast cancer, which means that about 7% of patients die annually. For Bulgaria, there are no data on the prevalence of the TNBC subtype. According to GLOBOCAN, 15% of all breast cancers are TNBC, which means that at least 600 patients develop this subtype each year.

Efficacy data

To evaluate the therapeutic efficacy and safety of atezolizumab, the results of one principal, ongoing clinical study (Impassion 130) and one network meta-analysis for indirect comparison of therapies were compared and analyzed.

Clinical study IMpassion 130 evaluated the safety and efficacy of atezolizumab (atezo), co-administered with nab-paclitaxel (nP) compared with placebo (Pl) in combination with nab-paclitaxel in patients with locally advanced or metastatic TNBC who have not received previous systemic therapy for metastatic breast cancer.

Therapeutic efficacy in the ITT population

Primary endpoint: investigator-assessed progression-free survival (PFS)
In the ITT population, a similar proportion of patients from both arms progressed or died by the date of completion of data collection for the assay (83.8% Pl + nP arm versus 79.4% in the atezo + nP arm). The addition of atezolizumab to nP resulted in a statistically significant prolongation of PFS, with a 20% reduction in relative risk compared to Pl + nP, thus reaching the primary endpoint. The median PFS was longer in the arm with atezo + nP (7.2 months) than in Pl + nP (5.5 months).

Primary endpoint: overall survival (OS).
First intermediate OS analysis. By the date of completion of data collection for the first interim analysis, a higher number of deaths had been found in the Pl + nP group (46.1%) compared to the atezo + nP group (40.1%). The 16% reduction in the risk of death in the atezo + nP group compared to Pl + nP was not statistically significant. The median OS was approximately 4 months longer for the atezo + nP group compared to Pl + nP (21.3 months versus 17.6 months).

S*econd intermediate OS analysis*. By the date of completion of the data collection for the second intermediate OS analysis, a higher number of deaths had been observed in the Pl + nP group (61.9%) compared to the atezo + nP group (56.5%). The 14% reduction in the risk of death in the atezo + nP group compared to Pl + nP was not statistically significant. The median OS was approximately 2 months longer for the atezo + nP group compared to Pl + nP (21.0 months versus 18.7 months).

Therapeutic efficacy in the PD-L1-positive patient population
Primary endpoint: investigator-assessed progression-free survival (PFS; PD-L1-positive population). Treatment with atezolizumab + nP compared with Pl + nP resulted in a statistically and clinically significant improvement in PFS with a 38% reduction in relative risk. The median PFS was longer in the arm with atezo + nP (7.5 months) compared to the Pl + nP arm (5.0 months); the one-year frequency without event was almost double for the atezo + nP arm (29.1% versus 16.4%, respectively).

Updated analysis of the investigator-assessed progression-free survival (PFS) (PD-L1-positive population). Treatment with atezolizumab + nP compared with Pl + nP resulted in a statistically and clinically significant improvement in PFS, with a 37% reduction in relative risk. The median PFS was longer in the athezo + nP arm (7.5 months) compared to the Pl + nP arm (5.3 months); the one-year frequency without event was almost double in the atezo + nP arm (30.3% versus 17.3%, respectively).

Second interim analysis of overall survival (PD-L1-positive patient population)
In the PD-L1-positive population, more patients from the Pl + nP arm (59.8%) died compared to the atezo + nP arm (50.8%) by the date of completion of the second interim analysis. A

clinically significant reduction in the risk of death of 29% was observed in patients receiving atezo + nP compared with Pl + nP. This was accompanied by a 7-month extension of the KM median of the OS for the atezo + nP arm compared to Pl + nP (25 months versus 18.0 months, respectively). Over two years, more than half of the patients in the atezo + nP arm lived 50.7%, compared with approximately 36.9% of patients in the Pl + nP arm.

A network meta-analysis for indirect comparison of therapies was performed, which indirectly compared, with respect to PFS, OS and ORR, treatment with atezolizumab + nab-paclitaxel with previously studied and currently used first-line therapies in patients with PD-L1-positive mTNBC. PFS and OS data show a statistically significant 5-year benefit (posterior median; 95% CI) for PFS for atezolizumab + nab-paclitaxel versus paclitaxel (4.08; 1.02-6.49 months) and docetaxel (5.31; 1.88-8.09 months), as well as a statistically significant 5-year OS benefit for atezolizumab + nab-paclitaxel compared to paclitaxel + bevacizumab (7.19; 0.52-13.1 months), paclitaxel (8.62; 1.95-14.37 months) and bevacizumab + capecitabine- (11.4; 1.72-19.36 months).

Safety data

The safety data of atezolizumab, used in combination with other medicinal products, were evaluated in 3425 patients with multiple tumor types. The most common adverse reactions (≥ 20%) were nausea (36.4%), anemia (36.1%), fatigue (35.0%), neutropenia (34.9%), alopecia (32.5%), diarrhea (29.2%), peripheral neuropathy (28.2%), rash (27.5%), constipation (26.8%), decreased appetite (24.8%), thrombocytopenia (23.8%) and musculoskeletal pain (20.6%).

Data on comparators

Taxane-based first-line chemotherapy (docetaxel, paclitaxel, nab-paclitaxel) and anthracycline-based therapy (epirubicin + cyclophosphamide) were selected as comparators.

Pharmacoeconomic indicators

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

NICE recommends Atezolizumab + nab-paclitaxel for the treatment of PD-L1-positive, triple-negative advanced breast cancer. The opinion of IQWiG is that Atezolizumab + nab-paclitaxel does not show additional health benefits, and HAS considers that the combination has no place in the first line of treatment of the disease.

Applied analysis

A cost-benefit pharmacoeconomic analysis has been applied. Health benefits for patients are measured as years of life gained and quality-adjusted life years gained. The perspective is of

the paying institution - the National Health Insurance Fund. The time horizon of the model is lifelong. Costs and benefits are discounted at an annual discount rate of 3.5%. The analysis uses a partitioned survival model, which divides total survival (OS) into progression-free survival (PFS) and post-progression survival. The three health conditions included in the model are PFS, progression, and death. The results of the cost-benefit analysis indicate that atezolizumab therapy in combination with nab-paclitaxel represents a treatment option with higher cost and higher health benefits compared to all comparative alternatives. The incremental ratio of the compared therapies has atezolizumab in combination with nab-paclitaxel outside the area of favorable cost-effectiveness in all cases considered. Uncertainty about future treatment costs is assessed through sensitivity analysis (probabilistic and one-way). Monte Carlo simulation was used.

Subgroup analyzes

Included are adult patients with inoperable locally advanced or metastatic triple-negative breast cancer (TNBC) with PD-L1 tumor expression ≥ 1% who have not received prior chemotherapy for metastatic disease.

Costs of the assessed health technology

The cost of treatment with atezolizumab in combination with nab-paclitaxel, the cost of treatment with alternatives, and the cost of medical services and ADR management were calculated.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the paying public institution - NHIF. The time horizon of the budget impact analysis is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 46 in the first year, reaching 61 in the fifth year. The reimbursement by the NHIF of the health technology atezolizumab in combination with nab-paclitaxel will increase the costs for the paying institution, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The advantage of the Tecentriq health technology, used in combination with nab-paclitaxel in the treatment of patients with inoperable, locally advanced or metastatic TNBC with PD-L1 tumor expression ≥ 1%, lies in the statistically and clinically significant improvement in progression-free survival without compromising patients' functioning or quality of life. The budget impact analysis shows that treatment costs are expected to increase in patients with inoperable locally advanced or metastatic TNBC with PD-L1 tumor expression ≥ 1% who have not received prior chemotherapy for metastatic disease with Tecentriq.