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

HEALTH TECHNOLOGY ASSESSMENT

Tecentriq

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

Atezolizumab

Therapeutic indication(s)	Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.
Start/end date of procedure	04.11.2020 - 22.12.2020
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 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

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver. The incidence of HCC varies depending on the prevalence of hepatitis B and C viruses. Approximately 80% of HCC cases are associated with HBV (~ 50%) or HCV (~ 30%) infection. Increasingly significant risk factors for the development of the disease are non-viral agents such as alcohol, obesity or other metabolic disorders. HCC is asymptomatic for most of the course of the disease. Non-specific symptoms associated with more advanced HCC may include jaundice, anorexia, weight loss, malaise, and upper abdominal pain. Physical signs of HCC may include hepatomegaly and ascites.

The five-year survival rate is lowest in patients diagnosed with cancer of the liver and intrahepatic bile duct.

In liver cancer, 44% of patients are diagnosed at an early stage of the disease. The five-year relative survival at this localized stage is 34.2%.

HCC continues to be associated with significant economic burden, morbidity, mortality and deteriorating quality of life (QoL).

Epidemiological data

Liver cancer is the fifth most common cause of death in men and the seventh most common cause of death in women. According to the European Cancer Information System (ECIS), the projected morbidity in Bulgaria for 2020 is 8.5% of all cancers for both sexes, and mortality 3%.

To date, there are only a few alternatives to systemic treatment, and the chemotherapy regimen has shown little effect in HCC. Non-systemic therapeutic alternatives, such as transarterial chemoembolization/embolization (TACE/TAE), are limited due to absolute or relative contraindications in some of the patients. There is unmet medical need for new systemic first-line treatment options in patients with unresectable HCC.

Efficacy data

The therapeutic efficacy and safety profile of atezolizumab in combination with bevacizumab in adult patients with advanced or unresectable hepatocellular carcinoma (HCC) have been evaluated in three clinical trials.

The main evidence of efficacy come from the phase III randomized controlled trial *IMbrave150*, with supporting evidence from phase Ib *GO30140*. The conducted network meta-analysis, including a study with sorafenib and other comparators, is also indirect evidence of the effectiveness of the combination atezolizumab + bevacizumab.

The clinical study *IMbrave150* (NCT03434379) evaluated the efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in patients with locally advanced and/or unresectable HCC, not amenable to curative surgical and/or locoregional treatment (LRT), or progressive disease after surgical and/or LRT. The results showed that treatment with atezolizumab plus bevacizumab was associated with significantly better overall survival (OS) and progression-free survival (PFS) than sorafenib in patients with advanced unresectable hepatocellular carcinoma who had not been previously treated with systemic therapy. The primary endpoints of the study - OS and PFS according to RECIST v1.1 - were reached in the ITT (intention to treat) population with statistically and clinically significant improvement in atezolizumab plus bevacizumab vs sorafenib. There was a 42% reduction in the risk of death in the atezolizumab plus bevacizumab arm compared to sorafenib arm; median OS: 13.2 months in the sorafenib arm compared to unachieved in atezolizumab plus bevacizumab arm. There was a 41% reduction in the risk of disease progression or death in atezolizumab plus bevacizumab arm compared with the sorafenib arm; median PFS: 4.3 months in sorafenib arm versus 6.8 months in atezolizumab plus bevacizumab arm. Treatment with atezolizumab plus bevacizumab resulted in a clinically significant delay in the deterioration of the patient-reported physical function, role function and quality of life compared to sorafenib.

Clinical study *GO30140* (NCT02715531) assessed the efficacy and safety of atezolizumab in combination with bevacizumab and/or other therapies in patients with solid tumors. The efficacy and safety data of GO30140 support the positive benefit-risk profile demonstrated by atezolizumab plus bevacizumab in the IMbrave150 study.

Safety data

The results of clinical trials confirm the good tolerability of the combination therapy atezolizumab plus bevacizumab. The most common adverse events are hypertension (29.8%), fatigue (20.4%) and proteinuria (20.1%). The incidence of severe adverse events was higher with atezolizumab plus bevacizumab combination therapy (38%) compared with sorafenib (30.8%); the incidence of treatment-related severe adverse events was similar (17% vs. 15.4%).

The percentage of patients with grade 3-4 adverse events (maximal grade) was comparable between sorafenib (55.1%) and atezolizumab plus bevacizumab (56.5%).

The incidence of treatment-related severe adverse events was comparable between sorafenib (15.4%) and atezolizumab plus bevacizumab (17.0%).

Data on comparators

According to the local guidelines for therapy, sorafenib, lenvatinib, epirubicin, as well as the triple chemotherapeutic combinations cisplatin + fluorouracil + epirubicin and cisplatin + fluorouracil + vincristine are indicated as first-line systemic therapy for inoperable or metastatic disease. The use of conventional chemotherapy is limited due to high resistance, impaired liver function and concomitant chronic liver disease (hepatitis and/or cirrhosis). The main comparator that can partially replace the assessed therapy with atezolizumab + bevacizumab is the multikinase inhibitor sorafenib.

Pharmacoeconomic indicators

Applied analysis

The chosen method for comparative assessment of the health technology is a cost-benefit analysis. In addition, a cost-effectiveness analysis was conducted. The outcome measures are quality adjusted life year and years of life gained. The perspective of the analysis is that of the paying institution – the NHIF. The time horizon is lifelong - 20 years. Discounting with an annual discount factor of 3.5% is applied. A partitioned survival model was used, with 3 stages - PFS, progression, death. The comparator is sorafenib. The therapy with atezolizumab + bevacizumab is associated with additional cost and with added years of life and QALY compared to sorafenib. From the point of view of the health care system in Bulgaria, atezolizumab + bevacizumab is not cost-effective compared to sorafenib, as the incremental ratio falls above the break-even point.
The performed sensitivity analyses confirm the conclusions made.

Subgroup analyses

No subgroup analysis was performed.

Cost of the assessed health technology

The analysis included atezolizumab in combination with bevacizumab medication cost and alternatives (sorafenib) medication cost, drug administration cost, medical services cost, adverse events management cost, outpatient monitoring cost, palliative care cost.

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the public payer – the NHIF. The time horizon is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 55 in the first year, reaching 110 in the fifth year.

Paying for Tecentriq with public funds will lead to additional cost for the NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Compared to standard treatment (sorafenib) in adult patients with advanced or unresectable hepatocellular carcinoma who have not received prior systemic therapy, the combination atezolizumab plus bevacizumab prolongs overall survival and progression-free survival, improves overall response rate and its duration, slows the quality of life deterioration. The payment of Tecentriq with public funds will lead to additional cost throughout the analysis period, with the additional cost being associated with additional benefits for patients.