



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



HEALTH TECHNOLOGY ASSESSMENT

Opdivo

10 mg/ml - 4 ml concentrate for solution for infusion x 1 vial

10 mg/ml - 10 ml concentrate for solution for infusion x 1 vial

INN Nivolumab

Therapeutic indication	In combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumors express PD-L1 with a combined positive score (CPS) ≥ 5 .
Start- end of the procedure	01.09.2022 – 22.12.2022
Final decision	Addition of a new therapeutic indication to Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act, and reimbursement by the NHIF beyond the value of the provided medical services.



Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Opdivo

Health problem

Gastroesophageal cancer is a heterogeneous disease with tumor manifestations in the esophagus, gastroesophageal junction, or stomach. Gastroesophageal adenocarcinomas are associated with high mortality. It has been established that infection with *Helicobacter pylori* (H. pylori) is an indisputable cause of approximately 65–80% of stomach cancer cases. Additional risk factors for both stomach cancer and gastroesophageal junction cancer include advanced age, male sex, smoking, race, family history, low physical activity, low fiber intake, exposure to radiation, low socioeconomic status, and a diet high in salty and smoked foods and low in fruits and vegetables. Stomach cancer is asymptomatic in early stages or is associated with nonspecific symptoms such as dyspepsia, bloating, mild nausea, loss of appetite, and/or acid reflux. Common symptoms at an advanced stage of the disease include difficulty swallowing (dysphagia), anorexia, weight loss, which may result from reduced appetite and/or a sensation of fullness after consuming only small amounts of food, localized persistent abdominal pain, ascites, jaundice, persistent acid reflux or dyspepsia, nausea, and vomiting. Patients may also experience gastrointestinal bleeding, which can lead to anemia, fatigue, and shortness of breath, as well as the presence of blood in the stools. Nivolumab is a fully humanized immunoglobulin G4 antibody, a PD-1 receptor inhibitor, which prevents the inactivation or reactivation of T-cells' ability to provide antitumor protection. Nivolumab binds with high affinity to PD-1 receptors on T-cells and selectively disrupts the inhibitory signaling activated by PD-L1 and programmed cell death ligand 2 (PD-L2), thereby restoring normal antitumor T-cell function. PD-1 expression on immune cells is elevated in patients with certain types of cancers, including stomach cancer, where approximately 14-65% of tumors express PD-1.

Epidemiological data

According to GLOBOCAN data (2020), stomach cancer ranks 9th in terms of incidence and 6th in terms of mortality among all cancers in Bulgaria. In 2020, the total number of newly diagnosed cases of stomach cancer in Bulgaria was 1,267 (3.5% of all diagnosed cancers). During the same period, there were 1,073 deaths (5.5% of all cancer-related deaths) in the country.

Also, according to GLOBOCAN data (2020), esophageal cancer ranks 22nd in terms of incidence and 19th in terms of mortality among all cancers in Bulgaria. In 2020, the total number of newly diagnosed cases of esophageal cancer in Bulgaria was 222 (0.61% of all diagnosed cancers). For the same period, there were 204 deaths (1.0% of all cancer-related deaths) in the country.



Efficacy data

The therapeutic efficacy and safety profile of nivolumab have been analyzed in one clinical trial.

The CheckMate 649 clinical trial is a randomized, open-label, phase 3 trial that evaluates the efficacy and safety of nivolumab plus ipilimumab or nivolumab plus chemotherapy (XELOX [capecitabine + oxaliplatin] or FOLFOX [leucovorin + 5-FU + oxaliplatin]) compared to chemotherapy (XELOX or FOLFOX) in patients with previously untreated advanced or metastatic stomach/gastroesophageal junction or esophageal cancer. Randomisation is 1:1:1 in all arms until completion of enrollment in the nivolumab + ipilimumab arm ECOG PS - Eastern Cooperative Oncology Group functional status; FOLFOX - leucovorin + 5-fluorouracil + oxaliplatin, GEJ - gastroesophageal junction; PD-L1 - programmed cell death receptor ligand 1; Q2W - every 2 weeks; Q3W - every 3 weeks; ROW - rest of the world; XELOX, capecitabine + oxaliplatin.

The primary endpoints are overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR). For overall survival (OS) with a minimum follow-up of 12.1 months, nivolumab plus chemotherapy demonstrated a statistically significant and clinically relevant 29% reduction in the risk of death compared to chemotherapy in patients with PD-L1 CPS ≥ 5 . The median OS was 3.3 months longer in the nivolumab plus chemotherapy arm compared to the chemotherapy arm: 14.4 months versus 11.1 months. In month 6, the OS rate was higher in the nivolumab plus chemotherapy arm compared to the chemotherapy arm: 81.4% versus 74.8%; in month 12, the rates were 57.3% and 46.4%, respectively. Progression-free survival (PFS): In patients with PD-L1 CPS ≥ 5 , nivolumab plus chemotherapy showed a statistically significant and clinically relevant 32% reduction in the risk of progression compared to chemotherapy. The median PFS was significantly improved by 1.7 months in the nivolumab plus chemotherapy arm compared to chemotherapy (7.7 months versus 6.0 months). The PFS rate was higher in the nivolumab plus chemotherapy arm compared to chemotherapy: 62.4% versus 50.1% in month 6 and 36.3% versus 21.9% in month 12. Objective response rate (ORR): For patients with measurable disease and PD-L1 CPS ≥ 5 , an improvement in ORR assessed by BICR was observed in those treated with nivolumab plus chemotherapy compared to chemotherapy. Overall, 12% of patients receiving nivolumab plus chemotherapy achieved a complete response (CR) compared to 7% of patients treated with chemotherapy. For all randomized patients with PD-L1 CPS ≥ 5 who had measurable disease and a response to treatment, the median time to response (TTR) was 1.5 months for both arms. The median duration of response (DOR) was longer in the nivolumab plus chemotherapy arm by 2.5 months compared to the chemotherapy arm. In all randomized patients with PD-L1 CPS ≥ 5 who had measurable disease and were treatment responders, the median TTR was 1.5 months in both arms. The median DOR (95% CI) was greater in the nivolumab plus chemotherapy arm by 2.5 months compared with the chemotherapy arm. A higher proportion of patients in the nivolumab plus chemotherapy arm had a longer DOR compared to the chemotherapy arm. Approximately 65% of responders receiving nivolumab plus chemotherapy had a DOR of at least 6 months compared to 56% of responders receiving chemotherapy. Around 43% and 30% of responders in each arm had a DOR of at least 12 months.



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Safety data

The most common adverse reactions (>10%) are nausea (53%), peripheral neuropathy (43%), fatigue (41%), diarrhea (37%), decreased appetite (35%), constipation (30%), vomiting (29%), stomatitis (25%), abdominal pain (23%), fever (19%), rash (17%), musculoskeletal pain (17%), cough (14%), edema (including peripheral edema) (14%), hypoalbuminemia (13%), and headache (10%).

Data on comparators

Comparative alternatives include the following therapies:

For esophageal cancer: cisplatin + fluorouracil, pembrolizumab + cisplatin + fluorouracil.

For stomach cancer: cisplatin + fluorouracil + epirubicin, etoposide + fluorouracil + leucovorin.

Pharmacoeconomic indicators

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

Two positive evaluations have been published by other governmental institutions: HAS (France) and CADTH (Canada). The conclusion of IQWiG (Germany) regarding the indication for adult patients with HER2-negative, advanced or metastatic esophageal adenocarcinoma with PD-L1 expression and CPS ≥ 5 as first-line therapy is that the additional benefit of nivolumab treatment has not been demonstrated. For the indication of adult patients with HER2-negative, advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction with PD-L1 expression and CPS ≥ 5 as first-line therapy, there is an indication of a quantitatively unmeasurable added benefit with nivolumab treatment.

Applied analysis

The applied pharmacoeconomic analysis is of cost-effectiveness (CEA) type, where the final outcome in terms of health benefits is expressed as life years gained (LYG). This analysis is further enhanced with a cost-utility analysis (CUA), where the final outcome is expressed as quality-adjusted life years (QALY) gained. The comparative alternatives selected are fluorouracil, epirubicin, cisplatin, and cisplatin + fluorouracil. The perspective of the analysis is that of the payer institution – the National Health Insurance Fund (NHIF). The chosen time horizon is 40 years or a lifetime horizon, which is deemed appropriate for the model and justified given the expected lifespan. Health benefits and costs are discounted at an annual discount rate of 3.5%. A survival model has been developed, including three health states: with disease progression, without disease progression, and death.

The results of the analysis show that the incremental cost-utility ratio (ICUR) for nivolumab + chemotherapy compared to the alternatives exceeds the threshold for favorable cost-effectiveness.



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The analysis demonstrates the high value of the new technology and a moderate improvement in survival. Exceeding the threshold of >1 year of overall survival is reported as a significant health benefit.

Costs for the assessed health technology

The model includes only direct medical costs – costs for treatment with the comparative alternatives, costs for chemotherapy in subsequent therapy, costs for the use of the health technology nivolumab + XELOX, costs for the use of the health technology nivolumab + FOLFOX, costs for the use of the comparative alternative FEP (fluorouracil, cisplatin, epirubicin), costs for the use of the comparative alternative cisplatin + fluorouracil, costs for subsequent chemotherapy with paclitaxel + ramucirumab, costs for medical diagnostic activities for patients with HER-2 negative, advanced or metastatic adenocarcinoma of the stomach, gastroesophageal junction, or esophagus, and costs for managing adverse events.

Subgroup analysis

Not attached

Budget impact analysis

The budget impact analysis has been conducted from the perspective of the public payer institution – the National Health Insurance Fund (NHIF). The time horizon for the budget impact analysis is 5 years. The expected number of patients treated with Opdivo in the first year is 164, and in the fifth year, it is 139. Two scenarios are presented: a world with Opdivo and a world without Opdivo. The model is structured in two variants – Variant 1: with dose intensity = 100%, and Variant 2: with dose intensity <100%. Variant 2 reflects actual clinical practice and correlates with data from the CheckMate-649 clinical trial.

The budget impact of reimbursing Opdivo as first-line therapy for adult patients with HER2-negative, advanced or metastatic adenocarcinoma of the stomach, gastroesophageal junction, or esophagus, whose tumors have PD-L1 expression with a combined positive score (CPS) ≥ 5 , with 100% and <100% reported dose intensity, forecasts an increase in NHIF expenses over a period of five years. Risk-sharing agreements and patient access schemes have not been considered.

Conclusion

According to GLOBOCAN data (2020), stomach cancer ranks 9th in terms of incidence and 6th in terms of mortality and esophageal cancer ranks 22nd in terms of incidence and 19th in terms of mortality among all cancers in Bulgaria. Stomach cancer is a socially significant disease, often diagnosed at an advanced stage, which is associated with low five-year survival rates and poor prognosis. The health technology Opdivo (nivolumab) in combination with fluoropyrimidine and platinum-based chemotherapy is indicated as first-line treatment for adult patients with HER2-negative, advanced or metastatic adenocarcinoma of the stomach, gastroesophageal junction, or esophagus, whose tumors have PD-L1 expression with a combined positive score (CPS) ≥ 5 . The



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analysis shows significant health benefits for the patient and a moderate improvement in survival as well as an increase in NHIF costs under full and partial reimbursement over a five-year period.