



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	As monotherapy, it is indicated for the adjuvant treatment of adult patients with esophageal carcinoma or gastroesophageal junction carcinoma who have residual pathologic disease following prior neoadjuvant chemotherapy.
Start- end of the procedure	10.10.2022 – 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

Esophageal cancers are primarily classified into squamous cell carcinoma of the esophagus (SCC) and esophageal adenocarcinoma (EAC), based on the histological characteristics of the disease. The disease involves malignant tumor formations in the epithelial tissue of the esophagus. Gastroesophageal cancers (GEC) are a heterogeneous group of diseases, typically divided into three different segments:

- Esophageal carcinoma (EC): where malignant cell clusters are found within the tissues of the esophagus.
- Gastroesophageal junction carcinoma (GEJC): where malignant cells form at the junction of the esophagus and the stomach, known as the gastroesophageal junction (GEJ).
- Stomach carcinoma (SC): where malignant cell clusters develop in the mucosa of the stomach.

In its early stages, esophageal carcinoma (EC) is often asymptomatic. Once symptoms appear, EC typically manifests as dysphagia (difficulty swallowing) with solid food and weight loss. These symptoms can persist for several months and combined with a history of smoking and alcohol consumption, are indicative of SCC. Other symptoms may include chest pain in the absence of myocardial ischemia and anemia. Chronic gastrointestinal bleeding from mucosal lesions is possible but more typical of EAC. These clinical signs and symptoms require further examination, endoscopic evaluation, and imaging studies.

Nivolumab is a fully humanized immunoglobulin type 4 antibody, a PD-1 receptor inhibitor, which prevents the inactivation or reactivates the ability of T-cells 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 PD-L2, thereby restoring normal antitumor T-cell function. Before the approval of nivolumab, patients with residual pathological disease who had undergone neoadjuvant chemoradiotherapy (CRT) and resection were monitored for recurrence according to current clinical practice.

Epidemiological data

According to data for Bulgaria in 2020, esophageal carcinoma (EC) ranks 22nd in terms of new cases and 19th in terms of mortality among all malignant tumors registered in the country. There were 222 new cases (0.61% of all diagnosed cancers), and 204 deaths (1% of all cancer-related deaths).



Efficacy data

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

CheckMate 577 is a global, phase 3, randomized, multicenter, double-blind, placebo-controlled trial evaluating adjuvant nivolumab in adults with resected esophageal carcinoma (EC) or gastroesophageal junction carcinoma (GEJC) who have residual pathological disease following prior neoadjuvant CRT. In the trial, 794 patients were randomized (2:1) to receive either nivolumab monotherapy or placebo. Randomization was stratified based on: PD-L1 ligand 1 expression in tumor cells ($\geq 1\%$ vs. $< 1\%$ or undefined); pathological lymph nodes (ypN0 vs. $\geq$ ypN1); and histology (squamous cell carcinoma vs. adenocarcinoma). Patients randomized to nivolumab received 240 mg intravenously every 2 weeks for 16 weeks (8 doses), followed by 480 mg intravenously every 4 weeks, starting from week 17 (2 weeks after the 8th dose). Patients received placebo, administered intravenously every 2 weeks for the same duration and frequency as nivolumab. Treatment continued until disease recurrence.

Disease-Free Survival (DFS) was defined as the primary endpoint.

In the primary analysis, adjuvant nivolumab demonstrated a statistically significant improvement in DFS versus placebo, with a 31% reduction in the risk of relapse or death. There was a sustained separation of DFS curves and a doubling of median DFS with a clinically meaningful improvement of 11.4 months compared to placebo (median DFS: 22.4 months with nivolumab and 11.0 months with placebo). At month 6, the DFS rate was 72% in the nivolumab arm and 63% in the placebo arm. In the primary analysis, a total of 396 DFS-related events were reported, with 241 (45.3%) patients in the nivolumab arm and 155 (59.2%) patients in the placebo arm. Of all observed DFS events, 366 were recurrences (219 in the nivolumab arm and 147 in the placebo arm), and 30 were deaths. Similarly, fewer locoregional recurrences were observed in the nivolumab arm compared to placebo (65 out of 532 patients [12%] vs. 44 out of 262 patients [17%]). The median distant metastasis-free survival was 28.3 months in the nivolumab group and 17.6 months in the placebo group; thus, the risk of distant recurrence or death was 26% lower with nivolumab than with placebo. In the ad hoc analysis with longer follow-up, a total of 439 DFS-related events were reported in 268 (50.4%) patients in the nivolumab arm and 171 (65.3%) patients in the placebo arm. Adjuvant nivolumab continued to demonstrate a statistically significant improvement in DFS versus placebo, with a 33% reduction in the risk of relapse or death.

In the primary analysis, subsequent therapy including systemic antitumor therapy, radiation therapy, and surgery was administered to 30% (157 out of 532) of patients in the nivolumab arm and 42% (111 out of 262) in the placebo arm. Of 214 patients who received subsequent systemic antitumor therapy, 125 (23%) were in the nivolumab arm and 89 (34%) were in the placebo arm. A small number of these patients received subsequent immunotherapy (4 out of 532 patients [$< 1\%$] and 19 out of 262 patients [7%], respectively). In an ad hoc analysis with longer follow-up, 35% (186 out of 532) of patients in the nivolumab arm and 47% (124 out of 262) in the placebo arm



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received subsequent therapy. Subsequent immunotherapy was administered to 1% (7 out of 532) of patients in the nivolumab arm and 10% (26 out of 262) of patients in the placebo arm.

In the ad hoc analysis with longer follow-up, a total of 439 DFS-related events were reported in 268 (50.4%) patients in the nivolumab arm and 171 (65.3%) patients in the placebo arm. Adjuvant nivolumab continued to demonstrate a statistically significant improvement in DFS versus placebo, with a 33% reduction in the risk of relapse or death.

Safety data

The most common adverse reactions ($\geq 10\%$) are fatigue (45%), musculoskeletal pain (31%), diarrhea (26%), cough (24%), rash (24%), nausea (23%), pruritus (19%), decreased appetite (18%), constipation (17%), dyspnea (17%), abdominal pain (16%), upper respiratory tract infection (16%), arthralgia (14%), pyrexia (14%), vomiting (14%), headache (13%), and edema (10%). The majority of adverse reactions are mild to moderate in severity (grade 1 or 2).

Data on comparators

The comparative alternatives are determined according to the Pharmacotherapeutic Guidelines for Medical Oncology and reimbursed by the National Health Insurance Fund (NHIF): cisplatin + paclitaxel, carboplatin + paclitaxel, cisplatin + irinotecan.

Pharmacoeconomic indicators

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

An evaluation has been conducted in five national institutions – in the United Kingdom (NICE), Germany (IQWiG), France (HAS), Scotland (SMC), and Canada (CADTH). IQWiG indicates a small added benefit for adjuvant treatment with nivolumab compared to placebo in the specific patient population. All other institutions recommend the inclusion of Opdivo in the reimbursement system.

Applied analysis

The selected pharmacoeconomic methods for analysis are cost-effectiveness analysis (CEA), where the outcome in terms of health benefits is presented as life-years gained (LYG), and cost-utility analysis (CUA), where the outcome in terms of health benefits is presented as quality-adjusted life-years (QALY) gained. The appropriate alternatives for the analysis are cisplatin + paclitaxel, carboplatin + paclitaxel, and cisplatin + irinotecan, with adjuvant chemotherapy applied for adenocarcinoma histology and pN+, as no proven effect is observed for squamous cell carcinoma and treatment is discussed only for selected patients. The perspective of the analysis is that of the paying institution – the National Health Insurance Fund (NHIF). The chosen time



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horizon is lifetime. Health benefits and costs are discounted at an annual discount factor of 3.5%. A Markov model, including three health states – pre-relapse, post-relapse, and death – was used in the analysis.

Considering the primary scenario – the treatment of adult patients with esophageal carcinoma or gastroesophageal junction carcinoma who have residual pathological disease after prior neoadjuvant chemotherapy with nivolumab / Opdivo – will lead to higher health benefits, namely more life-years gained and quality-adjusted life-years gained. Accordingly, the ICER/LYG falls below the threshold of favorable cost-effectiveness, i.e., nivolumab treatment is cost-effective. ICUR/QALY exceeds but not significantly the 3xGDP threshold. In the additional scenario, where a 10% compensation for NHIF is provided, a similar conclusion can be made. ICER/LYG falls below the threshold of favorable cost-effectiveness, making health technology a cost-effective choice for treating the specific patient population, while ICUR/QALY is slightly above the favorable threshold set by WHO.

Costs for the assessed health technology

The model includes only direct medical costs – costs for the treatment and administration of Opdivo and costs for the treatment and administration of the alternatives.

Subgroup analysis

Not attached

Budget impact analysis

The budget impact analysis is conducted from the perspective of the public payer – the National Health Insurance Fund (NHIF). The time horizon for the budget impact analysis is 5 years. The comparative alternatives selected are cisplatin + paclitaxel, carboplatin + paclitaxel, and cisplatin + irinotecan. The forecasted number of patients in the first year is 53, and in the fifth year - 67. The costs included in the analysis are calculated in two scenarios:

- World with the health technology Opdivo – the medicinal product will be used for treating patients with esophageal cancer or gastroesophageal junction cancer.
- World without the health technology Opdivo – the medicinal product will not be reimbursed by NHIF.

The analysis forecasts an increase in costs over a period of five years if Opdivo therapy is reimbursed by NHIF for treating adult patients with esophageal or gastroesophageal junction cancer who have residual pathological disease after previous neoadjuvant chemotherapy, without considering risk-sharing agreements and patient access schemes.

Conclusion

Nivolumab is a fully humanized immunoglobulin type 4 antibody, a PD-1 receptor inhibitor. Prior to the approval of nivolumab, patients with residual pathologic disease who received neoadjuvant chemo-/radiotherapy and resection were placed under surveillance for relapse according to current



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clinical practice. The health technology Opdivo/nivolumab is a cost-effective choice as a monotherapy for adjuvant treatment of adult patients with esophageal cancer or gastroesophageal junction cancer who have residual pathological disease after previous neoadjuvant chemotherapy. Adding this medicinal product with the new indication to the Positive Drug List (PDL) will inevitably increase costs for the healthcare system but will provide a therapeutic approach that increases the number of life-years gained and quality-adjusted life-years gained.