



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(s)	Opdivo is mainly used when cancers are advanced, unresectable (cannot be removed by surgery) or metastatic (have spread to other parts of the body), or when other treatments do not work.
Start/end date of procedure	21.09.2022 – 29.12.2022
Final decision	Inclusion in 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.



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

Health problem

Esophageal carcinoma (EC) is a disease in which malignant (cancer) cells form in the tissues of the esophagus, the muscular tube through which food and liquids move from the throat to the stomach. It is one of the most aggressive types of cancer. There are two main histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), which differ significantly in terms of physiology, epidemiology and risk factors. ESCC is the most common form in the European Union (EU), accounting for 85% of cases globally and it is the predominant histological type in Asia and most of Europe. Tumor obstruction symptoms include dysphagia, weight loss, pain and/or fatigue. Early EC is usually asymptomatic. Dysphagia to solid foods is the primary symptom leading ESCC patients to seek medical attention.

The preferred first-line treatments for metastatic ESCC are chemotherapy regimens based on platinum compounds (cisplatin, oxaliplatin), fluoropyrimidines (capecitabine, fluorouracil), taxanes, anthracyclines, such as epirubicin, and pembrolizumab. However, a large percentage (42%) of ESCC patients remain untreated after prior fluoropyrimidine- and platinum-based combination chemotherapy. Most patients with ESCC receive taxanes as a second-line treatment, but their use is associated with low long-term survival and adverse events, which can lead to treatment delays and dose reductions.

As a result, there is an urgent need for new treatments that can improve survival outcomes with a manageable safety profile, reducing the disease burden in this patient population with limited treatment options.

Opdivo (nivolumab) as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma following prior fluoropyrimidine- and platinum-based combination chemotherapy.

Epidemiological Data

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



Efficacy data

The therapeutic efficacy and safety profile of nivolumab as monotherapy in adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma following prior fluoropyrimidine- and platinum-based combination chemotherapy were analyzed in a clinical trial. The ATTRACTION-3 trial is an open-label, multicenter, phase 3 randomized trial evaluating nivolumab compared to taxane monotherapy. The trial included 419 patients with unresectable advanced or recurrent ESCC. The trial results showed:

Overall survival (OS): 10.9 months for nivolumab vs. 8.4 months for taxane monotherapy;

Objective response rate (ORR): 19% for nivolumab vs. 22% for taxane monotherapy;

Duration of response (DOR): 6.9 months for nivolumab vs. 3.9 months for taxane monotherapy;

Progression-free survival (PFS) at 12 months: 12% for nivolumab vs. 7% for taxane monotherapy.

Nivolumab demonstrated a statistically significant and clinically meaningful improvement in OS compared to taxane monotherapy, increasing survival by 2.5 months with nivolumab treatment and reducing the risk of death by 23%. At 12 and 18 months, 47% and 31% of patients treated with nivolumab were still alive compared to 34% and 21% of patients treated with taxane monotherapy, suggesting that nivolumab provides a durable OS benefit. The survival benefit with nivolumab was independent of PD-L1 expression in tumor cells.

Safety data

The most common adverse events in patients treated with nivolumab were diarrhea (11%), rash (11%) and decreased appetite (8%), while patients treated with taxane monotherapy experienced alopecia (47%), decreased neutrophil count (37%) and decreased leukocyte count (35%).

Data on comparators

The following therapies are used as comparative alternatives: Paclitaxel and Docetaxel, which is applied for adenocarcinoma histology and progression after ≥ 6 months following platinum/fluoropyrimidine-based chemotherapy.

Pharmacoeconomic indicators

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



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Three assessments from other national institutions—NICE (United Kingdom), SMC (Scotland), and HAS (France)—have been included. In the United Kingdom, nivolumab is provided according to a commercial agreement with the NHS (National Health Service), which ensures a confidential discount. The SMC has approved the product for reimbursement for the treatment of patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma following prior fluoropyrimidine- and platinum-based combination chemotherapy, under agreed conditions. However, the final reimbursement decision in France was not in favor of Opdivo.

Attached analysis

A cost-utility analysis (CUA) has been included, where the outcome in terms of health benefits is presented as quality-adjusted life years (QALY) gained, along with a cost-effectiveness analysis (CEA), where the outcome is presented as life years gained (LYG). The perspective of the analysis is that of the payer—the National Health Insurance Fund (NHIF). The chosen time horizon in the model is lifetime (20 years). The comparative alternative selected is taxane-based chemotherapy with paclitaxel (monotherapy). Health benefits and costs are discounted at an annual rate of 3.5%. A partitioned survival model (PSM) with three health states was used to model the health benefits and costs of nivolumab and the therapeutic alternative paclitaxel for the target patient group and to assess the incremental cost-utility ratio (ICUR) of nivolumab compared to paclitaxel.

The results of the analyses show that nivolumab therapy is associated with additional costs but also with the addition of QALY and LYG compared to paclitaxel. From the perspective of the healthcare system in Bulgaria, nivolumab therapy is not cost-effective. The incremental cost-effectiveness ratio (ICER) and cost-utility ratio (ICUR) of the compared regimens remain above the threshold for favorable cost-effectiveness. The probability that nivolumab therapy is cost-effective compared to paclitaxel is 1%. The results of the one-way sensitivity analysis indicate that the health benefits and the cost of nivolumab therapy have the greatest impact on the ICER.

Costs for the assessed health technology

The model includes only direct medical costs, such as the cost of drug therapy and comparative alternatives, administration costs of the drug therapies, costs of medical services for disease monitoring, costs for managing adverse events and costs of palliative care.

Subgroup analysis

Not provided.

Budget impact analysis

The budget impact analysis is conducted from the perspective of the public payer—NHIF. The time horizon of the budget impact analysis is five years. The target population includes adult patients with unresectable, advanced, recurrent, or metastatic esophageal squamous cell carcinoma following prior fluoropyrimidine- and platinum-based combination chemotherapy. The estimated number of patients for treatment with nivolumab is nine in the first year and nine in the fifth year. The budget impact analysis was conducted by developing two scenarios: "World



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with Opdivo" and "World without Opdivo." Paclitaxel was chosen as the alternative. Two calculation scenarios are presented:

Scenario 1: with 100% dose intensity;

Scenario 2: with relative dose intensity (RDI).

The analysis predicts an increase in costs over five years if Opdivo therapy is reimbursed by NHIF for the evaluated indication without taking into account risk-sharing agreements or patient access schemes.

Conclusion

Opdivo (nivolumab) as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma following prior fluoropyrimidine- and platinum-based combination chemotherapy. The analysis results indicate that nivolumab therapy is associated with additional costs but also with added QALY and LYG. From the perspective of the healthcare system in Bulgaria, nivolumab therapy is not cost-effective. Nevertheless, the evaluated therapy offers a treatment option for patients with EC, improving their survival and quality of life.