



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 – 22.12.2022
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

Malignant pleural mesothelioma (MPM) is a rare and highly aggressive malignancy of the mesothelium affecting the lungs and chest wall, primarily caused by asbestos exposure. Based on tumor location, malignant mesothelioma (MM) is classified into four types: pleural mesothelioma, peritoneal mesothelioma, pericardial mesothelioma and testicular/ovarian mesothelioma. Histologically, mesothelioma is categorized into three main types: epithelioid (60-80% of all mesothelioma cases) and non-epithelioid (sarcomatoid and biphasic). The symptoms of MPM are often nonspecific and can mimic other respiratory diseases. Early-stage MPM patients typically experience symptoms such as difficulty breathing, chest pain and pleural effusion. Advanced MPM is associated with fatigue, severe weight loss, muscle wasting (cachexia), fever and night sweats. The nonspecific nature of the symptoms and the latent period of up to 40 years make early diagnosis of MPM challenging.

Currently, there is no definitive cure for MPM. The chemotherapeutic regimens used as standard treatment for MPM are associated with poor outcomes and significant acute and chronic treatment-related adverse effects.

Nivolumab and ipilimumab are immuno-oncology therapies targeting separate, distinct, but complementary immune checkpoints (programmed death receptor ligand 1 [PD-1] and cytotoxic T-lymphocyte-associated protein [CTLA-4], respectively), enhancing the body's natural immune response to recognize and defend against tumor cells. The inhibition mediated by the combination of nivolumab and ipilimumab results in improved T-cell function, greater than when either antibody is used alone, and enhances the antitumor response in metastatic melanoma, advanced renal cell carcinoma, gastric cancer, metastatic colorectal cancer and non-small cell lung cancer (NSCLC).

Nivolumab plus ipilimumab is the first dual immunotherapy investigated in a Phase 3 trial for patients with unresectable MPM. Nivolumab plus low-dose ipilimumab (1 mg/kg) promises durable dual immuno-oncology efficacy due to a potentially synergistic mechanism of action, while also maintaining a predictable safety profile and being well-tolerated in three other tumor types: NSCLC, melanoma, and renal cell carcinoma (RCC).

Epidemiological Data

According to GLOBOCAN 2020, 56 cases of mesothelioma were registered in Bulgaria, with 51 deaths. The 5-year prevalence is 1.17 per 100,000.



Efficacy data

The therapeutic efficacy and safety profile of nivolumab has been analyzed in one clinical trial. The clinical trial CheckMate 743 (CM-743) is an open-label, multicenter, randomized Phase 3 trial evaluating nivolumab plus low-dose ipilimumab (1 mg/kg) compared to chemotherapy (pemetrexed with cisplatin or carboplatin) as first-line therapy in patients with previously untreated unresectable malignant pleural mesothelioma (MPM). Patients in CM-743 were randomized (1:1) to one of the following treatments: Arm A: nivolumab, administered intravenously (IV) over 30 minutes at a dose of 3 mg/kg Q2W, in combination with ipilimumab, administered IV over 30 minutes at a dose of 1 mg/kg Q6W for up to 2 years; Arm B: pemetrexed (500 mg/m²), combined with cisplatin (75 mg/m²) or carboplatin (area under the curve [AUC] 5), all on day 1 Q3W for six cycles or until disease progression or unacceptable toxicity. The trial involved 605 patients with previously untreated unresectable malignant pleural mesothelioma.

The primary endpoint was overall survival (OS), defined as the time from randomization to the date of death. Secondary endpoints included:

Objective response rate (ORR), defined as the proportion of all randomized participants whose best overall response (BOR) was complete response (CR) or partial response (PR) according to the modified RECIST criteria (mRECIST) and/or RECIST 1.1, assessed by blinded independent central review (BICR).

Disease control rate (DCR), defined as the proportion of all randomized participants whose BOR was CR, PR or stable disease (SD) according to the mRECIST and/or RECIST 1.1, assessed by BICR.

Progression-free survival (PFS), defined as the time from randomization to the date of the first documented tumor progression (according to m-RECIST and/or RECIST 1.1), assessed by BICR, or death from any cause.

Correlation of PD-L1 expression level and efficacy, defined by ORR, PFS and OS (PD-L1 expression level is determined as the percentage of tumor cells demonstrating any intensity of PD-L1 staining on the plasma membrane using the validated DAKO PD-L1 IHC test).

The CM-743 trial achieved its primary endpoint, with the primary endpoint results showing sustained survival benefit in the 2-year analysis: 2-year OS was 18.1 months for nivolumab + ipilimumab versus 14.1 months for chemotherapy. Subgroup analyses in CM-743 demonstrated that the efficacy of nivolumab plus low-dose ipilimumab (1 mg/kg) was consistent across subgroups, including histology and PD-L1 expression.

The results for the secondary endpoints were:



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



ORR: 40% for nivolumab + ipilimumab versus 43% for chemotherapy.

CR: 2% for nivolumab + ipilimumab versus 0% for chemotherapy.

PR: 38% for nivolumab + ipilimumab versus 43% for chemotherapy.

DCR: 77% for nivolumab + ipilimumab versus 85% for chemotherapy.

Time to response: 2.7 months for nivolumab + ipilimumab versus 2.5 months for chemotherapy.

Safety data

The most common adverse reactions ($\geq 10\%$) were fatigue (32%), rash (31%), diarrhea (27%), nausea (23%), pyrexia (21%), decreased appetite (20%), constipation (20%), musculoskeletal pain (19%), pruritus (19%), hypothyroidism (14%) and pneumonia (11%). Most adverse reactions were mild to moderate (grade 1 or 2).

Data on comparators

Comparative alternatives include Cisplatin + Pemetrexed and Carboplatin + Pemetrexed.

Pharmacoeconomic indicators

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

Three assessments of nivolumab + ipilimumab for the treatment of patients with malignant pleural mesothelioma have been published. NICE (United Kingdom) recommends it as a therapeutic option for untreated unresectable malignant pleural mesothelioma in adult patients only if: they have an ECOG performance status of 0 or 1, and the company provides it in accordance with the commercial agreement. Additionally, the cost-effectiveness of the therapeutic combination falls within acceptable limits according to NHS criteria. Nivolumab + ipilimumab is recommended for routine use in the NHS. G-BA (Germany) and SMC (Scotland) have issued positive opinions.

Applied analysis

The chosen method for the comparative assessment of the health technology nivolumab (in combination with ipilimumab) is a cost-utility analysis (CUA), where the health benefits are measured in terms of quality-adjusted life years (QALY). Data is also provided for a cost-effectiveness analysis (CEA), where the health benefits are measured in life years gained (LYG). The most suitable alternative chosen in the analysis is the chemotherapy regimen of pemetrexed + cisplatin/carboplatin. The perspective of the analysis is that of the paying institution—National Health Insurance Fund (NHIF). The selected time horizon in the model is lifetime (20 years). Health benefits and costs are discounted at an annual discount rate of 3.5%. A partitioned survival



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



model is used with three health states: "progression-free (PF)," "disease progression (PD)" and an absorbing health state ("death").

Therapy with nivolumab in combination with ipilimumab is associated with superiority in overall survival for a lifetime horizon, with added QALYs (improved survival with good quality). In the first year of combined nivolumab with ipilimumab treatment, patient survival is higher compared to chemotherapy, with this difference increasing in favor of nivolumab with ipilimumab in the second year. When accounting for the differences in costs and health benefits between nivolumab with ipilimumab and chemotherapy, the calculated incremental cost-effectiveness ratio falls into the first quadrant of the cost-effectiveness graph (higher cost with higher health benefits), exceeding the threshold of BGN 51,897/LYG/QALY.

In the sensitivity analysis for the incremental cost-effectiveness evaluation, it is found that in the probabilistic simulation, the combination of nivolumab with ipilimumab maintains a higher cost with a higher value of health benefits (QALY, LYG).

Costs for the assessed health technology

The model includes only direct medical costs—for drug therapy with nivolumab in combination with ipilimumab and the comparator alternatives, costs for drug administration, costs for medical services for disease monitoring by health state, costs for managing adverse events, costs for subsequent therapy and costs for palliative care.

Subgroup analysis

None applied.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the paying public institution—NHIF. The time horizon for the budget impact analysis is 5 years. The estimated number of patients for the evaluated therapy is 20 in the first year, increasing to 32 in the fifth year. The comparators selected are pemetrexed + cisplatin and pemetrexed + carboplatin. The costs included in the analysis are calculated under two scenarios:

Scenario 1: A world in which the candidate health technology Opdivo (INN nivolumab), in combination with ipilimumab, is introduced into specialized healthcare and reimbursed by NHIF for the treatment of adult patients with unresectable malignant pleural mesothelioma (a world with the health technology).

Scenario 2: A world in which the candidate health technology Opdivo (INN nivolumab), in combination with ipilimumab, is not introduced into specialized healthcare and not reimbursed by NHIF for the treatment of adult patients with unresectable malignant pleural mesothelioma (a world without the health technology).

The results of the budget impact analysis show that reimbursement of the health technology Opdivo for the specified indication adds costs for the paying institution over a 5-year period, without taking into account risk-sharing agreements and patient access schemes.



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



Conclusion

Pleural mesothelioma is an aggressive disease. Recommendations for systemic treatment of patients with unresectable malignant pleural mesothelioma are limited to chemotherapy, with not particularly good results in extending survival. Nivolumab and ipilimumab are immuno-oncology therapies targeting separate, distinct, but complementary checkpoint pathways (PD-1 and CTLA4, respectively), activating the body's natural immune response to recognize and protect against tumor cells. The inhibition mediated by the combination of nivolumab and ipilimumab leads to an improvement in T-cell function, greater than that of each antibody used alone and improves the anti-tumor response in metastatic melanoma. Compared to chemotherapy, significantly higher and clinically meaningful survival with treatment with Opdivo (nivolumab) in combination with ipilimumab justifies the added cost when paying for the health technology. Considering the health benefits of the evaluated therapies, demonstrated in the economic model, it can be summarized that the added life years with the new health technology are more than those with chemotherapy.