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

HEALTH TECHNOLOGY ASSESSMENT

IMFINZI
50 mg/ml - 2.4 ml concentrate for solution for infusion x 1 vial
50 mg/ml - 10 ml concentrate for solution for infusion x 1 vial
INN Durvalumab

Therapeutic indications	IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
Start date - end date of procedure	19.04.2019-30.09.2019
Final decision	Inclusion in Annex 2 of the Positive Drug List (PDL) *with restriction: after at least two cycles of platinum-based radiochemotherapy;* for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF outside of the value of the rendered medical services.

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

Health problem

Lung cancer is one of the most frequently diagnosed tumors worldwide and a leading cause of cancer death. Lung cancer prognosis is generally poor. The relative 5-year overall survival for Bulgaria is very low - 5.9% for men, 10.4% for women and 6.5% for both. It is much lower than the European average of 12.6%. The incidence increases with age and reaches its peak around the age of 70. The stages of non-small cell lung cancer (NSCLC) are determined on the basis of clinical and pathological characteristics. The clinical stage is determined by the results of physical examination, biopsies, imaging studies (computed tomography, X-ray, PET scanner) and others, while pathological characteristics derive from histology samples. According to the latest 8th revision of the TNM classification, patients are considered as locally advanced in IIIA, IIIB and IIIC clinical stage. The stage is defined as premetastatic, the main difference between stage III (locally advanced NSCLC) and stage IV being the absence of M1 (distant metastases). Patients' condition in clinical stage III is defined as very severe, as in most cases it implies a markedly shortened life expectancy with deteriorated quality of life.

Patients with lung cancer are most often diagnosed late after the onset of symptoms or accidentally during an X-ray exam. The symptoms and signs of lung cancer often depend on the location of primary lesion, the presence or absence of compression on adjacent thoracic structures, metastases, paraneoplastic syndrome. The most common symptoms include cough, shortness of breath, weight loss, chest pain and recurrent infections. These symptoms often resemble those of chronic obstructive pulmonary disease (COPD), that often being one of the reasons for delayed diagnosis.

Epidemiological data

According to global statistics data of Globocan for 2018, 2.1 million new cases and 1.8 million deaths were diagnosed (85% mortality).

In Bulgaria, lung cancer is the most common cancer in men and the seventh most common in women. According to the National Cancer Registry for 2014, this localization represents 18.2% of the incidence of malignancies among men and 5.2% in women. In 2014, 3793 new cases were registered of which 79.5% were men. The actual incidence is 85.8 per 100000 males and 20.9 per 100000 females. Lung cancer is the most common cause of death from cancer in men - 26.2% and the third most common in women - 9.9%. In 2014, 3475 died of lung cancer, 78.8% of them were men. The actual mortality is 78 per 100000 men and 19.8

per 100000 women. According to literature data, the majority - 85% (3225 patients) have non-small cell lung cancer (NSCLC), and in about one third (1000 patients) the disease is in a locally advanced stage (stage III disease). Paucity of data exist on the incidence of inoperable stage III NSCLC, but according to available studies about 41-79% of all patients in stage III are inoperable.

Efficacy data

The clinical efficacy of Imfinzi (durvalumab) was studied in the PACIFIC trial, a double-blind, randomized, placebo-controlled clinical trial in 20 countries worldwide (Australia, Belgium, Canada, Chile, Germany, Greece, Italy, Japan, Korea, Mexico, Poland, Singapore, Slovakia, South Africa, Taiwan, Thailand, Turkey, Great Britain, USA, Vietnam). A total of 713 patients with locally advanced and nonoperable NSCLC were included, who completed a minimum of 2 cycles of definitive combination radiochemotherapy (cytostatic: platinum product). Patients started IMFINZI between 1 and 42 days after the end of standard treatment and were in good general condition - ECOG PS 0-1. The study did not include patients who progressed after radiation chemotherapy, who received immunotherapy with anti-PD 1 and anti-PDL1 antibodies, who had a confirmed autoimmune disease, a history of immune deficiency, immunodeficiency conditions requiring corticosteroid administration, active tuberculosis, hepatitis B and C. Patients were randomized in a 2:1 ratio to receive either IMFINZI at a dose of 10 mg/kg or placebo at the same dose, and treatment was continued until completion of 12 months, progression or emergence of unacceptable toxicity. The study was randomized by sex, age, status in terms of smoking, and patients' inclusion in the program was independent of the level of PD-L1 status.

The two primary endpoints were progression-free survival (PFS) and overall survival (OS), secondary endpoints were PFS after 12 months and 18 months of randomization, as well as time from randomization to second progression.

The results of the study to date show that PFS of patients treated with IMFINZI was statistically longer than those who received placebo: HR 0.52 and $p<0.0001$. In terms of overall survival, the same relationship was observed – an improved benefit from immunotherapy compared to placebo: HR 0.68 and $p = 0.00251$. Improved progression-free and overall survival outcomes were observed in all follow-up subgroups regardless of gender, age, smoking, EGFR mutation and histology.

The clinical trial was a double-blind, placebo-controlled, phase III, randomized, multicenter, and included patients over 18 years of age with histologically confirmed, locally advanced, inoperable NSCLC who after at least two cycles of simultaneous radiochemotherapy and no disease progression were randomized with 2:1 ratio - IMFINZI 10 mg/kg or placebo 10mg/kg.

Inclusion in the study was done no later than 42 days after the completion of concomitant radiochemotherapy. Treatment was continued until completion of 12 months, occurrence of progression or unacceptable toxicity.
70% of included patients are male, 45% are over 65 years of age, Caucasian - 69%, ex-smokers - 75%, current smokers - 16%, ECOG PS 0 - 49%, ECOGPS 1 - 51%. As regards disease stage: IIIA (53%), IIIB (45%); with squamous cell histology - 46%, PD L1 expression was demonstrated in 451 patients out of all 713 patients.

PACIFIC is the first clinical trial so far to demonstrate a statistically significant benefit of immunotherapy, Imfinzi over placebo in terms of both progression-free and overall survival for patients with locally advanced NSCLC who underwent combination chemotherapy. The Imfinzi treatment arm had a 48% lower risk of disease progression compared to placebo ($p<0.0001$), and this trend was maintained in terms of overall survival - a 32% lower risk of death in treatment with anti PDl1 inhibitor, $p = 0.00251$. The median overall survival in Imfinzi arm was not reached, while the placebo arm was 28.7 months.

Relatively low progression-free survival was observed in PACIFIC patients receiving placebo. Currently, patients who have undergone combined radiochemotherapy, would then normally remain on active monitoring and subsequent treatment is started only in case of disease progression (local recurrence or distant spread of the disease). In various studies that compared other medicines as possible maintenance treatment (and with negative outcomes, unlike PACIFIC), the progression-free survival of patients in the placebo arm was reported as 10.7 months or 11.4 months, while in PACIFIC it is only 5.6 months. The measurement of progression-free survival was initiated at randomization after completion of radiation chemotherapy rather than at the beginning of treatment, with overall survival data being conclusive, demonstrating the benefit of durvalumab maintenance therapy in these patients.

As regards the secondary endpoints, the progression-free 12-month survival for durvalumab was 55.9%, while for placebo it was 35.3%; at the 18th month of follow-up, the same indicators were 44.2% and 27%, respectively. This shows a clear tendency for the effect of immunotherapy to persist for the time of follow-up. Thus, treatment with Imfinzi resulted in a higher percentage of patients who were alive and didn’t progress at 12 and 18 months of therapy compared with placebo group. In addition, when considering the Kaplan-Mayer curves for progression-free and overall survival - Figure 1, the early separation of the two arms at the very beginning of the graph is impressive.

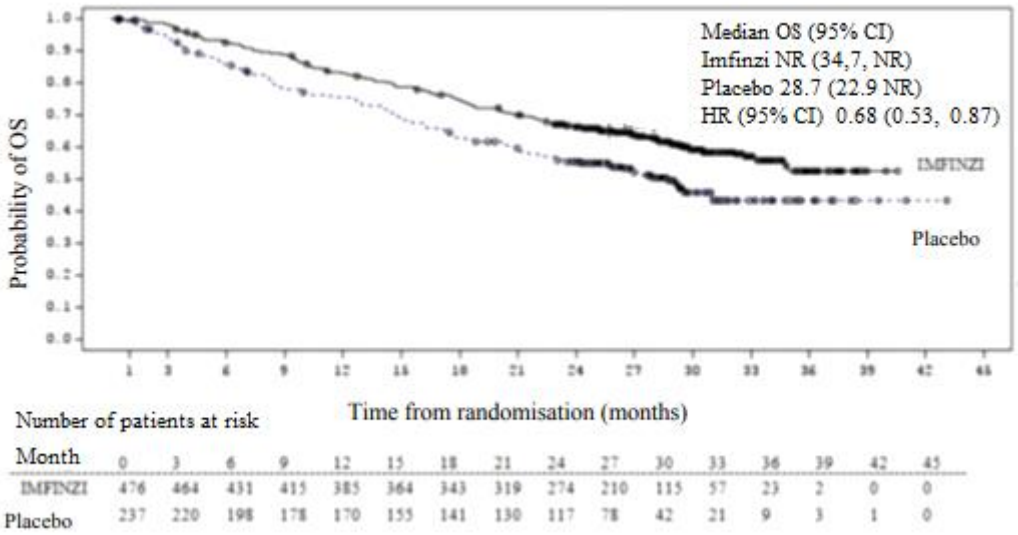
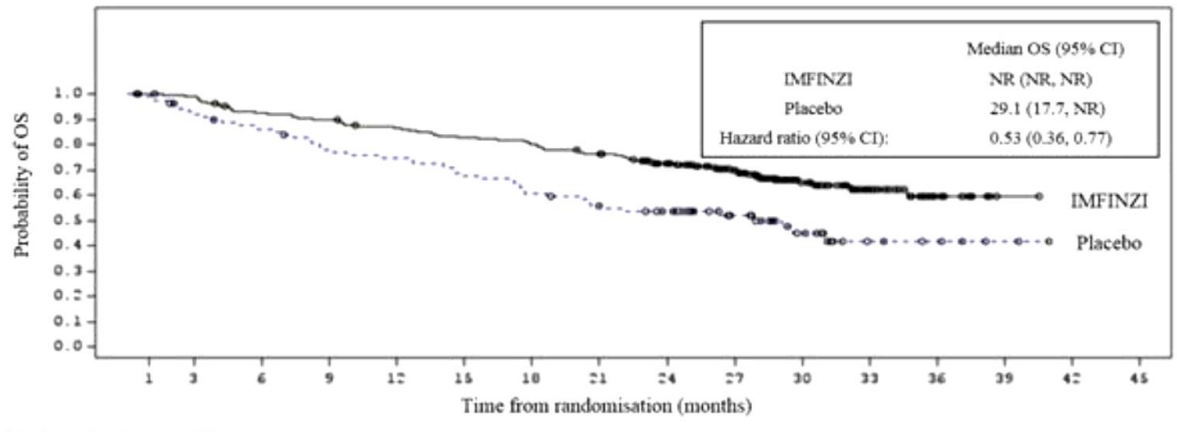


Figure 1. Kaplan-Mayer curve for overall survival according to PACIFIC

Subsequent post hoc analysis of progression-free and overall survival according to PDL1 status showed a clear benefit for the use of Imfinzi in patients with PDL1 > 1%. Thus, in these patients with PD L1> 1%, the mean overall survival was not reached for durvalumab, while for placebo it was 29.1 months - Figure 2.



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI	212	208	193	187	178	171	165	156	134	105	62	34	12	1	0	0
Placebo	91	81	75	67	64	58	52	46	41	29	17	7	5	2	0	0

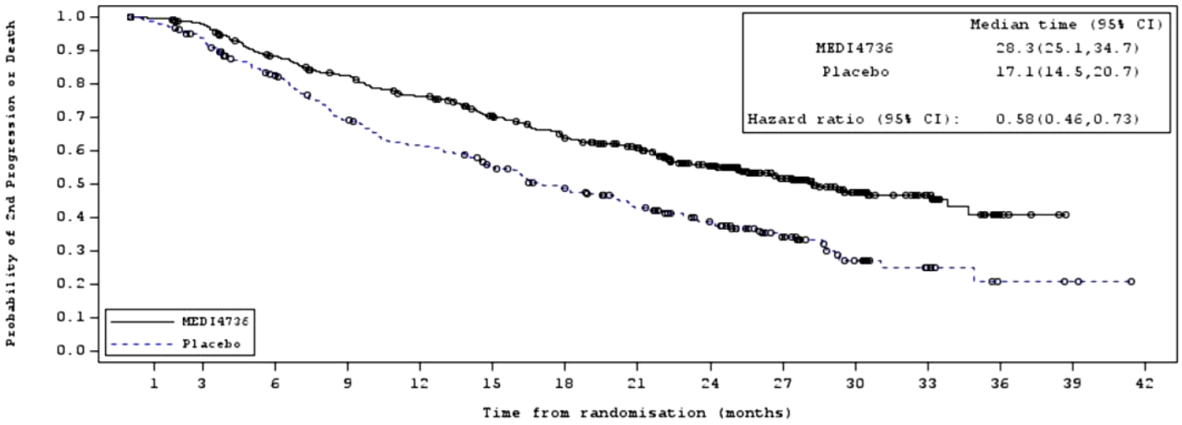
Figure 2. Kaplan-Mayer crisis for overall survival in patients with PDL1> 1%

The recommendation for use of the medicinal product is only in those patients in whom such expression is observed. With regard to progression-free survival, the same trend is observed - the benefit of durvalumab is established regardless of PDL1 status, but is most significant in

those patients with PDL1> 1%. A drawback of PACIFIC study is the relatively high percentage of patients in whom PDL1 status is unknown.

Further data analysis showed that durvalumab treatment resulted in a significantly longer median time to death or distant metastases by 47%. In addition, the time to second progression was significantly increased on the arm with immunotherapy compared to placebo therapy - 28.3 months compared to 17.1 months, respectively - Figure 3:

Figure 3



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
MEDI4736	476	455	404	373	342	307	274	249	192	126	65	36	5	0	0
Placebo	237	216	183	150	131	114	96	80	63	38	19	10	3	2	0

Figure 3: Time to second progression - Kaplan-Mayer curve

Brain metastases frequently undergo progression in patients with advanced NSCLC. The results show that during Imfinzi administration, the risk of brain progression was 6.3% compared to 11.8% for the placebo arm, which was statistically significant and associated with a improved quality of life in patients.

Analysis of data reported by patients

Patients' quality of life was assessed using a variety of scales, including those specific to lung cancer patients. Baseline levels between the two groups did not differ significantly in terms of symptoms, functional parameters and quality of life. Additionally, no difference in indicators was observed between durvalumab and placebo-treated patients in the course of treatment. Therefore, it was found that administration of immunotherapy does not lead to a deterioration in the quality of life of patients compared to those in whom it was not administered. Deterioration was only observed with respect to pain symptoms in patients on maintenance durvalumab therapy.

Safety data

The use of immunotherapy is associated with an increased risk of immune-related side effects. Data from PACIFIC study and two other studies (one in patients with solid tumors, the other in patients with locally advanced or metastatic lung cancer) were used to assess safety. In all three, durvalumab dosage was 10 mg/kg every two weeks.

One of the most common and serious adverse reactions is immune-related pneumonitis. In the three studies, this complication occurred in 4.2% of all patients, with grade 3 in 0.6%, grade 4 - < 0.1%, and grade 5 - 0.3%. In PACIFIC study, where development of pneumonitis is a risk due to pulmonary radiotherapy, this adverse event occurred in 10.7% of durvalumab-treated patients and 6.8% of placebo-treated patients. With regard to pneumonitis grade (3 and 4), the frequency between the two groups is relatively the same. Most frequently the treatment of this adverse event involved a corticosteroid and, in rare cases, the administration of infliximab.

Toxicity to the gastrointestinal tract - immune-related hepatitis or colitis, is relatively rare: observed in 1% and 1.6% of patients, respectively.

Immune-related endocrinopathies (hypo-hyperthyroidism, type I diabetes mellitus, adrenal insufficiency, hypophysitis/hypopituitarism) are rarely seen as a complication of Imfinzi, with grade 3 and above reported in less than 0.1% of all patients. The same is true for immuno-mediated nephritis and immune-related rash.

Assessment of all adverse events reported within PACIFIC alone indicates that 15.4% of durvalumab patients discontinued treatment due to adverse reactions, compared with 9.8% in the placebo group. However, the frequency of side effects leading to death were comparable between the two study groups.

Data on comparators

Patients in stage III of NSCLC are a heterogeneous group and most of them are inoperable. The operability of locally advanced NSCLC depends on a number of factors such as tumor location, number and location of affected lymph nodes, proximity to vital organs, comorbidities, general condition of the patient and decision of the thoracic surgeon, with 70 to 80% of patients being inoperable.

According to the World Recommendations for the Diagnosis, Treatment and Follow-up of Early and Locally Advanced (LA) NSCLC, the method of choice in patients with inoperable LA NSCLC is the use of concomitant radiochemotherapy and in cases where concomitant radiochemotherapy is not possible, a valid and effective alternative is the sequential

administration of chemotherapy and radiation therapy. Currently, about 10% of patients with inoperable LA NSCLC receive radiochemotherapy. The standard recommended doses are 60 - 66Gy conventional fractionated radiotherapy for the area of the primary tumor and the affected mediastinal lymph nodes. In the absence of progression after radiochemotherapy, patients remain under dynamic monitoring. There is no accepted method to apply in order to reduce the risk of recurrence or progression of the disease to a metastatic stage. Currently, following radiochemotherapy, the therapeutic strategy is based on active patient monitoring and best supportive care.

After radiochemotherapy, no additional treatment is given to patients who have not progressed. The therapeutic strategy consists of active monitoring and best possible supportive care. Patients are followed up with examinations and imaging studies, and in case of disease progression and/or recurrence, immunotherapy, chemotherapy or no treatment may be offered depending on the development of disease, the general condition of the patient and present comorbidity. Imfinzi is the only medicinal product and the only therapeutic alternative for the treatment of locally advanced, inoperable NSCLC in adults whose tumors express PD-L1 in ≥ 1% of tumor cells and whose disease has not progressed after platinum based radiochemotherapy. No active treatment is a suitable alternative compared to Imfinzi for current indications. Among patients in stage III NSCLC, there is a significant unmet need for active therapeutic alternatives that prolong survival and slow progression. With available treatment options, 89% of patients progress to metastatic NSCLC.

Pharmacoeconomic indicators

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

Assessments of health technologies from Great Britain, Germany, Sweden and France have been presented, all of which are positive and the medicinal product is reimbursed.

Applied analysis

A pharmacoeconomic cost-benefit method has been applied, as well as a cost-effectiveness analysis evaluating the value effectiveness of durvalumab in terms of progression-free time, with a measure of outcome an year of life gained (LYG). The data sources for both models are based on PACIFIC study. The costs are estimated on the basis of the actual therapeutic practice in Bulgaria.

The cost-effectiveness of durvalumab in terms of cost per 1 QALY and time for progression-free time in patients with NSCLC (measured by gained year of life) in Bulgaria was assessed from the point of view of the NHIF.

The best supportive care was chosen as an alternative for comparison, as the analysis used was based on data from the PACIFIC study, where durvalumab was compared to best supportive care. The practice of the best supportive care in Bulgaria is described. Patients with lung cancer have diverse and more pronounced symptoms than patients with other localizations, and often have comorbidity. Early assessment of the severity of symptoms allows individualization of interventions to respond to them. In patients with locally advanced NSCLC, carcinoma pain, fatigue, distress, cough and haemoptysis and dyspnoea may occur.

The time horizon of the analysis is 40 years, the analysis includes direct costs for the application of the compared alternatives, the costs are presented for 1 patient for 1 year. The cost structure includes drug therapy costs, drug administration costs, ADR treatment costs, and follow-up costs. After discontinuation of Imfinzi and a subsequent progression-free survival period, patients progress and move to further treatment, therefore post-progression costs have been included. Expenses have been discounted with a 3.5% discount rate.
The main measure of the result in the presented model in the cost-benefit analysis is the quality-adjusted life year (QALY) and life years gained (LYG) in the cost-effectiveness analysis.

A Markov model has been applied to model the development of the disease. The probabilities of 1 patient moving from one condition to another were calculated on the basis of Kaplan-Meier curves derived from PACIFIC study data.

The cost-benefit analysis shows that durvalumab is associated with incremental costs of BGN 114,465, but also with an incremental increase in quality-related years of life by 2.93 QALY, and the cost-effectiveness analysis shows an incremental increase in earned years of life by 3, 5998 LYG.
The incremental cost-effectiveness ratio for 1 earned year of life is BGN 31,797, and for one additional year of quality-adjusted life is BGN 39,066. The results of the sensitivity analysis show that durvalumab is a cost-effective alternative to the best maintenance care in patients with locally advanced, inoperable non-small cell lung cancer in adults.

Budget impact analysis
The analysis of the budget impact was conducted from the point of view of the paying public institution, the NHIF. The time horizon of the budget impact analysis is 5 years. The size of the target population was estimated on the basis of epidemiological data from the National Cancer Registry.
The projected number of patients for a five-year period is 46 for the first year, increasing to 144 by the fifth year, and the expected budget impact is positive with increasing NHIF expenditures, not taking into account risk-sharing agreements and patient access schemes.

Conclusion

Currently, patients with stage III NSCLC are treated with the best maintenance therapy. Durvalumab was associated with a statistically significant improvement in overall patient survival and quality of life and has a good safety profile.

Compared to current therapeutic practice, durvalumab is a cost-effective alternative with a profitability threshold of 3 times GDP/ capita.

The administration of Imfinzi at a dose of 10 mg/kg every two weeks as maintenance treatment in patients with locally advanced NSCLC who underwent at least two cycles of combination chemotherapy and with PD L1 expression greater than 1%, compared to the placebo group was associated with improved progression-free and overall survival, longer disease-free period and good quality of life without increased risk of adverse drug events.