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REVIEW ARTICLE

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Nivolumab in the treatment of thoracic cancer — new possibilities

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ABSTRACT

Immune checkpoint inhibitors have significantly changed the treatment of patients with advanced non-small cell lung cancer in recent years. The value of nivolumab was initially assessed in patients previously treated with systemic therapy. The association of nivolumab with ipilimumab and the interaction of these antibodies on different immune checkpoints have proven effective in solid tumors (melanoma and renal cell carcinoma). The CheckMate-9LA study assessed the value of dual immunotherapy combined with platinum-based chemotherapy in the first-line treatment of advanced non-small cell lung cancer. A clinical benefit – prolonged overall survival in patients receiving combination therapy – was documented. The results of the CheckMate743 trial for patients with pleural mesothelioma provide a basis for changing the current management algorithm for patients with this diagnosis. Patients diagnosed with mesothelioma of a non-epithelioid type particularly benefit from two-drug immunotherapy compared to chemotherapy. Maintaining the safety of treatment using immunotherapy targeting two immune checkpoints remains the challenge.

Key words: immunotherapy, immune checkpoint inhibitors, nivolumab, non-small cell lung cancer, pleural mesothelioma

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Introduction

Immune checkpoint inhibitors (ICIs) have significantly changed the treatment of advanced non-small cell lung cancer (NSCLC) patients in recent years [1]. They can be used in the first-line treatment either alone or in combination with chemotherapy, as well as after failure of the previously performed systemic treatment.

The value of nivolumab, which is a fully human antibody against programmed death receptor (anti-PD-1), was initially assessed in patients after failure of chemotherapy. The results of two pivotal phase III clinical trials (CheckMate-017 and CheckMate-057) led to registering the drug for patients with squamous and non-squamous NSCLC [2, 3]. Combined analysis of long-term results confirmed the significant clinical efficacy of nivolumab compared to docetaxel in terms of overall survival (OS) [4, 5].

Recently, indications for the use of nivolumab in patients with thoracic tumors have been expanded. Based on the results of the CheckMate-9LA study, a regimen consisting of nivolumab (anti-PD-1 antibody) and ipilimumab — an antibody directed against cytotoxic T cell antigen 4 (CTLA-4) — and two cycles of platinum-based chemotherapy in the first line of systemic treatment was registered [6]. The value of combination immunotherapy (nivolumab in combination with ipilimumab) in patients with pleural mesothelioma has also been documented [7].

This article discusses the theoretical basis of combining monoclonal antibodies, nivolumab, and ipilimumab, which inhibit the 2 most important immunological checkpoints (PD-1 and CTLA-4). The most important results of the studies that have become the basis for the registration of nivolumab after failure of chemo-

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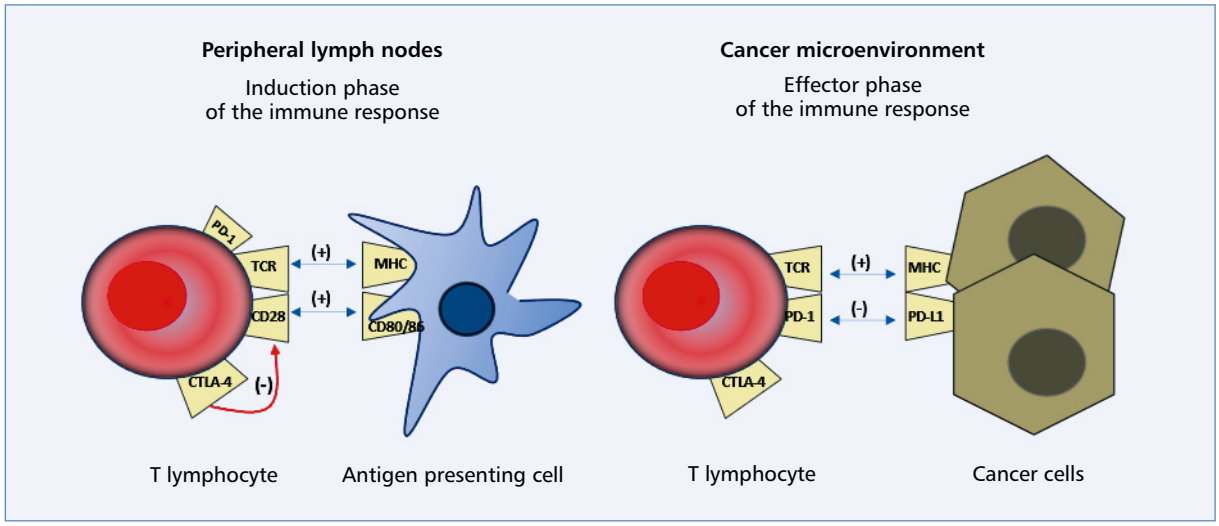

Figure 1. Induction of immune response in lymph nodes and tumor microenvironment (authors' own presentation)

therapy in NSCLC patients are summarized. The efficacy and safety data of immunotherapy with nivolumab and ipilimumab in thoracic cancers in which it has not been used so far (first-line treatment of advanced NSCLC and pleural mesothelioma) are also discussed in more detail.

Immune checkpoint inhibitors: should they be used alone or in combination?

The mechanism of action and clinical efficacy of combined treatment with nivolumab and ipilimumab result from the effect of antibodies on various immune checkpoints. The PD-1 molecule is constitutively expressed on all cells associated with specific immune response (T cells, B cells, and NK). Programmed death receptor ligand 1 (PD-L1) interacts with PD-1 and is present on non-specific immune cells (monocytes, dendritic cells, and tissue macrophages). In inflammatory states and in the environment of pro-inflammatory cytokines, such as tumor necrosis factor alfa (TNF-α) or interleukin 2 (IL-2), the expression of PD-1 and PD-L1 increases, and the interaction of PD-1 with PD-L1 inhibits the activity of PD-1-positive cells (lymphocytes), which is one of many mechanisms suppressing the excessive activity of T lymphocytes and protecting the body against possible autoimmune reactions [8]. PD-L1 can also be found on the surface of cancer cells, which is one of cancer immune escape mechanisms. Nivolumab inhibits PD-1 and reinvigorates T cell activity in cancer, lymph nodes, and tissues. Blocking the function of the PD-1 molecule takes place in the so-called "effector phase" of the immune response when lymphocytes should recognise and destroy tumor cells [8].

Stimulation of the CTLA-4 on the surface of T lymphocytes plays a role in inducing an immune reaction at the stage of antigen presentation (the so-called "early phase" of immune response induction) (Fig. 1). During the stimulation of T lymphocytes in the lymph nodes by antigen-presenting cells (APCs), specific receptor binding between these cells is formed [8, 9]. These interactions are called immunological synapses and involve a T-cell receptor (TCR) on T lymphocytes and major histocompatibility complex (MHC) molecules on APC, CD28 (cluster of differentiation 28) molecules on T lymphocytes and costimulatory molecules CD80 and CD86 on APC, as well as the cytokines network in the microenvironment. These interactions are necessary to stimulate T cells' activity. The CTLA-4 molecule is potent to displace CD28 from binding with CD80 and CD86, thereby disrupting the proper stimulation of T lymphocytes, resulting in inhibition of proliferation and activation of helper T cells and cytotoxic T cells. Moreover, such interaction sheds CD80 and CD86 molecules from the surface of antigen-presenting cells, leading to their inactivation. High CTLA-4 expression on T cells also induces the intracellular protein FoxP3 (forkhead box P3), resulting in turning them into regulatory T cells. The functioning of the CTLA-4 molecule is also one of the mechanisms regulating activity of the immune system [8–10].

The aforementioned interactions indicate a synergistic effect of PD-1 and CTLA-4 blocking, e.g. the combined use of nivolumab and ipilimumab consists in reactivating suppressed helper and cytotoxic T lymphocytes by blocking one of the strongest inhibitory signals (PD-1 and PD-L1 interaction) and restoration of essential (apart from antigen presentation) co-stimulatory signal (binding of CD28 by CD80 and CD86). The use of

Table 1. Roles of CTLA-4 and PD-1 molecules in the immune system and effects of their blocking (based on [8–11] with authors' own modification)

CTLA-4	PD-1
It appears on T lymphocytes during immunological synapse forming in the lymph node Present on activated T cells Ligands include CD80 (B7.1) and CD86 (B7.2) molecules present on many cells in the body	Present on the surface of T lymphocytes (constitutive expression), with increased expression after cell activation Ligands include PD-L1 and PD-L2 molecules, present on the surface of immune cells and cancer cells
Effect of blocking the molecule with an anti-CTLA-4 antibody	**Effect of blocking the molecule with an anti-PD-1 antibody**
Inhibition of T reg activity Increased cytotoxic activity of NK cells Increased phagocytic activity of non-specific immune cells Increased activation and proliferation of cytotoxic T lymphocytes	Increased activation of T lymphocytes not only in the tumor microenvironment but also in peripheral tissues

CTLA-4 — cytotoxic T cell antigen 4; PD-1 — programmed death receptor 1; PD-L1 — programmed death receptor ligand 1; NK — natural killer

ipilimumab additionally reduces the immunosuppressive effect of other cells. The synergistic effect of nivolumab and ipilimumab consists in restoring T lymphocyte activity in the early activation phase and the effector phase of the immune response [8–11]. Characteristics of both molecules' activity are summarized in Table 1.

The interaction of both immune checkpoint inhibitors is also strongly reflected in laboratory testing results. There is a significantly increased percentage of cytotoxic T lymphocytes in the peripheral blood in patients undergoing combined immunotherapy compared to monotherapy with either nivolumab or ipilimumab. High plasma levels of pro-inflammatory cytokines IL-2Rα, IL-1α, and chemokines (e.g. CXCL10) are reported in patients receiving combined immunotherapy, which cannot be obtained with nivolumab or ipilimumab alone. Responders to combined immunotherapy show an increased percentage of Eomes (eomesodermin)+, $CD69^+$, $CD45RO^+$ memory cytotoxic ($CD8^+$) T lymphocytes compared to baseline [9, 11, 12]. Moreover, low expression of other negative immune checkpoints, including T-cell immunoreceptors with Ig and ITIM domains (TIGIT) and lymphocyte-activation gene 3 (LAG3) on T lymphocytes is observed in responders. This phenomenon is not present in patients responding to nivolumab monotherapy. The expression of genes responsible for the immune response profile in peripheral blood leukocytes was also analyzed. In patients undergoing combined therapy, the expression of genes for granzymes A/B, proliferation marker Ki-67, IL-8, and HLA-DR (human leukocyte antigen-DR isotype) was reported, which proves the cytolytic and proliferative activity of cytotoxic T lymphocytes, as well as their potency to infiltrate neoplastic tissue. Patients receiving anti-PD-1 monotherapy have overexpressed genes determining the cytolytic activity of T lymphocytes (genes for granzymes *A*/*B*, *KLRF1*, and *FCRL3*), while patients receiving ipilimumab express genes producing specific cytokines (genes for *Ki-67* and *ICOS*) and related to the ability of T lymphocytes to proliferate. It seems that the gene expression profile after combined immunotherapy ensures both cytolytic and proliferative activity of T lymphocytes [9, 11, 12].

Detailed immunophenotyping of immune cells after combined immunotherapy and monotherapy was performed in animal models [11]. Wei et al. [11] divided the group of tumor-infiltrating cytotoxic T cells into 4 immunophenotypes: T cells with a functionally exhausted phenotype ($PD\text{-}1^{high}$, $LAG3^{++}$, $TIM3^{++}$), terminally differentiated T cells with an activated phenotype ($PD\text{-}1^+$, $LAG3^{int}$, $TIM3^{int}$), T cells in early differentiation stage ($Tbet^{int}$, $CD86^+$, $PD\text{-}1^{+/-}$, $Bcl2^+$), and apoptosis-resistant migrating T cells ($PD\text{-}1^-$, $CD62L^+$, $Bcl2^{++}$). The use of combined immunotherapy significantly increases the percentage of differentiated and activated lymphocytes and significantly reduces the percentage of functionally exhausted lymphocytes compared to nivolumab or ipilimumab alone. However, the type of therapy has no effect on the percentage of the remaining subpopulation of cytotoxic T lymphocytes in the peripheral blood. T helper lymphocytes also include subpopulations of different immunophenotypes: Th1 lymphocytes with an effector phenotype ($PD\text{-}1^+$, $GATA3^+$, $CD44^+$, $CXCR3^{++}$), T lymphocytes with a helper phenotype without chemokine receptors ($CD44^+$, $GATA3^+$, $CD44^+$, $CXCR3^-$), and apoptosis-resistant actively migrating lymphocytes ($PD\text{-}1^-$, $CD62L^+$, $Bcl2^{++}$). Combined immunotherapy significantly increases infiltration by Th1 effector lymphocytes compared to monotherapy with nivolumab or ipilimumab. The immunophenotype of regulatory T lymphocytes enables their division into 3 groups: Treg lymphocytes with a pro-tumor phenotype ($CTLA\text{-}4^{++}$, $FoxP3^+$, $CD25^+$), Treg lymphocytes with an incom-

plete differentiation phenotype (CTLA-4$^+$, FoxP3^{++}, CD25^{++}), and undifferentiated and depleted Treg lymphocytes (CTLA-4$^-$, FoxP3$^{+/-}$, CD25^{++}). Wei et al. [11] found smaller infiltrates by Treg lymphocytes with a pro-tumor immunophenotype in the animal model after using ipilimumab or combined therapy compared to nivolumab alone or untreated models. It was also shown that the percentage of Th1 effector lymphocytes negatively correlated, and the percentage of pro-tumor Treg lymphocytes positively correlated with tumor size [10, 11].

Based on theoretical assumptions, as well as the results of laboratory and clinical tests, other concepts of combining antibodies affecting different immune checkpoints have emerged. Clinical trials are currently ongoing in patients with advanced NSCLC, in which attempts are made to combine classic anti-PD-1 or anti-PD-L1 antibodies with antibodies against inducible T cell co-stimulator (ICOS), LAG-3, T cell immunoglobulin domain and mucin domain-3 (TIM-3), or TIGIT. Patients who did not respond to combined immunotherapy with nivolumab and ipilimumab showed a significantly higher percentage of T cells expressing these molecules. It seems that their presence may play a leading role in inhibiting the activation of T lymphocytes and inducing resistance to existing methods of immunotherapy [8, 10].

Nivolumab's value after chemotherapy failure

The safety and efficacy of nivolumab *versus* docetaxel in patients after chemotherapy failure were assessed in two randomized studies with similar designs. The differentiating factor was the histopathological diagnosis.

The CheckMate-057 study was designed for patients with non-squamous NSCLC. Patients with advanced or recurrent NSCLC and documented disease progression during or after platinum-based chemotherapy were eligible [3]. A total of 582 patients were assigned to two treatment arms: 292 patients to the group receiving nivolumab at a dose of 3 mg/kg every 2 weeks and 290 patients to the group receiving docetaxel at a dose of 75 mg/m^2 every 3 weeks. The primary endpoint was OS, and the secondary endpoints included objective response rate (ORR) and progression-free survival (PFS). The study demonstrated superiority of nivolumab over docetaxel with regard to the assumed endpoints. Median OS was 12.2 and 9.4 months, respectively [hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.59–0.89; p = 0.002]. ORRs were 19% for nivolumab *versus* 12% for docetaxel (p = 0.02). Overall, treatment-related adverse events (AEs) were reported in 69% of patients in the nivolumab group and 88% in the docetaxel group, while clinically significant adverse events (Grades 3–4) were reported in 10% of patients in the nivolumab group and 54% in the docetaxel group [3].

The CheckMate-017 study included 272 patients with advanced or recurrent squamous cell lung cancer — 135 patients were assigned to the nivolumab arm, and 137 patients were assigned to the docetaxel arm [2]. The advantage of nivolumab over docetaxel was confirmed. Median OS was 9.2 and 6.0 months, respectively (HR = 0.59; 95% CI 0.44–0.79; p < 0.001), and ORR was 20% and 9%, respectively (p = 0.008). Treatment-related AEs occurred in 58% of patients in the experimental arm and 86% in the control group. Grade 3 and 4 adverse events were observed in 7% and 55% of patients, respectively. Data regarding nivolumab's value in the second-line treatment are presented in Table 2.

Longer observations confirmed the value of nivolumab [4, 5]. The 4-year OS rates were 14% and 5%, respectively and the 5-year rates — 13.4% and 2.6%, respectively (HR = 0.68; 95% CI 0.59–0.78) [4, 5]. Greater clinical benefit was observed in patients who achieved an objective response to nivolumab treatment. The 4-year OS rate in patients with objective response was 58% in the nivolumab group and 12% in the docetaxel group [4].

Immunochemotherapy in first-line treatment of NSCLC

Immunochemotherapy is now a recognized standard of care in patients diagnosed with advanced NSCLC with PD-L1 expression < 50%, who remain in good general condition and have no significant contraindications to chemotherapy and immunotherapy. In Poland, it is possible to use a regimens based on pembrolizumab, and — from January 1st, 2023 — nivolumab and ipilimumab [13].

CheckMate-9LA — treatment effectiveness

The CheckMate-9LA study was the basis for the registration of a first-line treatment regimen with nivolumab in patients with advanced NSCLC [6]. The study included patients with good performance status (PS) 0–1 according to the Eastern Cooperative Oncology Group (ECOG) score, with no prior systemic treatment due to advanced NSCLC and without molecular disturbances in *EGFR* and *ALK* genes. A total of 719 patients were randomized 1:1 to receive chemotherapy (4 cycles of platinum-based chemotherapy) or immunochemotherapy. The treatment regimen in the experimental arm included 2 cycles of immunochemotherapy (nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg every 6 weeks in combination with platinum-based chemotherapy) followed by immunotherapy (for a total of two years or until the loss of clinical benefit) [6]. The stratification factors included sex, tumor histology, and PD-L1 expression. The primary endpoint was OS, and the secondary endpoint included

Table 2. Efficacy of nivolumab after chemotherapy failure [2, 3]

	CheckMate-017			CheckMate-057		
	Nivolumab	Docetaxel	HR	Nivolumab	Docetaxel	HR
Numer of patients	135	137		292	290	
ORR [%]	20	9	2.6; p = 0.008	19	12	p = 0.02
PFS [months]	3.5	2.8	0.62; p < 0.001	2.3	4.2	0.92; p = 0.39
OS [months]	9.2	6.0	0.59; p < 0.001	12.2	9.4	0.73; p = 0.002
AE (any) [%]	58	86		69	88	
AE (grade 3–4) [%]	7	55		10	54	

AE — adverse event; HR — hazard ratio; ORR — objective response rate; OS — overall survival; PFS — progression-free survival

ORR and PFS measured in an independent review. The advantage of immunochemotherapy in relation to the assumed endpoints was demonstrated in the whole analyzed population. The objective response rates were 38% and 25%, respectively. Median PFS was 6.8 months *versus* 5 months (HR = 0.7; 95% CI 0.57–0.86; p = 0.00012), and median OS was 14.1 months *versus* 10.7 month (HR = 0.69; 95% CI 0.55–0.87; p = 0.00065) [6]. The subgroup analysis showed no benefit of immunochemotherapy in terms of OS in patients over 75 years of age (HR = 1.21; 95% CI 0.69–2.12) and non-smokers (HR = 1.14; 95% CI 0.66–1.97). The predictive value of PD-L1 expression was also assessed with benefits noted in all subgroups (for patients with PD-L1 expression < 1% — HR = 0.62, for patients with PD-L1 expression ≥ 50% — HR = 0.66). Differences in survival parameters determined by the histological tumor type were found. In patients with non-squamous cell carcinoma, median PFS for immunochemotherapy and chemotherapy were 7 and 5.6 months, respectively (HR = 0.74; 95% CI 0.6–0.92), and median OS was 17 and 11.9 months, respectively (HR = 0.69; 95% CI 0.55–0.87). In patients with squamous cell carcinoma, median PFS and OS for immunochemotherapy and chemotherapy were 5.6 and 4.3 months (HR = 0.57; 95% CI 0.42–0.78) and 14.5 and 9.1 months (HR = 0.62; 95% CI 0.45–0.86), respectively [6]. Updated results from the CheckMate-9LA study were also published [14]. With a median follow-up of 30.7 months, the superiority of combined therapy was confirmed. The median OS was 15.8 and 11 months, respectively (HR = 0.72; 95% CI 0.61–0.86). The percentages of patients who were followed up after two years were 38% and 26%, respectively, and the percentages of patients who were free from disease progression were 20% and 8%, respectively [14, 15]. The efficacy data are summarized in Table 3.

During the 2021 World Conference on Lung Cancer, the results of the analysis evaluating the intracranial activity of this therapy regimen were presented [15]. The metastases in the central nervous system (CNS) were found in 51 patients treated with chemoimmunotherapy and in 50 patients receiving chemotherapy alone. The inclusion criterion in that study was the absence of neurological symptoms for 14 days preceding the administration of the first dose of investigational drugs and the completion of local treatment. There is a significant clinical benefit associated with the use of nivolumab and ipilimumab-based immunochemotherapy. Median PFS in this population was 13.5 and 4.6 months respectively (HR = 0.36; 95% CI 0.22–0.60), and the objective response rates were 20% and 10%, respectively. Longer OS was also observed in the group of patients with CNS metastases — median OS in patients with CNS lesions were 19.3 and 6.8 months, respectively (HR = 0.43; 95% CI 0.27–0.67), whereas in patients without CNS metastases they were 15.6 and 12.1 months, respectively (HR = 0.79; 95% CI 0.65–0.95) [15]. The data are summarized in Table 3.

Safety profile of immunochemotherapy

Treatment-related adverse events were observed in 92% of patients in the experimental group and 88% of patients in the control group [6]. Nausea (26%), diarrhea (23%), weakness, pruritus, anemia (21%), skin lesions, and hypothyroidism (19%) were most frequently observed during the administration of immunochemotherapy. In contrast, the most frequent AEs in the chemotherapy group were anemia (38%), nausea (36%), and weakness (18%).

The incidence of clinically significant treatment-related adverse events is summarized in Table 4 [6, 14].

Systemic treatment of patients with pleural mesothelioma

Approximately 360 patients in Poland are diagnosed annually with pleural mesothelioma [17]. Asbestos exposure is the greatest risk factor for cancer development, and the estimated time from exposure to disease onset is usually 30–40 years [18]. The diagnosis of pleural mesothelioma is based on the assessment of pleural specimens obtained during open biopsy or

Table 3. Efficacy of nivolumab in combination with ipilimumab and chemotherapy (based on [14, 16])

	Nivolumab/ipilimumab + + 2 cycles of chemotherapy (n = 361)	4 cycles of chemotherapy (n = 358)	HR
ORR [%]	37.7	25.1	
mPFS	6.8	5.0	0.7
mOS	18	12.6	0.66
mOS			
PD-L1 > 50%	18	12.6	0.66
PD-L1 1–49%	15.4	10.4	0.61
PD-L1 < 1%	17.7	9.8	0.67
mOS			
Squamous cell carcinoma	14.5	9.1	0.62
Non-squamous cell carcinoma	17	11.9	0.69
mOS			
CNS metastases (+)	19.3	6.8	0.43
CNS metastases (–)	15.6	12.1	0.79

CNS — central nervous system; HR — hazard ratio; mOS — median overall survival; mPFS — median progression-free survival; ORR — objective response rate; PD-L1 — programmed death receptor ligand 1

Table 4. Incidence of treatment-related adverse events in the CheckMate-9LA study [6, 14]

Adverse events	Nivolumab + ipilimumab + + chemotherapy (358 patients)		Chemotherapy (349 patients)	
	Any [%]	Grade 3–4 [%]	Any [%]	Grade 3–4 [%]
Any	92	47	88	38
Leading to treatment discontinuation	19	16	7	5
Serious	30	25.4	18	15

videothoracoscopy, including expression of immunohistochemical markers (calretinin, cytokeratin 5/6, WT-1). There are three histological types of malignant pleural mesothelioma (epithelial, sarcomatous, and mixed) with a different clinical course and sensitivity to systemic treatment [19]. The prognosis for pleural mesothelioma is poor, as most patients have advanced inoperable disease at diagnosis. Chemotherapy with cisplatin and pemetrexed is recognized as the standard first-line treatment; the superiority of the doublet regimen over cisplatin was demonstrated — median OS was 12.1 and 9.3 months, respectively (HR = 0.77; p = 0.020), and objective response rates were 41.3% and 16.7%, respectively [20]. Attempts to improve treatment outcomes by combining chemotherapy with anti-angiogenic drugs have failed [21, 22]. The effectiveness of chemotherapy is much lower in patients diagnosed with non-epithelial mesotheliomas — ORR does not exceed 15%, and OS is 4–6 months. Other negative prognostic factors were also determined, and apart from the tumor morphology, they include male sex, elevated lactate dehydrogenase level, weight loss, and thrombocythemia [23].

The chronic inflammatory response to asbestos fibers associated with carcinogenesis of pleural mesothelioma leads to the development of an immunosuppressive tumor microenvironment. Many studies also indicate that mesothelioma tissues are heavily infiltrated by immune cells, which can also be found in pleural effusion [24]. However, according to literature data, the immune system in patients with pleural mesothelioma is very tolerogenic (showing little activity against neoplastic cells) [24, 25]. It has been shown that although the total number of lymphocytes did not change in patients with mesothelioma, the percentages of some T lymphocyte populations (cytotoxic T cells, helper T cells, and NK cells) were significantly reduced [25, 26]. Biopsy studies have shown that despite the high infiltration by macrophages, $CD4^+$, and $CD8^+$ T lymphocytes in some tumors, there were no antigen-presenting cells necessary for antigen recognition and T cell activation. Many studies also show a significant increase in the percentage of regulatory T lymphocytes in the peripheral blood in patients with pleural mesothelioma [25, 26]. The above-mentioned premises theoretically justify the use of combined immunotherapy in mesothelioma [26, 27].

Table 5. Summary of treatment efficacy data [30]

	Nivolumab/Ipilimumab (303 patients)	Chemotherapy (302 patients)
ORR	39.6%	44%
CR	2.6%	–
PR	37%	44%
SD	37%	40.7%
PD	18.2%	4.3%
mPFS [months]	6.8	7.2
	HR = 0.92 (95% CI 0.76–1.11)	
mOS [months]	18.1	14.1
	HR = 0.75 (95% CI 0.63–0.90)	

CI — confidence interval; CR — complete response; HR — hazard ratio; mOS— median overall survival; mPFS — median progression-free survival; ORR — objective response rate; PD — progression disease; PR — partial response; SD — stable disease

In recent years, many studies have been conducted to assess the effectiveness of immune checkpoint inhibitors. Non-randomized studies in patients after chemotherapy failure indicated activity of immunotherapy — the ORR was 8–29%, and median OS was 10–17 months [28, 29].

Nivolumab in combination with ipilimumab in the treatment of patients with pleural mesothelioma

The efficacy and safety of a doublet regimen with dual immune checkpoint blockade were assessed in the CheckMate-743 study [7]. Patients diagnosed with advanced pleural mesothelioma, with good ECOG PS (0–1) and without contraindications for immunotherapy were eligible for treatment. Patients were randomized to receive nivolumab (3 mg/kg every 2 weeks) with ipilimumab (1 mg/kg every 6 weeks) for up to 2 years or to receive 6 cycles of platinum-based chemotherapy with pemetrexed [7]. Initial results and updates after 3 years of follow-up confirm the benefit of immunotherapy [7, 30]. Median OS was 18.1 and 14.1 months, respectively (HR = 0.73; 95% CI 0.61–0.87), and the percentage of patients who remained in follow-up after 3 years was 23% and 15%, respectively. Three years after treatment initiation, 14% of patients who received immunotherapy remained free from disease progression (1% in the chemotherapy arm). Data on survival and treatment response are presented in Table 5.

It should be emphasized that the activity of immunotherapy differs according to histological types of pleural mesothelioma. Patients with a non-epithelial type benefited significantly, as median OS was 18.1 and 8.8 months, respectively (HR = 0.48; 95% CI 0.34–0.69). In the group of patients with epithelial type, the impact on OS was limited, with median OS of 18.2 and 16.7 months, respectively (HR = 0.85; 95% CI 0.69–1.04).

The frequency of treatment-related adverse events (including grade ≥ 3) was similar in both groups (any AE in 80% of patients and grade ≥ 3 AEs in 30% of patients). Diarrhea (21%) and skin lesions (16%) were the most common in the group of patients undergoing immunotherapy, and nausea (37%), anemia (36%), and neutropenia (25%) were the most common in the group of patients receiving chemotherapy. The most common immune-related adverse events (irAEs) were rash (13% of patients), hypothyroidism/thyroiditis (12%), and colitis (9%). The most common grade 3/4 irAEs were hepatitis (5% of patients), colitis (4%), and rash (3%). The frequency of adverse events leading to temporary interruption or permanent discontinuation of treatment is presented in Table 6. In the experimental group, the most common causes of premature treatment discontinuation were colitis and diarrhea (2% of patients each) and anemia in the chemotherapy arm (4% of patients). It was also observed that premature treatment discontinuation due to an adverse event was a favorable prognostic factor in the analyzed group of patients.

Biomarkers assessment in patients diagnosed with pleural mesothelioma

The analysis of prognostic and predictive factors: clinical, morphological, and molecular, is an important part of research evaluating the value of modern anti-cancer therapies.

The CheckMate-743 study analyzed the predictive value of the signature of four genes encoding inflammatory proteins. It has been shown that in the group of patients with higher results receiving immunotherapy, OS was significantly longer than in patients treated with chemotherapy. Median OS was 21.8 and 16.8 months, respectively (HR 0.57; 95% CI 0.40–0.82), and the 3-year survival rates were 35% and 15%, respectively. These findings have not been demonstrated in the group of patients receiving chemotherapy [30].

Table 6. Incidence of treatment-related adverse events in the CheckMate-743 study [30]

Adverse events	Nivolumab + ipilimumab + + chemotherapy (300 patients)		Chemotherapy (284 patients)	
	Any [%]	Grade 3–4 [%]	Any [%]	Grade 3–4 [%]
Any	80	30.7	82	32
Leading to 1 drug discontinuation	22.7	15.3	15.8	7.4
Leading to all drugs discontinuation	17.3	13	1.7	4.6
Serious	21.3	15.7	7.7	6

The predictive value of tumor mutation burden (TMB) in relation to OS was not demonstrated (the analysis was performed in approximately 50% of patients in both groups with available TMB data).

The predictive value of PD-L1 expression was a secondary endpoint in the Check-Mate-743 study. The benefit of immunotherapy was demonstrated in the group of patients with PD-L1 expression ≥ 1% (HR = 0.69; 95% CI 0.55–0.87). In patients with PD-L1 expression < 1%, OS difference was not significant (HR = 0.94; 95% CI 0.62–1.40) [30].

Summary

The value of nivolumab in the second-line treatment of advanced NSCLC has been determined in randomized trials and confirmed in many publications based on real-world data. The synergistic effect of nivolumab and ipilimumab — as a consequence of restoring the activity of T lymphocytes in the early activation phase and in effector phase of immune response — is the basis for studies using both drugs. The results of the studies confirmed the effectiveness of nivolumab in combination with ipilimumab in patients with NSCLC (in combination with chemotherapy) and pleural mesothelioma (immunotherapy alone). The use of immunochemotherapy with dual immune checkpoints blockade allows for improving survival parameters in patients with NSCLC, regardless of histological type and PD-L1 expression level (including patients with PD-L1 expression < 1%). Clinical benefit is also noted in patients with CNS metastases. Age over 75 is probably a negative prognostic factor. Nivolumab in combination with ipilimumab is the first regimen using immune checkpoint inhibitors in pleural mesothelioma that is clinically proven and statistically superior to first-line chemotherapy. Patients with non-epithelial mesothelioma, for whom the systemic treatment methods available so far have shown little efficacy, can particularly benefit.

The use of a doublet immunotherapy regimen (including combination with chemotherapy) is associated with an increased risk of clinically significant adverse effects (including immune-related), which highlights a need for a thorough assessment of indications and contraindications for treatment at the time of patient selection and careful monitoring (especially in the first weeks of treatment).

Article Information and Declarations

Conflict of interest

M.K.-W.: honoraria for lectures from BMS and MSD.
K.W-K.: no conflict to declare.

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