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REVIEW ARTICLE

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Personalised treatment of non-small-cell lung cancer patients — review of current evidence

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ABSTRACT

The increasing number of scientific reports on the new-generation tyrosine kinase inhibitors and immunological checkpoint inhibitors in the management of patients with non-small-cell lung cancer (NSCLC) results in the necessity of frequent guidelines updating and constant preparing of treatment algorithms by scientific societies. This is accompanied by the continuous search for molecular predictive factors that could allow more personalised treatment and increased therapeutic benefits achieved by patients. Based on current recommendations, patients with mutated *EGFR* or rearranged *ALK* genes in advanced NSCLC should begin their treatment with tyrosine kinase inhibitors. The use of these agents within first- and second-line treatment may produce significant improvement of prognosis in selected patients. The improvement of survival may be achieved in patients with central nervous system metastases, who have poor prognosis. The role of immunotherapy increases as well, but negative results of some trials (e.g. MYSTIC or CheckMate 026) indicate difficulties in precise defining of groups of patients with the highest chances of benefit from immunotherapy. In view of the results from some trials (e.g. CheckMate 017, KEYNOTE 021, or PACIFIC), PD-L1 expression is not an optimal biomarker for immunotherapy. Initial results of some studies and retrospective analyses suggest the predictive value of other genetic or molecular abnormalities (e.g. high mutation load in tumour genome, microsatellite instability, or repair mechanism abnormalities). Precise definition of new biomarkers and ensuring the availability of genetic testing appears to be mandatory before widespread use of immunotherapy in clinical practice. Recently published positive results of studies testing new targeted agents, which have high value predictive factors, will probably influence the updates of scientific societies' guidelines and management algorithms. The aim of this review was to assess possibilities of personalised treatment in patients with advanced NSCLC with the use of new generation tyrosine kinase inhibitors and immune checkpoint inhibitors, in view of new scientific reports.

Key words: non-small-cell lung cancer, NSCLC, personalised treatment, EGFR inhibitors, ALK inhibitors, immunotherapy, immune checkpoints inhibitors

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Introduction

Lung cancer is the first cause of death due to cancer worldwide, as well as in Poland. In 2015, about 1.7 million deaths were recorded around the world [1]. Lung cancer is the most commonly diagnosed cancer in men, while in women it ranks second after breast cancer. Five-year overall survival rates (all histological types and stages) do not exceed 20% (in Poland approx. 13.5%). High mortality in lung cancer patients results mainly from too late diagnosis due to asymptomatic disease course at early stage. Approximately 80% of all lung cancers are non-small cell lung cancer (NSCLC), which is histologically classified into three types: squamous cell carcinoma (30%), adenocarcinoma (45%), and large-cell carcinoma (5%); the remaining 20% are small cell lung cancer (SCLC) [2].

The majority of patients with advanced-stage NSCLC receive systemic chemotherapy, whereas in pa-

tients with abnormalities in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and *ROS1* tyrosine kinase genes it is possible to use tyrosine kinase inhibitors. Due to rapidly occurring resistance to classic cytotoxic drugs, the results of chemotherapy are still unsatisfactory. Molecularly targeted drugs are more effective, but can be used only in patients with the aforementioned gene disorders (in Polish population they compromise approx. 12% of all NSCLC cases) [3]. The prerequisite for obtaining optimal therapeutic benefits in this group of patients is reliable assessment of status of genes being targets for targeted therapies.

The introduction of immune checkpoint inhibitors is promising in many cancers (including NSCLC) in clinical practice. These agents — monoclonal antibodies — bind to the programmed death receptor 1 (PD-1) or its ligand (PD-L1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA4). Contrary to traditional chemotherapy, the mechanisms of cancer immunotherapy are mainly based on:

— strengthening the immune system in the recognition of cancer cells;
— stimulation of the immune response;
— suppression of mechanisms that inhibit the immune system.

Historically, NSCLC was considered a non-immunogenic tumour — the opinion was partly due to unsuccessful attempts to modulate the immune system with interleukin 2, interferon or BCG (Latin Bacillus Calmette-Guerin) vaccine. However, as a result of better understanding of immune system mechanisms and the use of more advanced technologies, several drugs influencing the immune system (ipilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab) have been developed — these agents reduce the body's tolerance to cancer and increase the anti-cancer response.

The aim of the presented study is to summarise the most important results of clinical trials and conference reports on immunotherapy of NSCLC patients and treatment with molecularly targeted drugs of patients with activating mutations, and in particular the impact of these therapies on progression-free survival (PFS) and overall survival (OS). Considering the dynamic progress of knowledge, the negative results of some research, and increasing costs of sequential treatment, there is an urgent need for precise selection of patients and the development of an optimal algorithm for therapeutic treatment in advanced NSCLC.

Treatment of NSCLC patients harbouring *EGFR* mutation

Patients with the diagnosis of NSCLC and activating mutations within *EGFR* gene represent a special group. The frequency of mutations in *EGFR* gene is variable; in Caucasians it is about 12%, whereas in the Asian population it is found in about half of the patients. This mutation is most frequently detected in patients diagnosed with adenocarcinoma [4]. According to the majority of guidelines, genetic diagnosis of patients with non-squamous NSCLC should begin with *EGFR* gene status assessment, and in the absence of mutations it should also include *ALK* gene. The degree of histological differentiation has no effect on molecular diagnostic indications [5]. The current standard of treatment of patients with advanced NSCLC with deletion in exon 19 or substitution in exon 21 is the use of the first- or second-generation EGFR tyrosine kinase inhibitor (erlotinib, gefitinib, and afatinib). The probability of benefit following the use of EGFR tyrosine kinase inhibitors is about 50% higher in this group of patients as compared to standard chemotherapy. The main cause of resistance to treatment with EGFR inhibitors in the first-line setting is the appearance of secondary mutation T790M. The first drug registered by regulatory agencies in the United States and in Europe (Food and Drug Administration, FMA and European Medicine Agency, EMA, respectively), which showed high efficacy in case of this mutation after the failure of therapy with first-line EGFR inhibitors is osimertinib. Osimertinib is recommended by the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) in a dedicated group of patients after confirmed occurrence of T790M mutation [6].

Promising observations regarding the efficacy of osimertinib in first-line treatment were presented at the ESMO 2017 Congress. In the phase III study (FLAURA) the advantage of osimertinib was demonstrated relative to the standard of care (erlotinib or gefitinib) in terms of median progression-free survival (PFS) — 18.9 months compared to 10.2 months, which corresponds to a hazard ratio (HR) of 0.46 at the 95% confidence interval (CI) 0.37–0.57 and $p < 0.0001$. The median duration of response was 17.2 months and 8.5 months, respectively. The use of osimertinib in first-line treatment of patients with advanced NSCLC with mutation in *EGFR* gene resulted in reduced risk of disease progression or death by 54% compared to the standard use of first-generation tyrosine kinase inhibitors. It should be emphasised that advantage of osimertinib in terms of median PFS was also demonstrated in the subgroup of patients with central nervous system (CNS) metastases (15.2 months *vs.* 9.6 months, HR = 0.47, 95% CI 0.30–0.74; $p = 0.0009$). The median overall survival in the FLAURA study has not yet been achieved [7]. In October 2017, the FDA approved the accelerated registration of the drug in first-line treatment (justification — so-called breakthrough therapy) [8].

Treatment of patients with *ALK* rearrangement-positive NSCLC

ALK gene rearrangement occurs in 3–5% of all NSCLC patients and most often affects younger non-smokers. In patients with non-squamous NSCLC without *EGFR* mutations ESMO and ASCO guidelines recommend the determination of *ALK* and *ROS1* gene status (in particular in patients with adenocarcinoma or with mixed histology with predominant adenomatous component). In the treatment of patients with advanced NSCLC with *ALK* or *ROS1* rearrangements, ALK tyrosine kinase inhibitor — crizotinib — used in the first- or second-line of treatment is currently the standard of care.

The effect of crizotinib in the first-line treatment of patients with advanced NSCLC with *ALK* rearrangement was evaluated in the phase III study PROFILE 1014. The study demonstrated the superiority of crizotinib over standard platinum-based chemotherapy in terms of median PFS (10.9 months *vs.* 7.0 months, HR = 0, 45, 95% CI 0.35–0.60; p < 0.001). It should be noted that 84% of patients with the control arm received crizotinib (crossover) after the disease progression, which significantly influenced the results of overall survival analysis. The final results of the study published in 2017 showed the numerical higher activity of crizotinib in terms of OS as compared to chemotherapy (HR = 0.76, 95% CI 0.548–1.053; p = 0.0489 for one-sided test), but it did not reach the threshold of statistical significance [9]. The median OS was not reached in the crizotinib arm, but in control arm it was 47.5 months. Therefore, the impact of both interventions on OS was additionally estimated using the RPSFT (rank-preserving structural failure time) model, correcting the effect of transition of patients from control arm to treatment with crizotinib. Thereby, the estimated odds ratio (OR) for OS was 0.346 (stratified log-rank test) and 0.353 (stratified Wilcoxon test).

Not all patients with *ALK* gene rearrangement achieve response to treatment with crizotinib. Additionally, patients who have responded to this treatment acquire resistance after some time. If disease progresses during treatment with crizotinib, ESMO recommends the determination of *ALK* gene status on repeated biopsy and the use of second-generation ALK inhibitors (alectinib or ceritinib), which are characterised by higher affinity and stronger tyrosine kinase inhibition, as well as better penetration into (CNS). For alectinib this is confirmed by the results of the ALUR study, in which the value of this drug relative to standard chemotherapy (pemetrexed or docetaxel) was evaluated in patients previously receiving crizotinib or platinum-based chemotherapy [10]. Preliminary results of this study, presented during the ESMO 2017 Congress, indicate a significant advantage of alectinib against control intervention in terms of median investigator-assessed PFS (9.6 *vs*. 1.4 months, HR = 0.15, 95% CI 0.08–0.29; p < 0.001) and in an independent committee review (7.1 *vs.* 1.6 months, HR = 0.32, 95% CI 0.17–0.59; p < 0.001). It should also be noted that alectinib has a significant advantage compared to standard chemotherapy in patients with CNS metastases, for whom ORR in CNS reached 54.2% in the alectinib arm *versus* 0% in the control arm (difference 54.2%; 95% CI 0.23–0.78). Alectinib was also characterised by a more favourable safety profile and provided a better health-related quality of life (HRQoL) [11]. Grade 3 or higher adverse events occurred in 27.1% of patients in the alectinib arm and in 41.2% of patients in the control arm.

The efficacy and safety of another second-generation ALK inhibitor — ceritinib — was evaluated in a phase III study (ASCEND-5), which demonstrated superiority of this drug relative to standard chemotherapy in the second line of treatment in terms of median PFS (primary endpoint). The median PFS (ceritinib *vs.* pemetrexed *vs.* docetaxel) was 5.4 months *vs.* 2.9 months *vs.* 1.5 months, respectively [12]. Initial OS analysis at the data cut-off did not show significant differences in the median between ceritinib and chemotherapy (18.1 months *vs.* 20.1 months, HR = 1.0, 95% CI 0.67–1.49; p = 0.5). At the same time, severe adverse events have been reported more frequently in the ceritinib arm (43% and 32%, respectively).

In 2017, the results of a phase II clinical study (ALTA) were also published, comparing the efficacy and safety of two dosing regimens for another second-generation ALK inhibitor — brigatinib — in patients with advanced NSCLC with *ALK* rearrangement. The patients were randomly assigned to arm A (brigatinib 90 mg, once daily) or arm B (brigatinib 180 mg, once daily). The study showed the superiority of brigatinib at the higher dose in terms of median investigator-assessed PFS (arm A and B — 9.2 months *vs.* 12.9 months, respectively; HR = 0.55, 95% CI 0.35–0.86) and in independent committee review (9.2 months *vs*. 15.6 months). Brigatinib at a dose of 180 mg per day also showed an advantage in terms of one-year survival rate (arm A and B — 71% *vs.* 80%, respectively). ORR in patients with baseline measurable CNS metastases in an independent committee review reached the value of 42% in arm A compared to 67% in arm B. Treatment-emergent adverse events grade 3 or higher were reported in 21% of patients in arm A and 26% of patients in arm B. In April 2017, the FDA approved the accelerated registration of the drug in the treatment of patients with advanced NSCLC with *ALK* rearrangement, and with disease progression after crizotinib treatment or crizotinib intolerance (justification — so-called breakthrough therapy) [13, 14]. Currently, a phase III clinical study (ALTA-1L) is

ongoing, assessing the value of brigatinib in relation to crizotinib in the first line of treatment for patients with NSCLC with *ALK* rearrangement.

The current guidelines of scientific societies do not specify the preferred sequence of ALK inhibitors use due to the lack of studies directly comparing alectinib to ceritinib or brigatinib in second-line treatment. However, it is worth noting that in the ALEX study published in 2017, directly comparing alectinib to crizotinib in the first-line treatment of patients with advanced NSCLC with *ALK* rearrangement, an independent committee review showed a significant advantage of alectinib over crizotinib in terms of median PFS (25.7 months *vs.* 10.4 months; HR = 0.50; 95% CI 0.36–0.70; p < 0.001) and a rate of disease progression in CNS (12% *vs*. 45%, HR = 0.16, 95% CI 0.10–0.28; p < 0.0001) [15]. Based on the results of this study in October 2017, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion recommending the registration of the drug in the European Union in first-line treatment of patients with advanced NSCLC with *ALK* rearrangement, and the FDA registered the drug in this indication in November 2017 [16, 17]. As a consequence of the aforementioned research results and recommendations of government agencies, alectinib may soon become a new standard of treatment for patients with advanced NSCLC with *ALK* rearrangement.

The promising preliminary results of second-phase trials were also obtained for other new generation inhibitors of ALK and ROS1 (e.g. entrectinib, lorlatinib, and ensartinib) [18–20]. A summary of the effect of ALK inhibitors on PFS and OS and frequency of grade 3 or higher adverse events in the first- and second-line treatment of patients with advanced NSCLC with *ALK* rearrangement are shown in Table 1.

Monotherapy with monoclonal antibodies anti-PD-1 or anti-PD-L1

Pembrolizumab

In the phase I (KEYNOTE 001) and phase II/III studies (KEYNOTE 010), high expression of PD-L1 (> 50% of tumour cells) has been shown to predict a better response to pembrolizumab [21, 22]. In the phase III study (KEYNOTE 024), pembrolizumab was superior to platinum-based standard first-line chemotherapy in terms of median PFS (10.3 months *vs.* 6.0 months, HR = 0.50, 95% CI 0.37–0.68; p < 0.001) and ORR according to RECIST criteria (45.5% *vs*. 29.8%) as well as median OS (30.0 months *vs.* 14.2 months, HR = 0.63; 95% CI 0.47–0.86; p = 0.002) [23–25]. The mentioned benefits concerned NSCLC patients with high PD-L1 expression. It should be emphasised that an advantage of pembrolizumab in terms of OS was demonstrated despite the approved crossover of 62.3% of patients in the control arm undergoing chemotherapy, who had progression of the disease, to the pembrolizumab arm. Pembrolizumab was also superior in terms of its impact on quality of life and safety profile. Grade 3 and 4 adverse events occurred in 31.2% of patients *versus* 53.3% in the control arm [23]. Currently, a phase III trial (KEYNOTE 042) is being conducted in which pembrolizumab is compared to standard chemotherapy in the first line of treatment for NSCLC patients with PD-L1 expression at the level of ≥ 1%.

Nivolumab

Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 antigen. The drug was registered by the FDA and EMA for the treatment of patients with advanced NSCLC (regardless of PD-L1 expression) after the failure of standard platinum-based chemotherapy [25, 26].

The first multicentre studies evaluated the efficacy of nivolumab in patients with advanced squamous NSCLC (CheckMate 017) and advanced non-squamous NDRP (CheckMate 057) in a second-line setting. In a phase III study (CheckMate 017) involving 272 patients with advanced squamous NSCLC, who had previously received platinum-based chemotherapy, nivolumab and docetaxel were compared [27]. The study showed higher efficacy of nivolumab in the primary endpoint of OS (9.2 months *vs*. 6.0 months, HR = 0.59, 95% CI 0.44–0.79; p < 0.001). Benefits also included one-year survival rate (42% *vs.* 24%, HR = 0.59, 95% CI 0.44–0.79) and ORR (20% *vs.* 9%). However, progression-free survival did *not* favour *nivolumab* over docetaxel (median PFS — 3.5 months *vs*. 2.8 months, HR = 0.62, 95% CI 0.47–0.81; p < 0.001). Importantly, the higher expression of PD-L1 was not associated with greater clinical benefits of nivolumab in patients with squamous NSCLC. Treatment-emergent adverse events grade 3 or 4 were less frequent in patients receiving nivolumab (7% *vs.* 54%). The latest results of this study, presented at the ESMO 2017 Congress confirmed the higher survival benefits obtained by nivolumab-treated patients as compared to patients in the control arm (three-year survival rate — 16% *vs*. 6%, respectively) [28].

The efficacy of nivolumab against docetaxel in second-line treatment of patients with advanced non-squamous NSCLC was assessed in a phase III study (CheckMate 057), in which 582 patients participated [29, 30]. The study included patients who previously underwent standard platinum-based chemotherapy. Some patients with the presence of mutations in the *EGFR* gene or *ALK* rearrangements had also previ-

Table 1. Effect of ALK inhibitors on PFS and OS and frequency of grade 3 or higher adverse events in the first- and second-line treatment of patients with advanced NSCLC with *ALK* rearrangement

	ALK inhibitor	Effect on PFS as compared to control intervention		Effect on OS as compared to control intervention		Frequency of grade 3 or higher adverse events as compared to control intervention	Study
		Median (months)	HR	Median (months)	HR		
First-line treatment	Crizotinib	10.9 *vs.* 7.0 (crizotinib *vs.* standard chemotherapy)	0.45 (95% CI 0.35–0.60; p < 0.001)	Not reached *vs.* 47.5 (crizotinib *vs.* standard chemotherapy)	0.76 (95% CI 0.548–1.053; p = 0.0489 for one-side test)	Data not available	PROFILE 1014 (phase III study)
	Ceritinib	16.6 *vs.* 8.1 (ceritinib *vs.* standard chemotherapy)	0.55 (95% CI 0.42–0.73; p < 0.00001)	Not reached *vs.* 26.2 (ceritinib *vs.* standard chemotherapy)	0.73 (95% CI 0.50–1.08; p = 0.056)	78% *vs.* 62% (ceritinib *vs.* standard chemotherapy)	ASCEND-4 (phase III study)
	Alectinib	25.7 *vs.* 10.4 (alectinib *vs.* crizotinib) IRC assessment	0.50 (95% CI 0.36–0.70; p < 0.001)	Data not available		41% *vs.* 50% (alectinib *vs.* crizotinib)	ALEX (phase III study)
Second-line treatment (after failure of crizotinib treatment)	Alectinib	7.1 *vs.* 1.6 (alectinib *vs.* standard chemotherapy) IRC assessment	0.32 (95% CI 0.17–0.59; p < 0.001)	Data not available		27.1% *vs.* 41.2% (alectinib *vs.* standard chemotherapy)	ALUR (phase III study)
	Ceritinib	5.4 *vs.* 1.6 (ceritinib *vs.* standard chemotherapy) IRC assessment	0.49 (95% CI 0.36–0.67; p < 0.0001)	18.1 *vs.* 20.1 (ceritinib *vs.* standard chemotherapy)	1.0 (95% CI 0.67–1.49; p = 0.50)	43% *vs.* 32%* (ceritinib *vs.* standard chemotherapy)	ASCEND-5 (phase III study)
	Brigatinib	9.2 *vs.* 12.9 (brigatinib 90 mg q.d. *vs.* brigatinib 180 mg q.d.) Investigators assessment	0.55 (95% CI 0.35–0.86)	Data not available		21% *vs.* 26% (brigatinib 90 mg q.d. *vs.* brigatinib 180 mg q.d.)	ALTA (phase II study)
		9.2 *vs.* 15.6 (brigatinib 90 mg q.d. *vs.* brigatinib 180 mg q.d.) IRC assessment	Data not available				

*Serious adverse events. IRC — Independent Review Committee; q.d. — once daily

ously received EGFR or ALK inhibitors. The study showed the superiority of nivolumab in the primary endpoint of OS (12.2 months *vs.* 9.4 months, HR = 0.73, 96% CI 0.59–0.89; p = 0.002) and other efficacy parameters including: one-year survival rate (51% *vs.* 39%), 18-month survival rate (39% *vs.* 23%, HR = 0.72, 95% CI 0.60–0.88), ORR (19% *vs.* 12%), and median duration of response (17 *vs.* 6 months). The study showed a positive correlation of the effect of nivolumab on the survival in patients with PD-L1 expression — the higher the PD-L1 expression, the higher the survival benefits obtained by patients (Table 2). Among patients without

Table 2. Hazard ration (HR) values for the improvement of overall survival (OS) in patients with advanced non-squamous NSCLC in the nivolumab arm versus the docetaxel arm, depending on level of PD-L1 expression (CheckMate 057 study) [29]

Patients group	Hazard ratio (95% CI)	P value
PD-L1 expression < 1%	0.9 (0.66–1.24)	0.06
PD-L1 expression ≥ 1%	0.59 (0.43–0.82)	
PD-L1 expression ≥ 5%	0.43 (0.30–0.63)	0.0004
PD-L1 expression ≥ 10%	0.4 (0.26–0.59)	0.0002

PD-L1 expression, the survival in the nivolumab and docetaxel arms were similar.

The subgroup analysis results suggest superiority of nivolumab regarding improvement of survival in previously smokers (n = 458, HR = 0.7, 95% CI 0.56–0.86) with no advantage in never smokers (n = 118, HR = 1.02, 95% CI 0.64–1.61). Treatment-related grade 3 or 4 adverse events occurred less frequently in the nivolumab arm (10% vs. 54%). The long-term observation results presented at ESMO 2017 Congress confirmed consistent advantage of nivolumab over docetaxel in terms of overall survival (three-year survival rate — 18% *vs.* 9%, respectively) [28].

The value of nivolumab and standard chemotherapy in the first-line treatment was compared in a phase III clinical study (CheckMate 026). The study involved 423 patients with advanced NSCLC with PD-L1 expression > 5% [31]. Nivolumab was less effective than standard chemotherapy in the primary endpoint of PFS (4.2 months vs. 5.9 months, HR = 1.15, 95% CI 0.91–1.45; p = 0.251) and ORR (26.1% *vs*. 33.5%). The median OS was similar in both arms (14.4 months *vs.* 13.2 months, HR = 1.02, 95% CI 0.80–1.30). Grade 3 or 4 adverse events were less common in the experimental arm (17.6% *vs.* 50.6%). In 60% of patients in the control arm nivolumab was used after disease progression (crossover). The results of the study caused numerous discussions in the clinical environment regarding the optimal place of immunotherapy in the treatment of NSCLC patients and the actual causes of significant differences as compared to KEYNOTE 024 study. Although these differences may be partially explained by imbalanced characteristics of the studied populations (e.g. prior use of radiotherapy, differences in biomarker assessment, differences in the cut-off value for PD-L1 expression), it is generally considered necessary to define more precise predictive factors, that will allow more optimal selection of patients with a higher probability of obtaining benefits from anti-PD1 treatment. A retrospective exploratory subgroup analysis from the CheckMate 026 trial published in 2017 suggests that a high tumour mutational burden (TMB) may be a more reliable biomarker than PD-L1, or they should be used together [32]. According to the results of this analysis, patients with TMV ≥ 243 somatic mutations treated with nivolumab showed a trend towards improvement of PFS (HR = 0.62, 95% CI 0.38–1.00) and improvement of ORR (46.8% *vs.* 28.3%) as compared to the intervention in the control group.

The aim of another — currently conducted — phase III study (CheckMate 227) is to determine the most beneficial first-line treatment regimen for patients with NSCLC with use of nivolumab (monotherapy, combination with ipilimumab or chemotherapy).

Atezolizumab

Promising results of the studies on pembrolizumab and nivolumab justified attempts to determine the value of subsequent antibodies oriented on immune checkpoints. An example is atezolizumab, belonging to IgG1 class antibodies, registered by the FDA and EMA in the second-line treatment of patients with advanced NSCLC. Unlike nivolumab and pembrolizumab, which bind the PD-1 receptor on the surface of lymphocytes, atezolizumab targets PD-L1 ligand on the surface of tumour cells. Its efficacy against docetaxel was evaluated in second-line treatment in 1225 patients with advanced NSCLC in the phase III trial — OAK [33]. Analysis of results in the intent-to-treat (ITT) population showed the advantage of atezolizumab over docetaxel in terms of impact on primary endpoint, which was OS (13.8 months *vs.* 9.6 months; HR = 0.73; 95% CI 0.62–0.87; p = 0.0003) and median duration of response (16.3 months *vs.* 6.2 months, HR = 0.34, 95% CI 0.21–0.55; p < 0.0001), regardless of the histological type of NSCLC. The magnitude of advantage of atezolizumab over docetaxel was higher in the population of patients with PD-L1 expression ≥ 1% in tumour cells (TC) and infiltrating cells (IC), where the median OS was 15.7 months *vs*. 10.3 months in the atezolizumab and docetaxel arms, respectively (HR = 0.74, 95% CI 0.58–0.93; p = 0.0102). The greatest benefits of treatment with atezolizumab in terms of OS were observed in subgroup of patients with high PD-L1 expression (TC ≥ 50% and IC ≥ 10%) because the median OS was 20.5 months *vs.* 8.9 months, respectively (HR = 0.41, 95% CI 0.27–0.64; p < 0.0001). The median PFS and

ORR were similar in both arms and accounted for 2.8 months *vs.* 4.0 months, respectively (HR = 0.95, 95% CI 0.82–1.1; p = 0.49) and 14% *vs.* 13%. In patients receiving docetaxel, longer OS were noticed in the subgroup of patients with *EGFR* mutation (10.5 months *vs.* 16.2 months, HR = 1.24, 95% CI 0.71–2.18), which indicates lower benefits of immunotherapy. Atezolizumab was characterised by a more favourable safety profile.

The efficacy of atezolizumab in first-line treatment of patients with advanced NSCLC with PDH-L1 expression was assessed in the phase II study (BIRCH7) [34]. The study showed ORR of 25% and median PFS and OS of 7.3 months and 23.5 months, respectively. Grade 3 or higher adverse events occurred in 33% of patients. Direct comparison of atezolizumab to standard chemotherapy in the first-line treatment of NSCLC patients with PD-L1 expression ≥ 1% is currently carried out as part of the phase III IMpower 110 (NCT02409342) and IMpower 111 (NCT02409355) studies.

Durvalumab

Another promising antibody directed selectively against PD-L1 is durvalumab, which belongs to IgG1 class. In the phase I/II clinical study with use of durvalumab in the first-line treatment in patients with advanced NSCLC, an ORR of 28.6% (95% CI 16.6–43.3) and a disease control rate (disease stabilisation ≥ 24 weeks) of 42.9% (95% CI 28.8–57.8) were achieved [35]. Median PFS was 4.0 months (95% CI 2.3–9.1) while the median OS reached 21.0 months (95% CI 14.5–upper limit of the interval was not reached), and 72% of patients were still alive after 12 months (95% CI 56–83). There was no relationship between response rate and the histological type of the tumour. An open-label phase III clinical study (PEARL) is currently recruiting to assess the efficacy of durvalumab compared to standard chemotherapy in first-line treatment for NSCLC patients without *EGFR* mutations or *ALK* rearrangements with high PD-L1 expression (≥ 25%) [36].

In 2017, preliminary results of the phase III PACIFIC study were published — the study compared durvalumab with placebo in the consolidation treatment of patients with locally advanced NSCLC ineligible for resection the lung parenchyma and receiving platinum-based chemoradiotherapy (mostly concurrent). In this study durvalumab showed a significant advantage over the comparator in terms of ORR (28.4% *vs*. 16.0%; p < 0.001), median PFS (16.8 months *vs*. 5.6 months, HR = 0.52, 95% CI 0.42–0.65; p < 0.001) and median time to death or distant metastases (23.2 months *vs.* 14.6 months, 95% CI 10.6–18.6, HR = 0.52, 95% CI 0.39–0.69; p < 0.001) [37]. A significant advantage of durvalumab in terms of PFS was noticed regardless of the expression of PD-L1, with the criterion of positive expression at the level of 25% or greater (*vs.* lower percentage). Grade 3 or higher adverse events occurred in a similar percentage in both arms of the study (29.9% *vs.* 26.1%, respectively). Particularly important is the fact that in the group of patients receiving durvalumab radiation-induced pneumonia was not significantly more frequent. Results regarding effects on OS are not yet available, but the clinical benefit of durvalumab for the other endpoints assessed in the PACIFIC study suggests that in the near future durvalumab may be a valuable consolidation therapy in patients with locally advanced NSCLC after concomitant chemoradiation.

Avelumab

Another human anti-PD-L1 antibody tested for clinical use in treatment of NSCLC patients is avelumab. In a multi-cohort, phase I clinical study (JAVELIN SOLID TUMOURS), evaluating the efficacy of avelumab in the first-line treatment in 156 NSCLC patients with normal *EGFR* and *ALK* genes, ORR was 22.4%, and the median PFS reached 17.6 weeks (an objection to the study is the fact that PD-L1 expression is not verified) [38]. Treatment-emergent grade 3 adverse events occurred in 11% of patients. Currently, phase III clinical trials are underway in which avelumab is compared with standard first-line chemotherapy for patients with advanced NSCLC and with PD-L1 expression (JAVELIN Lung 100) and with docetaxel in the second-line treatment (JAVELIN Lung 200).

Anti-PD-1/anti-PD-L1 monoclonal antibodies combined with chemotherapy

Positive results of clinical trials with use of immune checkpoint inhibitors in monotherapy were a justification for attempts to determine the value of combination immunotherapy with chemotherapy. Preliminary results suggest that the combination of both treatments may offer greater clinical benefit to the patients.

The efficacy of combined treatment (pembrolizumab + pemetrexed + carboplatin) was compared with chemotherapy alone in first-line setting in patients with advanced non-squamous NSCLC in the phase I/II study (KEYNOTE 021, cohort G). The results presented at the ESMO 2017 Congress indicate that immunochemotherapy was superior to control intervention in terms of ORR (57% *vs.* 32%, 95% CI 7–41; p = 0.0029), median PFS (19.0 *vs.* 8.9 months, HR = 0.54, 95% CI 0.33–0.88; p = 0.0067), and 18-month survival rate (70% *vs.* 56%). The best results were achieved in patients with very high PD-L1 expression (50% or more); the responses in this group were more than twice as frequent after

immunochemotherapy (80% *vs.* 35%). It should be emphasised that 75% of patients in the control group received anti-PD-1/anti-PD-L1 treatment (including pembrolizumab) after disease progression. Data on median OS at the cut-off date could not be assessed due to insufficient long-term observation (median OS — not reachable *vs*. 20.9 months, HR = 0.59, 95% CI 0.34–1.05; p = 0.0344). Treatment-emergent adverse events grade 3 or higher were more common in patients receiving immunochemotherapy (41% *vs.* 29%) [39]. Currently, phase III clinical trials are ongoing (KEYNOTE 189, KEYNOTE 407), the aim of which is to further verify the efficacy of pembrolizumab combined with chemotherapy. The results of the study may help to explain the relationship between the degree of PD-L1 expression and the efficacy of combination therapy. Phase III studies are also underway to verify the value of atezolizumab combined with chemotherapy in the first-line treatment in NSCLC patients (IMpower 132, IMpower 130, IMpower 131, and IMpower 150).

Anti-PD-1/anti-PD-L1 monoclonal antibodies combined with CTL4 antibodies

Previous studies have not demonstrated the effect of ipilimumab combined with chemotherapy on OS in the first-line treatment in patients with NSCLC; however, attempts have been made to evaluate the effectiveness of the regimen involving so-called "double-block" of immune checkpoints (combined use of anti-PD-1/PD-L1 antibodies with ipilimumab) [40]. Clinical studies evaluating the combination of pembrolizumab with ipilimumab in the second-line treatment of patients with advanced NSCLC were started with the phase I/II clinical study (KEYNOTE 021, cohorts D and H). According to data presented at the ASCO 2016 Congress, patients receiving pembrolizumab combined with ipilimumab achieved median PFS and OS of 6 and 17 months, respectively. The results of the study indicate that use of pembrolizumab and ipilimumab is associated with increased toxicity and is no more effective in terms of ORR than monotherapy with pembrolizumab. No correlation was observed between PD-L1 expression and treatment outcomes [41].

The efficacy of nivolumab combined with ipilimumab (two dose schedules) in the first-line treatment of NSCLC patients was evaluated in a phase I clinical study (CheckMate 012) [42]. At the data cut-off point median PFS was longer in patients receiving ipilimumab every 12 weeks compared to the group with six-week dose intervals (8.1 months *vs.* 3.9 months). Two-year survival rates in these groups were 56% and 42% [43], respectively. Higher survival benefits were noted in patients with PD-L1 expression ≥ 1%; however, the study was not sufficiently statistically powered to show differences in survival between the groups. The incidence of grade 3 and 4 adverse events was similar for both ipilimumab regimens but significantly higher than for nivolumab monotherapy (CheckMate 026). It should be emphasised that the progression of the disease in patients receiving ipilimumab every six weeks occurred much earlier than in the group receiving drug every 12 weeks (the percentage of patients with progression or death before the first assessment in imaging tests — 44% and 18%, respectively). The presented results may suggest a difference between compared groups or potentially unfavourable effect of early immunotherapy in some patients. In patients with very high PD-L1 expression (50% or more of cells) ORR was significantly higher in the case of use of "dual blockade" (92% *vs.* 50%) with a 12-month survival rate of 100%. In case of low PD-L1 expression (< 1%), ORR after combination treatment did not significantly differ from the rates observed in other studies with nivolumab monotherapy in patients with NSCLC. In connection with CheckMate 026 study results, these data do not indicate that the patient may additionally benefit from use of nivolumab + ipilimumab regimen in the first-line treatment of NSCLC.

Phase III clinical trials are still ongoing, assessing the effectiveness of "dual blockade" of immune checkpoints (MYSTIC study — durvalumab alone or in combination with tremelimumab *vs.* chemotherapy; NEPTUNE study — durvalumab in combination with tremelimumab *vs.* chemotherapy; CheckMate 227 study — nivolumab, nivolumab with ipilimumab, nivolumab with chemotherapy as compared to first-line chemotherapy alone in patients with advanced NSCLC). In July 2017, preliminary results of the MYSTIC study were published, indicating that monotherapy with durvalumab or durvalumab in combination with tremelimumab (CTLA-4 inhibitor) used in the first-line treatment of patients with advanced NSCLC without disorders in *EGFR* and *ALK* genes did not show any advantage over platinum-based chemotherapy [44]. According to information issued by the drug manufacturer, the primary endpoint (PFS) was not achieved in any of the experimental arms of the study. The study has been continued, to evaluate the effect of durvalumab monotherapy and a regimen containing durvalumab and tremelimumab on the secondary endpoint (OS).

In conclusion, the preliminary results suggest that for the combination of anti-PD-1/PD-L1 antibodies with anti-CTLA4 antibody in NSCLC patients, there was no clinically significant added value in terms of ORR and PFS. The use of these schemes was associated with the risk of increased toxicity. The final conclusions regarding the "dual blockade" of immune checkpoints will be possible only after the publication of OS data and safety

Table 3. Treatment algorithm for patients with advanced NSCLC [47]

Histological type	Molecular disorders	PD-L1 status	First-line treatment	Maintaining treatment	Second-line treatment
Squamous NSCLC	NA	< 50%	Platinum derivatives, gemcitabine + cisplatin + necitumumab (EMA)	Necitumumab	Immunotherapy, chemotherapy, docetaxel + ramucirumab, afatinib
	NA	≥ 50%	Pembrolizumab	Pembrolizumab	Platinum derivatives
Non-squamous NSCLC	*EGFR* mutation	NA	Erlotinib + bevacizumab, erlotinib, afatinib, gefitinib	Erlotinib + bevacizumab, erlotinib, afatinib, gefitinib	Osimertinib, platinum derivatives
	ALK rearrangement	NA	Crizotinib (also in patients with *ROS1* mutation), ceritinib (FDA and EMA)	Crizotinib (also in patients with *ROS1* mutation), ceritinib (FDA and EMA)	Ceritinib, alectinib (after failure of crizotinib treatment), platinum derivatives
	Normal status of *EGFR* and *ALK* genes	< 50%	Platinum derivatives (in selected patients optionally bevacizumab)	Pemetrexed, bevacizumab	Immunotherapy, chemotherapy, docetaxel + ramucirumab, docetaxel + nintedanib (adenocarcinoma, EMA), erlotinib (EMA)
	Normal status of *EGFR* and *ALK* genes	≥ 50%	Pembrolizumab	Pembrolizumab	Platinum derivatives

NA — not applicable

data in the longer follow-up period, which confirm the lack of risk to patients from potential late toxicity.

Personalised treatment of patients with advanced NSCLC

Positive results of many studies on new immunotherapy options were reflected in the update of guidelines of scientific societies. ESMO 2017 guidelines for the management of patients with advanced NSCLC with normal *EGFR* and *ALK* genes recommend the use of pembrolizumab in the first-line treatment in patients with good performance status and PD-L1 expression ≥ 50% [45]. ASCO 2017 guidelines recommend the use of pembrolizumab in this group of patients provided that PD-L1 expression is ≥ 50% [46]. Patients with low PD-L1 expression should first receive standard chemotherapy. The use of other immunotherapeutic methods alone or in combination with chemotherapy is not recommended in the first-line setting. The algorithm for the management of patients with advanced NSCLC published in August 2017 indicates that pembrolizumab is the optimal option in patients with PD-L1 expression ≥ 50% (Table 3) [47]. New scientific reports on immunotherapy in NSCLC have been reflected in updated guidelines also for second-line treatment. Recommendations of ESMO immunotherapy for stage IV NSCLC patients with normal status of *EGFR* and *ALK* genes, who have progressed after the failure of first-line chemotherapy currently include nivolumab and pembrolizumab (for patients with PD-L1 expression > 1%) [45]. However, recommendations of ASCO immunotherapy of stage IV NSCLC patients with normal *EGFR* and *ALK* and *ROS1* genes and with PD-L1 expression ≥ 1% in second-line setting include monotherapy with nivolumab, pembrolizumab, and atezolizumab.

Therapeutic landscape

Currently, there are over 110 phase III clinical trials in the world assessing the effectiveness of new drugs in NSCLC patients, sponsored by pharmaceutical industry. In the near future, the results will allow the development of a comprehensive treatment algorithm that takes into

account new biomarkers [48]. Advances in the molecular biology of cancers and the high frequency of publications of new scientific reports mean that our knowledge on personalisation of treatment for patients with NSCLC is developing dynamically. In particular, we can observe this in the area of tyrosine kinase inhibitors and immunotherapy, which in some groups of patients allow therapeutic benefits with simultaneous reduction of toxicity as compared to standard chemotherapy. However, sequential use of new anticancer drugs and increasingly common administration of the studied drug to patients from the control arm on progression (crossover) make difficult the precise determination of effect of new drugs on OS [49]. In this context there is a growing role of studies based on clinical practice data. According to retrospective studies, the sequential use of molecularly targeted drugs of the new generation has led to median OS reaching even seven years (from the date of diagnosis of generalised disease) in patients with NSCLC with *ALK* rearrangement and six years in patients with NSCLC with *EGFR* mutation [50, 51]. The indicated values significantly exceed the recommended by ASCO experts the minimum values of expected increase in survival time, obtained due to new drugs registered for patients with non-squamous and squamous NSCLC [52].

Regarding immunotherapy, an example of a prospective study that showed OS improvement in the experimental arm, despite the admission of crossover, is the KEYNOTE-02 study. The study also showed PFS improvement in the subgroup of patients with advanced NSCLC with high PD-L1 expression (≥ 50%) receiving pembrolizumab within the first-line treatment as compared to standard platinum-based chemotherapy. Currently, pembrolizumab remains the sole inhibitor of immune checkpoints registered for the first-line treatment of NSCLC patients. Another promising example is the positive results of the PACIFIC study, suggesting that in the near future durvalumab may be an effective consolidation therapy after chemoradiation of patients with NSCLC at the local stage.

However, the collation of preliminary results of MYSTIC study with the negative results of CheckMate 026 study suggests that the use of immune checkpoint inhibitors does not always offer patients a clinically significant therapeutic benefit. It could result from difficulty in precisely defining the group of patients that benefit the most from treatment. In this context, the recent FDA accelerated approval of pembrolizumab combined with platinum-based chemotherapy in NSCLC patients without PD-L1 expression appears to be debatable. Considering that the results of two of the three large studies assessing the use of immunotherapy in the first-line treatment of patients with advanced NSCLC are negative, until full data from clinical trials have been published, the definition of a group of patients with advanced NSCLC who should be qualified for immunotherapy may raise doubts related to ambiguous research results.

The results of several clinical trials (e.g. CheckMate 017, KEYNOTE 021, PACIFIC) indicate that PD-L1 is not an optimal biomarker for immunotherapy. Differences in expression of PD-L1 in various parts of the tumour, in primary lesions and metastases, and variability over time cause doubts about the predictive value of PD-L1 for treatment with PD1/PD-L1 inhibitors in patients with NSCLC. Additionally, data indicating the lack of advantage of immunotherapy over docetaxel in second-line treatment in the group of patients with non-squamous NSCLC, who have never smoked (CheckMate 057), require further verification in subsequent studies. It is also necessary to confirm the value of all combination regimens, which due to the potential risk of late toxicity (including those different than in the case of monotherapy) require confirmation of the safety profile in a longer period of observation.

The tests currently used to evaluate PD-L1 expression are not equivalent to each other, which is an additional constraint in the formulation of conclusions. The threshold value determining the expression of PD-L1 may vary depending on the use of checkpoint inhibitors in monotherapy or in combination with other drugs.

The results of in-depth retrospective analysis of the CheckMate 026 study suggest that the predictive value may also have a high tumour mutational burden (TMB) value, and the simultaneous determination of PD-L1 expression and TMB may allow more precise selection of patients for treatment. Hence, further studies of the predictive value of microsatellite instability, TMB, mismatch repair deficiency, and the possibilities of practical use of the immune signature are being carried out [53–55]. The definition of new biomarkers seems necessary before the widespread use of immune checkpoint inhibitors in clinical practice.

Due to the key role of biomarkers in optimising the treatment of patients with NSCLC, further dynamic development and implementation of new diagnostic techniques should be predicted. An example is so-called "liquid biopsy", which involves the analysis of circulating free DNA (cfDNA). The advantage of these tests is reduced invasiveness and the possibility of frequent repetition to monitor the presence of new mutations occurring during treatment. The new possibilities will also make wider access to the digital polymerase chain reaction (PCR) and next-generation sequencing testing, which are currently more expensive, but offer much higher sensitivity than the commonly used real-time PCR. This translates into greater precision in qualifying patients for costly treatment methods.

The key role of biomarkers in the selection of patients for treatment is also starting to be noticed by the

regulatory agencies responsible for drug registration. In 2016 the FDA approved a first modern test for the determination of *EGFR* mutations from peripheral blood for clinical practice (EGFR Mutation Test v2 Cobas) [56]. In May 2017, for the first time in history, a medicinal product (pembrolizumab) was registered for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours, irrespective of tumour location and histological type. This decision marks a new direction in the US agency's approach to defining registration indications that can contribute to improving the availability of patients to modern molecularly targeted treatment. The adoption of an analogical approach in Europe by the EMA and its approval by the Agency for the Assessment of Medical Technology and Tariffs (AOTMiT) will have a decisive impact on the possibility of using modern anti-cancer drugs in Poland under programs that would not be limited by the location of cancer. With growing pressure from governmental health technology assessment agencies to more precisely define the population of patients eligible for treatment in reimbursement systems in most European countries, the importance of biomarkers used in oncology will gradually increase.

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