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REVIEW ARTICLE

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Pembrolizumab in combination with chemotherapy in patients with advanced squamous cell lung cancer — clinical trials and real-world data

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ABSTRACT

Advanced squamous-cell lung carcinoma remains a disease with an unfavorable prognosis. Until recently, chemotherapy was used in systemic treatment, and its effectiveness was limited. Implementation of immune check-point inhibitors allowed for an improvement in treatment results. The KEYNOTE-407 study included patients with squamous-cell lung cancer who received 4 immunochemotherapy cycles followed by maintenance treatment with pembrolizumab. Median overall survival of 17.2 months versus 11.6 months for chemotherapy was obtained (risk of death reduction by 29%) while the percentage of patients remaining in follow-up was 18%. Analysis of patients with good performance status treated in clinical practice confirms the results from the registration study and emphasizes the importance of taking into consideration clinical factors while qualifying patients for treatment.
Keywords: squamous-cell lung cancer; pembrolizumab, immunochemotherapy, prognostic and predictive factors

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Introduction

There are about 23000 newly diagnosed patients with non-small cell lung cancer (NSCLC) in Poland each year [1]. The therapy of choice in patients with generalized stage remains systemic treatment, and the therapeutic aim is to extend overall survival (OS) and improve quality of life (QoL). During qualification for treatment, apart from the patient's performance status (PS), comorbidities, results of laboratory tests, and status of biomarkers are also taken into account.

In patients with a documented presence of molecular disorders in the EGFR, *ALK* and *ROS1* genes, the management is based on use of molecularly targeted drugs. In other cases, chemotherapy, immunotherapy, or a combination of chemotherapy and immune checkpoint inhibitors (ICIs) may be considered. Immunotherapy mainly uses programmed death receptor type 1 (PD-1) inhibitors [2]. The biomarker that is decisive in qualifying for immunotherapy is the expression level of programmed death ligand 1 (PD-L1) on tumor cells (TCs) assessed by a validated immunohistochemical (IHC) assay. If PD-L1 expression is positive in ≥ 50% of cells, pembrolizumab, atezolizumab, or cemiplimab monotherapy should be considered. On the other hand, if the TC is < 50%, it is possible to use immunochemotherapy. Currently, regimens based on pembrolizumab and nivolumab combined with ipilimumab are available in Poland. Both regimens can be used regardless of the histological cancer type.

It is estimated that the incidence of squamous cell lung cancer (SCLC), among all types of NSCLC, is

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Table 1. Characteristics of the KEYNOTE-407 study population (based on [6])

	Pembrolizumab and chemotherapy (278 patients)	Placebo and chemotherapy (281 patients)
Median age (range) [years]	65 (29–87)	65 (36–88)
Patients > 65 years of age	54.6%	54.8%
Male sex	79.1%	83.6%
Asian race	19.4%	18.5%
ECOG performance status		
0	26.3%	32.0%
1	73.7%	68.0%
Non-smokers	7.9%	6.8%
Brain metastases	7.2%	8.5%
PD-L1 expression		
< 1%	34.2%	35.2%
1–49%	37.0%	30.0%
≥ 50%	26.3%	26.0%
Not assessed	2.5%	1.8%

ECOG — Eastern Cooperative Oncology Group; PD-L1 — programmed death ligand 1

currently 30–40% [3–5]. This study summarizes data from pivotal studies and observations from daily clinical practice (RWE) regarding SCLC patients qualified for immunochemotherapy with pembrolizumab.

Efficacy of immunochemotherapy — pivotal study results

The KEYNOTE-407 study enrolled patients diagnosed with SCLC who had not previously received systemic treatment due to generalized disease [6]. Patients receiving previous neoadjuvant or adjuvant treatment were still eligible for the study provided that the time between treatment cessation and disease dissemination was at least 12 months. Patients previously treated with pembrolizumab or other immune checkpoint inhibitors were not eligible for the study. In total, 559 patients were qualified for treatment, regardless of PD-L1 expression level (0–100%). The characteristics of the study population are presented in Table 1. Patients were randomly assigned to the chemotherapy arm [carboplatin for AUC 6 and paclitaxel 200 mg/m^2 every 21 days or nab-paclitaxel (nab-P) 100 mg/m^2 on days 1, 8, and 15] or to pembrolizumab-based immunochemotherapy. The treatment consisted of four cycles of immunochemotherapy or chemotherapy followed by maintenance treatment with pembrolizumab or placebo for a total of 35 cycles (2 years of treatment) [6]. After an initial follow-up period (with a median of 7.8 months), an advantage was observed in favor of pembrolizumab in combination with chemotherapy. Median OS for immunochemotherapy and chemotherapy were 15.9 and 11.3 months, respectively [hazard ratio (HR) was 0.64; 95% confidence interval (CI) 0.49–0.85; $p < 0.001$], and median PFS was 6.4 and 4.8 months, respectively (HR = 0.56; 95% CI 0.45–0.70; $p < 0.001$) [6]. The clinical benefit was independent of sex, age, PD-L1 expression level, and taxanes used (paclitaxel *vs*. nab-P) [6]. In the following years, updated data on the efficacy and safety of treatment were published (selected information is presented in Tab. 2) [7, 8]. It should be emphasized that in the experimental arm, 109 patients (39.2%) received systemic treatment after disease progression (including immunotherapy in 33 patients) while in the control arm, treatment was administered to 172 patients (61.4%), including 143 patients receiving immunotherapy. In the group of patients initially qualified for immunochemotherapy, 19.8% of patients completed the entire treatment planned and received 35 cycles of pembrolizumab [8]. In this subgroup, after another three years of follow-up, 60% of patients were still progression-free.

A special subgroup in this population included patients with a PD-L1 expression < 1%, who accounted for 35.2% of all patients included in the analysis in the KEYNOTE-407 study. The initially published results indicated that PD-L1 expression level does not significantly affect the likelihood of clinical benefit (HR = 0.61; 95% CI 0.38–0.98), but later analyses documented a limited advantage of immunochemotherapy over chemotherapy in the subgroup (HR = 0.79; 95% CI 0.56–1.11). However, it is worth noting the relatively high activity of chemotherapy used in the control arm in patients with a PD-L1 expression < 1% (median OS — 11 months). The percentage of patients

Table 2. Efficacy of treatment in the KEYNOTE-407 study (data for the general study population, based on the results of studies [6–8])

	ORR [%]	Median PFS [months]	PFS [%]	Median OS [months]	OS [%]
Paz-Ares (2018)	57.9 *vs.* 38.4	6.4 *vs.* 4.8 HR = 0.56; 95% CI 0.45–0.70; p < 0.001	–	15.9 *vs.* 11.3 HR = 0.64; 95% CI 0.49–0.85; p < 0.001	–
Paz-Ares (2020)	62.6 *vs.* 38.4	8 *vs.* 5.1 HR = 0.56; 95% CI 0.45–0.70; p < 0.001	After 12 months: 35.8 *vs.* 17.7	17.1 *vs.* 11.6 HR = 0.71; 95% CI 0.58–0.88; p < 0.001	After 12 months: 64.7 *vs.* 49.6
Novello (2023)	62.2 *vs.* 38.8	8 *vs.* 5.1 HR = 0.62; 95% CI 0.52–0.74	After 60 months: 10.8 *vs.* 3.5	17.2 *vs.* 11.6 HR = 0.71; 95% CI 0.59–0.85	After 60 months: 18.4 *vs.* 9.7

CI — confidence interval; HR — hazard ratio; ORR — objective response rate; OS — overall survival; PFS — progression-free survival

Table 3. Efficacy of pembrolizumab in combination with chemotherapy by PD-L1 expression level (based on study results [6–8])

	Median PFS [months] HR (95% CI)			Median OS [months] HR (95% CI)		
	< 1%	1–49%	≥ 50%	< 1%	1–49%	≥ 50%
Paz-Ares (2018)	0.68 (0.47–0.98)	0.56 (0.39–0.80)	0.37 (0.24–0.58)	0.61 (0.38–0.98)	0.57 (0.36–0.90)	0.64 (0.37–1.10)
Paz-Ares (2020)	0.67 (0.49–0.91)	0.50 (0.39–0.63)		0.79 (0.56–1.11)	0.67 (0.51–0.87)	
Novello (2023)	0.7 (0.52–0.95	0.6 (0.45–0.81)	0.48 (0.33–0.69)	0.83 (0.61–1.13)	0.61 (0.45–0.83)	0.68 (0.47–0.97)

CI — confidence interval; HR — hazard ratio; OS — overall survival; PFS — progression-free survival

with a PD-L1 expression < 1% remaining in follow-up after 5 years was 10.7% in the experimental arm and 13.1% in the control arm. A summary of treatment efficacy data in subgroups determined by PD-L1 expression level is presented in Table 3.

Efficacy of immunochemotherapy — real-world data

For a few years, immunochemotherapy based on pembrolizumab has been the standard of care in the first-line treatment of patients with advanced SCLC and PD-L1 expression levels < 50%. In Poland, this regimen has been financed since January 2021. Real-world data can establish the real value of immunochemotherapy and help identify subgroups of patients who benefit most from this treatment. Several reports concerning this clinical setting have been published recently.

Waterhouse et al. [9] analyzed a group of 4 271 patients, including 814 diagnosed with SCLC, who received immunochemotherapy (almost all patients were treated with pembrolizumab in combination with chemotherapy). Median OS was 10.6 months (95% CI 9.3–11.8). After 12 and 24 months of follow-up, 45.1% and 24.5% of patients were alive, respectively. Performance status had a significantly negative prognostic value. In patients with good performance status [0–1 according to the Eastern Cooperative Oncology Group (ECOG) scale], median OS was 11.6 months (95% CI 10.1–14.3), and in patients in average general condition (ECOG PS 2), OS was 8 months (95% CI 5.6–11.2). At the same time, significant differences were observed between the percentage of patients remaining in follow-up after 12 months (49.5% *vs.* 32.5%). An additional negative prognostic factor is the presence of brain metastases during qualification for treatment. Median OS for patients with and without brain metastases was 6.7 and 1.1 months, respectively, and the percentage of patients remaining in follow-up after 12 months was 32.1% and 45.9%, respectively [9].

In 364 patients diagnosed with SCLC, long-term clinical benefit after pembrolizumab-based immunochemotherapy was obtained in approximately 35% of

Table 4. Efficacy of pembrolizumab in combination with chemotherapy in squamous cell lung cancer patients — real-world data

	Number of patients		Median PFS [months] (95% CI)		Median OS [months] (95% CI)		OS at 12 months
	Total	PD-L1 < 1%	Total	PD-L1 < 1%	Total	PD-L1 < 1%	
Waterhouse (2021)	814	209 (35.9%)	ND		10.6 (9.3–11.8)	8.7 (7.7–12.4)	Total: 45.1% PD-L1 < 1%: 42.3% PD-L1 1–49%: 43.3% PD-L1 ≥ 50%: 50.9%
Liu (2022)	364	94 (35.3%)	6.5 (5.6–7.6)	5.8 (4.6–8.3)	15.3 (11.7–18.6)	17.2 (10.8–20.6)	Total: 54.9% PD-L1 < 1%: 57.0% PD-L1 1–49%: 56.0%
Wagenius (2023)	62	ND	ND	ND	18.9 (14.1, NE)	ND	71.3%

CI — confidence interval; HR — hazard ratio; ND — no date; NE — not estimable; OS — overall survival; PD-L1 — programmed death ligand 1; PFS — progression-free survival

patients (37% of patients remained in follow-up after 24 months) [10]. Median OS was 15.3 months (95% CI 11.7–18.6), and there were no differences related to PD-L1 expression level. In patients with a PD-L1 expression ≥ 1% and < 1%, median OS was 16.2 months (95% CI 10.3–20.6) and 17.2 months (95% CI 10.8––20.6), respectively [10]. The impact of other clinical and morphological factors on the prognosis in this group of patients was not assessed.

The SPINNAKER study included in the analysis a group of 308 patients (including 17% of patients diagnosed with SCLC) receiving pembrolizumab-based immunochemotherapy [11]. Median PFS for the general population was 8 months (95% CI 7.1–8.8), and median OS was 12.7 months (95% CI 10.2–15.2). The percentage of patients remaining in follow-up after 12 months was 52.2%. Detailed data on the SCLC patient subgroup were not presented. However, a multivariate analysis showed that a diagnosis of SCLC, presence of metastases in 3 or more sites, and a high value of the Systemic Inflammatory Index (SII) calculated based on platelet count and neutrophil-to-lymphocyte ratio (NLR) are negative prognostic factors for both PFS and OS. The performance status of patients also had a significant impact (ECOG: 0 *vs*. 1; HR = 1.46; 95% CI 1.06–2.02; p < 0.022) [11]. Selected real-world data regarding treatment efficacy are summarized in Table 4 [9, 10, 12].

Safety profile

A different mechanism of action of immune checkpoint inhibitors (including pembrolizumab) leads to the occurrence of immune-related adverse events (irAEs), which result from the activation of the immune system. In addition, due to the combined nature of the treatment, these patients also experience typical side effects of chemotherapy. In the KEYNOTE-407 study, adverse events were reported in 98.6% (74.8% grades 3–5), and irAEs were reported in 95.7% of patients (57.2% grades 3–5). Side effects led to discontinuation of one of the drugs in 28.8% of patients (in 17% of patients both immunotherapy and chemotherapy were discontinued). Complications of systemic treatment were considered the cause of death in 11% of patients. The frequency of adverse events is presented in Tables 5 and 6.

Table 5. Adverse events of pembrolizumab in combination with chemotherapy (based on the results of the KEYNOTE-407 study [8])

	Any grade [%]	Grade 3–5 [%]
Total	98.6	74.8
Anemia	54.7	15.8
Neutropenia	37.8	23.0
Nausea	36.3	1.4
Diarrhea	33.5	4.3
Thrombocytopenia	30.9	8.3
Loss of appetite	27.7	2.5
Joint pain	25.5	1.8
Asthenia	24.5	7.7
Peripheral neuropathy	21.9	1.1
Rash	18.7	0.7
Pruritus	18.3	0.4
Vomiting	18.3	0.4
Cough	17.6	0.7
Increased body temperature	15.1	0.7

In the aforementioned retrospective SPINNAKER study, irAEs of any grade were observed in 43% of patients (including 43 patients with grade 3 or 4).

Table 6. Immune-related adverse events (based on the results of the KEYNOTE-407 study [8])

	Any grade [%]	Grade 3–5 [%]
Total	35.6	13.3
Hypothyroidism	12.2	0.4
Pneumonitis	8.3	3.3
Hyperthyroidism	7.6	0.4
Infusion-related reaction	5.4	1.8
Colitis	3.5	2.5
Pituitary insufficiency	1.4	0.8

The occurrence of irAEs was a favorable prognostic factor — median OS was 17.5 months versus 10.1 months ($p < 0.001$) in the group of patients without adverse events [13].

Conclusions

Advanced SCLC is still associated with unfavorable prognosis, resulting from, among others, limited effectiveness of chemotherapy. Implementation of immune checkpoint inhibitors in the treatment of NSCLC patients, initially after chemotherapy failure, allowed for prolonged OS in some patients (long-term clinical benefit was observed in about 20% of cases) [14, 15]. Immunochemotherapy based on pembrolizumab is currently one of possible treatment options in this group of patients already in the first line of systemic treatment. The available data indicate the possibility of obtaining an objective treatment response in about 60% of patients and median OS of about 17 months [6–8]. In the KEYNOTE-407 study, 18.4% of patients in the immunochemotherapy arm remained in follow-up after 5 years from treatment initiation (*vs*. 9.7% in the chemotherapy arm).

However, it should be emphasized that the profile of patients who qualified for the pivotal study — consistent with inclusion criteria in the Drug Program in Poland — included good performance status (ECOG PS 0–1), absence of active brain metastases or molecular abnormalities in the *EGFR* and *ALK* genes. Publications based on real-world data confirm that performance status is an important prognostic factor. It seems reasonable to take into account other predictive and prognostic factors, which are discussed in the literature on immune checkpoint inhibitors in NSCLC patients. The presence of metastases in the skeletal system and liver, advanced stage of the disease, significant weight loss before treatment commencement, high activity of lactate dehydrogenase (LDH), elevated NLR and hypoalbuminemia may have a negative impact on the prognosis in patients undergoing immunochemotherapy [16–20]. In addition, the importance safety profile should be emphasized — in the KEYNOTE-407 study, approximately 30% of patients required treatment discontinuation due to adverse events.

Rational qualification for treatment of SCLC patients allows for their optimal selection and gives a chance for long-term clinical benefit.

Article information and declarations

Author contributions

M.K-W.: review of the literature, writing a preliminary version manuscript.
D.M.K.: verification and supervision.

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Conflict of interest

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Supplementary material

None.

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