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Immunochemotherapy in patients with non-squamous lung cancer

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Abstract

Immunochemotherapy is one of the main treatment options in patients with non-squamous non-small-cell lung cancer without molecular targeted abnormalities. In Poland, immunotherapy given concurrently with chemotherapy is available in patients with programmed death ligand 1 (PD-L1) expression below 50%. Pembrolizumab plus chemotherapy and nivolumab with ipilimumab with 2 cycles of chemotherapy are more efficient than chemotherapy alone with longer progression-free survival (PFS) and overall survival (OS). Other immunochemotherapy regimens including atezolizumab, durvalumab, tremelimumab, or cemiplimab are not used in daily practice in Poland. Benefits observed with immunochemotherapy are limited to patients in Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and without contraindications to immune checkpoint inhibitors and cytotoxic agents.

Keywords: immunotherapy, chemotherapy, non-small-cell lung cancer

Introduction

Immunotherapy is one of the main therapeutic options of molecularly targeted treatment available for patients with non-squamous cell lung cancer without molecular aberrations. In patients with expression of programmed death ligand 1 (PD-L1) on at least 50% of cells, stand-alone immunotherapy is the treatment of choice. In patients with lower PD-L1 expression, there are benefits from adding immunotherapy to standard platinum-based chemotherapy. The theoretical basis for the combination of immunotherapy with chemotherapy is probably the synergistic effect of both therapy modes by increasing tumor antigens presentation by immune system cells [1, 2], increasing the expression of PD-L1 on tumor cells, and stimulating the activity of effector T lymphocytes [3]. The effectiveness of the combination of immunotherapy with chemotherapy was assessed in several phase III studies with PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, durvalumab), and CTLA4 inhibitors (ipilimumab, tremelimumab) (Tab. 1).

Combination of pembrolizumab with chemotherapy

In the multicohort phase I/II Keynote-021 study [4], in a group of previously untreated patients with non-squamous cell lung cancer without *EGFR* or *ALK* genes aberrations and receiving pembrolizumab with pemetrexed and carboplatin, an objective response rate (ORR) was 55–71%, and median progression-free survival (PFS) was 10.2 months [95% confidence interval (CI) 6.2–15.2]. It was found that the benefits were not dependent on PD-L1 expression level [5]. The results of the phase I study were confirmed in a phase II extension study. The study constituting the basis for the registration of pembrolizumab in combination with chemotherapy was the phase III Keynote-189 study [6]. A group of 616 previously untreated patients with stage IV non-squamous cell lung cancer without *EGFR* and *ALK* gene disorders were randomly assigned to a group receiving

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Table 1. Selected phase III clinical trials with a combination of immune checkpoint inhibitors with chemotherapy in the first-line treatment of patients with advanced non-squamous non-small cell lung cancer (NSCLC)

Study	Histological type	PD-L1 expression	Treatment regimen	mPFS [months]	HR	mOS [months]	HR
KEYNOTE-189	N-SCC (100%)	Regardless of PD-L1 status	Pembrolizumab + chemotherapy	9 *vs.* 4.9	0.50	22 *vs.* 10.6	0.60
IMpower150	N-SCC (100%)	Regardless of PD-L1 status	Atezolizumab + bevacizumab + + chemotherapy*	8.4 *vs.* 6.8	0.57	19.5 *vs.* 14.7	0.80
EMPOWER-Lung 3	N-SCC (57.4%**)	Regardless of PD-L1 status	Cemiplimab + chemotherapy	7.9 *vs.* 5.7	0.53	19.4 *vs.* 12.4	0.64
CheckMate 9LA	N-SCC (69%**)	Regardless of PD-L1 status	Nivolumab + ipilimumab + + chemotherapy	7 *vs.* 6	0.72	17.8 *vs.* 12	0.78
POSEIDON	N-SCC (63.3%**)	Regardless of PD-L1 status	Durvalumab + tremelimumab + + chemotherapy	6.8 *vs.* 5.5	0.66	17.2 *vs.* 13.1	0.70

*Data for patients without molecular disorders (atezolizumab + bevacizumab + chemotherapy *vs.* bevacizumab + chemotherapy); **Percentage of patients with a diagnosis of non-squamous cell carcinoma in the experimental arm; HR — hazard ratio; mOS — median overall survival; mPFS — median progression-free survival; N-SCC — non-squamous-cell carcinoma; PD-L1 — programmed death ligand 1

doublet chemotherapy including platinum derivative and pemetrexed in combination with pembrolizumab (410 patients) or placebo (206 patients). The inclusion criterion was good or very good performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG). Scale. Patients were qualified for the study regardless of PD-L1 status, but PD-L1 expression level was one of the stratifying factors. Patients in the chemotherapy and combination arms could receive maintenance treatment with pemetrexed or pembrolizumab/placebo, respectively. Treatment with pembrolizumab or placebo was continued until disease progression, unacceptable toxicity, or a maximum of 35 three-week cycles. The primary endpoints of the study were overall survival (OS) and PFS. Among the qualified patients, the majority were men and former or current smokers. On enrollment, approximately 18% of patients had metastases in the central nervous system (CNS), previously treated in the majority of patients.

In the group receiving chemotherapy combined with pembrolizumab, a significant OS prolongation was observed (median 22 *vs.* 10.6 months in the chemotherapy alone group). Immunochemotherapy extended median PFS from 4.9 months to 9 months [7]. The objective response rate was higher in the pembrolizumab group (48.3% *vs.* 19.9%). The results updated after five years of follow-up confirmed the benefits of chemotherapy combined with pembrolizumab compared to doublet chemotherapy [8]. A 40% reduction in the relative risk of death was observed [hazard ratio (HR) = 0.60; 95% CI 0.50–0.72] and the relative risk of progression or death by 50% (HR = 0.50; 95% CI 0.42–0.60). The 5-year survival rate in the pembrolizumab group was 19.4% compared with 11.3% in the placebo group. No disease progression after 5 years was observed in 7.5% of patients treated with pembrolizumab compared to < 1% in the group receiving chemotherapy alone. Obtaining an objective response was one of the factors determining the long-term benefit of immunotherapy. It was found that the chance of obtaining an objective response correlated with PD-L1 expression level — in the group with PD-L1 expression < 1%, in the pembrolizumab arm, the percentage of the ORR was 33% compared to 62% in the group with high PD-L1 expression. Of 410 patients assigned to the pembrolizumab arm, 57 patients (14%) completed the planned 35 treatment cycles. In this group, the objective response rate was 86%, and almost 72% of patients lived at least 3 years after completing the two-year treatment. In the Keynote-189 study, the benefits in terms of improved survival were found across all analyzed subgroups and were independent of the PD-L1 expression level. Despite a similar incidence of adverse events of grade 3 and greater, including immune-related adverse events (irAEs), more patients in the pembrolizumab group discontinued treatment due to toxicity (36% *vs.* 17%).

Combination of atezolizumab with chemotherapy

Another registered combination of immunotherapy with chemotherapy in patients with non-squamous cell lung cancer is the combination of atezolizumab with chemotherapy containing carboplatin and paclitaxel and with bevacizumab. Unlike other immunochemotherapy regimens, patients with an *EGFR* mutation or *ALK* rearrangement were also eligible for the pivotal IMpower150 study. However, in patients with non-small cell lung cancer (NSCLC) with *EGFR* or *ALK* gene disorders, immunochemotherapy with atezolizumab and bevacizumab may be indicated only after failure of appropriate molecularly targeted drugs. On the other hand, the effectiveness of immunotherapy in the above-mentioned patient

population is debatable. The use of atezolizumab, carboplatin, paclitaxel, and bevacizumab was compared with chemotherapy combined with bevacizumab and chemotherapy with atezolizumab without an antiangiogenic agent. Patients were qualified for the study regardless of PD-L1 expression status. The use of the four-drug regimen compared to the regimen without atezolizumab improved OS from 15 to 19.8 months (HR = 0.8; 95% CI 0.68–0.95) and PFS from 6.8 to 8.3 months (HR = 0.59; 95% CI 0.5–0.7) [9]. A tendency to improve OS was also observed in the group of patients with *EGFR* gene mutations or *ALK* gene rearrangement, which, however, has not changed clinical practice due to the small sample size [10].

Combination of cemiplimab with chemotherapy

One of the newer drugs in the treatment of lung cancer patients is cemiplimab, an antibody against PD-1. The EMPOWER-Lung 3 study was a double-blind, placebo-controlled, phase III study evaluating cemiplimab in combination with chemotherapy in the first-line treatment of NSCLC patients, regardless of PD-L1 expression and histological tumor type. The study involved patients with good performance status (0–1 according to the ECOG scale) diagnosed with non-squamous or squamous NSCLC in clinical stages IV and III, not eligible for radical treatment [11]. A total of 466 patients were randomized to receive cemiplimab and chemotherapy (312 patients) or placebo and chemotherapy (154 patients). Cemiplimab was used at a dose of 350 mg every 3 weeks for up to 108 weeks in combination with chemotherapy (4 cycles with platinum derivatives), followed by maintenance treatment with pemetrexed as indicated. The primary endpoint was OS, and the secondary endpoints were response rate and PFS. In the entire analyzed population, there was a benefit from the use of immunochemotherapy in relation to the assumed study endpoints. In the cemiplimab plus chemotherapy group, median OS was 21.9 months compared to 13.0 months in the chemotherapy plus placebo group (HR = 0.71; 95% CI 0.53–0.93; p = 0.014), and median PFS reached 8.2 months versus 5.0 months, respectively (HR = 0.56; 95% CI 0.44–0.70; p < 0.0001). Treatment-related adverse events (TRAEs) were observed in 88.1% of patients in the experimental arm compared with 84.3% in the control arm. Immune-related adverse events occurred in 18.9% of patients treated with cemiplimab and chemotherapy, with grade 3 or greater toxicity occurring in 2.9% of patients [3].

The published update (after at least two years of follow-up) of the EMPOWER-Lung 3 study showed that in patients with non-squamous cell lung cancer, median PFS was 7.9 months *vs.* 5.7 months (HR = 0.53; 95% CI 0, 39–0.71) with cemiplimab compared to the control arm, and median OS reached 19.4 months versus 12.4 months, respectively (HR = 0.64; 95% CI 0.47–0.88). However, the benefits of immunochemotherapy were limited to patients with positive PD-L1 expression [12].

Combination of nivolumab with ipilimumab and chemotherapy

In the CheckMate 9LA study, 719 patients previously receiving systemic treatment for advanced NSCLC were randomly assigned to 4 cycles of platinum-based chemotherapy or immunochemotherapy. The treatment regimen in the experimental arm included a combination of nivolumab (at a dose of 360 mg every 3 weeks) with ipilimumab (at a dose of 1 mg/kg every 6 weeks in combination) and 2 cycles of platinum-based chemotherapy. Immunotherapy was continued for a maximum of 2 years or until disease progression [13]. The primary endpoint was OS, and the secondary endpoints were response rate and PFS assessed by an independent committee. In patients diagnosed with non-squamous cell lung cancer, median PFS was 7 months and 5.6 months (HR = 0.74; 95% CI 0.6–0.92), and OS was 17 and 11.9 months (HR = 0, 69; 95% CI 0.55–0.87) for the immunochemotherapy and chemotherapy arms, respectively. With a median follow-up of 30.7 months, the benefit of combined treatment was confirmed in terms of OS extension from 11 to 15.8 months (HR = 0.72; 95% CI 0.61–0.86) [14]. The results of treatment with nivolumab, ipilimumab, and chemotherapy were better regardless of tumor histology and PD-L1 expression level. In patients diagnosed with non-squamous cell carcinoma, median OS was 17.8 and 12 months (HR = 0.78; 95% CI 0.63–0.96), and median PFS was 7 *vs.* 6 months, respectively (HR = 0, 72; 95% CI, 0.59–0.88) [14]. TRAEs were observed in 92% of patients in the experimental group and 88% in the control arm [13].

Combination of durvalumab with tremelimumab and chemotherapy

Another example of dual immunotherapy in combination with chemotherapy is a regimen with durvalumab and tremelimumab in the first-line treatment of patients with advanced NSCLC. A total of 1013 patients diagnosed with NSCLC without genetic disorders were enrolled in the three-arm POSEIDON study and randomly assigned to the group receiving tremelimumab at a dose of 75 mg, durvalumab at a dose of 1500 mg and chemotherapy for a maximum of 4 cycles and one additional dose of tremelimumab. In both immunotherapy arms, durvalumab was administered every 4 weeks until progression [15]. The

primary endpoints for durvalumab plus chemotherapy versus chemotherapy were PFS and OS. The key secondary endpoints for the dual immune blockade arm compared with chemotherapy were PFS and OS. The combination of durvalumab with chemotherapy did not result in a significant improvement in OS compared to chemotherapy alone. In the group receiving dual blockade in combination with chemotherapy, a significant improvement in median PFS was observed in patients treated with chemotherapy alone (medians 6.2 *vs.* 4.8 months; HR = 0.72; 95% CI 0.60–0.86; p = 0.0003) and a prolongation of OS from 11.7 to 14.0 months (HR = 0.77; 95% CI 0.65–0.92). Over 60% of patients enrolled in the presented study were diagnosed with non-squamous cell carcinoma. Subgroup analysis comparing survival data in patients stratified by histological type showed that in the non-squamous cell carcinoma group, median PFS was 6.8 months for double immunochemotherapy versus 5.5 months for chemotherapy (HR = 0.66; 95% CI 0.52–0.84), and for the combination of durvalumab with chemotherapy versus chemotherapy, they reached 6.4 months and 5.5 months (HR = 0.77; 95% CI 0.61–0.96), respectively. The improvement in OS compared to the chemotherapy arm concerned the group receiving tremelimumab (17.2 *vs.* 13.1 months – HR = 0.70; 95% CI 0.56–0.87) and was not significant in the population receiving only durvalumab with chemotherapy (14.8 *vs.* 13.1 months — HR = 0.82; 95% CI 0.66–1.03). Both chemoimmunotherapy regimens were more likely to give an objective response, although the benefit was more pronounced in patients with non-squamous histology. Grade 3 or 4 TRAEs occurred in 51.8% of patients in the tremelimumab plus durvalumab plus chemotherapy group, 44.6% in the durvalumab plus chemotherapy group, and 44.4% in the chemotherapy group. Serious treatment-related adverse events occurred in 27.6%, 19.5%, and 17.7% of patients, respectively [15].

Conclusions

Currently, as part of the first-line systemic treatment of advanced NSCLC in Poland, it is possible to qualify patients for treatment with immune checkpoint inhibitors combined with chemotherapy. Possibilities of using immunochemotherapy in patients with non-squamous cell lung cancer include the combination of pembrolizumab with chemotherapy and nivolumab with ipilimumab and 2 cycles of platinum-based chemotherapy. The other immunochemotherapy regimens presented in this article have not yet been reimbursed in Poland. In patients with non-squamous cell lung cancer, the used chemotherapy regimen is platinum derivative combined with pemetrexed. Qualification for immunochemotherapy under the current drug program is possible in patients with documented PD-L1 expression in fewer than 50% of cells, regardless of the histological type of cancer. Patients diagnosed with advanced non-squamous cell lung cancer benefit from immunochemotherapy regardless of the PD-L1 expression level. However, it should be noted that in patients diagnosed with non-squamous cell carcinoma, the clinical benefits are primarily obtained by patients diagnosed with adenocarcinoma. Data on other types of non-squamous cell carcinoma are limited. All presented immunochemotherapy regimens demonstrated improved survival compared to chemotherapy in patients diagnosed with non-squamous cell lung cancer. On the other hand, the use of immunochemotherapy is less tolerated than chemotherapy and leads to a greater number of significant adverse events.

When qualifying patients for immunochemotherapy, parameters of organ efficiency, contraindications to particular therapeutic methods, and, above all, the performance status should be taken into account. Only patients with good and very good performance status according to the ECOG scale can benefit from immunochemotherapy. In other groups of patients, a different method of treatment should be chosen.

Article Information and Declarations

Author contributions

A. Płużański: concept, manuscript preparation, substantive supervision; A. Piórek: manuscript preparation.

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Conflict of interest

A. Płużański: lecture fees and participation in advisory board meetings of MSD, BMS, Astra, and Roche.
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Supplementary material

None.

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