VIA MEDICA

REVIEW ARTICLE

Aleksandra Piórek, Magdalena Zaborowska-Szmit

Department of Lung and Thoracic Cancer, The Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw

Atezolizumab — PD-L1 inhibitor in non-small-cell lung cancer

Address for correspondence:
Lek. Aleksandra Piórek
Klinika Nowotworów Płuca i Klatki Piersiowej, Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie w Warszawie
e-mail: opiorek@tlen.pl

Oncology in Clinical Practice
2017, Vol. 13, No. 5, 211–215
DOI: 10.5603/OCP.2017.0029
Translation:
dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

Advanced non-small-cell lung cancer is still a challenging disease. Chemotherapy and EGFR or ALK tyrosine kinase inhibitors are well-established options. Immunotherapy with immune-checkpoint inhibitors significantly improves survival both in first- and second-line treatment. Atezolizumab is one of the novel immunotherapies. This paper presents current data on mechanisms of action and clinical data of atezolizumab in second-line treatment of patients with advanced non-small-cell lung cancer.

Key words: non-small-cell lung cancer, advanced disease, immunotherapy, atezolizumab

Oncol Clin Pract 2017; 13, 5: 211–215

Introduction

The most valuable method of immunotherapy in patients with advanced non-small cell lung cancer (NSCLC) is the use of immune-checkpoint inhibitors, which include programmed death receptor type 1 (PD1) inhibitors — pembrolizumab and nivolumab — as well as an inhibitor for PD1 ligand (PD-L1) atezolizumab.

In October 2016 the US Food and Drug Administration (FDA) issued a positive decision for atezolizumab in the second-line treatment of patients with advanced NSCLC after failure of previous platinum-based doublet chemotherapy.

On 21. of September 2018, atezolizumab was registered in the European Union for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. The recommendation was based on coherent results of two randomised clinical trials (OAK and POPLAR), which demonstrated the superiority of atezolizumab as compared to docetaxel.

Atezolizumab has been identified as a drug that prolongs overall survival (OS) with a favourable safety profile. It should be emphasized that both studies have shown clinically relevant and statistically significant difference in overall survival in all patients included in intent to treat population (ITT) regardless of PD-L1 expression level.

Atezolizumab treatment was well tolerated and the incidence of immune-related adverse events (irAE) was low. The most common side effects in patients receiving atezolizumab were fatigue (> 20% of patients), decreased appetite, dyspnoea, cough, nausea, musculoskeletal pain, and constipation. Clinically relevant immune-related adverse events included pneumonia, hepatitis, colitis, and thyroid dysfunction. As yet, no relationship between the occurrence of immunological complications and long-term prognosis has been demonstrated [1]. The percentage of adverse events leading to discontinuation of the treatment in the OAK study was 8% for atezolizumab and 19% for the docetaxel group.

Mechanism of action of atezolizumab

Atezolizumab is a humanised monoclonal antibody IgG1 class with modified Fc region, which binds directly to PD-L1 provides dual blockade for PD-1 and B7.1 receptors and releases a suppressed PD-L1/PD-1-mediated immune response, including reactivation of anti-tumour immune responses without triggering cytotoxic antibody-dependent action. Atezolizumab

does not interfere with PD-L2/PD-1 interaction, so that inhibitory signals occurred via this signalling pathway can maintain.

Expression of programmed cell death 1 ligand (PD-L1) may occur on tumour cells and/or on tumour-infiltrating immune cells, contributing to the inhibition of antitumor immune response in the tumour microenvironment.

Constitutively occurs on antigen presenting cells (APCs) in lymphoid tissues, peripheral dendritic cells, macrophages and other cells involved in non-specific response.

PD-L1 expression is low in "immunological peace state", but it is rapidly stimulated during inflammation mediated by pro-inflammatory cytokines, mainly IFN-γ. Very high expression occurs on tumor cells (including NSCLC) [2]. It is estimated that 20–50% of human tumours express PD-L1.

The binding of PD-L1 to PD-1 and B7.1 receptors on T cells and antigen presenting cells inhibits cytotoxic activity and proliferation of T cell and cytokine production. PD-1 is expressed on the surface of activated T cells, B cells, and NK (natural killer) cells [3]. PD-1/PD-L1 interactions inhibit T-cell responses, induce apoptosis of tumour-specific T-lymphocytes, and promote the development of T-regulating lymphocytes (T_{regs}) [4]. T_{regs} lymphocytes have previously been referred to as suppressive because they are responsible for suppressing overly intense or autoreactive immune response.

Paradoxically, cancer cells use the natural PD-1/PD-L1 mechanism to escape from the immune response of the body. Atezolizumab blocks the aforementioned processes of inadequate and unfavourable "immune tolerance".

While PD-1 inhibitors (nivolumab, pembrolizumab) target PD-1 receptor on activated immune cells, PD-L1 inhibitors have a double action and block PD-L1 and PD-1 interactions as well as PD-L1 and B7.1 interactions (inhibiting receptor on T cells).

Predictive factors for treatment with atezolizumab

The results of a phase II clinical study (POPLAR) showed that OS — the primary endpoint — was significantly improved in patients on atezolizumab as compared to docetaxel, and the magnitude of OS benefit was associated with an increase in PD-L1 expression [5]. OS in the intention-to-treat (ITT) population was 12.6 months (95% CI 9.7–16.4) for atezolizumab as compared to 9.7 months (95% CI 8.6–12.0) in docetaxel group, which corresponded to reducing the risk of death by 27% [HR = 0.73 (95% CI 0.53–0.99); p = 0.04]. There was also a correlation between treatment efficacy and PD-L1 expression on tumour cell (TC) and tumour-infiltrating immune cell (IC) surface, which was evaluated on a four-step scale (0–3). The following HR values were found:

— for TC3 or IC3 — 0.49 (0.22–1.07; p = 0.068);
— for TC2/3 or IC2/3 — 0.54 (0.33–0.89; p = 0.014);
— for TC1/2/3 or IC1/2/3 — 0.59 (0.40–0.85; p = 0.005);
— for TC0 and IC0 — 1.04 (0.62–1.75; p = 0.871).

The limited percentage of objective responses to immunotherapy induced a discussion of predictive biomarkers, which could help to define the group of patients being good candidates for receiving immune-checkpoint inhibitors.

The most commonly studied predictive biomarker is expression of PD-L1 on tumour cells. Although objective responses to treatment are mainly noticed in patients with high expression, they are also seen in patients with low PD-L1 expression. Despite developing and approval of commercial immunohistochemistry (IHC) tests for PD-L1, their use as a predictive marker is limited by many unresolved issues, including various cut-off criteria, differences in terms of tissue preparation, differences between biopsy of primary and metastatic lesions, oncogene-induced changes in PD-L1 expression, heterogeneity of tumour tissue, differences in tumour cell staining compared to immune cells, and subjectivity of assessment [6, 7]. In addition, PD-L1 expression can be altered by prior or current treatment (radiotherapy and chemotherapy), which can occur after biopsy [8, 9]. Only SPI42 assay has been approved to evaluate PD-L1 expression in patients qualified for a treatment with atezolizumab. There is preliminary evidence that the SPI42 staining results differ from other tests [10].

Non-small cell lung cancer is characterised by increased genome instability, which can result in different mutations leading to the creation of new specific antigens. It has been hypothesised that efficacy of anti-PD-1 drugs is to a large extent related to the recognition of new antigens arising from various somatic mutations caused by carcinogens. It has been shown that greater number of tumour mutations correlates with better response to immunotherapy (e.g. pembrolizumab) [11]. Response rate to pembrolizumab in the KEYNOTE-001 study was 22.5% in active or ex-smokers compared to 10.3% in non-smokers and thereby with fewer smoking-related mutations [12].

Another issue is that response evaluation criteria in solid tumours (RECIST), which are basically used for chemotherapy are not fully relevant for comprehensive evaluation of immunotherapy effictiveness. Therefore, irRC (immune-related response criteria) has been proposed to describe atypical response patterns.

Characteristics of OAK study

OAK was a multicentre, open-label, phase III clinical study that compared efficacy and safety of atezolizumab alone with docetaxel in the second- or third-line treatment of patients with advanced NSCLC [13]. The study

included 1225 patients, who were stratified according to PD-L1 expression on immune cells (IC), number of previous chemotherapy lines, and NSCLC histologic type.

PD-L1 expression was assessed in a central laboratory using IHC VENTANA PD-L1 (SP142) assay. PD-L1 expression was evaluated on tumour cells (TC) and on tumour-infiltrating immune cells (IC). Table 1 presents how the degree of expression was defined. Patients were randomly assigned (1:1) to a group receiving atezolizumab at a fixed dose of 1200 mg intravenously or docetaxel 75 mg/m^2, both every three weeks. Treatment was continued until disease progression or unacceptable toxicity assessed by the investigator. It was allowed to continue treatment with atezolizumab beyond disease progression, which was received by 40% of patients. Patients with autoimmune diseases and symptomatic brain metastases treated with corticosteroids were excluded. Patients with *EGFR* activated mutation or *ALK* gene rearrangement were included into a study provided prior treatment was carried out with a tyrosine kinase inhibitor.

Table 1. PD-L1 expression level on tumour cells (TC) and tumour-infiltrating immune cells (IC) in OAK study

	PD-L1 expression level
TC (tumour cells)	
TC1/2/3	≥ 1%
TC2/3	≥ 5%
TC3	≥ 50%
TC0	< 1%
IC (tumour-infiltrating immune cells)	
IC1/2/3	≥ 1%
IC2/3	≥ 5%
IC3	≥ 10%
IC0	< 1%

Patient characteristics are shown in Table 2. Mean patients' age was 64 years (range, 33–85 years), with predominant male gender (61%), Caucasian race (70%), and patients with performance status (PS) 1 in ECOG scale (63%). *EGFR* activated mutations were detected in 10% of patients, and *ALK* rearrangement was present in less than 1%. Most of patients were former or current smokers (82%). Seventy-four per cent of patients were diagnosed with non-squamous cell NSCLC; 75% of patients received only one prior treatment line.

The primary endpoint was overall survival (OS) in the ITT population and in a population of patients with PD-L1 expression (TC1/2/3 or IC1/2/3). Secondary endpoints included ORR, PFS, DoR, and safety. Both primary endpoints were met after median follow-up of 21 months, and the primary analysis encompassed the first 850 randomised patients.

Statistically significant improvement in OS was observed in patients treated with atezolizumab compared to docetaxel in both the ITT population regardless of PD-L1 expression (median difference 4.2 months) [HR 0.73 (95% CI 0.62–0.87)] and in patients with PD-L1 expression ≥ 1% (5.4 months) [HR 0.74 (95% CI 0.58–0.93)]. Detailed results are presented in Table 3 and Figures 1 and 2.

The greatest benefit was achieved in the patients with the highest PD-L1 expression (TC3/IC3), but it was also observed in patients without PD-L1 expression (TC0 and IC0 population). Treatment with atezolizumab resulted

Table 2. Patients characteristics before treatment initiation, ITT (n = 850)

Data	Atezolizumab n = 425	Docetaxel n = 425
Median age (years)	63	64
≥ 65	45%	49%
Male	61%	61%
Histologic type		
Nonsquamous	74%	74%
Squamous	26%	26%
ECOG 0/1	37% / 64%	38% / 62%
Number of previous therapy lines, 1/2	75% / 25%	75% / 25%
Smoking history		
Never-smokers	20%	17%
Current/ex-smokers	14% / 66%	16% / 67%
CNS metastases, yes/no	9% / 91%	11% / 89%
Known EGFR status		
Mutation	10%	10%

Table 3. Summary of treatment outcomes — primary analysis in OAK study in ITT population and in PD-L1-positive population

	ITT			TC1/2/3 or IC1/2/3		
	Atezolizumab (n = 425)	**Docetaxel (n = 425)**	**p value**	**Atezolizumab (n = 241)**	**Docetaxel (n = 222)**	**p value**
OS months (95% CI)	13.8 (11.8–15.7)	9.6 (8.6–11.2)	p = 0.003	15.7 (12.6–18.0)	10.3 (8.8–12.0)	p = 0.0102
PFS months (95% CI)	2.8 (0.62–0.87)	4.0 (3.3–4.2)	p = 0.49	2.8 (2.6–4.0)	4.1 (2.9–4.3)	p = 0.38
ORR (%)	14	13		18	16	

ITT — intention-to-treat; CI — confidence interval; PFS — progression-free survival; OS — overall survival; ORR — objectve response rate

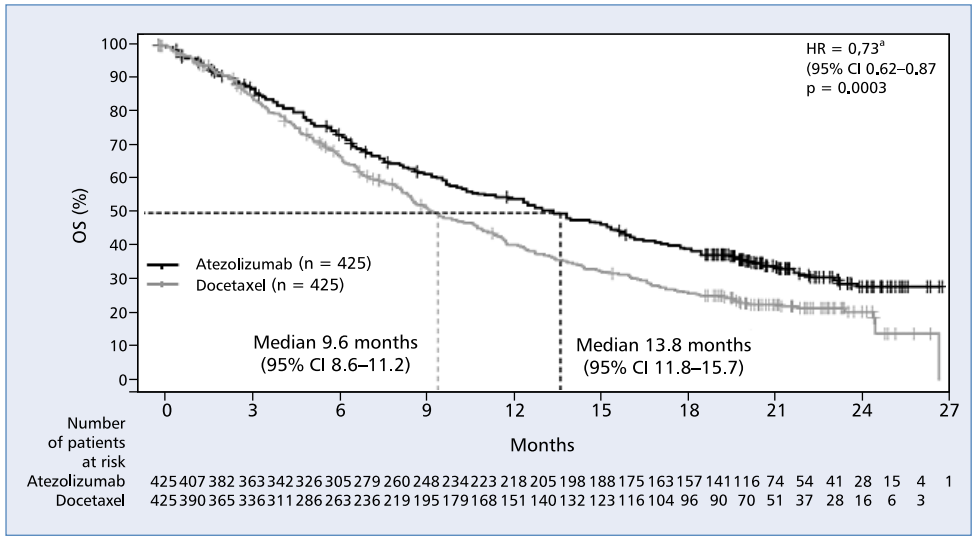

Figure 1. Overall survival in intention-to-treat population

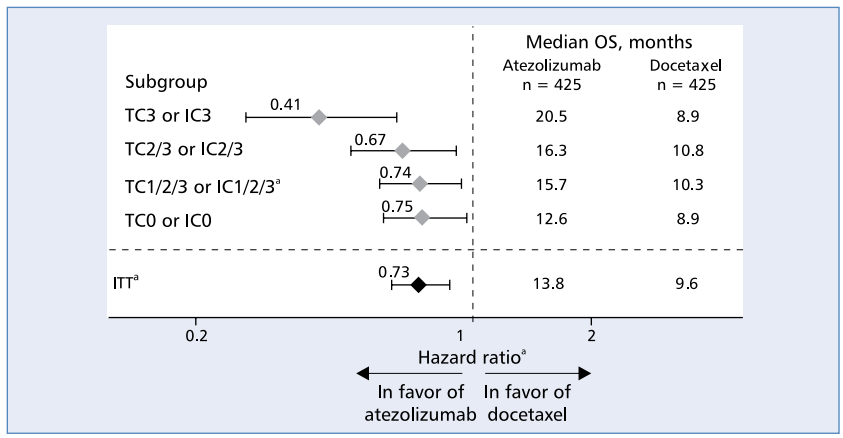

Figure 2. Overall survival according to PD-L1 expression

in a 25% reduction in the risk of death in subgroup TC0/IC0 as compared to docetaxel [HR 0.75 (95% CI 0.59–0.96)]. In comparison, the risk reduction in the POPLAR study was 22% [HR 0.88 (95% CI 0.55–1.43)].

The benefit of atezolizumab treatment was constantly noticed in all evaluated subgroups of patients (including patients with squamous and non-squamous cell carcinoma and patients with CNS metastases) except patients with confirmed *EGFR* activated mutation.

After completion of the study 17% of patients treated with docetaxel received immunotherapy (mainly nivolumab). The proportion of patients who received the

next line of chemotherapy (mainly docetaxel) was higher in the atezolizumab arm (41%) than in the docetaxel arm (31%). Despite the difference in median OS, no progression-free survival (PFS) benefits were achieved with numerically better PFS results in the docetaxel arm [2.8 months in atezolizumab arm and 4 months in the docetaxel arm, HR 0.95 (95% CI 0.82–1.1), p = 0.49]. Objective response rates were similar in both arms, but the mean response duration was significantly longer in patients receiving atezolizumab [16.3 months in the atezolizumab arm and 6.2 months in the docetaxel arm, HR 0.34 (95% CI 0.21–0.55), p < 0.0001].

Treatment with atezolizumab was also characterised by more favourable safety profile. The toxicity was similar to that observed in the POPLAR study. The incidence of grade 3/4 adverse events related to treatment was 15% for atezolizumab and 43% for docetaxel. Reported irAE included pneumonia [six patients (1%), four patients with grade 3 (< 1%)], hepatitis [two patients with grade 4 (< 1%)], and colitis [two patients with grade 2 (< 1%)]. No deaths associated with atezolizumab treatment were noted.

Challenges in lung cancer treatment

Non-small cell lung cancer is the most common cause of death from malignant neoplasms in Poland and worldwide. In approximately 60% of patients, at the time of diagnosis lung cancer is already locally advanced or disseminated. The standard first-line treatment of patients with advanced NSCLC is platinum-based doublet chemotherapy with the third-generation drug, with median OS in a range of 10–12 months, and one-year survival rate of about 30–40% [14]. In patients with *EGFR* gene activating mutations or rearrangement of *ALK* and *ROS1* genes the use of oral small-molecule tyrosine kinase inhibitors (TKIs) could be also considered. This treatment leads to objective response in about 60–70% of patients and median PFS within 9–14 months.

Finally, in the vast majority of patients with response to first-line treatment, progression of the disease occurs. Up to now the standard of care in this situation is the use of docetaxel or pemetrexed alone in patients with good performance status (PS). Currently — together with the results of phase III clinical studies — immunotherapy should be a valuable treatment method in the second-line setting.

Summary

Atezolizumab is the first anti-PD-L1 monoclonal antibody registered in Poland for a treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.

The results of the OAK and POPLAR studies have confirmed the role of PD-L1 as a potential therapeutic target, and once again documented the importance of immunotherapy in the treatment of patients with advanced NSCLC.

Both studies demonstrated a statistically significant and clinically relevant prevalence of atezolizumab over docetaxel as regards to overall survival in patients with advanced NSCLC. The observed therapeutic effect was independent of PD-L1 expression level.

Treatment with atezolizumab was characterized by a favorable safety profile and the rate of immune-related adverse events was low.

References

1. Postow MA. Managing immune checkpoint-blocking antibody side effects. Am Soc Clin Oncol Educ Book. 2015: 76–83, doi: 10.14694/EdBook_AM.2015.35.76, indexed in Pubmed: 25993145.
2. Konishi J, Yamazaki K, Azuma M, et al. B7-H1 expression on non--small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. Clin Cancer Res. 2004; 10(15): 5094–5100, doi: 10.1158/1078-0432.CCR-04-0428, indexed in Pubmed: 15297412.
3. Agata Y, Kawasaki A, Nishimura H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. Int Immunol. 1996; 8(5): 765–772, doi: 10.1093/intimm/8.5.765, indexed in Pubmed: 8671665.
4. Aerts JG, Hegmans JP. Tumor-specific cytotoxic T cells are crucial for efficacy of immunomodulatory antibodies in patients with lung cancer. Cancer Res. 2013; 73(8): 2381–2388, doi: 10.1158/0008-5472.CAN-12-3932, indexed in Pubmed: 23580578.
5. Fehrenbacher L, Spira A, Ballinger M, et al. POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016; 387(10030): 1837–1846, doi: 10.1016/S0140-6736(16)00587-0, indexed in Pubmed: 26970723.
6. McLaughlin J, Han G, Schalper K, et al. Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non–Small-Cell Lung Cancer. JAMA Oncology. 2016; 2(1): 46, doi: 10.1001/jamaoncol.2015.3638, indexed in Pubmed: 26562159.
7. Patel SP, Kurzrock R. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. Mol Cancer Ther. 2015; 14(4): 847–856, doi: 10.1158/1535-7163.MCT-14-0983, indexed in Pubmed: 25695955.
8. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015; 520(7547): 373–377, doi: 10.1038/nature14292, indexed in Pubmed: 25754329.
9. Sheng J, Fang W, Yu J, et al. Expression of programmed death ligand-1 on tumor cells varies pre and post chemotherapy in non-small cell lung cancer. Sci Rep. 2016; 6: 20090, doi: 10.1038/srep20090, indexed in Pubmed: 26822379.
10. Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J Thorac Oncol. 2017; 12(2): 208–222, doi: 10.1016/j.jtho.2016.11.2228, indexed in Pubmed: 27913228.
11. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015; 348(6230): 124–128, doi: 10.1126/science.aaa1348, indexed in Pubmed: 25765070.
12. Garon E, Rizvi N, Hui R, et al. Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. New England Journal of Medicine. 2015; 372(21): 2018–2028, doi: 10.1056/nejmoa1501824.
13. Rittmeyer A, Barlesi F, Waterkamp D, et al. OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017; 389(10066): 255–265, doi: 10.1016/S0140-6736(16)32517-X, indexed in Pubmed: 27979383.
14. Krzakowski M. Nowotwory płuca, opłucnej, śródpiersia. In: Krzakowski M, Potemski P, Warzocha K, Wysocki P. ed. Onkologia kliniczna tom II. Via Medica, Gdańsk 2015: 556–558.