Ahead of Print
Turk Thorac J
DOI: 10.5152/TurkThoracJ.2017.17006

REVIEW

Immune Checkpoint Inhibitors in Advanced-Stage Non-Small Cell Lung Cancer

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Cite this article as: Kazaz SN, Öztop İ. Immune Checkpoint Inhibitors in Advanced-Stage Non-Small Cell Lung Cancer. Turk Thorac J 2017: DOI: 10.5152/TurkThoracJ.2017.17006

Abstract

More than half of non-small cell lung cancer (NSCLC) patients are at an advanced stage at the time of diagnosis, and they have a poor prognosis. Systemic treatment is the basic treatment approach for advanced-stage NSCLC, and chemotherapy and targeted treatments are commonly used based on the molecular characteristics. Although targeted therapies have led to a significant level of improvement in terms of survival, the results are still unsatisfactory. However, considerable attention has been focused to the immunotherapy with recent positive results reported by studies on this field. In this context, a certain portion of clinical studies have shown dramatic results, and these have involved inhibitors developed particularly against the immune checkpoint protein programmed death receptor-1 and its ligand (programmed death ligand-1). This review aims to present the significance of immune checkpoint inhibitors in NSCLC and to summarize the findings of relevant contemporary clinical studies.

KEYWORDS: Non-small cell lung cancer, immunotherapy, checkpoint inhibitors

Received: *03.02.2017* ***Accepted:*** *15.05.2017* ***Available Online Date:*** *21.07.2017*

INTRODUCTION

Lung cancer is the leading cause of cancer-related death for both genders worldwide and poses a serious public health problem [1,2]. Non-small cell lung cancer (NSCLC) comprises approximately 85% of all lung cancers. More than 50% of NSCLC patients are at an advanced stage at the time of diagnosis, and they are characterized by a poor prognosis. In addition, 40-70% of the early stage NSCLC patients develop distant metastases throughout the course of the disease, despite curative surgical intervention [3-5]. Systemic treatment is the basic treatment approach for advanced-stage NSCLC; some patients receive radiotherapy if needed, and other specific patients may undergo surgical intervention. With regard to the planning of systemic treatment, the decision is made by taking patient- and tumor-related factors into account. Primary patient-related factors include age, performance status, and comorbidity, and main tumor-related factors include classification of the histological type and molecular analysis of the tumor, which are of key importance [6,7]. Today, recommended molecular analyses are epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) fusion oncogene and C-ros oncogene 1 analyses. After performing these analyses, relevant patients receive targeted treatments (erlotinib, gefitinib, afatinib, or crizotinib), while others are treated with systemic chemotherapy. These approaches extend the survival time and increase the quality of life. In addition, there are recent studies available on the BRAF, RAS, and MET pathways, all of which have reported considerably positive findings [8-10]. The agents targeting these pathways may be used in this field in the near future.

Recently, we have witnessed a key development in the field of immunotherapy for the treatment of NSCLC. A better identification of the immune pathways playing a role in tumor progression and growth in lung cancer, which is known to have a relatively low immunogenicity, and inhibitor agents specifically developed for them have led to renewed attention to immunotherapy. Following various pre-clinical and clinical studies demonstrating that blocked immune checkpoints increase the immune response and cause tumor regression, agents blocking these points have received considerable attention. This review aims to present the significance of immune checkpoint inhibitors in NSCLC and to summarize the findings of relevant contemporary clinical studies.

Immune Response

The immune response against tumors consists of four main phases. These are tumor identification, presentation of tumor antigens to antigen-presenting cells (APCs), presentation of APCs to immune effector cells after being processed (priming

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phase), and direct attack on the tumor with T-cell activation (effector phase). At the beginning of immune recognition, APCs internalize tumor antigens and migrate to lymph nodes. In lymph nodes, APCs present tumor antigens to resting T cells. The antigen-specific T-cell receptor complex plays a fundamental role in this process, and the interaction between B7.1 or B7.2 and CD28 contributes to this presentation (priming phase). Once activated, the T cell carries out an attack on the tumor cell and causes lysis of the tumor cell by releasing cytolytic enzymes such as perforin and granzyme (effector phase) [11,12]. All aforementioned phases of the immune response are controlled by various immune checkpoints that prevent excessive inflammation and autoimmunity. In the presence of malignancy, cancerous cells further activate these checkpoints and thus gain immunological tolerance [13].

Two significant checkpoints have been identified, and specific inhibitors for them have been developed. The first is cytotoxic T-lymphocyte antigen 4 (CTLA-4), which inhibits T-cell activity by competing with CD28 to bind to B7.1 and B7.2. The second checkpoint is programmed death receptor-1 (PD-1), which mainly takes place by the interaction of tumor and T cells. When programmed death ligand-1 (PD-L1) on the tumor cell binds to the PD-1 receptor on T cells, the T cells are inactivated and are unable to carry out the immune response against the tumor [14,15]. PD-L1 release from the tumor cell is reported to take place in two forms: inflammation through interferon gamma within the tumor microenvironment and oncogene-dependent tumor PD-L1 expression [16,17].

CTLA-4 Inhibitors

Ipilimumab

Ipilimumab is a full-human, IgG1 monoclonal antibody against CTLA-4. A randomized phase II study including advanced NSCLC patients without a history of systemic treatment examined the effectiveness of its addition to a carboplatin/paclitaxel combination in two different ways (concurrently or subsequently). The study concluded that adding ipilimumab was beneficial; however, the benefit was more visible in the squamous histology [18]. This study's Phase III design (carboplatin/paclitaxel/ipilimumab) is in progress.

PD-1 and PD-L1 Inhibitors

Nivolumab

Nivolumab is a full-human, IgG4 monoclonal antibody against PD-1 [19]. A phase I study in which it was examined as monotherapy in advanced-stage NSCLC treatment obtained an objective response rate (ORR) of approximately 20%, which increased by up to 31% in PD-L1-positive tumors and remained at around 10% in PD-L1-negative tumors [20]. However, in a phase II study including advanced-stage NSCLC patients with a squamous histology (Check-Mate 063), PD-L1-positive cases in a group of patients who had received two or more lines of treatment had an ORR of 24%, while this rate was 14% in PD-L1-negative cases [21]. Both studies considered a cut-off limit as 5% for PD-L1 positivity. Having demonstrated the benefit in case of squamous histology in a phase II study, the Check-Mate 017 study was conducted on advanced-stage NSCLC patients with the same histology. The study included 272 patients, and the patients who had received a line of treatment were randomized into nivolumab (3 mg/kg biweekly) or docetaxel (75 mg/m^2 every three weeks) groups. It was concluded that nivolumab was superior to docetaxel in terms of ORR (20% vs. 9%), median overall survival (OS) (9.2 months vs. 6.0 months), and 1-year survival (42% vs. 24%). The study considered ≥1% as the cut-off value for PD-L1 positivity, and the findings were reported to be independent of the PD-L1 expression status (Table 1) [22]. After those studies, nivolumab was approved by the Food and Drug Administration (FDA) in March 2015 to be used for the treatment of advanced-stage NSCLC patients with a squamous histology and progression after platinum-based chemotherapy.

There are other available studies conducted on the effectiveness of nivolumab in patients with a non-squamous histology. Check-Mate 057, a phase III study, included a total of 582 advanced-stage and non-squamous NSCLC patients who had previously received a line of treatment. The patients were randomized into nivolumab (3 mg/kg biweekly) or docetaxel (75 mg/m^2 every three weeks) groups. This study concluded that nivolumab was more effective than docetaxel in patients with a non-squamous histology (ORR: 19% vs. 12%; median OS: 12.2 months vs. 9.4 months, and 1-year survival: 51% vs. 39%, in support of nivolumab). This study also reported an association between survival advantage and PD-L1 positivity (Table 1) [23]. Following this study, the FDA expanded its approval to include patients with a non-squamous histology as well.

Recently, the results of the Check-Mate 026 trial evaluating the efficacy of nivolumab in the first-line treatment in advanced-stage NSCLC patients have been published [24]. The study considered ≥1% as the cut-off value for PD-L1 positivity, and a total of 541 subjects were randomized 1:1 into nivolumab (3 mg/kg biweekly) or platinum-based chemotherapy groups. The primary endpoint was progression free survival (PFS) as assessed by the Independent Radiology Review Committee in patients with ≥5% PD-L1 tumor expression. It was concluded that there were no differences between the two arms in terms of PFS [4.2 months vs. 5.9 months, hazard ratio (HR): 1.15] or median OS (14.4 months vs. 13.2 months, HR: 1.02) (Table 1). However, the high rate of crossover to nivolumab on the chemotherapy arm, the higher overall survival rates in the chemotherapy arm than in historical controls, a greater proportion of Asian patients included in the study, and patients with a broad range of PD-L1 expression (≥1%) might have affected the results [24].

Pembrolizumab

Pembrolizumab is a humanized, type IgG4, monoclonal antibody against PD-1. A phase I study (KEYNOTE-001) was conducted with pembrolizumab on an advanced-stage NSCLC patient group, majority of whom had received prior treatment. Pembrolizumab was administered at varying doses, and the study found an ORR of 19.4%, a median duration of response time of 12.5 months, and a median OS of 12 months. The study reported similar responses for both histologies, but the response rate was higher (around 45%)

Table 1. Results of completed clinical studies on PD-1 and PD-L1 inhibitors

Study	Author	Design	Phase	Patient characteristics	Results
Check-Mate 063	Rizvi et al. [21]	Nivolumab 3 mg/kg, bi-weekly	II	Advanced-stage NSCLC patients with squamous cells who received >2 lines of treatment	ORR in the whole group: 20% ORR in PD-L1-positive group: 31% ORR in PD-L1-negative group: 10%
Check-Mate 017	Brahmer et al.[22]	Nivolumab 3 mg/kg, bi-weekly vs. Docetaxel 75 mg/m^2	III	Advanced-stage NSCLC patients who progressed after the platinum-based combination CT	ORR: 20% vs. 9% Median OS: 9.2 months vs. 6.0 months 1-year survival: 42% vs. 24%
Check-Mate 057	Borghaei et al.[23]	Nivolumab 3 mg/kg, bi-weekly vs. Docetaxel 75 mg/m^2	III	Advanced-stage NSCLC patients with non-squamous histology, progressed after the first line of CT	ORR: 19% vs. 12% Median OS: 12.2 months vs. 9.4 months 1-year survival: 51% vs. 39%
Check-Mate 026	Socinski et al. [24]	Nivolumab 3 mg/kg, bi-weekly vs. Platinum-based chemotherapy	III	Previously untreated, advanced-stage NSCLC patients	PFS: 4.2 months vs. 5.9 months, HR:1.15 OS: 14.4 months vs. 13.2 months, HR:1.02
KEYNOTE-001	Garon et al.[25], Rizvi et al.[26]	Pembrolizumab 2 mg/kg, bi-weekly	I	Advanced-stage NSCLC patients with squamous cells who received >2 lines of treatment	ORR: 45% in the group with PD-L1 positivity of ≥50%
KEYNOTE-010	Herbst et al.[27]	Pembrolizumab 2 mg/kg, bi-weekly; 3 mg/kg, bi-weekly vs. Docetaxel 75 mg/m^2	II/III	Advanced-stage NSCLC patients with squamous cells who received >1 line of treatment	ORR: 18%, 18%, and 9% in patients with PD-L1≥1% 30%, 29%, and 8% in patients with PD-L1≥50% Median OS: 10.4 months, 12.7 months, and 8.5 months in patients with PD-L1≥1% 14.9 months, 17.3 months, and 8.2 months in patients with PD-L1≥50%
KEYNOTE-024	Reck et al.[28]	Pembrolizumab 200 mg, every three weeks vs. Platinum-based chemotherapy	III	Previously untreated, advanced-stage NSCLC patients	ORR: 45% vs. 28%, p<0.001 Median PFS: 10.3 months vs. 6.0 months, p<0.001 Median OS not reached in both arms
POPLAR	Fehrenba-cher et al.[30]	Atezolizumab 1200 mg, every three weeks vs. Docetaxel 75 mg/m^2	II	Advanced-stage NSCLC patients who progressed after the CT, platinum-based combination	ORR: 15% vs. 15% Response duration time: 14.3 months vs. 7.2 months Median OS: 11.4 months vs. 9.5 months
OAK	Rittmeyer A et al.[31]	Atezolizumab 1200 mg, every three weeks vs. Docetaxel 75 mg/m^2	III	Advanced-stage NSCLC patients who progressed after the platinum-based combination CT (2./3.line)	Median PFS: 4.0 months vs. 2.8 months Median OS: 13.8 months vs. 9.6 months Efficacy is correlated with PD-L1 expression
BIRCH	Besse et al.[32]	Atezolizumab 1200 mg, every three weeks	II	Advanced-stage NSCLC patients who had received/not received treatment	ORR in the whole group: Received treatment: 17% Not received treatment: 19% PD-L1 expression: ORR in TC≥50% or IC≥10%: Received treatment: 25% Not received treatment: 25%
Durvalumab study	Higgs et al.[33]	Durvalumab 10 mg/kg, bi-weekly	I	Advanced-stage NSCLC patients who received multiple lines of treatment in the past	ORR: Whole group: 16% Squamous group: 21% Non-squamous group: 13% PD-L1-positive group: 27% PD-L1-negative group: 5%
Avelumab study	Gulley et al.[34]	Avelumab 10 mg/kg, bi-weekly	Ib	184 advanced-stage patients who progressed after platinum-based chemotherapy	ORR: 12%, SD: 38%, and median PFS: 11.6 weeks

NSCLC: non-small cell lung cancer; CT: chemotherapy; ORR: objective response rate; SD: stable disease; PFS: progression-free survival; OS: overall survival; PD-1: programmed death receptor-1; PD-L1: programmed death ligand-1; TC: tumor cell; IC: immune cell

among those who had not received prior treatment and among those with PD-L1 expression higher than 50% (Table 1) [25,26]. Following this study, pembrolizumab was approved by the FDA in October 2014 to be administered to NSCLC patients who progress after platinum-based chemotherapy, who have a negative EGFR mutation and ALK rearrangement, and who express PD-L1.

A recent phase II/III study investigated the effectiveness of pembrolizumab on advanced-stage and progressive NSCLC patients who had received chemotherapy at least once. Including a total of 1,034 patients with PD-L1 expression of ≥%1, this study (KEYNOTE-10) randomized the patients into a pembrolizumab group at two different doses (2 mg/kg or 10 mg/kg every three weeks) or a docetaxel group (75 mg/m^2 every three weeks). The study concluded that pembrolizumab was superior to docetaxel in terms of ORR and survival, with no significant difference between the two doses of pembrolizumab. The study analyzed the results under two categories (PD-L1 positivity≥1% and ≥50%) and reported that both groups benefited from the drug, which was in support of the use of pembrolizumab. The patients with PD-L1≥1% presented ORR of 18%, 18%, and 9% for 2 mg/kg and 10 mg/kg pembrolizumab and 75 mg/m^2 docetaxel, respectively, while the corresponding rates were 30%, 29%, and 8% for those with PD-L1≥50%. Similarly, the patients with PD-L1≥1% presented median survival times of 10.4 months, 12.7 months, and 8.5 months for 2 mg/kg and 10 mg/kg pembrolizumab and 75 mg/m^2 docetaxel, respectively, while the corresponding rates were 14.9 months, 17.3 months, and 8.2 months for those with PD-L1≥50%. This study demonstrated that pembrolizumab was beneficial for the PD-L1≥1% group and the PD-L1≥50% group (Table 1) [27]. There are ongoing studies investigating the role of pembrolizumab as monotherapy or combination therapy in various lines of treatment. Those studies include PD-L1-positive patients.

The effectiveness of pembrolizumab was recently evaluated in a phase III study (KEYNOTE-024) in a first-line setting in advanced-stage NSCLC patients. A total of 305 patients with PD-L1 expression of ≥50% were randomized into pembrolizumab (200 mg/every three weeks) or platinum-based chemotherapy groups. This study showed that pembrolizumab was more effective than chemotherapy in terms of ORR (45% vs. 28%, p<0.001), median PFS (10.3 months vs. 6.0 months, p<0.001), and median OS (not reached in both arms, p=0.005). Further, less frequent grade 3/4 toxicities were reported in the pembrolizumab arm (26% vs. 51%) (Table 1) [28].

Atezolizumab

Atexolizumab is a humanized, type IgG1, monoclonal antibody against PD-L1. It was created through a special process to prevent the antibody-dependent cellular cytotoxicity that might be caused by active T cells. The phase I study reported an ORR of around 23% and a median survival of 16 months for the advanced-stage NSCLC patients who had received multiple lines of treatment [29]. This study evaluated PD-L1 expression in both tumor cells and immune cells infiltrating the tumor, and it reported a correlation between increased PD-L1 expression and increased response rates and survival times in those cells. The patients with a PD-L1 expression of ≥50% in tumor cells or ≥10% in immune cells had an ORR of 48% and a median OS of 18 months. The subsequent phase II POPLAR study randomized a total of 287 advanced-stage NSCLC patients who had received at least one line of systemic treatment into atezolizumab (1200 mg fixed dose, every three weeks) or docetaxel (75 mg/m^2 every three weeks). The study obtained a similar response rate (15%) in both arms, and the results supported atezolizumab in terms of response duration time (14.3 months vs. 7.2 months) and median survival (11.4 months vs. 9.5 months) (Table 1). This study evaluated PD-L1 expression in both tumor cells and immune cells infiltrating the tumor, and it reported a positive correlation between increased PD-L1 expression and survival time in those cells [30].

In a phase III trial (OAK trial), a total of 1,225 patients who had received a previous line of treatment were randomized into atezolizumab (1200 mg fixed dose, every three weeks) or docetaxel (75 mg/m^2 every three weeks). It was concluded that atezolizumab was superior in terms of median PFS (4.0 months vs. 2.8 months) and median OS (13.8 months vs. 9.6 months). Also, a positive correlation was reported between PD-L1 expression and response [31]. Based on these results, atezolizumab was approved by the FDA in October 2016 to be used for the treatment of advanced-stage NSCLC patients who had progressed after platinum-based chemotherapy (Table 1).

Recently, a phase II BIRCH study examined atezolizumab in a PD-L1-positive patient group, including patients with and without a history of treatment [32]. The study included a total of 659 patients, and PD-L1 positivity was defined as membranous staining in at least 5% of the tumor cells and/or immune cells in the tumorous area. The patient groups with and without a history of prior treatment had response rates of 17% and 19%, respectively. The findings were correlated with PD-L1 expression, and the group with a higher PD-L1 expression (≥50% in tumor cells or ≥10% in immune cells) displayed a response rate of 25%, which was more or less the same for both groups (Table 1) [32]. The studies on atezolizumab are ongoing for both first and later lines of treatment, including its application both as monotherapy and combined with chemotherapy.

Durvalumab

Durvalumab is a full-human, type IgG1, monoclonal antibody against PD-L1. It was subjected to a special process to prevent the antibody-dependent cellular cytotoxicity that might be caused by active T cells. As part of the phase I study, 200 advanced-stage NSCLC patients with a history of multiple lines of treatment received durvalumab (10 mg/kg biweekly) with a 16% response rate. In terms of histological sub-types, the squamous group had a higher response rate than the non-squamous group (21% vs. 13%). This study defined PD-L1 positivity as ≥25% membranous staining in tumor cells. The total response rate was 27% in the PD-L1-positive group, while it remained around 5% in the PD-L1-negative group (Table 1) [33]. There are ongoing studies on the administration of durvalumab both as part of the first line treatment and combined with curative chemoradiotherapy in advanced-stage local diseases.

Avelumab

Avelumab is a full-human, type IgG1, monoclonal antibody against PD-L1. As part of a phase Ib study including 184 advanced-stage NSCLC patients who progressed after platinum-based chemotherapy, avelumab was administered biweekly at a dose of 10 mg/kg and the ORR, stable disease (SD), and median PFS were 12%, 38%, and 11.6 weeks, respectively. The study considered ≥1% staining in the tumor cell to indicate PD-L1 positivity, and the ORR and median PFS were 14.4% and 11.7 weeks in the PD-L1 positive group, respectively, and 10.0% and 5.9 weeks, respectively, in the PD-L1-negative group [34]. As part of a phase Ib study including 145 metastatic NSCLC patients without a history of prior treatment, avelumab was administered biweekly at a dose of 10 mg/kg, and the ORR, SD, disease control rate, and median PFS were 18.7%, 45.3%, 64.0%, and 11.6 weeks, respectively. The study considered ≥1% staining in the tumor cell to indicate PD-L1 positivity, and the ORR was 20% in the PD-L1-positive group and 0.0% in the PD-L1-negative group (Table 1) [35]. There are other ongoing studies concerning different lines of treatment, especially Javelin Lung 200 that compares avelumab to docetaxel as second-line treatment.

Toxicity

Alongside their distinctive mechanisms of action, immune checkpoint inhibitors have demonstrated specific characteristics of toxicity. These toxicities are generally associated with the activation of the immune system and manifest themselves as skin rash, colitis, hepatitis, pneumonitis, endocrinopathies, and infusion reactions. These toxicities also exhibit a different pattern in terms of their time of occurrence; skin toxicities appear earlier, while endocrinopathies may occur relatively later. In an evaluation of basic grade 3/4 toxicities, the Check-Mate 063 study [21] reported 17% toxicity with nivolumab and diarrhea and pneumonitis were both observed at rates of 3%. The Check-Mate 017 [22] study reported total grade 3/4 toxicity rates of 7% and 55% for nivolumab and docetaxel, respectively. The KEYNOTE-010 [27] study reported rates of 13% and 35% for pembrolizumab and docetaxel, respectively. Alongside the monitoring of effectiveness, it is very important to thoroughly monitor and manage these specific toxicities through the follow-up and treatment processes of patients treated with checkpoint inhibitors.

Biomarker Status

Because the response rate obtained through immunotherapy has remained at around 15-20% and results depend on a series of factors associated with patients and tumors, researchers have felt it necessary to identify biomarkers [22,23,29,30]. Two biomarkers have gained prominence thus far: PD-L1 expression and mutational load status.

PD-L1 Expression Status

The PD-L1 positivity rate is reported to be approximately 50-60% in NSCLC. Regarding studies concerning the role of PD-L1 expression as a biomarker, some report that results obtained with immunotherapy are not related to PD-L1 expression, while others suggest a relation and a correlation with the positivity rate [22,23,27,30,31]. However, there are some issues concerning the consideration of PD-L1 expression as a biomarker. The first problem is the variable character of PD-L1 expression; a significant variability is reported between the biopsy material and resection material as well as between the primary tumor and metastasis. The second problem concerns the non-uniform character of the evaluation methods. The examination of PD-L1 expression in various studies with different methods and in the context of different cell groups [in the tumor cell (TC) or in both the TC and immune cell (IC)] leads to further heterogeneity [36-39]. The third problem pertains to the difference of cut-off limits assumed by studies. For instance, nivolumab studies take cut-off limits as ≥1%, 5%, 10%, 25%, and 50%, whereas pembrolizumab studies assume those limits to be <1% (low), 1%-49% (medium), and ≥50% (high). In atezolizumab studies, these values are scored as 0: <1% (TC/IC), 1: ≥1-<5% (TC/IC), 2: ≥5%-<50% (TC), ≥5%-<10% (IC), and 3: ≥50% (TC), ≥10% (IC) [29-32]. The International Association for the Study of Lung Cancer performs standardization studies in order to minimize all problems brought about by the heterogeneity of the evaluation methods for PD-L1 expression.

Regarding the role of PD-L1 expression as a biomarker, some studies (Check-Mate 063 and Check-Mate 017) report results independent of PD-L1 expression, while others (Check-Mate 057, KEYNOTE-001, KEYNOTE-010, and POPLAR) report results related to PD-L1 expression and even report a correlation with higher levels of PD-L1 expression (KEYNOTE-010, POPLAR). Two recent meta-analyses [17,40] and the aforementioned studies suggest that the effectiveness of PD-1/PD-L1 inhibitors is related to PD-L1 expression; while there was no benefit to PD-L1-negative cases, PD-L1-positive cases exhibited a significant level of benefit, which was observable beginning from ≥1%.

Mutational Load

Rizvi et al. [41] investigated the relationship between the mutational load and effectiveness in advanced-stage NSCLC patients receiving PD-1 inhibitor treatment and demonstrated that those with a non-synonymous mutational load had better rates of objective response, clinical benefit, and survival compared with those without non-synonymous mutational load. Likewise, they have also reported a correlation between a molecular smoking signature, higher neoantigen burden and DNA repair pathway mutations.

In conclusion, highly positive results consistent with immunotherapy-checkpoint inhibitors in particular-have been obtained in the treatment of advanced-stage NSCLC. Although the beneficial effect appears to be independent of PD-L1 expression, both clinical studies and meta-analyses indicate a significant level of benefits for PD-L1-positive cases and a positive correlation between the PD-L1 expression rate and response. However, further standardized examinations are required in order for PD-L1 expression to be utilized as a biomarker. Due to the high cost of immunotherapy drugs, biomarker studies are highly important for determining which groups of patients are likely to receive more benefits from such treatments. There are ongoing studies investigating the effectiveness of immunotherapy agents

utilized as monotherapy in different lines of treatment and combined with other treatment methods, particularly targeted agents. The findings of such studies are anxiously awaited.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.N.K., İ.Ö.; Design - S.N.K., İ.Ö.; Supervision - S.N.K., İ.Ö.; Analysis and/or Interpretation - S.N.K., İ.Ö.; Literature Search - S.N.K., İ.Ö.; Writing Manuscript - S.N.K., İ.Ö.; Critical Review - S.N.K., İ.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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