

REVIEW

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Immunotherapy for Lung Cancer

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ABSTRACT Lung cancer is one of the leading causes of cancer-related deaths in men and women. Similar to the approach with other cancer types, lung cancer staging is crucial in planning an effective treatment plan and predicting patient prognosis. Effective immunotherapies for patients with non-small cell lung cancer and non-genomic driver mutations are rapidly evolving. Moreover, anti-programmed death receptor-1 (PD-1)/programmed death ligand 1 (PD-L1)-based treatments have become the first-line standard of care. Despite shortcomings, PD-L1 expression level seems currently to be a relatively reliable predictor of the clinical efficacy of treatment with anti-PD-1/PD-L1 antibodies. However, additional biomarkers are required to better personalize treatment options for these patients. This review aimed to increase awareness of lung cancer and immunotherapy treatment options, depending on patient and disease stage characteristics.

Keywords: Biomarker; immune checkpoint inhibitor; immunotherapy; mutation; non-small cell lung cancer

We highlight the following in this review: increasing lung cancer awareness; considerations for accessing immunotherapy; guiding the most rational and appropriate use of immunotherapy; and specifying the proper administration of immunotherapy to suitable patients appropriately and promptly.

EPIDEMIOLOGY

Lung cancer is the leading cause of cancer-related death in men and second in women, accounting for 25% of all cancer-related deaths, with an estimated

1.8 million deaths worldwide.¹ The factors influencing the rates and trends of lung cancer worldwide are sex, age, race/ethnicity, and geography. For example, lung cancer mortality rates are highest in men, African-Americans, and those in the mid-southern region of the United States.² The Türkiye Globocan factsheet showed that lung cancer is the most encountered cancer type in men, whereas it is the fourth (after breast, thyroid, and colorectal cancer) in women (Figure 1A, Figure 1B).³

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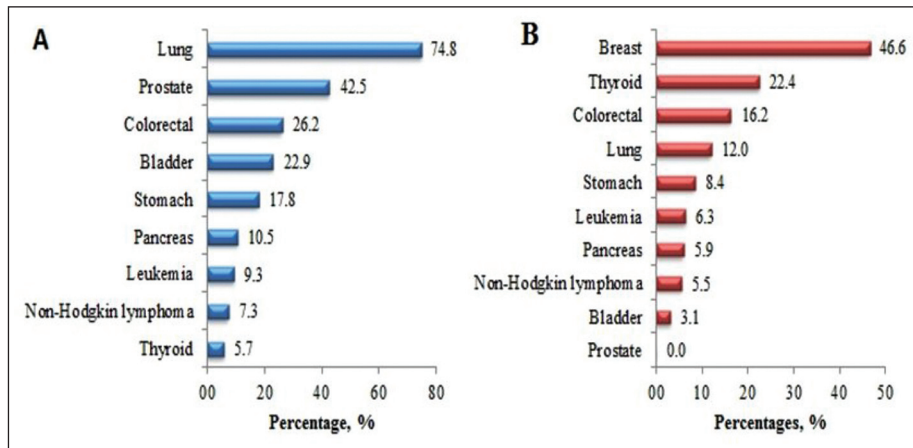


FIGURE 1: Prevalence of ten most common types of cancer in men (A) and women (B) in Turkish republic, standardized by age (World standard population per 100,000).³

ETIOLOGY AND RISK FACTORS

Behavioral and environmental risks responsible for the majority of lung cancer cases are cigarette smoking and exposure to factors, such as environmental tobacco smoke, radon, and asbestos. Moreover, genetic predisposition, infections, and inflammatory processes also contribute to the risk.⁴ Of these, the roles of smoking and asbestos exposure in the development of lung cancer have been studied extensively.⁵ In Türkiye, environmental asbestos exposure is an important problem in rural areas.^{6,7}

SCREENING, DIAGNOSIS, AND STAGING

Patients presenting with respiratory complaints often have advanced disease during the diagnosis. Therefore, early detection of cancer is important to increase the possibility of successful treatment. Early screening and diagnosis are 2 components of early cancer detection. Effective screening tests allow cancer diagnosis at an earlier stage, thereby reducing the probability of cancer-related deaths. Lung cancer mortality has decreased in multi-center, randomized, controlled screening studies of American and European origins.^{8,9}

Lung cancer is diagnosed by cellular/cytological or tissue/pathological analysis of the biopsy specimen. Compared with imaging methods [contrast-enhanced computerized tomography (CT) scanning, positron emission tomography (PET)/CT], fiberoptic

bronchoscopy, percutaneous fine needle aspiration, mediastinoscopy, thoracoscopy, and/or thoracentesis are preferred. Thus, the aim was to choose the most appropriate method to obtain a sufficient diagnostic sample in terms of immune markers and molecular analyses.¹⁰

Similar to other cancer types, staging in lung cancer is of fundamental importance in planning an effective treatment approach and predicting prognosis. The International Association for the Study of Lung Cancer (IASLC) TNM staging system is used in lung cancer.¹¹ The minimum requirements for staging include thoracic CT scans, whole-body fluorodeoxyglucose-PET/CT, and contrast-enhanced brain magnetic resonance imaging. Additionally, histological evaluation of mediastinal lymph nodes is performed in resectable cases, except in patients with peripherally located stage I lung cancer.

PATHOLOGY-DEPENDENT TREATMENT OF LUNG CANCER

With driver mutations, occurring mostly in a small group of lung adenocarcinoma, significant gains in clinical management have been achieved.¹² Although squamous cell carcinoma has similar characteristics to non-squamous cell carcinoma, these driver mutations show a quite different pattern.¹³

Differentiation of non-squamous and squamous cell carcinoma based on morphological and im-

munophenotypic characteristics is necessary to recognize different oncogenic alterations and determine appropriate chemotherapeutic agents. Considering the established clinical efficacy of immune checkpoint inhibitors (ICIs) or particular tyrosine kinase inhibitors (TKIs) as first-line therapies for patients with advanced non-small cell lung cancer (NSCLC), molecular profiling of tumors is necessary before initiating targeted systemic therapies to patients.¹⁴ Furthermore, patients with advanced NSCLC should at least be tested for sensitizing epidermal growth factor receptor (*EGFR*) mutations, B-Raf proto-oncogene (*BRAF*) mutations, *ROS* proto-oncogene 1 (*ROS1*) rearrangements, anaplastic lymphoma kinase (*ALK*) gene rearrangements, and programmed death ligand 1 (PD-L1) expression levels.¹⁵

Based on the recent guidelines regarding molecular testing in patients with lung cancer, which are established by a consensus of the College of American Pathologists (CAP), IASLC, and Association for Molecular Pathology (AMP), *EGFR* mutations and *ALK* and *ROS1* rearrangements should be tested in all patients with advanced non-squamous cell carcinoma or those with an adenocarcinoma component, irrespective of clinical characteristics.¹⁶ Testing for *BRAF*, *ERBB2* (HER2), *RET*, *NTRK*, *MET*, and *KRAS* alterations are not suggested as a single gene testing but are considered appropriate as part of larger multiplex panels to identify treatment choices besides minimal recommendations.¹⁶ Subsequently, the American Society of Clinical Oncology (ASCO) recommends *BRAF* as a stand-alone test for all patients with lung adenocarcinoma, irrespective of clinical characteristics.¹⁷

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) recommend biomarker testing in eligible patients with metastatic NSCLC for the following biomarkers: *EGFR*, *ALK*, *BRAF*, *ROS1*, *MET* exon 14 skipping mutations, *KRAS*, *NTRK1/2/3*, *RET*, and PD-L1.¹⁸ Moreover, biomarker testing is also recommended for emerging biomarkers, such as *ERBB2* (HER2) mutations and high-level *MET* amplification.¹⁸ Molecular biomarker testing is recommended for all patients with metastatic non-squamous

NSCLC and in some patients with metastatic squamous NSCLC, as well as after progression on targeted therapies; for example, testing for *EGFR* T790M.¹⁸ Currently, only PD-L1 immunohistochemistry (IHC) is required for squamous cell carcinomas; however, the landscape is changing.

Despite the lower prevalence of PD-L1 expression in NSCLC in Türkiye, no differences were observed between the frequencies of these mutations in Türkiye compared with those in Europe and the United States. In a study conducted on 2,798 patients with NSCLC in Türkiye, PD-L1 expression was high ($\geq 50\%$) and low (1-49%) in 23% and 21% of the patients, respectively. However, 56% had no PD-L1 expression ($< 1\%$) in the largest reference center.¹⁹ Therefore, all patients with advanced NSCLC should undergo mutational analysis before initiating therapy.

Recently, a review summarized the guidelines on the selection of patients with lung cancer suitable for TKI treatment.¹⁶ These updated guidelines, derived from the CAP, IASLC, and AMP, have indicated that adenocarcinoma, non-small cell carcinoma with adenocarcinoma component, including adenosquamous and pleomorphic carcinoma, large cell carcinoma, and NSCLC not otherwise specified should be tested. Because of the occurrence of underlying targetable oncogenic alterations, other rare NSCLC subtypes, such as sarcomatoid and large-cell neuroendocrine carcinomas, should also be molecularly tested, if clinically necessary. Never/light smokers can develop targetable oncogenic alterations, and if they are diagnosed with lung cancer, it would most probably be an adenocarcinoma. However, most patients with a smoking history develop lung adenocarcinomas. Despite a significant relationship between smoking and squamous cell lung carcinoma, a small percentage of never/light smokers develop squamous cell lung carcinoma. Thus, adenosquamous and pure squamous carcinomas with adenocarcinoma-type oncogenic driver mutations may be under-sampled. Therefore, all patients with NSCLC with a history of never/light smoking should be profiled for tumor mutations.¹⁶

PD-L1 TESTING

The evaluation of PD-L1 expression and its receptor in NSCLC is of great therapeutic importance. These

molecules can be expressed on tumor cell membranes and/or immune system elements. Moreover, lymphocytes in the tumor microenvironment are mainly CD4 T cells, T and B regulatory cells, natural killer cells, monocytes, and dendritic cells.²⁰

The interpretation of PD-L1 IHC has various scoring systems. Tumor proportion score and percentage of PD-L1 positive tumor cells are recommended in assessing NSCLC. Additionally, several PD-L1 antibody clones are available for IHC testing, such as DAKO 22C3, DAKO 28-8, Ventana SP263, and Ventana SP142.²¹ Many studies showed good expression correlations between the first 3 clones; thus, any of the first 3 clones is most commonly used in routine diagnostics.²²

TUMOR MUTATION BURDEN AND IMMUNE MICROENVIRONMENT

Currently, the PD-L1 IHC biomarker is the only method that plays a role in deciding on the ICI treatment and has been approved by the Food and Drug Administration (FDA). However, areas of discussion regarding the PD-L1 IHC remain, including spatial and temporal heterogeneities between PD-L1 expressions in tumor tissues. However, in various IHC platforms, the requirement of specific PD-L1 IHC assays for each anti-PD-1/PD-L1 agent also creates issues for this method. Considering these factors, PD-L1 expression is not a perfect method to predict ICI treatment response.²³ Furthermore, tumor mutational burden and immune microenvironment components are considered promising biomarkers.²⁴

TREATMENT OF ADVANCED NSCLC

Palliative approach is the basis of the treatment in patients with advanced NSCLC. Systemic therapy options include targeted therapy, immunotherapy, and cytotoxic chemotherapy. Surgical resection or definitive irradiation may be the treatment choice for patients with solitary metastasis.

The studies investigating the benefit of targeted therapy, which compared patients with oncogenic mutation who received targeted therapy vs. chemotherapy, reported increased median survival with targeted agents.^{18,25} Tumor burden and symptoms decreased, whereas the quality of life (QoL) in-

creased. In eligible patients with advanced NSCLC, the NCCN recommends testing for *ALK*, *EGFR*, *BRAF*, *KRAS*, *NTRK1/2/3*, *MET* exon 14 skipping, *RET*, and *ROSI*. Moreover, specific targeted agents are available for patients with these biomarkers.¹⁸ In *EGFR* mutation-positive patients, *EGFR*-specific TKIs should be used as first-line treatment because of their favorable prognosis over chemotherapy.^{18,25} A repeat biopsy is required to identify the acquired resistance in cases of progression during therapy. *ALK* inhibitors are recommended as first-line treatment for *ALK* mutation-positive patients.^{18,26} Emerging biomarkers in the NCCN Guidelines® include *ERBB2 (HER2)* and high-level *MET* amplification, and specific targeted agents are recommended for these mutations.¹⁸

Histological subtypes should be used to select the optimal chemotherapy regimen for patients with advanced NSCLC but without actionable driver mutations. The initial chemotherapy regimen in advanced adenocarcinoma and squamous cell NSCLC is generally 4 to 6 cycles of carboplatin+pemetrexed and carboplatin+paclitaxel, respectively.²⁷

The management of distant metastases is based on the site. Radiotherapy (RT) and palliative care may be necessary for brain and bone metastases, respectively. Moreover, local therapies can be used for limited-site oligometastatic disease. The administration of curative-intent retreatment could be possible with early identification of disease recurrence, which provides longer survival. Prospective, randomized-controlled follow-up studies are necessary to verify the effectiveness of convenient follow-up approaches.²⁸

IMMUNOTHERAPY IN LUNG CANCER, CURRENT DATA

Currently, the standard of care in the first-line and later lines (as monotherapy) in treating advanced NSCLC without driver mutation is immunotherapy as monotherapy, immunotherapy combined with chemotherapy, or dual immunotherapy in combination with/without chemotherapy. Although immunotherapy for lung cancer is approved in Türkiye, it has yet to be reimbursed. Therefore, access to im-

munotherapy is limited to patients enrolled in clinical trials and early access programs and those with private insurance.

FRONTLINE TREATMENT OF ADVANCED NSCLC

Immunotherapy as Monotherapy

ICI monotherapy is superior to platinum-based doublet chemotherapy in selected patients with high PD-L1 expression ($\geq 50\%$).²⁹ Table 1 shows the results of randomized trials comparing ICI monotherapy and chemotherapy.

ICI monotherapy with pembrolizumab, atezolizumab, or cemiplimab is appropriate for patients with tumors expressing $\geq 50\%$ PD-L1 if they have no rapidly progressive disease or rapid tumor response not relevant due to high tumor burden or symptomatic disease. In the interim overall survival (OS) analysis results of the IMpower110 study, atezolizumab was statistically superior compared with chemotherapy in the PD-L1-high patient population. However, current exploratory follow-up results (median: 31.3 months) showed that the hazard ratio (HR) decreased, and the confidence interval (CI) crossed one.³⁰

IMMUNOTHERAPY COMBINED WITH CHEMOTHERAPY

The combination of chemotherapy and immunotherapy is a more appropriate treatment strategy in patients with $< 50\%$ or $\geq 50\%$ PD-L1 expression with a high tumor burden who require rapid response.³¹ ICIs combined with platinum-based doublet chemotherapy have been compared with platinum-based chemotherapy as frontline treatment for advanced NSCLC (Table 2).

Compared with platinum-based doublet chemotherapy, pembrolizumab with pemetrexed and platinum combination and pembrolizumab with paclitaxel/nabpaclitaxel and carboplatin combination improved the OS and progression-free survival (PFS) in advanced non-squamous and squamous NSCLC, respectively.^{32,33} After 4 cycles of combined chemotherapy and pembrolizumab, treatment is continued as pemetrexed+pembrolizumab and pembrolizumab alone for up to 35 cycles in non-squamous and squamous NSCLC, respectively.

Atezolizumab is an alternative to pembrolizumab in advanced non-squamous NSCLC. The combination of atezolizumab with bevacizumab, carboplatin, and paclitaxel significantly improved the PFS and OS compared with the same regimen without atezolizumab.³⁴ In the IMpower130 trial, the combination of atezolizumab with nabpaclitaxel and carboplatin improved PFS and OS in non-squamous NSCLC.³⁵ However, improvement in OS was not

TABLE 1: Randomized phase 3 trials comparing immune checkpoint inhibitor monotherapy with chemotherapy in the first-line treatment of NSCLC.

Study	n	Selection criteria	Experimental arm	Control arm	ORR	Median		Median follow-up
						PFS	OS	
KEYNOTE-024 trial ²⁹	305	$\geq 50\%$ PD-L1	Pembrolizumab	Platinum-doublet chemotherapy	46.1% vs. 31.1%	7.7 mon. vs. 5.5 mon.	26.3 mon. vs. 13.4 mon.	59.9 mon.
IMpower110 study ³⁰	555	$\geq 1\%$ PD-L1	Atezolizumab	Platinum-doublet chemotherapy	In PD-L1 $\geq 50\%$ subgroup: 40.2% vs. 28.6%	In PD-L1 $\geq 50\%$ subgroup: 8.2 mon. vs. 5 mon.	HR: 0.62 (95% CI, 0.48-0.81) In PD-L1 $\geq 50\%$ subgroup: 20.2 mon. vs. 14.7 mon.	31.3 mon.
EMPOWER-Lung 1 study ³¹	710	$\geq 50\%$ PD-L1	Cemiplimab	Platinum-doublet chemotherapy	39% vs. 20% p<0.0001	HR: 0.59 (95% CI, 0.43-0.81) 8.2 mon. vs. 5.7 mon.	HR: 0.76 (95% CI, 0.54-1.09) NR vs. 14.2 mon.	10.8 mon.
						HR: 0.54 (95% CI, 0.43-0.68)	HR: 0.57 (95% CI, 0.42-0.77)	

NSCLC: Non-small cell lung cancer; ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival; PD-L1: Programmed death ligand-1; HR: Hazard ratio; CI: Confidence interval; mon: Months; NR: Not reported.

TABLE 2: Randomized phase 3 trials comparing chemotherapy plus immunotherapy versus chemotherapy in the first-line treatment of NSCLC.

Study	n	Histological subtype	Experimental arm	Control arm	ORR	Median PFS	Median OS	Effect of PD-L1 expression	Median follow-up
KEYNOTE 189 trial ³²	616	Nonsquamous	Pembrolizumab+ chemotherapy	Pemetrexed+ cisplatin/ carboplatin	48% vs. 20% p <0.0001	9.0 mon. vs. 4.9 mon. HR: 0.50 (95% CI, 0.41-0.59)	22.0 mon. vs. 10.6 mon. HR: 0.60 (95% CI, 0.50-0.72)	Independent	46.3 mon.
KEYNOTE 407 trial ¹³	559	Squamous	Pembrolizumab+ chemotherapy	Paclitaxel/ nabpaclitaxel+ carboplatin	62.6% vs. 38.8% p <0.0001	8.0 mon. vs. 5.1 mon. HR: 0.59 (95% CI, 0.49-0.71)	17.2 mon. vs. 11.6 mon. HR: 0.71 (95% CI, 0.59-0.86)	Independent	40.1 mon.
IMpower150 study ³⁴	1202	Nonsquamous	Atezolizumab+ chemotherapy+ bevacizumab	Paclitaxel+ carboplatin+ bevacizumab	63.5% vs. 48%	8.3 mon. vs. 6.8 mon. HR: 0.59 (95% CI, 0.50-0.70)	19.5 mon. vs. 14.7 mon. HR: 0.80 (95% CI, 0.67-0.95)	Independent	39.8 mon.
IMpower130 study ³⁵	724	Nonsquamous	Atezolizumab+ chemotherapy	Nabpaclitaxel+ carboplatin	49% vs. 32%	7.0 mon. vs. 5.5 mon. HR: 0.64 (95% CI, 0.54-0.77)	18.6 mon. vs. 13.9 mon. HR: 0.79 (95% CI, 0.64-0.98)	Independent	19 mon.
IMpower132 study ³⁶	578	Nonsquamous	Atezolizumab+ chemotherapy	Pemetrexed+ carboplatin	47% vs. 32%	7.7 mon. vs. 5.2 mon. HR: 0.56 (95% CI, 0.47-0.62)	17.5 mon. vs. 13.6 mon. HR: 0.86 (95% CI, 0.71-1.06)	ITT: OS results were not statistically significant. OS improved in PD-L1 negative subgroup	28.4 mon.
IMpower131 study ³⁷	1021	Squamous	Atezolizumab+ chemotherapy	Paclitaxel/ nabpaclitaxel+ carboplatin	49.7% vs. 41%	6.3 mon. vs. 5.6 mon. HR: 0.71 (95% CI, 0.60-0.85)	14.2 mon. vs. 13.5 mon. HR: 0.88 (95% CI, 0.73-1.05)	ITT: OS results were not statistically significant. OS improved in PD-L1 high subgroup	26.8 mon.

[†]In these trials, patients were enrolled regardless of PD-L1 expression level; i.e. patients with no PD-L1 expression were also included; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; mon: Months; ITT: Intention-to-treat; NR: Not reported; PD-L1: Programmed death ligand-1.

significant when atezolizumab was added to pemetrexed and carboplatin in patients with advanced non-squamous NSCLC.³⁶ Therefore, in advanced non-squamous NSCLC patients, atezolizumab can be an option if administered with either nab-paclitaxel and carboplatin combination or bevacizumab, carboplatin, and paclitaxel combination.³⁴ Compared with chemotherapy, atezolizumab in combination with chemotherapy did not improve OS in advanced squamous NSCLC.³⁷

Immunotherapy has not been recommended as a first-line therapy in patients with driver mutations because of low response rates and low PFS. In the IMpower150 trial, 14% of patients had *EGFR* mutation or *ALK* rearrangement and were administered at least one prior line of targeted therapy.³⁴ In this subgroup, the addition of atezolizumab in the bevacizumab-carboplatin-paclitaxel combination improved OS. However, this was not observed in the IMpower130 trial, wherein atezolizumab was administered in combination with nabpaclitaxel and carboplatin.³⁵

IMMUNOTHERAPY COMBINATION WITH/WITHOUT CHEMOTHERAPY

Another option in patients with advanced NSCLC without driver mutation is dual immunotherapy combination, such as nivolumab and ipilimumab, with or without chemotherapy. Table 3 shows the results of immunotherapy combination strategies tested in randomized phase 3 trials.

In the CheckMate 227 trial, nivolumab+ipilimumab was superior to chemotherapy in terms of survival, irre-

TABLE 3: Randomized phase 3 trials comparing combination immunotherapy with/without chemotherapy versus chemotherapy in the first-line treatment of NSCLC.

Study	n	Selection criteria	Experimental arm	Control arm	ORR	Median PFS	Median OS	Median follow-up
CheckMate-9LA trial ³⁸	719	All PD-L1 levels	Nivolumab+ ipilimumab + only 2 cycles of chemotherapy [†]	Chemotherapy [†]	38% 25%	6.7 mon. 5.3 mon. HR: 0.67 (95% CI, 0.56-0.79)	15.8 mon. vs. 11.0 mon. HR: 0.72 (95% CI, 0.61-0.86)	30.7 mon.
Checkmate-227 trial ³⁹	1189	PD-L1 ≥1%	Nivolumab+ ipilimumab Nivolumab Chemotherapy [‡]		36.4% 27.5% 30.0%	5.1 mon. 4.2 mon. 5.6 mon. Nivolumab+ipilimumab vs. chemotherapy: HR: 0.81 (95% CI, 0.68-0.96) Nivolumab vs. chemotherapy: HR: 0.98 (95% CI, 0.83-1.15)	17.1 mon. 15.7 mon. 14.9 mon. Nivolumab+ipilimumab vs. chemotherapy: HR: 0.76 (95% CI, 0.65-0.90) Nivolumab vs. chemotherapy: HR: 0.91 (95% CI, 0.76-1.06)	54.6 mon.
	550	PD-L1 <1%	Nivolumab + ipilimumab Nivolumab Chemotherapy [‡]		27.3% 37.9% 23.1%	5.1 mon. 5.6 mon. 4.7 mon. Nivolumab+ipilimumab vs. chemotherapy: HR: 0.74 (95% CI, 0.58-0.94) Nivolumab vs. chemotherapy: HR: 0.72 (95% CI, 0.57-0.91)	17.2 mon. 15.2 mon. 12.2 mon. Nivolumab+ipilimumab vs. chemotherapy: HR: 0.64 (95% CI, 0.51-0.81) Nivolumab vs. chemotherapy: HR: 0.82 (95% CI, 0.65-1.02)	20.6 mon.
KEYNOTE-598 trial ⁴⁰	588	PD-L1 ≥50%	Pembrolizumab+ ipilimumab	Pembrolizumab	45.4% 45.4%	8.2 mon. 8.4 mon. HR: 1.06 (95% CI, 0.86 to 1.30) p=0.72	21.4 mon. 21.9 mon. HR: 1.08 (95% CI, 0.85-1.37) p=0.74	
MYSTIC trial ⁴¹	1118	PD-L1 ≥25%	Durvalumab Durvalumab+ tremelimumab Chemotherapy [§]		35.6% 34.4%	4.7 mon. 3.9 mon. Durvalumab vs. chemotherapy: HR: 0.87 (99.5% CI, 0.59-1.29) Durvalumab+tremelimumab vs. chemotherapy: HR: 1.05 (99.5% CI, 0.72-1.53) p=0.71	16.3 mon. 11.9 mon. Durvalumab vs. chemotherapy: HR: 0.76 (97.54% CI, 0.56-1.02) p=0.04 Durvalumab+tremelimumab vs. chemotherapy: HR: 0.85 (96.77% CI, 0.61-1.17) p=0.20	30.2 mon.
POSEIDON trial ⁴²	1013	PD-L1 ≥50%	Durvalumab+ chemotherapy Durvalumab+ tremelimumab+ chemotherapy Chemotherapy [¶]		41.5% 38.8% 24.4%	5.5 mon. 6.2 mon. 4.8 mon. Durvalumab+chemotherapy vs. chemotherapy: HR: 0.74 (95% CI, 0.62-0.89) p=0.00093 Durvalumab+tremelimumab+chemotherapy vs. chemotherapy: HR: 0.77 (95% CI, 0.60-0.96) p=0.0003	13.3 mon. 14.0 mon. 11.7 mon. Durvalumab+chemotherapy vs. chemotherapy: HR: 0.86 (95% CI, 0.72-1.02) p=0.07581 Durvalumab+tremelimumab + chemotherapy vs. chemotherapy: HR: 0.77 (95% CI 0.65-0.92) p=0.00304	34.9 mon.

[†]Nonsquamous: pemetrexed+cisplatin or carboplatin; squamous: pemetrexed+cisplatin or carboplatin; [‡]Nonsquamous: pemetrexed+carboplatin, or gemcitabine+carboplatin; [§]Nonsquamous: pemetrexed+cisplatin or carboplatin; squamous: gemcitabine+carboplatin; [¶]Nonsquamous: pemetrexed+cisplatin or carboplatin; squamous: pemetrexed+cisplatin or carboplatin; ^{||}Nonsquamous: platinum+pemetrexed (maintenance pemetrexed permitted); squamous: platinum+gemcitabine, or carboplatin+nab-paclitaxel; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; PFS: Progression-free survival; OS: Overall survival; CI: Confidence interval; mon: Months; ITT: Intention-to-treat; PD-L1: Programmed death ligand-1.

spective of PD-L1 expression.³⁹ The median OS was 17.1 and 13.9 months with nivolumab+ipilimumab and chemotherapy, respectively (HR, 0.73; 95% CI, 0.64-0.84).³⁸ Compared with chemotherapy, nivolumab+ipilimumab had better OS in the subsets of patients with PD-L1 expression of <1% and ≥50%. By contrast, the median OS was similar (15.1 months in both arms) in patients with tumor PD-L1 expression of 1-49%.³⁹ The FDA has approved the use of nivolumab and ipilimumab combination in patients with tumors expressing PD-L1 ≥1%.

In the KEYNOTE-598 trial, ipilimumab+pembrolizumab did not improve the PFS and OS compared with pembrolizumab monotherapy as first-line treatment for advanced NSCLC with PD-L1 ≥50%.⁴⁰ However, considering the delayed separation of the curves at ~18 months in other dual immunotherapy studies, their OS results should be evaluated, wherein available data was ~12 months of follow-up.

The MYSTIC trial data showed that durvalumab as first-line treatment did not significantly improve OS compared with chemotherapy (HR, 0.76; 95% CI, 0.56-1.02) or durvalumab+tremelimumab did not significantly improve the OS and PFS compared with chemotherapy (HR, 0.85; 95% CI, 0.61-1.17 for OS; HR, 1.05, 99.5% CI, 0.72-1.53 for PFS) in patients with metastatic NSCLC and tumor cell PD-L1 expression ≥25%.⁴¹

In the POSEIDON trial, compared with patients on chemotherapy alone, both patients receiving first-line durvalumab+chemotherapy (HR, 0.74; 95% CI, 0.62-0.89 for PFS; HR, 0.86; 95% CI, 0.72-1.02 for OS) and first-line durvalumab+tremelimumab+chemotherapy (HR, 0.72; 95% CI, 0.60-0.86 for PFS; HR, 0.77; 95% CI, 0.65-0.92 for OS) had clinically significantly improved PFS and OS.⁴²

Based on the long-term survival and durable response results in the nivolumab and ipilimumab combination trials, the CheckMate 9LA trial was designed with the rationale that adding 2 chemotherapy cycles to this combination could provide rapid initial disease control.³⁸ Therefore, patients were randomized into 2 groups: those receiving nivolumab+ipilimumab+2 cycles of platinum-doublet chemotherapy and those receiving nivolumab+ipilimumab+4

cycles of platinum-doublet chemotherapy.³⁸ Compared with patients receiving chemotherapy in the 2-year updated results, those receiving nivolumab+ipilimumab+chemotherapy had improved median OS (15.8 vs. 11.0 months; HR, 0.72; 95% CI, 0.61-0.86), median PFS (6.7 vs. 5.3 months; HR, 0.67; 95% CI, 0.56-0.79), and objective response rate (38% vs. 25%).

IMMUNOTHERAPY IN PRETREATED ADVANCED NSCLC

In patients receiving systemic agents as frontline treatment, anti-PD-1 or anti-PD-L1 agents are used as second-line treatment, rather than chemotherapy. Table 4 shows the results of randomized phase 3 trials comparing immunotherapy and chemotherapy (consisting of docetaxel) in pretreated advanced NSCLC.

In pretreated patients, ICIs doubled the objective response rate and improved OS. Compared with docetaxel, immunotherapy had a significantly longer response duration in the responding patients.⁴³⁻⁴⁷ The combined analysis of CheckMate 017 and CheckMate 057 showed that the 5-year pooled OS rates were 13.4% and 2.6% for those receiving nivolumab and docetaxel, respectively.⁴⁵ Compared with docetaxel, nivolumab had significantly improved OS without considering tumor histology and PD-L1 status. Notably, the squamous histology was not statistically significant in the OAK and KEYNOTE-010 trials; however, the inclusion of squamous histology as a subgroup analysis for both trials should be considered.^{46,47}

IMMUNOTHERAPY IN LOCALLY ADVANCED NSCLC

The prognosis of locally advanced NSCLC remains poor despite multimodality treatment. In the PACIFIC trial, patients who did not improve after concomitant chemoradiotherapy were randomized into durvalumab for 1 year and placebo.⁴⁸ At 5 years, durvalumab increased the median PFS (16.9 vs. 5.6 months; HR, 0.55; 95% CI, 0.45-0.68) and median OS (47.5 vs. 29.1 months; HR, 0.72; 95% CI, 0.59-0.89). Additionally, the benefit of durvalumab was

TABLE 4: Randomized phase 3 trials comparing immunotherapy versus chemotherapy in pretreated advanced NSCLC.

Agent	Trial	Patient characteristics	ORR	Median OS	OS HR	Median duration of response	Median follow-up
Nivolumab	CheckMate-057 trial ⁴¹	Nonsquamous	19% vs. 12%	12.2 mon. vs. 9.5 mon.	HR: 0.70 (95% CI, 0.58-0.83)	17 mon. vs. 6 mon.	69.4 mon.
	CheckMate-017 trial ⁴⁴	Squamous	20% vs. 9%	9.2 mon. vs. 6 mon.	HR: 0.62 (95% CI, 0.48-0.79)	25 mon. vs. 8 mon.	69.5 mon.
	5-year pooled analysis ⁴⁵	All histology	20% vs 11%	11.1 mon. vs 8.1 mon.	HR: 0.68 (95% CI, 0.59-0.78)	20 mon. vs 5.6 mon.	Nonsquamous: 69.4 mon. Squamous: 69.5 mon.
Atezolizumab	OAK trial ⁴⁶	Nonsquamous	N/A	14.3 mon. vs. 11.4 mon.	HR: 0.77 (95% CI, 0.66-0.89)	N/A	47.7 mon.
		Squamous	N/A	9.2 mon. vs 7.8 mon.	HR: 0.79 (95% CI, 0.62-1.00)	N/A	
		All histology	14% vs. 12%	13.3 mon. vs. 9.8 mon.	HR: 0.78 (95% CI, 0.68-0.89)	24.0 mon. vs. 6.3 mon.	
Pembrolizumab	KEYNOTE-010 trial ⁴⁷	Nonsquamous	N/A	N/A	HR: 0.69 (95% CI, 0.58-0.81)	N/A	67.4 mon.
		Squamous	N/A	N/A	HR: 0.85 (95% CI, 0.62-1.18)	N/A	
		All histology	21% vs. 10%	11.8 mon. vs. 8.4 mon.	HR: 0.70 (95% CI, 0.61-0.80)	68.4 mon. vs. 7.5 mon.	

NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; mon: Months; N/A: Not available; PD-L1: Programmed death ligand-1.

not observed in patients with PD-L1 expression <1%.⁴⁹ Currently, the administration of durvalumab for 1 year is the standard treatment in patients with unresectable stage III NSCLC without disease progression after concurrent chemoradiotherapy.

NEOADJUVANT IMMUNOTHERAPY IN NSCLC

The CheckMate 816 trial evaluated pathological complete response as the primary endpoint in patients with resectable NSCLC who underwent nivolumab+platinum-doublet chemotherapy or chemotherapy as neoadjuvant treatment.⁵⁰ Compared with chemotherapy, nivolumab+platinum-doublet chemotherapy significantly increased the pathological complete response rate [24.0% vs. 2.2%; odds ratio, 13.94 (99% CI, 3.49-55.75); $p < 0.0001$].⁵⁰

RADIATION TREATMENT AND IMMUNOTHERAPY IN LUNG CANCER

The general standard in treating locally advanced NSCLC is concurrent chemoradiotherapy, which is usually administered during 6 weeks of RT. The conventional fractionated method of 2 Gy is often preferred during RT. Additionally, dosing schedules are variable in patients undergoing palliative RT. Regimens ranging from 8 Gy in one fraction to 30 Gy in 10 fractions can be administered. An appropriate option for medically inoperable patients with early-stage disease is stereotactic body RT (SBRT), generally delivered as 45-60 Gy in 3 fractions for peripherally located tumors or 25-34 Gy in a single fraction for small peripheral tumors. Central tumors should be treated with more protracted SBRT fractionation schedules. Compared with conventionally fractionated RT, SBRT provides remarkable results in these patients.⁵¹

Radiation therapy influences the immune system, whereas combined RT and immunotherapy may improve lung cancer treatment.⁵² A recent review of different trials evaluated the mechanisms of the synergistic role of RT with immunotherapy in effective

immune stimulation.⁵³ A recent review evaluating preclinical and clinical studies on the potential interaction of combination therapies of radiation and immune checkpoint blockade reported on the synergy of radiation between the immune system and anti-tumor immunity via a combined-modality manner, which integrates radiation and immunotherapies.⁵⁴ In the multicenter, randomized controlled open-label phase 2 ImmunoSABR study, conducted in 14 centers in 6 countries, the combination of stereotactic ablative body RT and tumor-selective immunocytokine L19-IL2 was tested to increase PFS in patients with limited metastatic NSCLC.⁵⁵ The initial results will be available at the end of 2023. The phase 2 ETOP NICOLAS trial evaluated the safety and efficacy of nivolumab+chemoradiotherapy in patients with stage III NSCLC, who were administered 3 cycles of platinum-based chemotherapy and concurrent RT (66 Gy/33 fractions).⁵⁶ The ETOP NICOLAS trial demonstrated the feasibility of chemotherapy+RT with concurrent and maintenance nivolumab in patients with unresectable stage III NSCLC.⁵⁶ This trial did not report unexpected adverse events or risk of increased severe pneumonitis.⁵⁶ Another study described patients with oligometastatic NSCLC as a special group in stage IV NSCLC and reported promising results with the combination of stereotactic ablative body RT with immunotherapy.⁵⁷ Administration of SBRT before pembrolizumab is well tolerated. Moreover, positive results were largely influenced by the PD-L1-negative subgroup, which can significantly improve PFS and OS.⁵⁸ Recently, SBRT has started to achieve highly effective results in providing local control of limited metastatic disease (in oligo-metastatic, oligo-progressive, etc.).

TREATMENT APPROACH WITH GUIDELINES

The European Society for Medical Oncology has updated the recommendations for the treatment of advanced NSCLC.⁵⁹ Additionally, the ASCO and Cancer Care Ontario recently updated a joint guideline on systemic therapy for stage IV NSCLC without driver mutations.⁶⁰ Moreover, the NCCN Guidelines for NSCLC are frequently updated throughout the year, and testing for PD-L1 expres-

sion is currently recommended in all patients with advanced NSCLC before deciding on first-line treatment, if clinically feasible.¹⁸ A recent review summarized various immunotherapy-based treatments for patients with advanced or metastatic NSCLC.⁶¹

MANAGEMENT OF IMMUNE-RELATED PULMONARY TOXICITIES

A meta-analysis showed that PD-1/PD-L1 inhibitors, such as nivolumab, atezolizumab, and pembrolizumab, enhanced the risk of all-grade pneumonitis compared with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor (ipilimumab).⁶² The risk of grade 3-5 pneumonitis was significantly higher only in pembrolizumab compared with chemotherapy.⁶² Another meta-analysis of 19 trials showed an increased incidence of pneumonitis with PD-1 inhibitors compared with PD-L1 inhibitors, and this adverse effect was more frequent in patients receiving immunotherapy as first-line treatment.⁶³ The incidence of pneumonitis was also higher and more severe with dual-immunotherapy (anti-PD-1/PD-L1 and anti-CTLA-4) than that with monotherapy (6.6% vs. 1.6%; $p < 0.001$).⁶⁴ Besides, no association was observed between the increased risk of pneumonitis and immunotherapy (pembrolizumab)+chemotherapy combination in lung cancer.⁶⁵ Lung toxicity was also increased in patients with locally advanced NSCLC who received maintenance immunotherapy (durvalumab) after definitive chemoradiation.⁶⁶

Recently, pulmonary toxicities occur earlier in patients with NSCLC than those with other tumors and are not predictive for better patient outcomes by contrast to other immune-related adverse events (irAEs).⁶⁷ Patients with immune-related pulmonary toxicities frequently present with relatively non-specific symptoms, such as dyspnea, cough, chest discomfort, and/or infrequently fever. Chest X-ray or CT may reveal ground-glass opacities, findings consistent with organizing pneumonia, or interstitial pneumonia. Furthermore, it may present with only radiographic findings (grade 1), mild-to-moderate respiratory complaints (grade 2), severe respiratory complaints requiring oxygen sup-

port (grade 3), and life-threatening conditions (grade 4).

Withholding ICIs is the initial step in asymptomatic pneumonitis cases.⁶⁸ Generally, corticosteroids (equivalent of prednisone 1 mg/kg daily) are rapidly initiated in patients with pneumonitis with symptomatic grade ≥ 2 .^{68,69}

MANAGEMENT OF IMMUNE-RELATED NON-PULMONARY TOXICITIES

Dermatologic toxicities, such as rash and pruritus, are frequently observed with anti-CTLA-4 treatment (ipilimumab) and can occur in approximately 50% of patients.⁷⁰ Some important irAEs include immune hepatitis and gastrointestinal toxicity (diarrhea and colitis).⁷¹ A meta-analysis showed that immune gastrointestinal toxicities were not significantly different in diverse solid cancers.⁷² CTLA-4 and PD-1 inhibitors can lead to autoimmune hepatotoxicity, which causes elevated transaminase and total bilirubin levels.^{70,73}

The most common endocrine toxicity is autoimmune thyroid disease, manifesting as hypothyroidism or hyperthyroidism. The occurrence of other endocrine toxicities, such as thyroiditis, hypophysitis, Type I diabetes, and primary adrenal insufficiency, have been reported but are rare.⁷¹ Although PD-1/PD-L1 inhibitors more frequently lead to thyroid dysfunction, CTLA-4 inhibitors more frequently cause hypophysitis.⁷⁴

The occurrence of cardiovascular toxicities, such as cardiomyopathy (particularly myocarditis), pericardial disease, and valvular disease, have been linked with ICIs in lung cancer.⁷⁵

The most common multisystem irAEs were immune-thyroiditis with pneumonitis, hepatitis, or dermatitis, and dermatitis-pneumonitis in a study conducted in a multicenter cohort of 623 patients with NSCLC treated with anti-PD-1/PD-L1 monotherapy.⁷⁶ In patients with advanced NSCLC treated with ICIs, a link was observed between the occurrence of multisystem irAEs and improved survival.⁷⁶ Generally, moderate or severe irAEs are treated with cessation of checkpoint inhibitors and administration of glucocorticoid immunosuppression.

DISCUSSION AND CONCLUSIONS

The most important element of first-line therapy are treatments consisting of anti-PD-1/PD-L1 antibodies. Their benefits in long-term survival can be examined through long-term follow-up data. Despite shortcomings, PD-L1 level currently seems to be a relatively reliable predictor for distinguishing patients who will benefit from immunotherapy.²³ However, new biomarkers are necessary for individualized treatment options for patients. Furthermore, we believe that advances in this area will require detailed identification, such as demonstrating the predictive role of genetic mutations, allowing a deeper understanding of the dynamic changes in the tumor microenvironment.

Although current immunotherapy options are groundbreaking in cancer treatment, their long-term effectiveness may be limited. Thus, studies on effective immunotherapy agents through new pathways are continuing. Moreover, one of the markers guiding the studies of new immunotherapy generation is lymphocyte activation gene 3 protein (LAG-3), a molecule proven in preclinical studies to stay at a key point as an immune checkpoint *in vivo*. It is considered to play a vital role in cancer pathogenesis and possesses a stabilizing effect on the immune system. Currently, LAG-3 inhibitors are recognized as next-generation immunotherapy agents and are anticipated to play a fundamental role in future cancer treatment approaches.⁷⁷ For example, the randomized phase 2 RELATIVITY-104 study is testing nivolumab+relatlimab (anti-LAG-3)+chemotherapy compared with nivolumab+chemotherapy in NSCLC.⁷⁸ Therefore, anti-LAG-3-based drugs in lung cancer immunotherapy may be used in daily practice in the near future.

Currently, immunotherapy is considered the mainstay treatment in advanced, driver-negative NSCLC. Its contribution to PFS, OS, and QoL was shown in mature clinical trial data. Furthermore, our patients had improved PFS, OS, and QoL because immunotherapy was used in early access programs and accessible through clinical study opportunities in

our country. We hope immunotherapy will be easily accessible for every eligible patient with lung cancer in the near future.

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Conflict of Interest

Dr. Karadurmuş is on Speaker's Bureau for Bristol Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Pfizer, Amgen, Novartis, and Astellas and is on Advisory Boards of Amgen, BMS, MSD, Pfizer, Roche, Novartis, Astellas, and Takeda; all outside the submitted work. Dr. Akyürek is on Speaker's Bureau for BMS, MSD, Pfizer, Roche, and Astra Zeneca and is on Advisory Boards of Amgen and Novartis; all outside the submitted work. Dr. Aydınler has declared no conflict of interest. Dr. Savaş has declared no conflict of interest. Dr. Sönmez has declared no conflict of inter-

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Authorship Contributions

All authors contributed equally while this study preparing.

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