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REVIEW

First-line immunotherapy-based regimens for metastatic non-small cell lung cancer: A network meta-analysis of landmark trials

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ABSTRACT

First-line immunotherapy-based regimens for metastatic non-small cell lung cancer: A network meta-analysis of landmark trials

Introduction: First-line immunotherapy, alone or with chemotherapy, has revolutionized the treatment of metastatic non-small cell lung cancer (NSCLC). However, with multiple approved regimens, the optimal therapeutic choice is undefined due to a lack of direct comparative trials. This network meta-analysis was conducted to establish a hierarchy of efficacy for five landmark immunotherapy-based regimens to inform clinical and policy decisions.

Materials and Methods: A network meta-analysis of five pivotal phase III trials (KEYNOTE-024, KEYNOTE-189, KEYNOTE-407, CheckMate 9LA, IMpower 110), all recently reimbursed in our country, was performed. We synthesized overall survival (OS) data for the total population and across subgroups defined by histology (squamous vs. non-squamous) and PD-L1 expression (<1%, 1-49%, ≥50%), with chemotherapy as the common comparator.

Results: Pembrolizumab-based therapies ranked consistently high. In non-squamous NSCLC, pembrolizumab-chemotherapy was highest-ranked and significantly superior to the nivolumab-based combination (HR: 0.76, 95% CI: 0.58-0.99). In squamous disease, the combination of nivolumab, ipilimumab, and chemotherapy emerged as the highest-ranked regimen (SUCRA: 78.3%). By PD-L1 status, pembrolizumab monotherapy was top-ranked for ≥50% expression (SUCRA: 82.8%), while pembrolizumab-chemotherapy was superior for the 1-49% subgroup (SUCRA: 87.5%). For PD-L1 negative (<1%) patients, a subgroup with substantial heterogeneity, no regimen showed a statistically significant OS benefit over chemotherapy.

Conclusion: Our analysis indicates pembrolizumab-based regimens, as monotherapy or with chemotherapy, offer the most robust and highest-ranking survival advantage across most key NSCLC subgroups. These findings provide a critical, evidence-based framework to guide individualized first-line treatment selection.

Key words: Non-small cell lung cancer; immunotherapy; network meta-analysis; overall survival; pembrolizumab

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ÖZ

Metastatik küçük hücreli dışı akciğer kanserinde birinci basamak immünoterapi temelli rejimler: Dönüm noktası çalışmalarının network meta-analizi

Giriş: Tek başına veya kemoterapi ile birlikte uygulanan birinci basamak immünoterapi, metastatik küçük hücreli dışı akciğer kanseri (KHDAK) tedavisinde devrim niteliğinde bir gelişme olmuştur. Ancak, çok sayıda onaylanmış rejim olması ve doğrudan karşılaştırmalı çalışmaların bulunmaması nedeniyle, optimal tedavi seçimi belirsizdir. Bu ağ meta-analizi, klinik ve politika kararlarına bilgi sağlamak amacıyla, beş önemli immünoterapi bazlı rejimin etkinlik hiyerarşisini belirlemek için gerçekleştirilmiştir.

Materyal ve Metod: Ülkemizde yakın zamanda geri ödeme kapsamına alınan beş önemli faz III denemenin (KEYNOTE-024, KEYNOTE-189, KEYNOTE-407, CheckMate 9LA, IMpower 110) ağ meta analizi gerçekleştirilmiştir. Toplam popülasyon ve histoloji (skuamöz vs. skuamöz olmayan) ve PD-L1 ekspresyonu ($<1\%$, $1-49\%$, $\geq 50\%$) ile tanımlanan alt gruplar için genel sağkalım (OS) verilerini, kemoterapi ortak karşılaştırıcı olarak kullanarak sentezledik.

Bulgular: Pembrolizumab bazlı tedaviler tutarlı bir şekilde yüksek sıralamada yer aldı. Skuamöz olmayan KHDAK'de pembrolizumab-kemoterapi en yüksek sıralamayı aldı ve nivolumab bazlı kombinasyondan önemli ölçüde üstündü (HR: 0.76, 95% CI: 0.58-0.99). Skuamöz hastalıkta, nivolumab, ipilimumab ve kemoterapi kombinasyonu en yüksek sıralamayı alan rejim olarak ortaya çıktı (SUCRA: 78.3%). PD-L1 durumuna göre, pembrolizumab monoterapisi $\geq 50\%$ ekspresyon için en yüksek sıralamaya sahipti (SUCRA: 82.8%), pembrolizumab-kemoterapi ise $1-49\%$ alt grubu için üstündü (SUCRA: 87.5%). PD-L1 negatif ($<1\%$) hastalar için, önemli heterojenliğe sahip bir alt grupta, hiçbir rejim kemoterapiye göre istatistiksel olarak anlamlı bir OS faydası göstermedi.

Sonuç: Analizimiz, pembrolizumab bazlı rejimlerin, monoterapi olarak veya kemoterapi ile birlikte, çoğu önemli KHDAK alt grubunda en sağlam ve en yüksek sıralamaya sahip sağkalım avantajı sağladığını göstermektedir. Bu bulgular, bireyselleştirilmiş birinci basamak tedavi seçimine rehberlik edecek, kanıta dayalı kritik bir çerçeveye sunmaktadır.

Anahtar kelimeler: Küçük hücreli olmayan akciğer kanseri; immünoterapi; network meta-analizi; genel sağkalım; pembrolizumab

INTRODUCTION

The treatment landscape for metastatic non-small cell lung cancer (NSCLC) has been transformed over the past decade, significantly improving survival outcomes for many patients (1). Immune checkpoint inhibitors (ICIs) that target the programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathways are now the cornerstone of first-line therapy for patients who do not have targetable oncogenic driver mutations. Current standards of care include ICI monotherapy, dual ICI combinations, and ICIs combined with chemotherapy, which are selected based on factors like PD-L1 expression and tumor histology (2,3). Landmark phase III trials such as KEYNOTE-024, KEYNOTE-189, KEYNOTE-407, CheckMate 9LA, and IMpower 110 have established the clinical efficacy of these approaches in diverse patient populations with varying histologies and PD-L1 expression levels (4-8). Despite this progress, direct head-to-head comparisons of these regimens are lacking, leaving clinicians with uncertainty regarding the optimal choice of therapy, particularly for patients with intermediate or low PD-L1 expression or for those with differing histological subtypes (3).

In this context, network meta-analysis (NMA) offers a robust methodological framework to synthesize evidence across multiple randomized controlled trials

(RCTs) by integrating both direct and indirect comparisons. This is particularly valuable for assessing the relative efficacy of immunotherapy-based regimens where head-to-head trials are absent. Several meta-analysis have previously attempted to compare first-line ICI regimens in NSCLC, yet most were conducted before the availability of long-term survival data or the approval of novel combination strategies such as nivolumab plus ipilimumab with limited chemotherapy (9-12).

Underscoring the clinical relevance of this issue, in July 2025, the Social Security Institution in our country formally included five immunotherapy-based protocols—CheckMate 9LA, KEYNOTE-189, KEYNOTE-407, KEYNOTE-024, and IMpower 110—into the reimbursement list for first-line treatment of metastatic NSCLC (13). This development has heightened the clinical importance of understanding the comparative effectiveness of these regimens in clinical practice. Therefore, the objective of this study was to conduct a comprehensive NMA of pivotal phase III randomized trials to compare the overall survival (OS) benefit of first-line immunotherapy-based regimens against chemotherapy in patients with metastatic NSCLC. The analysis incorporated data from five major trials and evaluated the outcomes across the overall population as well as clinically relevant subgroups defined by histological subtype (non-squamous vs. squamous) and PD-L1 expression

levels (<1%, 1-49%, and ≥50%). By synthesizing the most updated survival data, this study aimed to inform evidence-based decision-making and provide a practical guide for clinicians in selecting optimal first-line treatment strategies for patients with meta-static NSCLC.

MATERIALS and METHODS

Study identification and selection criteria

This NMA was designed and reported following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Network Meta-Analyses (PRISMA-NMA) (14). The systematic review protocol was registered on PROSPERO under the number 1141509. Unlike a conventional systematic review with a broad literature search, this study was specifically designed to compare the pivotal clinical trials corresponding to the five first-line immunotherapy-based regimens for metastatic NSCLC recently included in the national reimbursement list in our country (Social Security Institution, Official Gazette, July 10, 2025) (13). This focused approach was chosen to directly inform clinical and policy decisions within the new local healthcare landscape. Consequently, the following five pivotal phase III RCTs were pre-selected for inclusion: KEYNOTE-024, KEYNOTE-189, KEYNOTE-407, IMpower 110, and CheckMate 9LA. The eligibility of these five trials was confirmed based on the following criteria: (1) being a phase III RCT; (2)

enrolling adult patients with previously untreated, metastatic NSCLC without sensitizing EGFR or ALK alterations; and (3) reporting OS outcomes. Data on OS, presented as hazard ratios (HRs) with 95% confidence intervals (CIs), were extracted from the final or most updated publications of these trials (15-19). Key characteristics of the five pivotal trials included in this NMA, including study design, patient populations, and PD-L1 assessment methods, are summarized in Table 1.

Data extraction and endpoints

Aggregate data from the selected publications were extracted for the following treatment arms: nivolumab plus ipilimumab and chemotherapy (from CheckMate 9LA), pembrolizumab plus chemotherapy (from KEYNOTE-189 and KEYNOTE-407), pembrolizumab monotherapy (from KEYNOTE-024), and atezolizumab monotherapy (from IMpower 110). As the IMpower110 trial did not demonstrate a significant OS benefit in the broader PD-L1 ≥1% population, formal analysis was limited to the PD-L1-high subgroup [tumor cell (TC) ≥50% or immune cell (IC) ≥10%]. Chemotherapy served as the common comparator in all trials. The primary endpoint of this NMA was OS. Data were analyzed for the overall population and for prespecified subgroups based on tumor histology (non-squamous and squamous) and PD-L1 expression levels (<1%, 1-49%, and ≥50%).

Table 1. Baseline features and study design of the included pivotal trials					
Feature	KEYNOTE-024	KEYNOTE-189	KEYNOTE-407	IMpower 110	CheckMate 9LA
Histology	Non-squamous/ Squamous	Non-squamous only	Squamous only	Non-squamous/ Squamous	Non-squamous/ Squamous
PD-L1 inclusion criteria	PD-L1 TPS ≥50% only	All-comers (any PD-L1 level)	All-comers (any PD-L1 level)	PD-L1 TC/IC ≥1% only	All-comers (any PD-L1 level)
PD-L1 assay used	22C3 pharmDx	22C3 pharmDx	22C3 pharmDx	SP142	28-8 pharmDx
Experimental arm	Pembro monotherapy	Pembro + chemo	Pembro + chemo	Atezo monotherapy	Nivo + Ipi + 2 cycles chemo
Comparator arm	Platinum-doublet chemo	Pemetrexed + platinum	Carboplatin + (nab-)paclitaxel	Platinum-doublet chemo	Platinum-doublet chemo (four cycles)
Total patients (n)	305	616	559	554	719
Median age (years)	65	65	65	64	65
Sex (% , male)	61%	59%	81%	70%	70%
PD-L1 TPS distribution					
<1%	N/A	31%	35%	N/A	37%
1-49%	N/A	30%	37%	29%	32%
≥50%	100%	33%	26%	49%	24%
IC: Immune cell, N/A,: Not available, PD-L1: Programmed death-ligand 1, TC: Tumor cell, TPS: Tumor proportion score.					

Statistical Analysis

All statistical analyses were performed using R software (version 4.5.0), primarily with the *netmeta* package for frequentist NMA. A random-effects model was applied to account for clinical and methodological heterogeneity across trials. HRs were logarithmically transformed (log-HRs), and their corresponding standard errors were derived from the reported 95% CIs in the source publications. Chemotherapy was established as the common reference comparator across all networks. The network geometry for each subgroup analysis, illustrating the direct comparisons between treatments, was visualized using the *netgraph()* function.

To evaluate the relative efficacy and establish a hierarchy of the competing treatments, we calculated the surface under the cumulative ranking curve (SUCRA) scores and corresponding ranks for each regimen using the *netrank()* function. A higher SUCRA score (ranging from 0% to 100%) indicates a greater probability of a treatment being the most effective option. Comprehensive pairwise comparisons of all treatments within each network, incorporating both direct and indirect evidence, were summarized in league

tables generated by the *netleague()* function. These tables present the estimated HRs and corresponding 95% CIs for each potential treatment comparison. The results of the NMA, comparing each active regimen against the chemotherapy reference, were visualized using forest plots generated with the *forest()* function. Network consistency was assessed using the I^2 statistic to quantify overall heterogeneity. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Network heterogeneity

Statistical heterogeneity was low to non-existent across most networks, with I^2 values of 0% for the non-squamous, squamous, PD-L1 1-49%, and PD-L1 $\geq 50\%$ subgroups. Moderate heterogeneity was observed in the overall population network ($I^2=39\%$). In contrast, substantial heterogeneity was detected in the PD-L1 <1% subgroup ($I^2=68.4\%$), indicating that the comparative efficacy results for this specific subgroup should be interpreted with caution. The network geometries for each subgroup analysis are depicted in Figure 1.

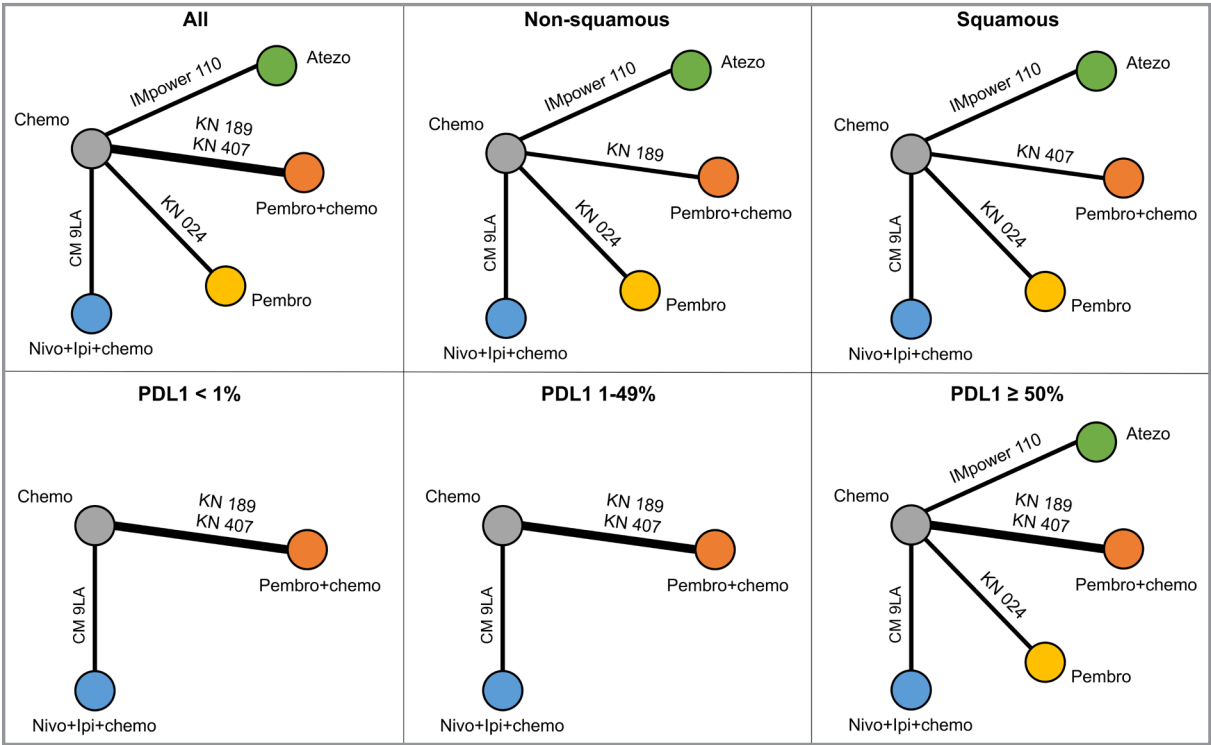


Figure 1. Network diagrams of treatment comparisons across all patients and prespecified subgroups.

Overall population

In the analysis of the entire patient population, most immunotherapy-based treatments demonstrated a significant improvement in OS compared to chemotherapy. Pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and the combination of nivolumab, ipilimumab, and chemotherapy all showed a statistically significant OS benefit. Atezolizumab showed a trend towards improved OS, but this did not reach statistical significance (HR: 0.76, 95% CI: 0.52-1.11). Based on SUCRA scores, pembrolizumab monotherapy had the highest probability of being the most effective treatment (80.9%), followed by pembrolizumab plus chemotherapy (74.1%), nivolumab plus ipilimumab and chemotherapy (47.5%), and atezolizumab (45.4%) (Table 2). Pairwise comparisons between the immunothera-

py regimens did not reveal any statistically significant differences in OS in the overall population, as shown in the league table (Table 3).

Histological subgroups

Non-squamous histology

For patients with non-squamous NSCLC, pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and nivolumab plus ipilimumab and chemotherapy provided a significant survival advantage over chemotherapy. Atezolizumab did not demonstrate a statistically significant benefit (HR: 0.72, 95% CI: 0.48-1.08). Pembrolizumab monotherapy was ranked as the most effective treatment with a SUCRA score of 82.1%, closely followed by pembrolizumab plus chemotherapy at 80.1% (Table 2). A statistically significant benefit in OS was observed for the pembrolizumab plus chemotherapy regimen when

Table 2. Comparative efficacy of immunotherapy-based regimens versus chemotherapy for overall survival: a random-effects network meta-analysis with SUCRA rankings

Subgroups	Treatments	HR (95% CI)	SUCRA score (%)
All	Atezo	0.76 [0.52; 1.11]	45.4
	Nivo+Ipi+chemo	0.74 [0.60; 0.92]	47.5
	Pembro+chemo	0.65 [0.55; 0.77]	74.1
	Pembro	0.62 [0.46; 0.84]	80.9
Non-squamous	Nivo+Ipi+chemo	0.79 [0.65; 0.96]	35.6
	Atezo	0.72 [0.48; 1.08]	50.7
	Pembro+chemo	0.60 [0.50; 0.72]	80.1
	Pembro	0.58 [0.41; 0.83]	82.1
Squamous	Atezo	0.91 [0.45; 1.84]	34.3
	Pembro	0.73 [0.38; 1.40]	58.6
	Pembro+chemo	0.71 [0.59; 0.85]	64.5
	Nivo+Ipi+chemo	0.65 [0.49; 0.86]	78.3
PDL1 < 1%	Pembro+chemo	0.68 [0.45; 1.02]	70.1
	Nivo+Ipi+chemo	0.64 [0.37; 1.10]	75.7
PDL1 1-49%	Nivo+Ipi+chemo	0.71 [0.54; 0.94]	62.1
	Pembro+chemo	0.63 [0.50; 0.79]	87.5
PDL1 ≥ 50%	Nivo+Ipi+chemo	0.76 [0.55; 1.05]	46.1
	Atezo	0.73 [0.54; 0.99]	53.1
	Pembro+chemo	0.68 [0.53; 0.87]	66.2
	Pembro	0.62 [0.48; 0.80]	82.8

CI: Confidence interval, HR: Hazard ratio, PD-L1: Programmed death-ligand 1, SUCRA: Surface under the cumulative ranking curve.

Table 3. League table of pairwise hazard ratios for overall survival among immunotherapy-based regimens across clinical subgroups				
Subgroups	Treatments			
	Reference	Pembro	Pembro+chemo	Nivo+Ipi+chemo
All	Pembro			
	Pembro+chemo	0.95 (0.68-1.34)		
	Nivo+Ipi+chemo	0.84 (0.58-1.21)	0.88 (0.67-1.16)	
	Atezo	0.82 (0.50-1.32)	0.86 (0.57-1.30)	0.97 (0.63-1.51)
Non-squamous		Pembro	Pembro+chemo	Atezo
	Pembro			
	Pembro+chemo	0.97 (0.65-1.44)		
	Atezo	0.81 (0.47-1.38)	0.83 (0.53-1.30)	
Squamous				
	Nivo+Ipi+chemo	0.73 (0.49-1.10)	0.76 (0.58-0.99)	0.91 (0.58-1.43)
		Nivo+Ipi+chemo	Pembro+chemo	Pembro
	Nivo+Ipi+chemo			
PDL1 < 1%	Pembro+chemo	0.92 (0.66-1.27)	0.97 (0.50-1.91)	
	Pembro	0.89 (0.44-1.80)	0.78 (0.38-1.61)	0.80 (0.31-2.09)
	Atezo	0.71 (0.34-1.52)		
		Nivo+Ipi+chemo	Pembro+chemo	
PDL1 1-49%				
	Nivo+Ipi+chemo	0.94 (0.48-1.85)		
		Pembro+chemo	Nivo+Ipi+chemo	
	Pembro+chemo			
PDL1 ≥ 50%				
	Nivo+Ipi+chemo	0.88 (0.62-1.26)		
		Pembro	Pembro+chemo	Atezo
	Pembro			
PDL1 ≥ 50%	Pembro+chemo	0.91 (0.64-1.31)	0.93 (0.63-1.38)	
	Atezo	0.85 (0.57-1.27)	0.89 (0.60-1.34)	0.96 (0.62-1.50)
	Nivo+Ipi+chemo	0.82 (0.54-1.24)		
Pairwise comparisons display hazard ratios with 95% confidence intervals, comparing column treatments versus row treatments.				

compared indirectly to the nivolumab-based combination (HR: 0.76, 95% CI: 0.58-0.99) (Table 3).

Squamous histology

In the squamous histology subgroup, the combination of nivolumab, ipilimumab, and chemotherapy (SUCRA: 78.3%) and pembrolizumab plus chemotherapy (SUCRA: 64.5%) showed a significant OS benefit compared to chemotherapy. In contrast, pembrolizumab monotherapy and atezolizumab did not demonstrate a statistically significant survival improvement over chemotherapy in this subgroup (Table 2). No significant differences were found in the pairwise comparisons between the active treatment regimens (Table 3).

PD-L1 expression subgroups

PD-L1 < 1%

In the subgroup with PD-L1 expression below 1%, neither nivolumab plus ipilimumab and chemotherapy nor pembrolizumab plus chemotherapy demon-

strated a statistically significant survival benefit over chemotherapy, as their confidence intervals crossed 1.0. The nivolumab-based combination ranked highest with a SUCRA score of 75.7%, followed by the pembrolizumab-based combination at 70.1% (Table 2). The pairwise comparison between the two active treatments did not show a significant difference (Table 3).

PD-L1 = 1-49%

For patients with PD-L1 expression between 1% and 49%, both pembrolizumab plus chemotherapy and nivolumab plus ipilimumab and chemotherapy demonstrated a significant OS benefit over chemotherapy. Pembrolizumab plus chemotherapy was ranked as the most effective treatment, achieving a SUCRA score of 87.5% (Table 2). The comparison between these two active regimens did not yield a statistically significant difference (Table 3).

PD-L1 ≥ 50%

In the high PD-L1 expression subgroup ($\geq 50\%$), pembrolizumab monotherapy, pembrolizumab plus chemotherapy, and atezolizumab each showed a significant OS improvement compared to chemotherapy. The combination of nivolumab, ipilimumab, and chemotherapy did not reach statistical significance (HR: 0.76, 95% CI: 0.55-1.05). Pembrolizumab monotherapy was the top-ranked treatment with a SUCRA score of 82.8% (Table 2). There were no statistically significant differences in OS among the various immunotherapy-based treatments in the pairwise comparisons for this subgroup (Table 3).

DISCUSSION

This NMA was conducted to evaluate the comparative efficacy of five first-line immunotherapy-based regimens for metastatic NSCLC, which have recently been included in our national reimbursement list. The primary finding of our study is that immunotherapy-based combination regimens offer a superior OS advantage compared to chemotherapy alone. Notably, across many analyzed subgroups, pembrolizumab-based regimens—particularly in combination with chemotherapy—demonstrated the highest probability of being the most effective treatment according to SUCRA rankings. In a therapeutic area where direct head-to-head trial data is unavailable, this study provides a crucial evidence-based framework to guide decision-making for both clinicians and healthcare policymakers.

Our findings in the overall population confirm the foundational results of the pivotal trials that established these regimens as standards of care. The significant survival improvements observed with pembrolizumab plus chemotherapy, nivolumab plus ipilimumab plus chemotherapy, and pembrolizumab monotherapy relative to chemotherapy are consistent with the outcomes of the KEYNOTE-189, KEYNOTE-407, CheckMate 9LA, and KEYNOTE-024 trials. An interesting observation was the high SUCRA score for pembrolizumab monotherapy in the overall population. This is likely attributable to a “weighting” effect, as the KEYNOTE-024 trial exclusively enrolled patients with high PD-L1 expression ($\geq 50\%$), a population known to derive substantial benefit from this treatment. Our results align with previous NMAs that have also shown the superiority of immunotherapy combinations over chemotherapy (20). However, our analysis provides an updated perspective by including data from the CheckMate 9LA trial, which other analyses had not fully incorporated (9,21).

The analysis of histological subgroups revealed clinically significant distinctions. For patients with non-squamous NSCLC, our NMA showed a statistically significant OS advantage for pembrolizumab plus chemotherapy compared to nivolumab plus ipilimumab with chemotherapy (HR: 0.76). This indirect comparison highlights a potentially critical difference for clinical practice, possibly explained by the synergistic effect of pemetrexed, a chemotherapy agent used specifically in the non-squamous KEYNOTE-189 trial. In contrast, for patients with squamous histology, the combination of nivolumab, ipilimumab, and chemotherapy emerged as the top-ranked regimen by SUCRA score, though it was not statistically superior to pembrolizumab plus chemotherapy. This finding suggests that a strategy combining dual immunotherapy with a limited course of chemotherapy is a potent option in this difficult-to-treat population. As expected, immunotherapy monotherapies were not effective in the squamous subgroup.

The most critical insights from our analysis are derived from the subgroups based on PD-L1 expression, the primary biomarker for treatment selection. In patients with high PD-L1 expression ($\geq 50\%$), pembrolizumab monotherapy ranked as the most effective treatment, with no statistically significant difference compared to more intensive combination regimens. This confirms the practice-changing findings of the KEYNOTE-024 trial and suggests that in this population, adding chemotherapy or a second ICI may not confer additional survival benefits but would increase the risk of toxicity and overall costs (22). For the “grey zone” of patients with PD-L1 expression between 1-49%, pembrolizumab combined with chemotherapy stood out as the most effective regimen, providing valuable guidance for this large patient cohort. Interpretation of the PD-L1 negative ($<1\%$) subgroup must be approached with caution due to the substantial statistical heterogeneity observed ($I^2 = 68.4\%$). In this group, neither nivolumab plus ipilimumab and chemotherapy nor pembrolizumab plus chemotherapy demonstrated a statistically significant survival benefit over chemotherapy alone, as the confidence intervals for the HRs included 1.0. Although these regimens had high SUCRA scores, this discordance underscores the uncertainty of their benefit, compelling clinicians to carefully balance the potential for efficacy against the risk of toxicity.

Efficacy is not the sole determinant of treatment selection; the safety and tolerability of a regimen are equally important. This is particularly relevant in older patients, who constitute the majority of the NSCLC population, as factors such as comorbidities, polypharmacy, and frailty can significantly influence treatment tolerability. The pivotal trials included in our analysis reported varying toxicity profiles. For instance, pembrolizumab monotherapy in KEYNOTE-024 was associated with substantially fewer grade 3 or higher treatment-related adverse events (TRAEs) compared to chemotherapy (26.6% vs. 53.3%) (4). In contrast, the addition of pembrolizumab to chemotherapy in the KEYNOTE-189 and KEYNOTE-407 trials did not significantly increase the rate of high-grade TRAEs compared to chemotherapy alone (67.2% vs. 65.8% and 69.8% vs. 68.2%, respectively) (5,6). The CheckMate 9LA regimen, which combines dual immunotherapy with two cycles of chemotherapy, was associated with a higher rate of serious TRAEs compared to chemotherapy alone (30% vs. 18%), though rates of grade 3-4 TRAEs were manageable (7). A NMA focused on safety has confirmed that adding chemotherapy to ICI increases the overall risk of TRAEs, but not necessarily immune-related adverse events (23). Therefore, our finding that pembrolizumab monotherapy is the preferred option for PD-L1 high patients is reinforced by its more favorable safety profile, while the choice between different combination therapies in other subgroups must involve a careful discussion of these efficacy-toxicity trade-offs.

Our study has several limitations inherent to its design. First, significant statistical heterogeneity was noted in the analyses of the overall population and, most prominently, the PD-L1 <1% subgroup. This heterogeneity likely stems from cross-trial differences in patient characteristics, chemotherapy backbones, and, notably, the different PD-L1 assays used (22C3, 28-8, and SP142), which have known analytical and clinical differences. Second, as a NMA, our findings are based on indirect comparisons between trials, which, while statistically valid, are not a substitute for direct evidence from head-to-head RCTs. Third, the analysis utilized aggregate data from publications rather than individual patient data, which would have allowed for more granular adjustments for patient-level confounders. Finally, SUCRA scores provide a probabilistic ranking and should not be misconstrued as definitive proof of superiority, par-

ticularly when the confidence intervals of competing treatments show considerable overlap.

Despite these limitations, our study possesses significant strengths. Its greatest strength is its pragmatic design, which directly addresses a focused clinical question prompted by recent national reimbursement decision and ensures that our findings are of immediate relevance to local clinical practice and health policy. Furthermore, this analysis is comprehensive, incorporating the five most up-to-date, landmark phase III trials that define the modern first-line treatment landscape for metastatic NSCLC. The extensive subgroup analyses based on histology and PD-L1 expression mirror the critical decision-making pathways used by clinicians daily. This was all accomplished using a robust and accepted statistical methodology, including a random-effects model and SUCRA rankings to provide a clear hierarchy of treatments.

The clinical and policy implications of this analysis are direct and actionable. Our study provides an evidence-based hierarchy that can help oncologists in our country navigate the selection of the most appropriate regimen from the five newly reimbursed options. Based on our findings, a potential treatment algorithm could be proposed: for patients with PD-L1 $\geq 50\%$ tumors, pembrolizumab monotherapy represents a powerful initial choice, offering comparable efficacy with lower toxicity and cost; for those with non-squamous tumors and PD-L1 expression of 1-49%, pembrolizumab with chemotherapy appears to be the most strongly supported option; for patients with squamous histology, either pembrolizumab with chemotherapy or nivolumab plus ipilimumab with chemotherapy are strong contenders. The decision for PD-L1 negative patients remains the most challenging, where the uncertain benefit of IO-based combinations must be carefully weighed against their toxicity. From a policy perspective, our findings may also inform cost-effectiveness evaluations, highlighting patient subgroups where less intensive (and less costly) monotherapy may be as effective as more expensive combination strategies, thereby promoting efficient resource allocation (24).

This analysis also illuminates key areas for future research. There is a clear need for head-to-head randomized trials to directly compare the most competitive regimens, particularly pembrolizumab plus chemotherapy versus nivolumab plus ipilimumab

with chemotherapy in patients with non-squamous NSCLC. Further research into predictive biomarkers beyond PD-L1 and histology, such as tumor mutational burden or specific gene expression profiles, is essential to refine patient selection and personalize treatment. Most importantly, now that these therapies are reimbursed, it is critical to establish a national registry to collect real-world evidence from the Turkish patient population. Such data will be invaluable for validating the findings of this NMA and understanding the effectiveness and safety of these regimens in a real-world setting.

CONCLUSION

In conclusion, this NMA indicates that pembrolizumab-based regimens, especially when combined with chemotherapy, provide the most consistent and highest-ranking OS benefit across most clinically relevant subgroups of patients with metastatic NSCLC. By synthesizing the evidence from five pivotal trials, this study offers a critical, evidence-based framework to guide first-line treatment selection for clinicians and policymakers.

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CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: All of authors

Analysis/Interpretation: All of authors

Data acquisition: RI

Writing: RI

Clinical Revision: ÖA

Final Approval: All of authors

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