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RESEARCH

Real-world effectiveness and safety of first-line chemoimmunotherapy combinations in metastatic non-small cell lung cancer with programmed death ligand-1 < 50%: results from an Italian observational study

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Abstract

Introduction This multi-center, observational cohort study aimed to evaluate the real-world effectiveness and safety of two first-line chemoimmunotherapy combinations—pembrolizumab plus chemotherapy and nivolumab/ipilimumab plus chemotherapy—in patients with metastatic non-small cell lung cancer (NSCLC) and programmed death ligand-1 (PD-L1) expression < 50%.

Patients and Methods The primary objectives were progression-free survival (PFS) and overall survival (OS) in the overall population. Secondary objectives included the incidence of chemotherapy-related and immune-related adverse events (irAEs).

Results A total of 495 patients were enrolled, with 348 (70.3%) receiving pembrolizumab plus chemotherapy and 147 (29.7%) treated with nivolumab/ipilimumab plus chemotherapy. Overall, median follow-up was 11 (95% CI: 10.2 12.2) months. The median PFS was 10.9 months (95% CI: 9.6–13), and the median OS was 21.1 months (95% CI: 16.8–NR) in the overall population. In multivariable analysis, ECOG PS ≥ 2, PD-L1 expression < 1%, squamous histology, baseline steroid use, and the presence of CNS, bone, or liver metastases were significantly associated with shorter survival. No significant differences were observed between the pembrolizumab and nivolumab/ipilimumab cohorts in terms of PFS (11.83 vs. 9.83 months; HR 0.86, 95% CI: 0.67–1.11, $p = 0.3$) or OS (21.3 vs. 20.6 months; HR 1.03, 95% CI: 0.76–1.39, $p = 0.9$). Chemotherapy-related adverse events were more frequent in the pembrolizumab cohort, whereas irAEs were more common in the nivolumab/ipilimumab cohort.

Conclusion In this real-world study, chemoimmunotherapy combinations demonstrated manageable toxicity profiles, with effectiveness comparable to that reported in pivotal phase 3 randomized trials. Pembrolizumab and nivolumab/ipilimumab showed similar real-world effectiveness but significantly different toxicity profiles.

Keywords Pembrolizumab · Nivolumab · Ipilimumab · Chemotherapy · NSCLC · PD-L1

Introduction

Immunotherapy, in the form of immune checkpoint inhibitors (ICIs) targeting programmed death cell protein-1 (PD-1), programmed death ligand-1 (PD-L1), or cytotoxic T-lymphocyte antigen-4 (CTLA-4), is currently the cornerstone of first-line treatment for metastatic non-small cell lung cancer (mNSCLC) without oncogenic alterations [1]. Notably, single-agent anti-PD-1 (pembrolizumab, cemiplimab) or anti-PD-L1 (atezolizumab) therapies have shown superior efficacy compared to platinum-based chemotherapy in non-oncogene-addicted mNSCLC with PD-L1 ≥ 50%

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[2–4]. Furthermore, adding ICIs to platinum-based chemotherapy (i.e., chemoimmunotherapy) has improved outcomes over chemotherapy alone, regardless of PD-L1 expression levels. Thus, for non-oncogene-addicted mNSCLC, both immunotherapy with single-agent anti-PD-(L)1 or chemoimmunotherapy are viable options for patients with PD-L1 expression ≥ 50%, while chemoimmunotherapy is the preferred approach for PD-L1 < 50% [1].

Several chemoimmunotherapy strategies have demonstrated an overall survival (OS) benefit compared to chemotherapy alone in randomized, phase 3 trials:

- Anti-PD-1 agents (pembrolizumab or cemiplimab) combined with histology-driven platinum-based chemotherapy (4 cycles), followed by maintenance with the anti-PD-1 agent (combined with pemetrexed in non-squamous histology) [5–7].
- Dual immune checkpoint blockade with anti-PD-1/anti-CTLA-4 (nivolumab plus ipilimumab), combined with a short course of platinum-based chemotherapy (2 cycles), followed by maintenance with nivolumab plus ipilimumab [8].
- Dual immune checkpoint blockade with anti-PD-L1/anti-CTLA-4 (durvalumab plus tremelimumab), combined with a standard course of platinum-based chemotherapy (4 cycles), followed by maintenance with durvalumab (including a fifth dose of tremelimumab post-chemotherapy, and pemetrexed for non-squamous histology) [9].
- Anti-PD-L1 (atezolizumab) combined with an anti-VEGF (bevacizumab) plus chemotherapy (4 cycles of carboplatin and paclitaxel, followed by maintenance with atezolizumab and bevacizumab), or combined with chemotherapy alone (4 cycles of carboplatin and nab-paclitaxel, followed by atezolizumab maintenance)—limited to non-squamous histology [10, 11].

To date, no direct comparative studies are available between these strategies, aside from a Japanese randomized phase 3 trial (JCOG2007) that evaluated chemotherapy combined with either nivolumab/ipilimumab or pembrolizumab. This study found no significant differences in progression-free survival (PFS) and OS between the two regimens [12]. However, because the enrolled patients were exclusively Asian, these results cannot be directly generalized to Western populations. Additionally, the trial was closed early due to a high incidence of treatment-related deaths in the nivolumab/ipilimumab arm, limiting the possibility of drawing definitive conclusions.

Furthermore, real-world data on the effectiveness and safety of these combinations remain scarce, as real-world populations often differ from those selected under the stringent criteria of randomized trials. Therefore, real-world observational studies can be extremely useful in this context.

Here we report the results of the Real-Combo Lung study, an Italian observational study of two different chemoimmunotherapy combinations (pembrolizumab plus chemotherapy and nivolumab/ipilimumab plus chemotherapy) in patients with non-oncogene-addicted mNSCLC and PD-L1 expression < 50%, in a real-world setting.

Methods

The Real-Combo Lung study is an ambispective, observational study conducted across 23 centers in Italy. The study enrolled patients with mNSCLC who had no *EGFR* mutations or *ALK* rearrangements and a PD-L1 expression level of less than 50%. Patients were treated with chemoimmunotherapy combinations from April 1, 2022, to December 31, 2023. Retrospective data collection was permitted for centers that began enrollment after April 1, 2022. The present analysis was conducted based on a data cut-off of June 30, 2024.

Data were collected anonymously through a clinical record form specifically designed for the study. During the enrollment period, the chemoimmunotherapy combinations approved and funded by the Italian National Health System were limited to pembrolizumab plus chemotherapy and nivolumab/ipilimumab plus chemotherapy.

The primary objective of the study was to assess the effectiveness of chemoimmunotherapy combinations in a real-world setting, evaluated in terms of PFS and OS across the entire population. PFS was defined as the time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurred first. OS was defined as the time from treatment initiation to death from any cause. Patients without events were censored at the date of their last follow-up.

Secondary objectives included safety, assessed by the incidence of treatment-related adverse events. Adverse events were defined and graded according to the NCI CTCAE v. 5.0. Exploratory objectives included evaluating differences in the clinical characteristics and outcomes of patients treated with different chemoimmunotherapy combinations, particularly regarding subgroup defined according to histology (squamous vs. non-squamous) and PD-L1 expression level (< 1% vs. 1–49%), as well as assessing potential prognostic factors in the overall population and in the two treatment cohorts.

Given the descriptive nature of this study, neither statistical hypothesis was formulated nor a sample size calculation was performed. Categorical variables were expressed as frequencies and percentages and compared using Pearson's Chi-squared test or Fisher's exact test. Age was expressed as median and interquartile range (IQR) and compared between groups using the Wilcoxon rank sum test. Kaplan–Meier curves were generated to estimate PFS and OS. Median PFS

and OS, along with their 95% confidence intervals (CIs), were estimated overall and stratified by treatment cohorts. The log-rank test was used to assess statistical differences in survival probabilities between groups. Risk factors for PFS and OS, including age, gender, PD-L1 expression, ECOG status, histology, smoking status, number of comorbidities, baseline steroid use, number of metastatic sites, and presence of CNS, bone, or liver metastases, as well as treatment, were evaluated using univariable Cox regression analysis. Variables with p-values < 0.1, were subsequently included in a multivariable Cox regression model. The proportional hazards assumption was assessed using weighted Schoenfeld residuals. We considered p-values of less than 0.05 as indicating statistical significance. All analyses were performed using R statistical software (version 4.4.1) [13].

The study protocol was approved by the ethics committee at each participating center, and the study was conducted in accordance with Good Clinical Practice guidelines. Written informed consent was obtained from all patients.

Results

The study enrolled 495 patients with mNSCLC without *EGFR* mutations and *ALK* rearrangements, and with PD-L1 expression of < 50%, that started chemoimmunotherapy from April 1, 2022 to December 31, 2023. Of the 495 patients included in the study, 348 (70.3%) were treated with pembrolizumab plus platinum-based chemotherapy and 147 (29.7%) with nivolumab/ipilimumab plus platinum-based chemotherapy.

In the overall population, the median age of the patients was 68.2 years (IQR: 61.3, 73.4). Most patients had ECOG PS of 0–1, and were current or former smokers. The baseline characteristics of the patients are reported in Table 1. In the cohort treated with nivolumab/ipilimumab, there were significantly more patients with tumor harboring PD-L1 expression < 1% (57.6% vs. 39.5%, $p < 0.001$) and treated with baseline steroids (37.3% vs. 23.9%, $p = 0.003$), and fewer patients aged > 75 (11.6% vs. 20.7%, $p = 0.019$), never smokers (4.2% vs. 11.9%, $p = 0.009$) and with bone metastases (27% vs. 37.8%, $p = 0.024$), compared to the cohort treated with pembrolizumab. No other significant differences in the characteristics of the two cohorts were observed, particularly regarding tumor histology, number of comorbidities, ECOG PS, number of metastatic sites or the presence of brain or liver metastases.

Overall, the median follow-up was 11 (95% CI: 10.2 12.2) months. The median PFS was 10.9 (95% CI 9.6–13.0) months, and the median OS was 21.1 (95% CI 16.8–NR) months in the overall population (Fig. 1A, B). In patients with PD-L1 < 1%, median PFS was 9.9 (95% CI 9.3–12.9) and median OS was 16.7 (95% CI 13.5–21.1), whereas in patients with PD-L1 1–49% median PFS was 11.7 (95% CI 9.6–15.7) months, and median OS was not reached.

No significant differences in PFS and OS were observed between the two treatment cohorts (Fig. 2A, B). Specifically, in the pembrolizumab cohort, the median PFS was 11.8 months (95% CI: 9.8–14.3) compared to 9.8 months (95% CI: 7.5–15.7) in the nivolumab/ipilimumab cohort (unadj HR 0.86, 95% CI: 0.67–1.11, $p = 0.3$). The median OS was 21.3 months (95% CI: 16.1–NR) in the pembrolizumab cohort and 20.6 months (95% CI: 15.4–NR) in the nivolumab/ipilimumab cohort (unadj HR 1.03, 95% CI: 0.76–1.39, $p = 0.9$).

At multivariable analysis, ECOG PS ≥ 2, PD-L1 expression < 1%, squamous histology, baseline steroids, and presence of CNS, bone or liver metastases, were significantly associated with a worse outcome, both in terms of PFS and OS. Univariable and multivariable analysis for PFS and OS are shown in Tables 2 and 3.

In subgroups based on histology (squamous and non-squamous) and PD-L1 expression (< 1% and 1–49%), there was no significant difference in terms of PFS between the two treatment cohorts (Supplementary Figs. 1A, B and 2A, B). Regarding OS, there was no difference between the two treatment cohorts according to histology or in the subgroup with PD-L1 expression < 1% (Supplementary Figs. 3A, B, 4A). However, in the subgroup with PD-L1 expression 1–49%, patients treated with nivolumab/ipilimumab had a better median OS compared to those treated with pembrolizumab (NR vs. 22.4 months, unadj HR 2.10, 95% CI: 1.19–3.70, $p = 0.011$) (Supplementary Fig. 4B).

In terms of safety, in the overall population, the incidence of chemotherapy-related adverse events of any grade and grade 3–4 was 63.8 and 14.5%, respectively (Table 4). The incidence of immune-related adverse events (irAEs) of any grade and grade 3–4 was 41.8 and 12.1%, respectively. Chemotherapy-related adverse events were more frequent in the pembrolizumab cohort, both for any grade (71.8% vs. 44.9%, $p < 0.001$) and grade 3–4 (17.8% vs. 6.8%, $p = 0.002$). Conversely, irAEs were more common in the nivolumab/ipilimumab cohort, both for any grade (52.4% vs. 37.4%, $p = 0.002$) and grade 3–4 (21.7% vs. 8.1%, $p < 0.001$). However, no significant differences were observed between the two cohorts in the incidence of adverse events leading to treatment discontinuation or death. Specifically, 42 patients (12.1%) in the pembrolizumab cohort and 20 patients (13.6%) in the nivolumab/ipilimumab cohort discontinued treatment due to toxicity. Overall, two treatment-related deaths were reported, one in each cohort.

Table 1 Patients' characteristics in the overall population and in the two treatment cohorts

Characteristic	Overall $N=495$	Nivo/Ipi $N=147$ (29.7%)	Pembro $N=348$ (70.3%)	p*
Age				**0.025**
Median (range)	68.2 (28—88)	68.4 (45–83)	67.3 (28–88)	
> 75 yo—no. (%)	89 (18.0)	17 (11.6)	72 (20.7)	**0.016**
≤ 75 yo—no. (%)	406 (82.0)	130 (88.4)	276 (79.3)	
Sex—no. (%)				> 0.9
Male	321 (64.8)	95 (64.6)	226 (64.9)	
Female	174 (35.2)	52 (35.4)	122 (35.1)	
Smoking status—no (%)				**0.009**
Current/Former	439 (90.3)	136 (95.8)	303 (88.1)	
Never	47 (9.7)	6 (4.2)	41 (11.9)	
Unknown	9	5	4	
ECOG PS—no. (%)				0.4
0–1	445 (90.1%)	134 (91.8)	311 (89.4)	
≥ 2	49 (9.9%)	12 (8.2)	37 (10.6)	
Unknown	1	1	–	
Number of comorbidities				0.3
0–2	250 (56.7)	76 (60.3)	174 (55.2)	
> 2	191 (43.3)	50 (39.7)	141 (44.8)	
Unknown	54	21	33	
Baseline steroids				**0.003**
Yes	128 (28.1)	53 (37.3)	75 (23.9)	
No	328 (71.9)	89 (62.7)	239 (76.1)	
Unknown	39	5	34	
Histology—no. (%)				0.4
Non-squamous	389 (79.1)	112 (76.7)	277 (80.1)	
Squamous	103 (20.9)	34 (23.3)	69 (19.9)	
Unknown	3	1	2	
PD-L1—no (%)				**< 0.001**
< 1%	219 (44.9)	83 (57.6)	136 (39.5)	
1–49%	269 (55.1)	61 (42.4)	208 (60.5)	
Unknown	7	3	4	
Number of metastatic sites—no (%)				0.075
≤ 2	315 (67)	98 (73.1)	217 (64.6)	
> 2	155 (33)	36 (26.9)	119 (35.4)	
Unknown	25	13	12	
Bone metastases—no (%)				**0.024**
Yes	163 (34.5)	38 (27)	125 (37.8)	
No	309 (65.5)	103 (73)	206 (62.2)	
Unknown	23	6	17	
Liver metastases—no (%)				0.5
Yes	40 (8.5	14 (9.9)	26 (7.9)	
No	431 (91.5)	127 (90.1)	304 (92.1)	
Unknown	24	6	18	
CNS metastases—no (%)				0.8
Yes	89 (18.8)	26 (18.2)	63 (19)	
No	385 (81.2)	117 (81.8)	268 (81)	
Unknown	21	4	17	

*Wilcoxon rank sum test; Pearson's Chi-squared test

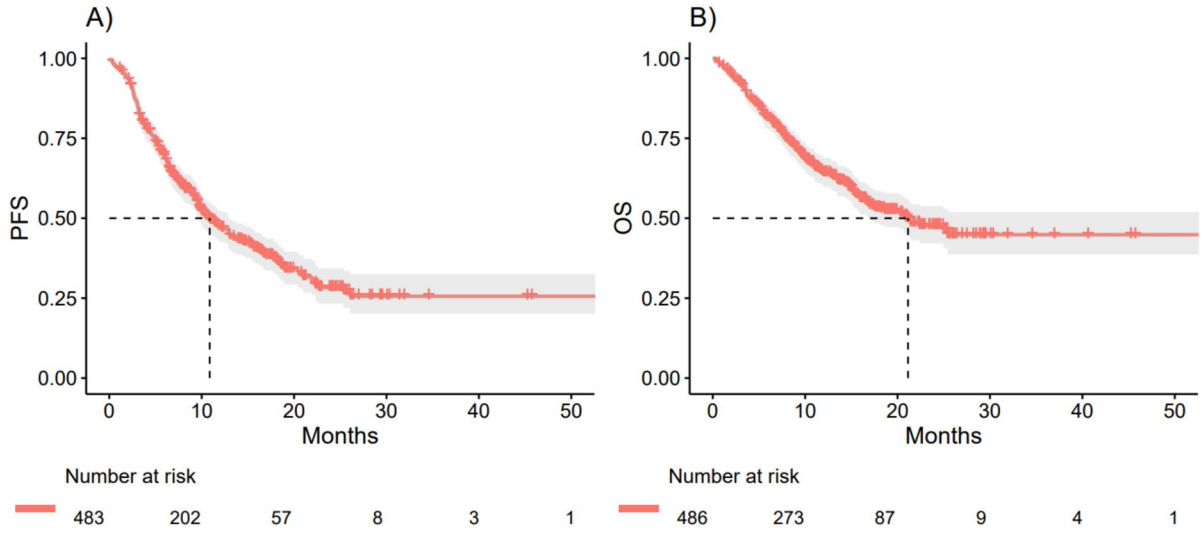

Fig. 1 PFS (**A**) and OS (**B**) in the overall population. PFS: progression free survival. *OS* overall survival

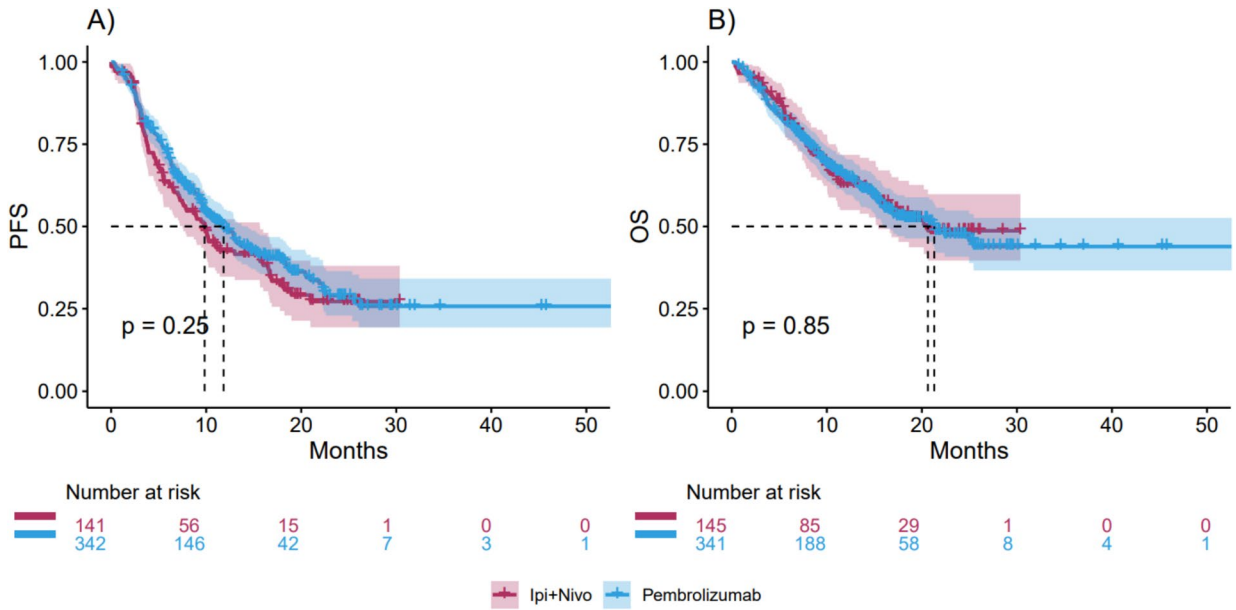

Fig. 2 PFS (**A**) and OS (**B**) in the two treatment cohorts. *PFS* progression free survival, *OS* overall survival. *p* value refers to the log-rank test

Discussion

This observational study reported median PFS of 10.9 (95% CI 9.6–13) and OS of 21.1 (95% CI 16.8–NR) months for patients with mNSCLC without *EGFR* mutations and *ALK* rearrangements and with PD-L1 expression level < 50% treated with first-line chemoimmunotherapy combinations, specifically pembrolizumab plus chemotherapy and nivolumab/ipilimumab plus chemotherapy.

In our study, patient characteristics differed from those of the highly selected populations enrolled in randomized clinical trials (RCTs) investigating pembrolizumab plus chemotherapy (KEYNOTE-189 and KEYNOTE-407 for non-squamous and squamous histology, respectively) [14, 15] or nivolumab/ipilimumab plus chemotherapy (CheckMate-9LA, both histologies) [16], compared with chemotherapy alone. Notably, patients with ECOG PS ≥ 2 or receiving baseline steroids, who were generally excluded from these RCTs, were included in our study, representing 10% and 28% of the entire population, respectively. Moreover, the

Table 2 Univariable and multivariable Cox proportional hazards regression models for PFS

Variable	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*p*
Age		0.3	–	–
< 75	–			
≥ 75	0.84 (0.61–1.16)			
Sex		0.7	–	–
Female	–			
Male	1.04 (0.82–1.33)			
Smoking status		0.7	–	–
Current/Former	–			
Never	0.93 (0.63–1.37)			
ECOG PS		**< 0.001**		**0.001**
0–1	–		–	
≥ 2	2.49 (1.79–3.48)		1.80 (1.25–2.57)	
Number of comorbidities		0.6	–	–
0–2	–			
> 2	0.93 (0.73–1.20)			
Baseline steroids		**< 0.001**		**0.004**
No	–		–	
Yes	1.86 (1.44–2.40)		1.51 (1.14–1.99)	
Histology		**0.003**		**< 0.001**
Non-squamous	–		–	
Squamous	1.50 (1.15–1.97)		1.76 (1.31–2.37)	
PD-L1—no (%)		0.063		0.076
< 1%	–		–	
1–49	0.80 (0.63–1.01)		0.80 (0.62–1.02)	
Number of metastatic sites		**< 0.001**		0.14
≤ 2	–		–	
> 2	1.56 (1.22–1.99)		1.24 (0.93–1.66)	
Bone metastases		**< 0.001**		**0.016**
No	–		–	
Yes	1.53 (1.20–1.95)		1.40 (1.06–1.85)	
Liver metastases		0.066		**0.027**
No	–		–	
Yes	1.46 (0.98–2.19)		1.65 (1.06–2.56)	
CNS metastases		**0.003**		**0.018**
No	–		–	
Yes	1.54 (1.16–2.05)		1.49 (1.07–2.07)	
Treatment		0.3	–	–
Ipi/nivo	–			
Pembro	0.86 (0.67–1.11)			

HR hazard ratio, *CI* confidence interval

median age in our study was higher than that reported in RCTs (68.2 vs. 65 years), with 18% of patients aged > 75 years [14–16].

Despite these differences, the PFS and OS observed in our study were consistent with those reported in pivotal RCTs. Specifically, median PFS was 9.0 months (95% CI: 8.1–10.4), 8.0 months (95% CI: 6.3–8.5), and 6.7 months (95% CI: 5.6–8.0), while median OS was 22.0 months (95% CI: 19.5–24.5), 17.2 months (95% CI: 14.4–19.7), and 15.8 months (95% CI: 13.9–19.7) in the overall populations of KEYNOTE-189 [14], KEYNOTE-407 [15], and CheckMate-9LA [16], respectively. It is worth noting that these RCTs included not only patients with PD-L1 < 50% but also those with PD-L1 ≥ 50%, a subgroup that generally derives greater benefit from immunotherapy.

When considering different PD-L1 subgroups, in the present study patients with PD-L1 1–49% had a median PFS of 11.7 months (95% CI: 9.6–15.7), while median

Table 3 Univariable and multivariable Cox proportional hazards regression models for OS

Variable	Univariate HR (95% IC)	*p*	Multivariate HR (95% IC)	*p*
Age		0.6	–	
< 75	–			
≥ 75	1.09 (0.76–1.56)			
Sex		0.3	–	
Female	–			
Male	1.17 (0.87–1.58)			
Smoking status		0.061		0.074
Current/former	–		–	
Never	0.58 (0.33–1.03)		0.59 (0.33–1.05)	
ECOG PS		**< 0.001**		**0.021**
0–1	–		–	
≥ 2	2.52 (1.74–3.67)		1.64 (1.08–2.49)	
Number of comorbidities		0.8	–	
0–2	–			
> 2	1.05 (0.78–1.40)			
Baseline steroids		**< 0.001**		**0.010**
No	–		–	
Yes	2.21 (1.65–2.96)		1.52 (1.11–2.10)	
Histology		**0.046**		**0.007**
Non-squamous	–		–	
Squamous	1.39 (1.01–1.92)		1.64 (1.15–2.35)	
PD-L1—no (%)		**0.021**		**0.029**
< 1%	–		–	
1–49	0.72 (0.55–0.95)		0.72 (0.53–0.97)	
Number of metastatic sites		**0.002**		0.7
≤ 2	–		–	
> 2	1.56 (1.17–2.09)		1.07 (0.76–1.50)	
Bone metastases				**0.003**
No	–		–	
Yes	1.76 (1.32–2.34)	**< 0.001**	1.64 (1.18–2.27)	
Liver metastases		**0.003**		**0.003**
No	–		–	
Yes	1.93 (1.26–2.96)		2.02 (1.26–3.24)	
CNS metastases		**< 0.001**		**0.001**
No	–		–	
Yes	1.97 (1.43–2.70)		1.86 (1.28–2.69)	
Treatment		0.9	–	–
Ipi/nivo	–			
Pembro	1.03 (0.76–1.39)			

HR hazard ratio, *CI* confidence interval

OS was not reached (95% CI: 21.3–NR). In the KEYNOTE-189, KEYNOTE-407, and CheckMate-9LA trials, median PFS in this subgroup was 9.4 months (95% CI: 8.1–13.8), 8.2 months (95% CI: 6.2–11.4), and 6.7 months (95% CI: 4.5–8.5), respectively, while median OS was 21.8 months (95% CI: 17.7–25.6), 18.0 months (95% CI: 13.6–22.8), and 15.2 months (95% CI: 12.6–21.2) [14–16].

Among patients with PD-L1 < 1%, we observed a median PFS of 9.9 months (95% CI: 9.3–12.9) and a median OS of 17.7 months (95% CI: 13.7–20.3). In the KEYNOTE-189, KEYNOTE-407, and CheckMate-9LA trials, median PFS in this subgroup was 6.2 months (95% CI: 4.9–8.3), 6.3 months (95% CI: 6.1–8.5), and 5.8 months (95% CI: 4.4–7.7), respectively, while median OS was 17.2 months (95% CI: 13.8–22.8), 15.0 months (95% CI: 13.2–19.4), and 17.7 months (95% CI: 13.7–20.3) [14–16].

In our study, multivariable analysis identified ECOG PS ≥ 2, PD-L1 expression < 1%, squamous histology,

Table 4 Treatment-related adverse events

Adverse events	Overall, *n* (%) *N* = 495	Ipi/Nivo, *n* (%) *N* = 147	Pembro, *n* (%) *N* = 348	*p**
Chemotherapy-related				
Any grade	316 (63.8)	66 (44.9)	250 (71.8)	**< 0.001**
G3–G4	72 (14.5)	10 (6.8)	62 (17.8)	**0.002**
Neutropenia				
Any grade	92 (18.6)	22 (15.0)	70 (20.1)	ns
G3–G4	32 (6.5)	8 (5.4)	24 (6.9)	ns
Thrombocytopenia				
Any grade	34 (6.9)	5 (3.4)	29 (8.3)	**0.047**
G3–G4	8 (1.6)	1 (0.7)	7 (2.0)	ns
Anemia				
Any grade	176 (35.6)	26 (17.7)	150 (43.1)	**< 0.001**
G3–G4	23 (4.6)	2 (1.4)	21 (6.0)	**0.024**
Nausea/vomiting				
Any grade	91 (18.4)	23 (15.6)	68 (19.5)	ns
G3–G4	5 (1.0)	0 (0.0)	5 (1.4)	ns
Peripheral neuropathy				
Any grade	29 (5.9)	8 (5.4)	21 (6.0)	Ns
G3–G4	0 (0.0)	0 (0.0)	0 (0.0)	–
Immune-related				
Any grade	207 (41.8)	77 (52.4)	130 (37.4)	**0.002**
G3–G4	60 (12.1)	32 (21.7)	28 (8.1)	**< 0.001**
Endocrine				
Any grade	48 (9.7)	23 (15.6)	25 (7.2)	**0.004**
G3–G4	7 (1.4)	6 (4.1)	1 (0.3)	**0.003**
Rash				
Any grade	57 (11.5)	24 (16.3)	33 (9.5)	**0.029**
G3–G4	9 (1.8)	4 (2.7)	5 (1.4)	ns
Hepatitis				
Any grade	27 (5.5)	12 (8.2)	15 (4.3)	ns
G3–G4	9 (1.8)	7 (4.8)	2 (0.6)	**0.004**
Colitis				
Any grade	56 (11.3)	27 (18.4)	29 (8.3)	**0.001**
G3–G4	16 (3.2)	8 (5.4)	8 (2.3)	ns
Pneumonitis				
Any grade	25 (5.1)	7 (4.8)	18 (5.2)	ns
G3–G4	8 (1.6)	3 (2.0)	5 (1.4)	ns
Leading to discontinuation	62 (12.5)	20 (13.6)	42 (12.1)	0.66
Leading to death	2 (0.4)	1 (0.7)	1 (0.3)	0.51

*Pearson's Chi-squared test; Fisher's exact test

baseline steroid use, and the presence of CNS, bone, or liver metastases as significant predictors of worse PFS and OS. This result is consistent with expectations, as these characteristics are well-established prognostic factors for NSCLC patients receiving chemoimmunotherapy. Similar findings have also been reported in other observational studies in this setting. [17–23].

Notably, age seemed not to have a significant prognostic impact, as patients aged ≥ 75 had a similar outcome compared to younger patients, in terms both of PFS (HR 0.84; 95% CI 0.61–1.16) and OS (HR 1.09, 95% CI 0.76–1.56). Given that patients aged ≥ 75 years represented a non-negligible proportion (89 patients, 18%) of the whole population enrolled in our study, this finding reliably suggests that chemoimmunotherapy may be an effective option in this age group. This is particularly relevant, as the efficacy of chemoimmunotherapy combinations in elderly patients with mNSCLC remains unconclusive. In

the KEYNOTE-189 and KEYNOTE-407 studies, HR for OS in patients aged ≥ 65 was 0.64 (95% CI 0.43–0.95) and 0.74 (95% CI 0.51–1.07), respectively, indicating that these patients may derive a benefit from chemoimmunotherapy comparable to that observed in younger patients [5, 6]. However, HR for patients aged ≥ 75 years was not reported, raising uncertainties about the efficacy of chemoimmunotherapy combinations in very elderly patients. In contrast, the Checkmate-9LA study reported an HR for OS of 1.21 (95% CI 0.69–2.12) in patients aged ≥ 75, suggesting a limited or even absent benefit from chemoimmunotherapy compared to chemotherapy alone [8].

Similarly, real-world studies indicate that chemoimmunotherapy combinations may not provide additional benefit over ICI monotherapy in elderly patients, while posing a significant risk of toxicity. A Chinese retrospective study of 110 patients with mNSCLC aged ≥ 75 found no significant differences in median PFS (5.3 vs. 5.5 months, $p = 0.70$) or OS (10.7 vs. 20.3 months, $p = 0.995$) between those treated with chemoimmunotherapy ($n = 20$) and those receiving ICI alone ($n = 30$). However, the chemoimmunotherapy group had a higher treatment discontinuation rate due to toxicity (40% vs. 20%) ($n = 30$) [24]. Another retrospective study of 156 mNSCLC patients aged ≥ 70 compared pembrolizumab plus chemotherapy ($n = 95$) with pembrolizumab monotherapy ($n = 61$, all with PD-L1 > 50%). No differences were observed in median PFS (7 vs. 8 months) or OS (16 vs. 14 months), but chemoimmunotherapy was associated with significantly higher rates of adverse events (91% vs. 51%, $p < 0.001$), treatment discontinuation (37% vs. 21%, $p = 0.034$), and hospitalization (56% vs. 23%, $p < 0.001$) [25].

In terms of PFS and OS, the results of our study also compare favorably with those of other real-world studies on chemoimmunotherapy combinations for mNSCLC, which reported median PFS ranging from 6.2 to 8.6 months and median OS ranging from 11.8 to 24 months [17–23]. The relatively wide variability in survival outcomes across observational studies can likely be attributed to differences in study design, median follow-up duration, specific chemoimmunotherapy regimens, and the prognostic profile of enrolled patients, including ECOG PS, histology, disease burden, comorbidities, and the distribution of PD-L1 expression levels.

Among these observational studies, most focused on non-squamous histology and pembrolizumab-based chemoimmunotherapy, thus real-world data on squamous histology or nivolumab/ipilimumab plus chemotherapy are still limited. Specifically, an international real-world study from USA, Europe and Japan, reported the outcomes of 430 patients with NSCLC treated with different first-line chemoimmunotherapy combinations, including anti-PD-(L)1 plus chemotherapy (84.6%), anti-PD-(L)1 plus anti-CTLA-4 with or without chemotherapy (11.9%), and anti-PD-(L)1 plus chemotherapy and anti-vascular endothelial growth factor receptor (3.5%) [23]. The median OS was 21.7 months (PD-L1 < 1%: 18.3 months; PD-L1 1–49%: 21.6 months; PD-L1 ≥ 50%: 24.0 months). However, the study was limited to non-squamous histology and the authors did not report the outcomes according to the specific chemoimmunotherapy regimens.

Thus, to our knowledge, this is the first real-world study that included both squamous and non-squamous histology and reported the outcomes of patients treated with either pembrolizumab plus chemotherapy or nivolumab/ipilimumab plus chemotherapy. Specifically, compared with the pembrolizumab cohort, patients treated with nivolumab/ipilimumab were younger, more likely to have tumors with PD-L1 expression < 1%, have a history of current or former smoking, and receive baseline steroids, while they were less likely to have bone metastases. Despite these differences, we did not observe any differences in PFS and OS between the two cohorts. This finding is consistent with the results of the only randomized study comparing pembrolizumab with nivolumab/ipilimumab plus chemotherapy, although those results were unconclusive because the study was prematurely closed due to a high incidence of treatment-related deaths in the nivolumab/ipilimumab arm [12].

When considering PD-L1 subgroups in our study, there was no difference in PFS and OS between the two treatment cohorts in patients with PD-L1 < 1%, whereas in patients with PD-L1 1–49% median OS was longer in the nivolumab/ipilimumab cohort compared to the pembrolizumab cohort. This observation contrasts with indirect comparisons between randomized clinical trials. A recently analysis based on reconstructed individual patients data from Kaplan-Maier curves of pivotal phase 3 trials reported that, in patients with PD-L1 < 1%, nivolumab/ipilimumab plus chemotherapy was associated with longer restricted mean survival time (RMST) compared to pembrolizumab plus chemotherapy in squamous histology (24.9 months vs. 22.8 months). In contrast, in patients with PD-L1 > 1% pembrolizumab plus chemotherapy achieved better RMST than nivolumab/ipilimumab, both in squamous and non-squamous histology [26]. Therefore, our results in the population with PD-L1 1–49% should be interpreted with caution. Without randomization, an altered distribution of known or unknown prognostic factors, including difficulty-to-quantify variables—such as tumor burden, severity of disease-related symptoms or general clinical conditions beyond ECOG PS—may have led to the selection of a more favorable population in the cohort of patients with PD-L1 1–49% treated with nivolumab/ipilimumab, potentially explaining the observed differences in outcomes. Alternatively, this difference may be purely due to chance. A definitive conclusion on the differential efficacy

of these regimens across PD-L1-defined subgroups can only be drawn from randomized studies.

As expected, the toxicity profiles were significantly different between the two treatment cohorts. Specifically, irAEs were more frequent in the nivolumab/ipilimumab cohort, where patients received dual immune checkpoint blockade, whereas chemotherapy-related adverse events were more common in the pembrolizumab cohort, where patients underwent a longer course of chemotherapy. However, toxicity was acceptable and manageable in both cohorts, with no significant differences in events leading to treatment discontinuation (12.1% in the nivolumab/ipilimumab and 13.6% in the pembrolizumab cohort) or to death.

Our study has several limitations. First, it is a non-randomized observational study, and the comparison between the treatment cohorts may be affected by selection bias and unmeasured confounding factors. Second, PD-L1 expression was not centrally assessed, leading to heterogeneity in methods and interpretation across centers. Third, the median follow-up was relatively short, potentially limiting the ability to detect delayed survival benefits. Fourth, as with all retrospective studies, adverse events may have been underreported and should therefore be interpreted with caution. In addition, although molecular characteristics—which may influence prognosis and treatment outcomes—were collected, a detailed analysis was not included in the present study and will be reported separately. Finally, the impact of post-progression treatments on OS was not evaluated. Overall, the findings of this study should be interpreted in light of the inherent limitations of non-randomized designs. Although covariate adjustment preserved the full sample size and statistical power, unmeasured confounders not accounted for in the analyses may have influenced comparisons between treatment cohorts.

Conclusions

In conclusion, this is the first real-world observational study to evaluate the outcomes of two different first-line chemoimmunotherapy treatment for mNSCLC with PD-L1 expression ≤ 50%. We observed PFS and OS consistent with those reported by correspondent phase 3 randomized clinical trials, with acceptable and manageable toxicity. Interestingly, elderly patients achieved similar PFS and OS to younger patients. Despite the limitations of a non-randomized study, we found no significant differences in real-world effectiveness between pembrolizumab and nivolumab/ipilimumab, although the safety profiles differed.

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Data availability All data supporting the results of the study can be found in the article. Researchers can contact the corresponding author of this article by email and indicate the required research materials and purpose. We will be glad to provide relevant materials for this study after approval and discussion.

Declarations

Conflict of interest Alessandro Inno: honoraria/advisory board roles from Amgen, Astra Zeneca, Merck Sharp-Dome, Novartis, Roche. Carlo Genova: honoraria/advisory board roles from Amgen, Astra Zeneca, Bristol-Myers-Squibb, Daiichi-Sankyo, Eli Lilly, Merck-Sharp-Dohme, Novartis, Pierre Fabre, Regeneron, Roche, Takeda. The other authors declare no conflicts of interest.

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