

Original Article

Concomitant Metformin Use During Nivolumab Therapy for Advanced Non-Small Cell Lung Cancer: A Real-World Analysis of Survival Outcomes

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ABSTRACT

Aim: The effect of metformin on antitumor immunity has been investigated in experimental studies, but its clinical value during immune checkpoint inhibitor therapy remains uncertain. This study examined whether metformin use was associated with survival outcomes in patients with advanced non-small cell lung cancer (NSCLC) who were receiving nivolumab.

Methods: We retrospectively reviewed the medical records of patients with advanced or metastatic NSCLC who received nivolumab after platinum-based chemotherapy between December 2022 and December 2025. Patients were categorized according to metformin use during nivolumab therapy. The main endpoint was overall survival from nivolumab initiation. Secondary outcomes included overall survival from initial diagnosis, adverse event categories, and progression-free survival (PFS) from nivolumab initiation. Survival outcomes were assessed using Kaplan-Meier estimation, the log-rank test, and Cox regression.

Results: The cohort included 119 patients, of whom 33 (27.7%) used metformin. Compared with non-users, metformin users had higher body mass index, a higher proportion with performance status 2, and higher baseline neutrophil counts. Median overall survival from nivolumab initiation was 9.26 months in the non-metformin group and 9.00 months in the metformin group (log-rank $p=0.061$). After adjustment for Eastern Cooperative Oncology Group performance status, sex, body mass index, and neutrophil count, metformin use was not significantly associated with the risk of death (adjusted hazard ratio=1.15; 95% confidence interval, 0.66-2.03; $p=0.620$). In an exploratory analysis, overall survival from diagnosis did not differ significantly between groups (19.4 vs. 20.1 months; log-rank $p=0.348$). Adverse event categories did not differ significantly. PFS was shorter in unadjusted analysis but was no longer statistically significant after multivariable adjustment.

Conclusion: In this real-world cohort, metformin use during nivolumab therapy was not associated with longer overall survival. The initial difference in PFS appeared to be influenced by baseline differences between groups.

Keywords: Non-small cell lung cancer, nivolumab, metformin, overall survival, progression-free survival

Introduction

Lung cancer is one of the most common malignancies worldwide and remains responsible for more cancer-related deaths than any other tumor type [1]. Non-small cell lung cancer (NSCLC) constitutes the largest subgroup of lung cancers, representing approximately 85% of all cases [2]. In advanced NSCLC without targetable molecular alterations, immune checkpoint blockade has become an integral part of current systemic treatment strategies [3]. Nivolumab is an IgG4 antibody that inhibits the programmed death-1 pathway

and is an established treatment option following platinum-based chemotherapy for patients with advanced NSCLC. In the phase III CheckMate 017 and CheckMate 057 trials, nivolumab provided longer survival than docetaxel in both squamous and nonsquamous NSCLC, with a more favorable safety profile [4-6]. Nevertheless, outcomes achieved with nivolumab in routine practice may vary according to patient-related factors such as performance status, comorbidities, and concomitant medications.

Metformin is a widely prescribed first-line oral agent for the management of type 2 diabetes mellitus and has attracted

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increasing interest in oncology because of its potential anticancer and immunomodulatory properties [7,8]. Beyond its metabolic effects, preclinical studies and emerging clinical observations suggest that metformin may influence the tumor immune microenvironment and thereby modify responses to immune checkpoint inhibitors [9,10]. Several mechanisms have been proposed, including downregulation of Programmed death-ligand 1 (PD-L1) expression, reduction of tumor oxygen consumption, attenuation of tumor hypoxia, and enhancement of cytotoxic T-cell activity [11,12]. Metformin has also been proposed to affect the gut microbiota, which may represent another pathway through which it could influence antitumor immune responses [13]. Nevertheless, the extent to which these biological effects translate into clinically meaningful benefit during immune checkpoint inhibitor therapy remains unclear.

Given this background, we investigated whether concomitant metformin use was associated with survival outcomes in patients with advanced NSCLC who were receiving nivolumab. Overall and progression-free survival (PFS) from nivolumab initiation were defined as the primary and secondary endpoints, respectively.

Methods

Study Design

We performed a single-center retrospective review of patients with advanced or metastatic NSCLC who were treated with nivolumab between December 2022 and December 2025. Inclusion required age ≥ 18 years, histologic confirmation of NSCLC, previous platinum-based chemotherapy, and receipt of nivolumab as later-line immunotherapy. Patients were included only if they had received at least two cycles of nivolumab for metastatic disease. This criterion was used to ensure a minimum level of treatment exposure and evaluable follow-up after nivolumab initiation. Eight patients who received fewer than two cycles of nivolumab were excluded. All patients received nivolumab as monotherapy at a dose of 240 mg every two weeks.

Patients were included if baseline clinical data, laboratory results, treatment details, adverse event records, and survival status were available. Patients were excluded if they had missing clinical or survival data, a second active malignancy, an active infection at nivolumab initiation, or targetable driver alterations, including EGFR, ALK, or ROS1. Patients receiving glucose-lowering agents other than metformin were also excluded. Patients with type 2 diabetes mellitus who were receiving oral metformin at a daily dose of 500–2000 mg before and during nivolumab therapy were classified as metformin users. Patients who initiated metformin after starting nivolumab were excluded. The comparison group consisted exclusively of patients without diabetes.

PD-L1 status, when reported, was recorded from pathology reports. Adverse events were identified retrospectively from clinical records and classified according to the documented

event category. Common Terminology Criteria for Adverse Events grades and specific immune-related adverse event classifications were not consistently available. Therefore, the adverse-event analysis was considered exploratory. Ethics approval was obtained from the Ankara Etlik City Hospital Ethics Committee (approval no: AEŞH-BADEK1-2025-128, date: 14 May 2025). Owing to the retrospective design and use of existing patient records, individual informed consent was waived.

Data Collection and Outcomes

Clinical information was retrieved from hospital electronic records. The variables reviewed included age at diagnosis, sex, Eastern Cooperative Oncology Group performance status, smoking history, histologic subtype, metastatic sites, PD-L1 expression when available, body mass index, baseline laboratory values, number of nivolumab administrations, metformin use, adverse event records, and survival status. Baseline laboratory values were defined as measurements obtained within the 7 days before nivolumab initiation. The primary survival endpoint was overall survival, defined as the time from nivolumab initiation (first dose) to death from any cause. Overall survival from initial diagnosis was evaluated as a separate exploratory endpoint. Patients still alive at the end of follow-up were censored at their last documented visit. Adverse events were collected from clinical records and classified according to the recorded event type. PFS was analyzed as a secondary endpoint, defined as the time from nivolumab initiation to documented disease progression or death from any cause. Radiological progression was determined retrospectively from imaging reports and clinical records documenting disease progression. Patients without progression or death were censored at their final follow-up visit. The database cutoff date for survival follow-up was June 30, 2026.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA), and R software (R Foundation for Statistical Computing, Vienna, Austria). Normality of continuous variables was assessed using the Shapiro-Wilk test. Variables with normal distribution were summarized as mean $\pm$ standard deviation, while non-normally distributed variables were summarized as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages.

For comparisons between metformin groups, continuous variables were analyzed using the independent-samples t-test or Mann-Whitney U test according to data distribution. Categorical variables were assessed using Pearson's chi-square test, Fisher's exact test, or the Monte Carlo exact test, as appropriate.

Overall survival was estimated using the Kaplan-Meier approach, and comparisons between metformin groups were performed with the log-rank test. For overall survival measured from nivolumab initiation, the association between

metformin use and mortality risk was additionally evaluated using univariable and multivariable Cox proportional hazards regression. The multivariable model included metformin use, Eastern Cooperative Oncology Group (ECOG) performance status, sex, body mass index, and neutrophil count, which corresponded to the baseline variables that differed significantly between the metformin groups. Effect estimates were reported as hazard ratios with 95% confidence intervals (CIs). A two-sided *p* value of less than 0.05 was considered statistically significant.

For PFS, the relationship between metformin use and event risk was assessed with univariate and multivariable Cox regression analyses, and effect sizes were expressed as hazard ratios with 95% CIs. Model assumptions were evaluated using Schoenfeld residuals, with no relevant violations observed for the variables in the multivariable model. Baseline group differences were further addressed using propensity-score-based inverse probability of treatment weighting (IPTW) with stabilized weights. The propensity model included ECOG performance status, sex, body mass index, and neutrophil count; these variables were selected because they differed significantly between the metformin groups at baseline. Covariate balance after weighting was assessed using standardized mean differences (SMDs), with an absolute SMD <0.10 considered indicative of adequate balance. As a sensitivity analysis, weights were trimmed at the 1st and 99th percentiles.

Results

A total of 119 patients with advanced NSCLC who were treated with nivolumab were included. The median age was 66 years, and most patients were male. Stage IV disease was present at diagnosis in 58.0% of patients, while ECOG performance status of 1 was observed in 91.6% of patients. The most common histology was adenocarcinoma, followed by squamous cell carcinoma. Metformin was used by 33 patients (27.7%) during nivolumab therapy. No adverse events were documented in 70.6% of patients. Overall, baseline data are presented in Table 1.

Compared with non-users, patients receiving metformin were more often female (33.3% vs. 11.6%; *p*=0.005) and more frequently had an ECOG performance status of 2 (24.2% vs. 2.3%; *p*=0.001). Body mass index (BMI) was also higher among metformin users [27.34 (24.89-29.69) vs. 23.82 (21.49-26.05) kg/m²; *p*<0.001]. Baseline neutrophil count was also higher in the metformin group [5.72 (4.38-8.11) vs. 4.78 (3.48-6.22) ×10³/μL; *p*=0.032]. No statistically significant between-group differences were observed in stage at diagnosis, smoking status, histologic subtype, PD-L1 expression, metastatic sites, chemotherapy regimen, number of chemotherapy cycles, number of nivolumab administrations, hemoglobin, albumin, lymphocyte count, platelet count, or distribution of adverse events. Baseline characteristics by metformin status are presented in Table 2.

The median observed follow-up time after nivolumab initiation was 10.12 months (IQR, 4.73-17.15). During follow-up, 89

deaths (74.8% of the cohort) were recorded. The median overall survival from nivolumab initiation was 9.26 months (95% CI, 7.25-11.27). The corresponding median values were 9.26 months (95% CI, 6.97-11.56) for non-users and 9.00 months (95% CI, 4.42-13.58) for metformin users. Survival measured from nivolumab initiation did not differ significantly by metformin use (log-rank *p*=0.061). In univariable Cox regression, the HR for metformin use was 1.54 (95% CI, 0.98-2.44; *p*=0.064). After adjustment for ECOG performance status, sex, body mass index, and neutrophil count, metformin use was not significantly associated with the risk of death (adjusted HR=1.15; 95% CI, 0.66-2.03; *p*=0.620). ECOG performance status 2 (adjusted HR=2.55; 95% CI, 1.20-5.40; *p*=0.014) and higher neutrophil count (adjusted HR=1.19; 95% CI, 1.09-1.30; *p*<0.001) were independently associated with a higher risk of death. Overall survival, calculated from nivolumab initiation, is summarized in Table 3.

In an exploratory analysis, overall survival from diagnosis was assessed in all 119 patients, among whom 89 (74.8%) deaths occurred during follow-up. The median value was 19.7 months (95% CI, 17.53-21.96) in the whole cohort. By metformin use status, the median survival from diagnosis was 19.4 months (95% CI, 16.51-22.38) among non-users and 20.1 months (95% CI, 17.15-23.13) among metformin users. No significant difference was observed between groups (log-rank *p*=0.348). Findings are presented in Table 4.

Nivolumab PFS, stratified by metformin status, is shown in Table 5. In the overall cohort, 103 of 119 patients (86.6%) experienced PFS events, with a median PFS of 4.80 months (95% CI, 3.80-5.80). In univariable analysis, metformin users had a shorter PFS than non-users [3.81 vs. 5.45 months; log-rank *p*=0.008; HR=1.77; 95% CI, 1.15-2.71; *p*=0.009]. After adjustment for ECOG performance status, sex, BMI, hemoglobin, albumin, and neutrophil count, the association weakened and was no longer statistically significant [adjusted HR=1.10; 95% CI, 0.65-1.87; *p*=0.711; Table 6]. These findings suggest that the unadjusted difference in PFS may have been influenced by baseline clinical and laboratory differences between the groups, rather than reflecting a direct effect of metformin. Propensity-score-based IPTW sensitivity analyses produced estimates in the same direction; however, statistical significance differed by the weighting approach [stabilized-weight HR=1.49; 95% CI, 0.96-2.32; *p*=0.078; weight-trimmed HR=1.58; 95% CI, 1.01-2.48; *p*=0.045; Table 6]. Covariate balance improved after stabilized weighting, but adequate balance was not achieved for all variables; the absolute SMDs after weighting were 0.246 for ECOG performance status, 0.036 for sex, 0.109 for body mass index, and 0.191 for neutrophil count. Accordingly, some residual imbalance and uncertainty remained across the sensitivity analyses. Assessment using Schoenfeld residuals did not indicate a violation of the proportional hazards assumption for metformin use or other covariates in the multivariable model (all *p*>0.10). Therefore, the PFS results should be interpreted together with the primary overall survival findings and in the context of baseline group imbalances.

Table 1. Baseline clinical and demographic characteristics of the overall cohort

Variable	Overall cohort
Age at diagnosis, years	66 (58-69)
Sex	
Female	21 (17.6)
Male	98 (82.4)
Stage at diagnosis	
II	8 (6.7)
III	42 (35.3)
IV	69 (58.0)
ECOG performance status	
1	109 (91.6)
2	10 (8.4)
Smoking status	
Never smoker	17 (14.3)
Former smoker	51 (42.9)
Current smoker	51 (42.9)
Smoking exposure, pack-years	45 (35-60)
Histology	
Adenocarcinoma	53 (44.5)
Squamous cell carcinoma	49 (41.2)
Other	17 (14.3)
PD-L1 expression, %	1 (0-20)
PD-L1 expression category	
<1%	52 (49.1)
1-49%	36 (34.0)
≥50%	18 (17.0)
Brain metastasis	
No	90 (75.6)
Yes	29 (24.4)
Contralateral lung metastasis	
No	84 (70.6)
Yes	35 (29.4)
Adrenal metastasis	
No	101 (84.9)
Yes	18 (15.1)
Bone metastasis	
No	77 (64.7)
Yes	42 (35.3)
Liver metastasis	
No	109 (91.6)
Yes	10 (8.4)
Pleural metastasis	
No	101 (84.9)
Yes	18 (15.1)
Mediastinal metastasis	
No	68 (57.1)
Yes	51 (42.9)
Number of metastatic sites	2 (1-2)
Number of metastatic sites category	
1	47 (39.5)
2	61 (51.3)
≥3	11 (9.2)

Table 1. Continued

Variable	Overall cohort
First-line/adjvant chemotherapy regimen	
Carboplatin-paclitaxel	77 (64.7)
Gemcitabine-cisplatin	20 (16.8)
Cisplatin-pemetrexed	22 (18.5)
Number of first-line/adjvant chemotherapy cycles	6 (4-6)
Metformin use	
No	86 (72.3)
Yes	33 (27.7)
Height, m	1.66±0.08
Weight, kg	68 (60-76)
BMI, kg/m ²	24.49 (22.04-27.55)
Hemoglobin, g/dL	12.12±1.99
Albumin, g/L	39.82±4.87
Lymphocyte count, ×10 ³ /μL	1.48 (1.06-2.13)
Neutrophil count, ×10 ³ /μL	4.98 (3.90-6.77)
Platelet count, ×10 ³ /μL	263 (213-343)
Number of nivolumab administrations	7 (6-18)
Adverse event category	
None	84 (70.6)
Gastrointestinal	8 (6.7)
Respiratory	6 (5.0)
Dermatologic	3 (2.5)
Renal	2 (1.7)
Thyroid	11 (9.2)
Hematologic	5 (4.2)
Values are presented as mean±standard deviation, median (interquartile range), or n (%), as appropriate. Percentages were calculated using available data. PD-L1 expression category was available for 106 patients, and smoking exposure was available for 102 patients. ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, PD-L1: Programmed death-ligand 1	

Discussion

In this real-world analysis of patients with advanced NSCLC treated with nivolumab, concomitant use of metformin was not associated with improved overall survival. Documented adverse event categories were also comparable by metformin status. For PFS, metformin users showed shorter survival in the unadjusted analysis; however, this association lost statistical significance after adjustment for baseline clinical and laboratory variables. These findings suggest that the biologically plausible interaction between metformin and antitumor immunity may not translate into a measurable survival advantage among patients receiving nivolumab in routine clinical practice.

The literature regarding the relationship between metformin and immune checkpoint inhibitors remains inconsistent. NSCLC-focused retrospective studies, such as those by Surmeli et al. [14] and Afzal et al. [15], have suggested that concomitant metformin use may be associated with favorable immunotherapy outcomes. Among these studies, Surmeli et al. [14] evaluated a closely comparable cohort of patients

Table 2. Baseline characteristics according to metformin use

Variable	Non-metformin (n=86)	Metformin (n=33)	p value
Age at diagnosis, years	63.52±8.52	66.42±6.82	0.083
Sex			0.005
Female	10 (11.6)	11 (33.3)	
Male	76 (88.4)	22 (66.7)	
Stage at diagnosis			0.405
II	5 (5.8)	3 (9.1)	
III	28 (32.6)	14 (42.4)	
IV	53 (61.6)	16 (48.5)	
ECOG performance status			0.001
1	84 (97.7)	25 (75.8)	
2	2 (2.3)	8 (24.2)	
Smoking status			0.962
Never smoker	13 (15.1)	4 (12.1)	
Former smoker	36 (41.9)	15 (45.5)	
Current smoker	37 (43.0)	14 (42.4)	
Smoking exposure, pack-years	50 (40-60)	40 (30-55)	0.144
Histology			0.614
Adenocarcinoma	40 (46.5)	13 (39.4)	
Squamous cell carcinoma	33 (38.4)	16 (48.5)	
Other	13 (15.1)	4 (12.1)	
PD-L1 expression, %	1 (0-30)	1 (0-10)	0.417
PD-L1 expression category			0.475
<1%	38 (49.4)	14 (48.3)	
1-49%	24 (31.2)	12 (41.4)	
≥50%	15 (19.5)	3 (10.3)	
Brain metastasis			0.147
No	62 (72.1)	28 (84.8)	
Yes	24 (27.9)	5 (15.2)	
Contralateral lung metastasis			0.303
No	63 (73.3)	21 (63.6)	
Yes	23 (26.7)	12 (36.4)	
Adrenal metastasis			0.776
No	72 (83.7)	29 (87.9)	
Yes	14 (16.3)	4 (12.1)	
Bone metastasis			0.562
No	57 (66.3)	20 (60.6)	
Yes	29 (33.7)	13 (39.4)	
Liver metastasis			0.138
No	81 (94.2)	28 (84.8)	
Yes	5 (5.8)	5 (15.2)	
Pleural metastasis			0.263
No	75 (87.2)	26 (78.8)	
Yes	11 (12.8)	7 (21.2)	
Mediastinal metastasis			0.636
No	48 (55.8)	20 (60.6)	
Yes	38 (44.2)	13 (39.4)	

Table 2. Continued

Variable	Non-metformin (n=86)	Metformin (n=33)	p value
Number of metastatic sites	2 (1-2)	2 (1-2)	0.536
Number of metastatic sites category			0.752
1	35 (40.7)	12 (36.4)	
2	44 (51.2)	17 (51.5)	
≥3	7 (8.1)	4 (12.1)	
First-line/adjuvant chemotherapy regimen			0.723
Carboplatin-paclitaxel	57 (66.3)	20 (60.6)	
Gemcitabine-cisplatin	13 (15.1)	7 (21.2)	
Cisplatin-pemetrexed	16 (18.6)	6 (18.2)	
Number of first-line/adjuvant chemotherapy cycles	6 (4-6)	6 (4-6)	0.913
BMI, kg/m ²	23.82 (21.49-26.05)	27.34 (24.89-29.69)	<0.001
Hemoglobin, g/dL	12.30±1.94	11.65±2.08	0.110
Albumin, g/L	40.14±4.56	38.97±5.58	0.242
Number of nivolumab administrations	8 (6-25)	7 (6-12)	0.221
Lymphocyte count, ×10 ³ /μL	1.58 (1.05-2.15)	1.38 (1.12-1.86)	0.430
Neutrophil count, ×10 ³ /μL	4.78 (3.48-6.22)	5.72 (4.38-8.11)	0.032
Platelet count, ×10 ³ /μL	259 (210-336.25)	288 (220.5-365.5)	0.409
Adverse event category			0.354
Gastrointestinal	5 (5.8)	3 (9.1)	
Respiratory	5 (5.8)	1 (3.0)	
Dermatologic	3 (3.5)	0 (0.0)	
Renal	2 (2.3)	0 (0.0)	
Thyroid	10 (11.6)	1 (3.0)	
Hematologic	2 (2.3)	3 (9.1)	
None	59 (68.6)	25 (75.8)	

Values are presented as mean±standard deviation, median(interquartile range), or n(%), as appropriate. Percentages are column percentages. Continuous variables were compared using the independent-samples t-test or Mann-Whitney U test according to distribution normality. Categorical variables were compared using Pearson's chi-square test, Fisher's exact test, or Monte Carlo exact test, as appropriate. PD-L1 expression category was available for 106 patients. ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, PD-L1: Programmed death-ligand 1

with metastatic NSCLC receiving nivolumab and reported significantly longer overall survival among metformin users, whereas PFS did not differ significantly between groups. In our cohort, however, we did not observe an overall survival benefit from metformin, even after adjustment for baseline differences. This discrepancy may partly reflect differences in patient characteristics, metformin exposure definitions, and analytical approaches. Consistent with our findings, studies including broader and more heterogeneous patient

Table 3. Overall survival from nivolumab initiation according to metformin use

Variable	n	Deaths, n (%)	Median OS from nivolumab initiation, months (95% CI)	Log-rank p
Overall	119	89 (74.8)	9.26 (7.25-11.27)	-
Metformin use				0.061
Non-metformin group	86	61 (70.9)	9.26 (6.97-11.56)	-
Metformin group	33	28 (84.8)	9.00 (4.42-13.58)	-

OS was defined as the time from nivolumab initiation to death from any cause. Patients who were alive at the last follow-up were censored on the date of last contact. Median OS was estimated using the Kaplan-Meier method, and groups were compared using the log-rank test.

CI: Confidence interval, OS: Overall survival

Table 4. Overall survival from diagnosis according to metformin use

Variable	n	Deaths, n (%)	Median OS from diagnosis, months (95% CI)	Log-rank p
Overall	119	89 (74.8)	19.7 (17.53-21.96)	-
Metformin use				0.348
Non-metformin group	86	61 (70.9)	19.4 (16.51-22.38)	-
Metformin group	33	28 (84.8)	20.1 (17.15-23.13)	-

OS was defined as the time from initial diagnosis to death from any cause. Patients who were alive at the last follow-up were censored on the date of last contact. Median OS was estimated using the Kaplan-Meier method, and groups were compared using the log-rank test.

CI: Confidence interval, OS: Overall survival

Table 5. Nivolumab PFS according to metformin use

Variable	n	Events, n (%)	Median PFS, months (95% CI)	Log-rank p
Overall	119	103 (86.6)	4.80 (3.80-5.80)	-
Metformin use				0.008
Non-metformin group	86	71 (82.6)	5.45 (4.11-6.80)	-
Metformin group	33	32 (97.0)	3.81 (3.40-4.22)	-

PFS was defined as the time from nivolumab initiation to progression or death from any cause. Patients without progression or death were censored at the date of last follow-up. Median PFS was estimated using the Kaplan-Meier method, and groups were compared using the log-rank test. This analysis was secondary and exploratory. PFS, progression-free survival from nivolumab initiation.

CI: Confidence interval, PFS: Progression-free survival

Table 6. Association between metformin use and nivolumab PFS across unadjusted, adjusted, and propensity-score-weighted models

Model	Covariates included	HR (95% CI)	p
Univariate Cox	None	1.77 (1.15-2.71)	0.009
Multivariable Cox	ECOG performance status, sex, BMI, hemoglobin, albumin, neutrophil count	1.10 (0.65-1.87)	0.711
IPTW, stabilized weights	Propensity score: ECOG performance status, sex, BMI, neutrophil count	1.49 (0.96-2.32)	0.078
IPTW, weights trimmed (1 st -99 th percentile)	Same propensity-score model, extreme weights trimmed	1.58 (1.01-2.48)	0.045

HR are for metformin use (yes vs. no) on nivolumab PFS. The multivariable model included metformin use, ECOG performance status, sex, body mass index, hemoglobin, albumin, and neutrophil count (n=119, 103 events). The propensity score for the IPTW models was estimated by logistic regression using ECOG performance status, sex, body mass index, and neutrophil count — the baseline covariates that differed significantly between metformin groups (Table 2)— and stabilized weights were applied to a weighted Cox model; weights were additionally trimmed at the 1st and 99th percentiles as a sensitivity analysis. The proportional hazards assumption was verified using Schoenfeld residuals (all p>0.10). All PFS analyses were secondary and exploratory.

HR: Hazard ratio, CI: Confidence interval, IPTW: Inverse probability of treatment weighting, ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index

populations have reported that the clinical relevance of this association remains uncertain, and some analyses have found no survival advantage associated with metformin use [16,17]. The study by Buti et al. [17] is also relevant in showing that concomitant medications used during immunotherapy may influence outcomes; however, such effects may be closely intertwined with patient characteristics, comorbidities, and the overall clinical context rather than being attributable solely to the medication itself.

Prospective data on the combination of metformin with immune checkpoint blockade also suggest that biological and immunologic activities do not necessarily translate into clinical benefit. Akce et al. [18] evaluated nivolumab plus metformin in a Phase II trial involving patients with treatment-refractory, microsatellite-stable metastatic colorectal cancer. Although tolerability was acceptable, the trial did not show objective tumor responses; stable disease was reported in only two patients, and enrollment was discontinued

because of futility. Interestingly, correlative analyses showed some evidence of immune modulation, including increased tumor-infiltrating leukocytes after combined metformin and nivolumab treatment; however, these immunologic changes did not result in meaningful clinical efficacy. Consistent with the neutral survival findings of our study, these results support the notion that metformin's potential effects on the tumor immune microenvironment may be insufficient alone to produce a measurable survival advantage in patients receiving immune checkpoint inhibitors.

In our cohort, patients receiving metformin had higher BMI, poorer ECOG performance status, and higher baseline neutrophil counts, indicating that metformin users represented a clinically distinct subgroup with a less favorable baseline clinical profile. Poor performance status and systemic inflammation are well-recognized adverse prognostic factors in patients with advanced NSCLC treated with immune checkpoint inhibitors [19,20]. Therefore, these baseline imbalances may have influenced the unadjusted associations between metformin use and survival outcomes. Overall, these findings suggest that the relationship between metformin and immunotherapy outcomes in real-world cohorts may be substantially influenced by patient selection and baseline clinical characteristics.

The PFS results should be considered in light of the baseline differences between groups. Although metformin use appeared to be linked to shorter PFS before adjustment, this relationship lost statistical significance after clinical and laboratory covariates were included in the model. However, the IPTW sensitivity analyses were not fully concordant, and residual covariate imbalance remained after weighting. Therefore, some uncertainty regarding the PFS association persists. The association of baseline laboratory variables, including hemoglobin, albumin, and neutrophil count, with PFS in this cohort further supports this interpretation. Therefore, the crude PFS difference should not be interpreted as evidence of a direct negative effect of metformin on tumor control. Instead, it emphasizes that unadjusted PFS comparisons may be difficult to interpret when clinically relevant baseline imbalances are present.

Study Limitations

This study has several limitations. Its retrospective and single-center nature may introduce selection bias and restrict the applicability of the findings to broader patient populations. The requirement for at least two cycles of nivolumab may have introduced selection bias by excluding patients with early death, rapid progression, or early treatment discontinuation. In addition, the relatively small number of metformin users may have reduced the ability to identify small differences in survival outcomes. Detailed information on diabetes duration, glycemic control, treatment adherence, and cumulative metformin exposure was not available, and this may also have affected the interpretation of the findings. Because adverse events were obtained retrospectively from routine clinical records, their severity and immune-related nature could not

be consistently assessed, and under-documentation cannot be excluded. Because PFS was analyzed as a secondary outcome, these results should be interpreted with caution. These limitations should be considered when evaluating the neutral survival results of this study.

Conclusion

Concomitant use of metformin was not associated with improved overall survival in patients with advanced NSCLC treated with nivolumab. Although PFS was shorter in the metformin group before adjustment, the association attenuated after adjusting for baseline clinical and laboratory imbalances. Overall, this real-world cohort did not provide evidence of an independent, measurable effect of metformin on survival during nivolumab therapy. Future studies with detailed data on diabetes characteristics, glycemic control, and metformin exposure may help define this relationship more clearly.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the Ankara Etlik City Hospital Ethics Committee (approval no: AEŞH-BADEK1-2025-128, date: 14 May 2025).

Informed Consent: Owing to the retrospective design and use of existing patient records, individual informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.A.S., M.A., H.Ş., Concept: H.A.S., H.Ş., Design: H.A.S., H.Ş., Data Collection or Processing: H.A.S., M.A., H.Ş., Analysis or Interpretation: H.A.S., M.A., H.Ş., Literature Search: H.A.S., M.A., Writing: H.A.S., M.A., H.Ş.

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

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Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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