Treatment patterns and clinical outcomes of patients with resectable non–small cell lung cancer receiving neoadjuvant immunochemotherapy: A large-scale, multicenter, real-world study (NeoR-World)

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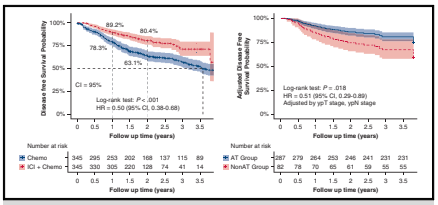
ABSTRACT

Background: Neoadjuvant immunotherapy has ushered in a new era of perioperative treatment for resectable non–small cell lung cancer (NSCLC). However, large-scale data for verifying the efficacy and optimizing the therapeutic strategies of neoadjuvant immunochemotherapy in routine clinical practice are scarce.

Methods: NeoR-World (NCT05974007) was a multicenter, retrospective cohort study involving patients who received neoadjuvant immunotherapy plus chemotherapy or chemotherapy alone in routine clinical practice from 11 medical centers in China between January 2010 and March 2022. Propensity score matching was performed to address indication bias.

Results: A total of 408 patients receiving neoadjuvant immunochemotherapy and 684 patients receiving neoadjuvant chemotherapy were included. The pathologic complete response (pCR) and major pathologic response (MPR) rates of the real-world neoadjuvant immunochemotherapy cohort were 32.8% and 58.1%, respectively. Notably, patients with squamous cell carcinoma exhibited significantly higher pCR and MPR rates than those with adenocarcinoma (pCR, 39.2% vs 16.5% [$P < .001$]; MPR, 66.6% vs 36.5% [$P < .001$]), whereas pCR and MPR rates were comparable among patients receiving different neoadjuvant cycles. In addition, the 2-year rates of disease-free survival (DFS) and overall survival (OS) rate were 82.0% and 93.1%, respectively. Multivariate analyses identified adjuvant therapy as an independent prognostic factor for DFS (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.29-0.89; $P = .018$) and OS (HR, 0.28; 95% CI, 0.13-0.58; $P < .001$). A significantly longer DFS with adjuvant therapy was observed in patients with non-pCR or 2 neoadjuvant cycles. We observed significant benefits in pCR rate (32.4% vs 6.4%; $P < .001$), DFS (HR, 0.50; 95% CI, 0.38-0.68; $P < .001$) and OS (HR, 0.61; 95% CI, 0.40-0.94; $P = .024$) with immunotherapy plus chemotherapy compared to chemotherapy alone both in the primary propensity-matched cohort and across most key subgroups.

Conclusions: The study validates the superior efficacy of neoadjuvant immunochemotherapy over chemotherapy alone for NSCLC. Adjuvant therapy could prolong DFS in patients receiving neoadjuvant immunochemotherapy, and patients with non-pCR or those who underwent 2 neoadjuvant cycles were identified as potential beneficiaries of adjuvant therapy. (J Thorac Cardiovasc Surg 2024;168:1245-58)



Neoadjuvant Chemo-IO showed better DFS, and adjuvant therapy was a prognostic factor.

CENTRAL MESSAGE

Superior disease-free survival (DFS) was observed with neoadjuvant immunochemotherapy compared with chemotherapy, and adjuvant therapy was an independent prognostic factor for DFS in patients with neoadjuvant immunochemotherapy.

PERSPECTIVE

The study validates the superior efficacy of neoadjuvant immunochemotherapy over chemotherapy alone for non–small cell lung cancer. Adjuvant therapy could prolong disease-free survival in patients receiving neoadjuvant immunochemotherapy. The study sheds light on the potential beneficiaries and optimized therapeutic strategies of neoadjuvant immunochemotherapy, helping guide future treatment selection and clinical trial design.

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Abbreviations and Acronyms

DFS = disease-free survival
MPR = major pathologic response
NSCLC = non−small cell lung cancer
OS = overall survival
pCR = pathologic complete response
PSM = propensity score matching

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Globally, lung cancer ranks as the second most common malignancy with the highest morbidity.[1] Locally advanced lung cancer, with a 5-year overall survival (OS) ranging from 26% to 68%, remains a major challenge in clinical practice.[2] The high recurrence rate, particularly after radical surgery, calls for more effective perioperative therapeutic strategies.[3-5] Recent studies have demonstrated superior pathologic response and survival in resectable locally advanced non−small cell lung cancer (NSCLC) with neoadjuvant immunotherapy.[6-10] CheckMate-816, the first prospective randomized phase III study of neoadjuvant immunotherapy in NSCLC, revealed significantly improved event-free survival (EFS) and pathologic response in patients receiving neoadjuvant chemotherapy plus immunotherapy.[6] On March 4, 2022, the US Food and Drug Administration approved nivolumab in combination with platinum-based doublet chemotherapy for neoadjuvant therapy in patients with resectable NSCLC, heralding a new era of perioperative treatment for NSCLC.[11]

Although the application of neoadjuvant immunotherapy for NSCLC has introduced a new treatment option for many patients, most evidence is derived from interventional clinical trials,[12] leaving a gap in evidence from routine clinical practice. Given the diverse clinicopathologic characteristics of patients and various therapeutic strategies in routine practice, studies outside of clinical trials could provide more data to supplement interventional clinical trials, identifying the potential beneficiaries and optimizing the therapeutic strategies of neoadjuvant immunochemotherapy. Moreover, studies outside of clinical trials could help address important but controversial issues, allowing for direct comparison among different strategies, including treatment cycles, regimens, and others that are difficult to directly compare in clinical trials.

In the present study, we examined the clinicopathologic characteristics and treatment patterns of patients receiving neoadjuvant immunochemotherapy in routine clinical practice. Our aim was to identify the potential beneficiaries and optimize therapeutic strategies of neoadjuvant immunochemotherapy. Furthermore, we compared the efficacy of neoadjuvant immunochemotherapy and chemotherapy in a propensity score–matched cohort.

METHODS

Patients

The study enrolled patients with NSCLC who received neoadjuvant therapy and underwent surgery from 11 medical centers in China between January 2010 and March 2022, (ClinicalTrials.gov identifier NCT05974007) (Table E1). The eligibility criteria were (1) a pathologic diagnosis of lung squamous cell carcinoma or adenocarcinoma; (2) receipt of neoadjuvant platinum-based doublet chemotherapy with or without immunotherapy; and (3) receipt of surgery after neoadjuvant therapy. Exclusion criteria were (1) enrollment in an interventional clinical trial; (2) another condition that might affect survival; (3) a second primary tumor requiring treatment; (4) unavailability of detailed clinicopathologic and follow-up information; and (5) death within 30 days after surgery. Figure E1 provides a diagram of the study design. This retrospective study was approved by the Ethics Committees of the 11 participating centers (approval 22/093-3294) on March 9, 2022, and the need for informed consent was waived.

Data Collection

All the patients underwent cervical, chest, and abdominal computed tomography scanning; brain magnetic resonance imaging; and whole-body bone scintigraphy for clinical staging and surgery evaluation. The staging

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criteria followed the eighth edition of the American Joint Committee on Cancer's TNM classification of lung cancer. Radiologic response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[13] Local multidisciplinary expert teams determined the treatment plans based on National Comprehensive Cancer Network and Chinese Society of Clinical Oncology guidelines, the Expert Consensus on Perioperative Treatment for Non−Small Cell Lung Cancer,[14] or latest results of the clinical trials. Our study did not require the enrolled patients to have results of PD-L1 expression and molecular testing. A uniform case report form (CRF) was designed to collect detailed demographic, imaging, pathology, treatment, and survival information from electronic medical records, clinical databases, or patients' families. The patients were followed up until May 15, 2023, or until the time of death. All data were pooled and reviewed by 2 thoracic surgeons, and only data that passed quality control examination were included.

Pathologic Assessment

The pathologic evaluation was performed by experienced pathologists at each medical center. According to the principles of pathologic assessment of lung cancer after neoadjuvant therapy recommended by the International Association for the Study of Lung Cancer,[15] pathologic complete response (pCR) was defined as 0% residual viable tumor cells in the primary tumor and sampled lymph nodes, and major pathologic response (MPR) was characterized by the presence of $\leq$10% residual viable tumor cells in the primary tumor.

Clinical Outcomes

The primary outcomes of this study were pCR and disease-free survival (DFS), defined as the interval between surgery and disease recurrence, progression, or death. The secondary outcomes included overall survival (OS); 1-year, 2-year, and 5-year DFS rate; 2-year and 5-year OS rate; and MPR.

Statistical Analysis

We focused on the real-world neoadjuvant immunochemotherapy cohort to explore the factors that influence clinical outcomes. Associations between clinicopathologic characteristics and pathologic response were evaluated using the Fisher exact test or Pearson χ^2 test. Univariate and multivariate survival analyses were performed with Cox proportional hazards models. Kaplan-Meier curves stratified by neoadjuvant therapeutic strategies and the use of adjuvant treatment were used in survival analysis. Subgroup analysis adjusted by ypT stage and ypN stage was performed to investigate the impact of adjuvant treatment on survival outcomes.

To balance the clinicopathologic characteristics between the immunochemotherapy group and the chemotherapy group, 1:1 nearest-neighbor propensity score matching (PSM) without replacement (caliper size, 0.05) was performed. The matched cohort facilitated a comparison of survival and pathologic response between the 2 treatment groups. Survival analysis was conducted using Kaplan-Meier curves, and univariate analysis was performed using Cox proportional hazards models. Pathologic response was compared between treatment groups using a stratified 2-sided Cochran-Mantel-Haenszel test. PSM between the 2 treatment groups was performed for each subgroup prior to the subgroup analysis of pathologic response and survival.

Categorical variables were summarized by count and frequency, and continuous variables were summarized by median and interquartile range. The Fisher exact test or Pearson χ^2 test was applied for statistical analysis of categorical variables, and the Wilcoxon test was used for continuous variables. All statistical analyses were conducted using R version 4.1.3 (R Foundation for Statistical Computing). A 2-tailed P value < .05 was considered statistically significant.

RESULTS

Patient Enrollment

Between January 2010 and March 2022, a total of 1092 patients with NSCLC from 11 medical centers in China participated in this study. Among these, 408 patients received neoadjuvant immunotherapy plus chemotherapy and 684 received neoadjuvant chemotherapy. The patients' clinicopathologic features are summarized in Table 1. A total of 716 patients (65.6%) were diagnosed with squamous cell carcinoma, and 376 (34.4%) were diagnosed with lung adenocarcinoma. At the time of diagnosis, 102 patients

TABLE 1. Baseline clinicopathologic characteristics of patients who received neoadjuvant chemotherapy with or without immunotherapy before and after PSM

	Before PSM (N = 1092)			After PSM (N = 690)		
Characteristic	Chemo (N = 684)	ICI + Chemo (N = 408)	*P* value*	Chemo (N = 345)	ICI + Chemo (N = 345)	*P* value†
Age, y, median (IQR)	59 (53-64)	61 (56-66)	<.001	60 (55-65)	60 (55-66)	.80
Sex, n (%)			<.001			.70
Female	133 (19.4)	39 (9.6)		36 (10.4)	39 (11.3)	
Male	551 (80.6)	369 (90.4)		309 (89.6)	306 (88.7)	
Smoking, n (%)			.033			.70
No	169 (24.7)	125 (30.6)		75 (21.7)	79 (22.9)	
Yes/ever	515 (75.3)	283 (69.4)		270 (78.3)	266 (77.1)	
Histologic type, n (%)			<.001			.90
ADC	261 (38.2)	115 (28.2)		102 (29.6)	104 (30.1)	
SCC	423 (61.8)	293 (71.8)		243 (70.4)	241 (69.9)	
cTNM stage, n (%)			.87			.60
I	67 (9.8)	35 (8.6)		25 (7.2)	31 (9.0)	
II	133 (19.4)	80 (19.6)		67 (19.4)	72 (20.9)	
III	484 (70.8)	293 (71.8)		253 (73.3)	242 (70.1)	

PSM, Propensity score matching; *ICI*, immune checkpoint inhibitor; *IQR*, interquartile range; *ADC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *cTNM stage*, clinical stage based on 8th edition of TNM staging of lung cancer. *Wilcoxon rank-sum test, Pearson χ^2 test. †Wilcoxon rank-sum test, Pearson's χ^2 test, Fisher exact test.

(9.3%) were categorized as clinical stage I, 213 (19.5%) as stage II, and 777 (71.2%) as stage III. The median duration of follow-up for patients alive at last contact was 24.0 months (95% confidence interval [CI], 23.0-25.0 months) in the neoadjuvant immunochemotherapy group and 49.2 months (95% CI, 45.1-54.0 months) in the neoadjuvant chemotherapy group.

PSM was performed to compare the clinical outcomes of neoadjuvant immunochemotherapy and neoadjuvant chemotherapy. A total of 690 patients, distributed equally with 345 in each group, were included in subsequent analyses. The clinical characteristics of the 2 groups in the matched cohort exhibited a well-balanced distribution (Table 1, Figure E2). Figure E3 provides a CONSORT diagram of the study, and Figure 1 provides a graphical abstract.

Clinicopathologic Characteristics of Patients Receiving Neoadjuvant Immunotherapy Plus Chemotherapy in Routine Clinical Practice

The clinicopathologic characteristics of the 408 patients who received neoadjuvant immunotherapy plus chemotherapy in routine clinical practice are summarized in Table 2. The cohort had a preponderance of males (90.4%) and smokers (69.4%) and included 293 patients with squamous cell carcinoma (71.8%) and 114 patients with adenocarcinoma (28.2%). At diagnosis, 35 patients (8.6%) were classified as clinical stage I, 80 (19.6%) as stage II, and 293 (71.8%) as stage III. Of the 115 patients with adenocarcinoma, 61 (53.0%) underwent examination for oncogenic driver mutations before treatment. More than one-half of the patients (55.4%) received 2 cycles of neoadjuvant therapy. Platinum plus paclitaxel (90.4% in squamous cell carcinoma) and platinum plus pemetrexed (77.4% in adenocarcinoma) were the most commonly used regimens for patients with squamous cell carcinoma and adenocarcinoma, respectively. The median time to surgery after neoadjuvant immunochemotherapy was 33 days (interquartile range, 27-42 days). All patients underwent pulmonary surgery, including pneumonectomy in 48 (11.8%), bilobectomy in 30 (7.4%), 268 (65.7%) lobectomy in 268 (65.7%), sleeve lobectomy in 53 (13.0%), and wedge resection/segmentectomy in 9 (2.2%). The postoperative surgical outcomes of the cohort are shown in Table E2. Patients receiving $\geq$4 cycles of neoadjuvant immunochemotherapy had a relatively higher conversion rate from video-assisted thoracoscopic surgery/robotic-assisted thoracic surgery to open surgery, as well as relatively longer duration of chest tube insertion and length of stay.

Pathologic Response

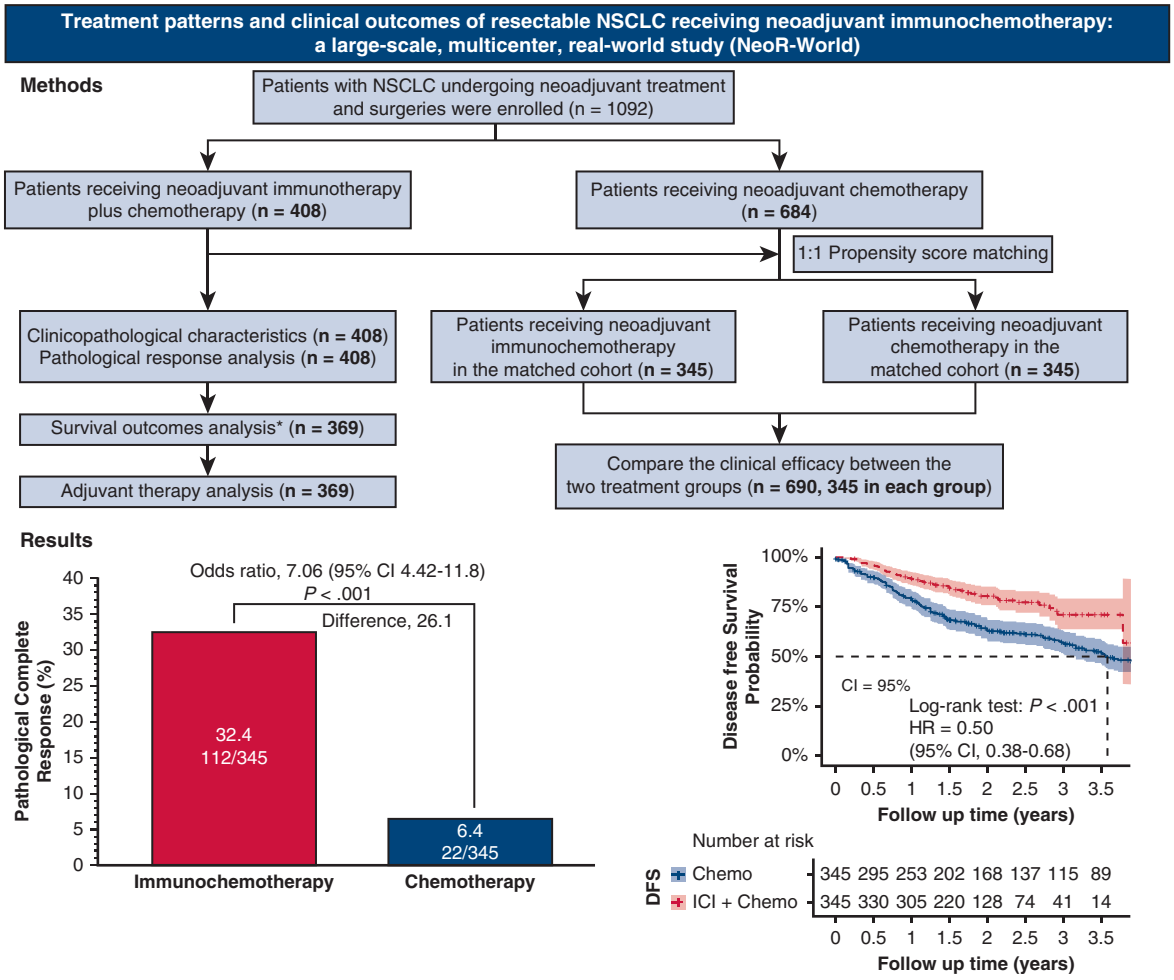
In the real-world neoadjuvant immunochemotherapy cohort, 134 patients (32.8%) achieved pCR and 237 (58.1%) achieved MPR (Table E3). Patients with squamous cell carcinoma (pCR, 39.2% vs 16.5% [$P < .001$]; MPR, 66.6% vs 36.5% [$P < .001$]) and superior radiologic response (pCR, 36.2% vs 25.4% [$P = .04$]; MPR, 65.2% vs 42.1% [$P < .001$]) demonstrated significantly higher rates of pCR and MPR (Table 3). Patients with PD-L1 $\geq$1% had a relatively higher pCR rate than those with PD-L1 <1% (38.1% vs 24.5%). pCR and MPR rates were comparable among patients receiving different neoadjuvant cycles (pCR, $P = .6$; MPR, $P = .5$) or different platinum regimens (pCR, $P = .14$; MPR, $P = .8$) (Table 3).

In the matched cohort, pCR was achieved by 32.5% (112 of 345) of the patients receiving immunotherapy plus chemotherapy and by 6.4% (22 of 345) of those receiving chemotherapy alone ($P < .001$) (Figure 2, *A*, Table E3). This observed benefit with immunotherapy plus chemotherapy was seen across most key subgroups, including those based on histologic type and those based on cTNM stage (Figure 2, *B*). The MPR rate was significantly higher among patients receiving immunotherapy plus chemotherapy than among those receiving chemotherapy alone, both in the primary matched cohort (57.1% vs 21.7%; $P < .001$) (Table E3) and across most key subgroups (Figure E4, *A* and *B*). Patients with squamous cell carcinoma and stage II-III cancer received a greater benefit from neoadjuvant immunochemotherapy in terms of pathologic response. Significant benefits in pCR and MPR with neoadjuvant immunochemotherapy also were observed in patients without oncogenic mutations after PSM (Figure E5, *A* and *B*).

Survival Outcomes

The median DFS and OS were not reached in the real-world neoadjuvant immunochemotherapy cohort. In this cohort, the 2-year DFS rate was 82.0% (95% CI, 78.0%-86.2%), and the 2-year OS rate was 93.1% (95% CI, 90.4%-95.9%) (Figure E6). Univariate analyses revealed that patients with pCR (hazard ratio [HR], 0.46; 95% CI, 0.26-0.83; $P < .01$), MPR (HR, 0.40, 95% CI, 0.25-0.63; $P < .001$), and early ypTNM stage exhibited longer DFS (Table E4). Meanwhile, MPR (HR, 0.28; 95% CI, 0.14-0.57; $P < .001$) and early ypTNM stage were associated with longer OS (Table E4). Multivariate analyses identified advanced ypTNM stage and the absence of adjuvant therapy as independent prognostic factors for shorter DFS and OS (Table 4).

In the matched cohort, the DFS was significantly longer in the immunochemotherapy group compared with the chemotherapy group (HR, 0.50; 95% CI, 0.38-0.68; $P < .001$) (Figure 3, *A*). DFS across most key subgroups favored immunotherapy plus chemotherapy (Figure 3, *B*). Patients with stage III and N2 exhibited a greater magnitude of benefit in DFS than those with stage I-II and N0-1. Exploratory analyses showed a DFS benefit in the neoadjuvant immunochemotherapy group regardless of whether patients had a pCR (Figure E7, *A*) or a MPR (Figure E7, *B*). There was a significant DFS benefit in patients receiving



Clinicopathological characteristic	DFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ypT stage				
T0	1 [Reference]		1 [Reference]	
T1-2	1.30 (0.70-2.41)	.4	1.06 (0.44-2.54)	.90
T3-4	2.67 (1.14-6.26)	.024	2.17 (0.66-7.08)	.20
ypN stage				
N0	1 [Reference]		1 [Reference]	
N1	2.97 (1.54-5.70)	.001	3.33 (1.24-8.96)	.017
N2	3.09 (1.68-5.71)	< .001	5.96 (2.53-14.0)	< .001
Adjuvant therapy				
No	1 [Reference]		1 [Reference]	
Yes	0.51 (0.29-0.89)	.018	0.28 (0.13-0.58)	< .001

Implications

The study validated the superior efficacy of neoadjuvant immunochemotherapy over chemotherapy alone for NSCLC. Adjuvant therapy could prolong DFS of patients receiving neoadjuvant immunochemotherapy, and patients with non-pCR or 2 neoadjuvant cycles were potential beneficiaries of adjuvant therapy.

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FIGURE 1. Graphical abstract. Treatment patterns and clinical outcomes of patients with resectable non–small cell lung cancer receiving neoadjuvant immunochemotherapy: a large-scale, multicenter, real-world study (NeoR-World). *CI*, Confidence interval; *HR*, hazard ratio; *DFS*, disease-free survival; *OS*, overall survival.

TABLE 2. Clinicopathologic characteristics of patients in the real-world neoadjuvant immunochemotherapy cohort

Characteristic	Overall (N = 408)	ADC (N = 115)	(SCC, N = 293)	*P* value*
Age, y, median (IQR)	61 (56-66)	59 (54-65)	62 (56-67)	.014
Sex, n (%)				<.001
Female	39 (9.6)	28 (24.3)	11 (3.8)	
Male	369 (90.4)	87 (75.7)	282 (96.2)	
Smoking, n (%)				<.001
No	125 (30.6)	51 (44.3)	74 (25.3)	
Yes/ever	283 (69.4)	64 (55.7)	219 (74.7)	
Neoadjuvant regimen, n (%)				<.001
Platinum + gemcitabine	16 (3.9)	0 (0)	16 (5.5)	
Platinum + paclitaxel	291 (71.3)	26 (22.6)	265 (90.4)	
Platinum + pemetrexed	101 (24.8)	89 (77.4)	12 (4.1)	
Platinum regimen, n (%)				.21
Carboplatin	269 (66.0)	83 (72.1)	186 (63.5)	
Cisplatin	98 (24.0)	24 (20.9)	74 (25.2)	
Others†	41 (10.0)	8 (7.0)	33 (11.3)	
Immunotherapy regimen, n (%)				
Camrelizumab	84 (20.6)	25 (21.7)	59 (20.1)	
Durvalumab	4 (1.0)	2 (1.7)	2 (0.7)	
Nivolumab	45 (11.0)	13 (11.3)	32 (10.9)	
Pembrolizumab	143 (35.0)	51 (44.3)	92 (31.4)	
Sintilimab	61 (15.0)	13 (11.3)	48 (16.4)	
Sintilimab + nivolumab	1 (0.2)	0 (0.0)	1 (0.3)	
Tislelizumab	69 (16.9)	10 (8.7)	59 (20.1)	
Toripalimab	1 (0.2)	1 (0.9)	0 (0.0)	
Neoadjuvant cycles, n (%)				.083
≤2	239 (58.6)	61 (53.1)	178 (60.7)	
3	103 (25.2)	28 (24.3)	75 (25.6)	
≥4	66 (16.2)	26 (22.6)	40 (13.7)	
cT stage, n (%)				.52
T1	76 (18.6)	24 (20.9)	52 (17.7)	
T2	160 (39.2)	49 (42.6)	111 (37.9)	
T3	107 (26.2)	25 (21.7)	82 (28.0)	
T4	65 (16.0)	17 (14.8)	48 (16.4)	
Tumor diameter, n (%)				.22
≤4 cm	171 (41.9)	56 (48.7)	115 (39.2)	
4-7 cm	173 (42.4)	43 (37.4)	130 (44.4)	
>7 cm	64 (15.7)	16 (13.9)	48 (16.4)	
cN stage, n (%)				.68
N0	86 (21.1)	25 (21.7)	61 (20.8)	
N1	69 (16.9)	22 (19.1)	47 (16.0)	
N2	236 (57.8)	62 (53.9)	174 (59.4)	
N3	17 (4.2)	6 (5.3)	11 (3.8)	
cTNM stage, n (%)				.62
I	35 (8.6)	9 (7.8)	26 (8.9)	
II	80 (19.6)	26 (22.6)	54 (18.4)	
III	293 (71.8)	80 (69.6)	213 (72.7)	
ypT stage, n (%)				<.001
T0	153 (37.5)	24 (20.9)	129 (44.0)	
T1	191 (46.8)	63 (54.8)	128 (43.7)	
T2	34 (8.3)	14 (12.2)	20 (6.8)	
T3	19 (4.7)	9 (7.8)	10 (3.4)	
T4	11 (2.7)	5 (4.3)	6 (2.1)	

(Continued)

TABLE 2. Continued

Characteristic	Overall (N = 408)	ADC (N = 115)	(SCC, N = 293)	*P* value*
ypN stage, n (%)				<.001
0	274 (67.2)	71 (61.7)	203 (69.3)	
1	57 (14.0)	8 (7.0)	49 (16.7)	
2	77 (18.9)	36 (31.3)	41 (14.0)	
ypTNM stage, n (%)				<.001
0	134 (32.8)	19 (16.5)	116 (39.2)	
I	122 (29.9)	45 (39.1)	76 (26.3)	
II	63 (15.5)	10 (8.7)	53 (18.1)	
III	89 (21.8)	41 (35.7)	48 (16.4)	
Resection completeness, n (%)				.40
R0	392 (96.1)	109 (94.8)	283 (96.6)	
R+	16 (3.9)	6 (5.2)	10 (3.4)	
Surgery, n (%)				<.001
Bilobectomy	30 (7.4)	9 (7.8)	21 (7.2)	
Lobectomy	268 (65.7)	92 (80.0)	176 (60.1)	
Lobectomy-sleeve	53 (13.0)	3 (2.6)	50 (17.1)	
Pneumonectomy	48 (11.8)	7 (6.1)	41 (14.0)	
Wedge resection + segmentectomy	9 (2.2)	4 (3.5)	5 (1.7)	
Radiologic response, n (%)				.009
CR	13 (3.2)	1 (0.9)	12 (4.1)	
PR	269 (65.9)	66 (57.3)	203 (69.3)	
SD	122 (29.9)	46 (40.0)	76 (25.9)	
PD	4 (1.0)	2 (1.7)	2 (0.7)	
PD-L1 (1% cutoff), n (%)				.001
<1%	53 (13.0)	17 (14.8)	36 (12.3)	
≥1%	63 (15.4)	29 (25.2)	34 (11.6)	
Unknown	292 (71.6)	69 (60.0)	223 (76.1)	

ADC, Adenocarcinoma; *SCC*, squamous cell carcinoma; *IQR*, interquartile range; *cTNM stage*, clinical stage based on 8th edition of TNM staging of lung cancer; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease. *Wilcoxon rank-sum test; Pearson χ^2 test, Fisher exact test. †Others include nedaplatin, oxaliplatin, and loplatin.

neoadjuvant immunochemotherapy without oncogenic mutations after PSM (HR, 0.50; 95% CI, 0.36-0.70; $P < .001$) (Figure E8).

The median OS of the matched cohort was not reached in either the immunochemotherapy group or the chemotherapy group (HR, 0.61; 95% CI, 0.40-0.94; $P = .024$). Patients receiving immunotherapy plus chemotherapy exhibited significantly longer OS than those receiving chemotherapy alone, both in the primary analysis cohort (Figure E9, *A*) and across most key subgroups (Figure E9, *B*).

Association of Adjuvant Treatment With Survival in Routine Clinical Practice

Of the 392 patients who underwent R0 resection in the neoadjuvant immunochemotherapy setting, 82 (20.9%) did not receive adjuvant therapy. Among the remaining patients, 56 (14.3%) received adjuvant chemotherapy, 23 (5.9%) received EGFR-TKI therapy, 35 (8.9%) received immunotherapy, and 196 (50.0%) received immunotherapy plus chemotherapy. Our analysis revealed that older patients (odds [OR], 0.96; 95% CI, 0.93-0.99; $P = .008$) and patients who received ≥4 cycles of neoadjuvant treatment (OR, 0.36; 95% CI, 0.20-0.67; $P = .002$) were less likely to receive adjuvant therapy in routine clinical practice (Table E5).

Patients who received adjuvant therapy tended to have longer DFS (HR, 0.61; 95% CI, 0.35-1.05; $P = .075$), and had significantly longer OS (HR, 0.37; 95% CI, 0.18-0.75; $P = .006$) (Table E4). Adjuvant immunotherapy did not exhibit a significant impact on DFS or OS (Table E4). Multivariate analyses identified adjuvant therapy as an independent prognostic factor for longer DFS (HR, 0.51; 95% CI, 0.29-0.89; $P = .018$) and OS (HR, 0.28; 95% CI, 0.13-0.58; $P < .001$) (Table 4, Figure 4, *A* and *B*).

A subgroup analysis adjusted by ypT stage and ypN stage was performed to identify the potential beneficiaries of adjuvant therapy (Table E6) and adjuvant immunotherapy (Table E7). We observed a significantly longer DFS with adjuvant therapy in smokers, patients with non-pCR, patients with non-MPR, and patients who underwent 2 cycles of neoadjuvant therapy and a significantly longer DFS with adjuvant immunotherapy in patients with no oncogenic mutations.

TABLE 3. Pathologic response of neoadjuvant immunotherapy plus chemotherapy in routine clinical practice

Variable	Non-pCR (N = 274)	pCR (N = 134)	*P* value	Non-MPR (N = 171)	MPR (N = 237)	*P* value
Age, y, median (IQR)	61 (55-66)	61 (56-67)	.5	60 (55-66)	62 (56-67)	.10
Sex, n (%)			.005			.054
Female	34 (12.4)	5 (3.7)		22 (12.9)	17 (7.2)	
Male	240 (87.6)	129 (96.3)		149 (87.1)	220 (92.8)	
Smoking, n (%)			.038			.2
No	93 (33.9)	32 (23.9)		58 (33.9)	67 (28.3)	
Yes/ever	181 (66.1)	102 (76.1)		113 (66.1)	170 (71.7)	
cT stage, n (%)			.11			.2
T1-2	151 (55.1)	85 (63.4)		105 (61.4)	131 (55.3)	
T3-4	123 (44.9)	49 (36.6)		66 (38.6)	106 (44.7)	
cN stage, n (%)			.2			.058
N0-1	111 (40.5)	44 (32.8)		70 (41.0)	85 (35.9)	
N2	150 (54.8)	86 (64.2)		90 (52.6)	146 (61.6)	
N3	13 (4.7)	4 (3.0)		11 (6.4)	6 (2.5)	
cTNM stage, n (%)			.11			.3
I	25 (9.1)	10 (7.5)		18 (10.5)	17 (7.2)	
II	61 (22.3)	19 (14.2)		37 (21.6)	43 (18.1)	
III	188 (68.6)	105 (78.4)		116 (67.9)	177 (74.7)	
Histologic type, n (%)			<.001			<.001
ADC	96 (35.0)	19 (14.2)		73 (42.7)	42 (17.7)	
SCC	178 (65.0)	115 (85.8)		98 (57.3)	195 (82.3)	
Platinum regimen, n (%)			.14			.8
Carboplatin	186 (67.9)	83 (61.9)		110 (64.3)	159 (67.1)	
Cisplatin	66 (24.1)	32 (23.9)		42 (24.6)	56 (23.6)	
Others*	22 (8.0)	19 (14.2)		19 (11.1)	22 (9.3)	
Neoadjuvant cycles, n (%)			.6			.5
≤2	156 (56.9)	83 (61.9)		94 (55.0)	145 (61.2)	
3	71 (25.9)	32 (23.9)		47 (27.5)	56 (23.6)	
≥4	47 (17.2)	19 (14.2)		30 (17.5)	36 (15.2)	
Radiologic response, n (%)			.040			<.001
CR/PR	180 (65.7)	102 (76.1)		98 (57.3)	184 (77.6)	
SD/PD	94 (34.3)	32 (23.9)		73 (42.7)	53 (22.4)	
PD-L1 (1% cutoff), n (%)			.29			.84
<1%	40 (14.6)	13 (9.7)		21 (12.3)	32 (13.5)	
≥1%	39 (14.2)	24 (17.9)		25 (14.6)	38 (16.0)	
Unknown	195 (71.2)	97 (72.4)		125 (73.1)	167 (70.5)	

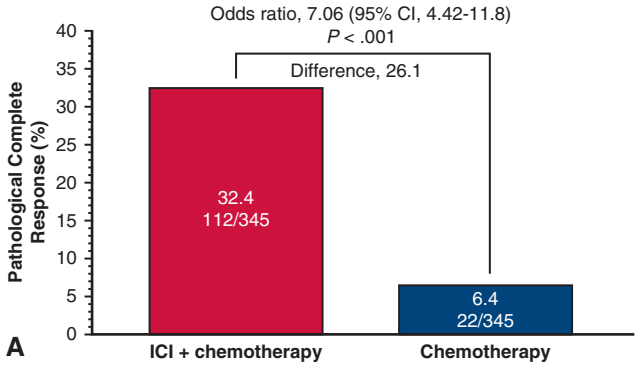
pCR, Pathologic complete response; *MPR*, major pathologic response; *IQR*, interquartile range; *cTNM stage*, clinical stage based on 8th edition of TNM staging of lung cancer; *ADC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease. *Others include nedaplatin, oxaliplatin, and loplatin.

Clinical Outcomes in Patients With Driver Gene Mutations

In the entire cohort, *EGFR* mutations were identified in 126 patients (34 in the immunochemotherapy group, 92 in the chemotherapy group), *KRAS* mutations were seen in 43 patients (14 in the immunochemotherapy group, 29 in the chemotherapy group), and other driver gene mutations (*ALK*, *HER-2*, *ROS1*, *RET*, *NTRK1*, and others) were seen in 24 patients (10 in the immunochemotherapy group, 14 in the chemotherapy group). The MPR rate was significantly higher in the immunochemotherapy group than in the chemotherapy group in both the patients with *EGFR* mutations (23.5% vs 4.4%; $P = .003$) and those with *KRAS* mutations (50.0% vs 6.9%; $P = .003$) (Table E8). Meanwhile, in the crude dataset, a significant benefit in DFS (HR, 0.31; 95% CI, 0.11-0.87; $P = .026$) with neoadjuvant immunochemotherapy was observed in patients with *EGFR* mutations (Figure E10).

DISCUSSION

Since the phase II NADIM trial demonstrated superior progression-free survival and pCR rate for NSCLC after neoadjuvant immunotherapy plus chemotherapy, this treatment mode has been widely researched in several phase III randomized controlled trials.[8] The Phase III CheckMate-816 study and Keynote-671 study further revealed that



Subgroups	N	Chemo	ICI_Chemo	RD %(95% CI)
All patients	690	6.4 (4.0 to 9.5)	32.5 (27.5 to 37.7)	26.1 (19.5 to 32.7)
Age				
< 60	320	6.2 (3.0 to 11.2)	32.5 (25.3 to 40.3)	26.3 (16.6 to 35.9)
≥ 60	400	7.0 (3.9 to 11.5)	33.0 (26.5 to 40.0)	26.0 (17.2 to 34.8)
Sex				
Male	648	6.8 (4.3 to 10.1)	34.6 (29.4 to 40.0)	27.8 (20.8 to 34.8)
Female	76	5.3 (0.6 to 17.7)	13.2 (4.4 to 28.1)	7.9 (–5.8 to 21.5)
Smoking				
Yes	566	7.4 (4.7 to 11.1)	36.0 (30.4 to 41.9)	28.6 (20.9 to 36.3)
No	182	3.3 (0.7 to 9.3)	18.7 (11.3 to 28.2)	15.4 (5.8 to 25.0)
Histologic type				
SCC	492	8.1 (5.0 to 12.3)	39.4 (33.3 to 45.8)	31.3 (22.7 to 39.9)
ADC	228	3.5 (1.0 to 8.7)	16.7 (10.3 to 24.8)	13.2 (4.9 to 21.4)
cTNM stage				
I	60	10.0 (2.1 to 26.5)	33.3 (17.3 to 52.8)	23.3 (–0.2 to 46.9)
II	150	4.0 (0.8 to 11.2)	24.0 (14.9 to 35.3)	20.0 (8.0 to 32.0)
III	510	7.1 (4.2 to 10.9)	34.9 (29.1 to 41.1)	27.8 (19.9 to 35.8)
cT stage				
T1-2	402	5.5 (2.8 to 9.6)	36.3 (29.7 to 43.4)	30.8 (21.9 to 39.8)
T3-4	288	7.6 (3.9 to 13.3)	27.8 (20.6 to 35.8)	33.3 (21.3 to 45.4)
cN stage				
N0-N1	296	6.8 (3.5 to 12)	29.1 (21.8 to 37.1)	22.3 (12.7 to 31.9)
N2	384	6.2 (3.3 to 10.7)	37.0 (30.1 to 44.2)	30.7 (21.4 to 40.0)
Radiological response				
CR	14	28.6 (3.7 to 71.0)	85.7 (42.1 to 99.6)	57.1 (–22.1 to 136.3)
PR	448	4.9 (2.5 to 8.6)	33.0 (26.9 to 39.6)	28.1 (20.1 to 36.2)
SD	212	0.9 (< 0.1 to 5.1)	26.4 (18.3 to 35.9)	25.5 (15.5 to 35.4)
PD	-			
EGFR				
Yes	42	0.0 (0.0 to 16.1)	0.0 (11.3 to 52.2)	
No	120	1.7 (0.0 to 8.9)	25.0 (14.7 to 37.9)	23.3 (10.3 to 36.4)
Unknown	488	8.6 (5.4 to 12.9)	39.8 (33.6 to 46.2)	31.1 (22.4 to 39.9)
ALK				
No	242	2.5 (0.5 to 7.1)	19.0 (12.4 to 27.1)	16.5 (8.3 to 24.8)
Unknown	458	9.2 (5.8 to 13.7)	41.0 (34.6 to 47.7)	31.9 (22.7 to 41.1)
Year of diagnosis				
2018~2022	390	3.1 (1.1 to 6.6)	29.7 (23.4 to 36.7)	26.7 (18.6 to 34.7)

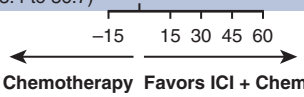


FIGURE 2. Pathologic complete response (pCR) in the matched cohort. A, Barplots showing the pCR rates in the immunochemotherapy group and chemotherapy group in the primary matched cohort. B, pCR in patient subgroups of the matched cohort. *CI*, Confidence interval; *ICI*, immune checkpoint inhibitor; *RD*, rate difference; *SCC*, squamous cell carcinoma; *ADC*, adenocarcinoma; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease.

TABLE 4. Multivariate analysis for DFS and OS in the real-world neoadjuvant immunochemotherapy cohort

Clinicopathologic characteristic (n = 369*)	DFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
ypT stage				
T0	1 [Reference]		1 [Reference]	
T1-2	1.30 (0.70-2.41)	.4	1.06 (0.44-2.54)	.90
T3-4	2.67 (1.14-6.26)	.024	2.17 (0.66-7.08)	.20
ypN stage				
N0	1 [Reference]		1 [Reference]	
N1	2.97 (1.54-5.70)	.001	3.33 (1.24-8.96)	.017
N2	3.09 (1.68-5.71)	<.001	5.96 (2.53-14.0)	<.001
Adjuvant therapy				
No	1 [Reference]		1 [Reference]	
Yes	0.51 (0.29-0.89)	.018	0.28 (0.13-0.58)	<.001

DFS, Disease-free survival; *OS*, overall survival; *HR*, hazard ratio; *CI*, confidence interval. *Patients receiving EGFR-TKI adjuvant therapy were excluded (n = 23).

THOR

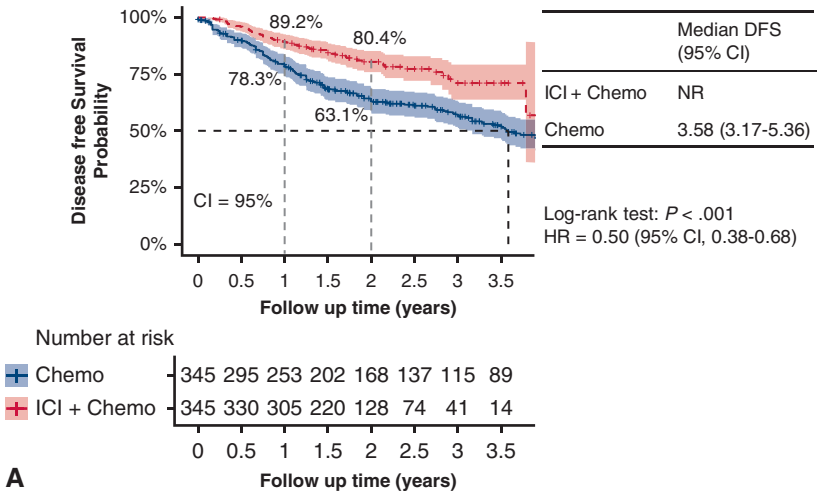
compared with neoadjuvant chemotherapy, neoadjuvant immunotherapy plus chemotherapy improved the EFS and pathologic response of NSCLC, setting up a standard treatment for locally advanced resectable NSCLC.[6,9] However, there remains a lack of evidence in routine clinical practice to identify the potential beneficiaries and optimize the therapeutic strategies of neoadjuvant immunochemotherapy, especially in a broader patient population.

The clinicopathologic features of and treatment strategies for patients receiving neoadjuvant immunotherapy plus chemotherapy in routine clinical practice differed from those in clinical trials (Table E9).[6,10,16,17] In clinical trials, more robust lymph node sampling and pathologic evaluation have been performed at baseline, whereas in routine clinical practice, it is more common to use simplified radiologic evaluation for N stage, resulting in more early-stage patients receiving neoadjuvant therapy in routine clinical practice. In addition, clinical trials often exclude patients with clinical stage I, whereas in our cohort, 8.6% of the patients receiving neoadjuvant immunochemotherapy were in clinical stage I at diagnosis. All these patients had central lung cancer with one of the following features: involving the main bronchus, adjacent to the pulmonary artery, or associated with atelectasis or obstructive pneumonitis. Neoadjuvant therapy for these patients might reduce the surgical risk, increase the R0 resection rate, and reduce the possibility of recurrence, making selected patients with clinical stage I potential beneficiaries of neoadjuvant immunochemotherapy.

The percentage of patients with squamous cell carcinoma in our real-world cohort was significantly higher than the proportions reported in Phase III clinical trials (CheckMate-816, Keynote-671, AEGEAN),[6,9,10] suggesting a clinical preference for neoadjuvant immunochemotherapy for patients with squamous cell carcinoma. Phase III clinical trials frequently use 3 cycles (CheckMate-816, Neotorch) or 4 cycles (Keynote-671, AEGEAN) of neoadjuvant therapy, whereas in routine clinical practice, patients mainly receive 2 to 4 cycles of neoadjuvant therapy, most commonly 2 cycles. In addition, the therapeutic strategies of adjuvant treatment are more flexible in routine clinical practice, including adjuvant chemotherapy, EGFR-TKI, immunotherapy, and immunotherapy plus chemotherapy.

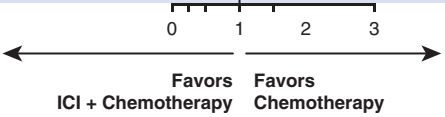
In our real-world neoadjuvant immunochemotherapy cohort, the rates of pCR and MPR were 32.8% and 58.1%, respectively, higher than those reported in clinical trials (pCR rate, 17.2%-24.8%; MPR rate, 30.2%-48.5%). The discrepancy can be attributed in part to the higher proportion of squamous cell carcinoma cases in our cohort, as patients with squamous cell carcinoma had much higher pCR and MPR rates in our real-world cohort. In addition, expression of PD-L1, a predictive biomarker for immunotherapy, as well as inconsistencies in the pathologic evaluation might account for the differences in pathologic response among cohorts. The 2-year DFS rate of 82.0% and 2-year OS rate of 93.1% in our real-world neoadjuvant immunochemotherapy cohort were higher than those reported in the aforementioned clinical trials. This might be attributed to a greater pathologic response, earlier clinical stage, and overestimation of clinical stage by computed tomography evaluation. Patients with pCR and MPR exhibited longer DFS and OS, further validating pathologic response as a prognostic marker for NSCLC patients receiving neoadjuvant immunotherapy.

The optimal neoadjuvant immunotherapy cycle for NSCLC remains a matter of debate.[18] The neoSCORE study compared the efficacy of 2 cycles and 3 cycles of neoadjuvant immunotherapy plus chemotherapy, and the results apparently showed a higher MPR in the recipients of 3-cycle therapy.[19] However, patients receiving different neoadjuvant immunotherapy cycles did not show different pathologic response rates and DFS in our real-world cohort, implying that 2 cycles of neoadjuvant immunotherapy might be sufficient to achieve a satisfactory pathologic response, and that patients should be evaluated for surgery after 2 cycles. Larger randomized controlled trials are needed to further investigate this issue.



A

Subgroups	N	Event N	HR (95% CI)	*P*-value
All patients	690	221	0.50 (0.38 to 0.68)	< .001
Age				
< 60	320	104	0.51 (0.33 to 0.78)	< .01
≥ 60	400	133	0.49 (0.34 to 0.71)	< .001
Sex				
Male	648	216	0.46 (0.34 to 0.62)	< .001
Female	76	21	0.58 (0.23 to 1.47)	.25
Smoking				
Yes	566	187	0.49 (0.35 to 0.67)	< .001
No	182	59	0.35 (0.20 to 0.63)	< .001
Histologic type				
SCC	492	157	0.47 (0.33 to 0.67)	< .001
ADC	228	78	0.50 (0.31 to 0.81)	< .01
cTNM stage				
I	60	12	0.33 (0.07 to 1.59)	.17
II	150	39	0.94 (0.49 to 1.79)	.84
III	510	185	0.42 (0.30 to 0.58)	< .001
cT stage				
T1-2	402	131	0.42 (0.28 to 0.61)	< .001
T3-4	288	91	0.51 (0.33 to 0.80)	< .01
cN stage				
N0-N1	296	77	0.71 (0.44 to 1.15)	.16
N2	384	144	0.34 (0.24 to 0.50)	< .001
EGFR				
Yes	42	13	0.12 (0.02 to 0.99)	.05
No	120	49	0.33 (0.18 to 0.60)	< .001
Unknown	488	146	0.48 (0.34 to 0.69)	< .001
ALK				
No	242	99	0.38 (0.24 to 0.59)	< .001
Unknown	458	135	0.49 (0.34 to 0.72)	< .001
Year of diagnosis				
2018~2022	390	123	0.59 (0.41 to 0.85)	< .01



B

FIGURE 3. Disease-free survival (*DFS*) in the matched cohort. A, Kaplan-Meier curves showing the DFS of the immunochemotherapy group and chemotherapy group in the primary matched cohort. B, DFS in patient subgroups of the matched cohort. *CI*, Confidence interval; *ICI*, immune checkpoint inhibitor; *NR*, not reached; *HR*, hazard ratio; *SCC*, squamous cell carcinoma; *ADC*, adenocarcinoma.

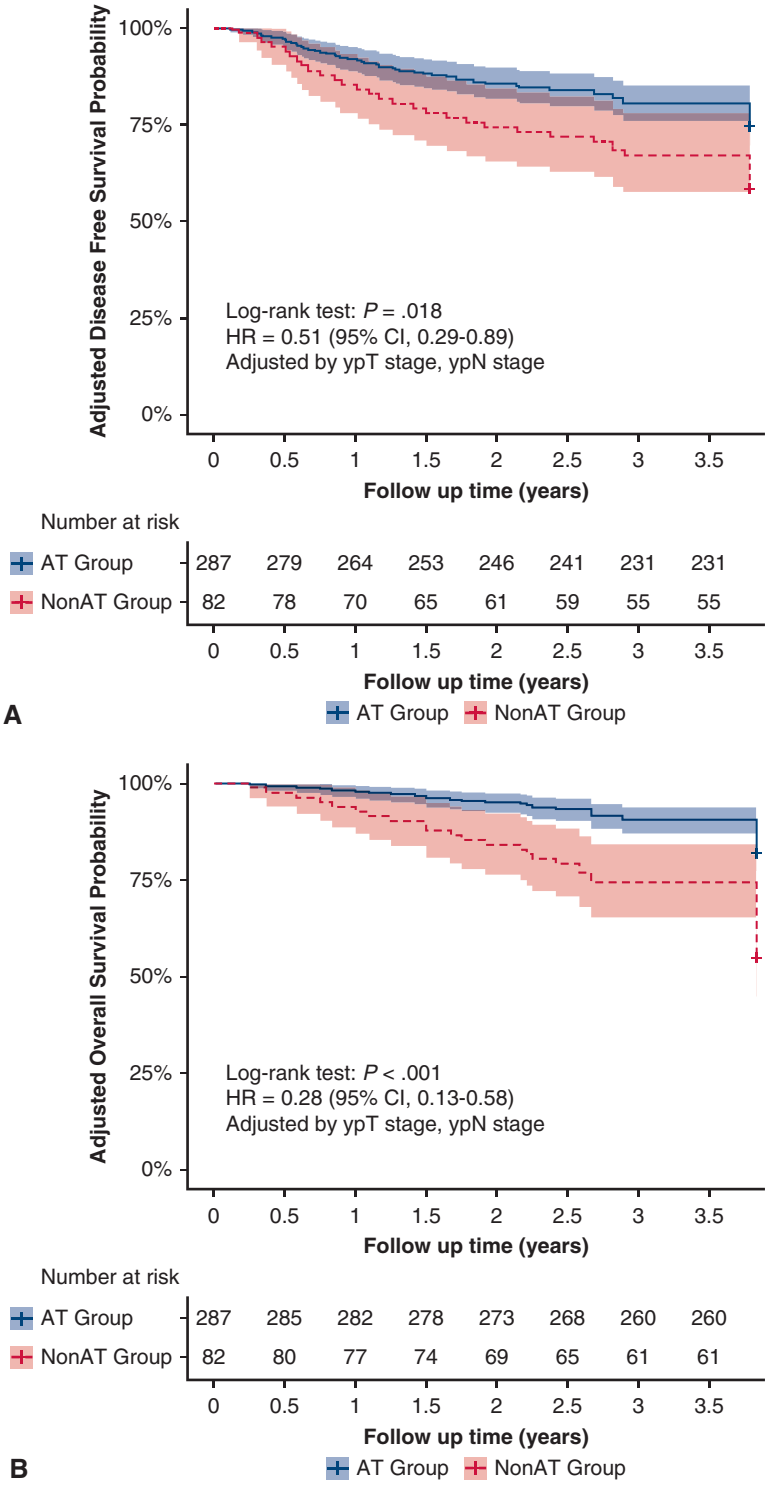


FIGURE 4. Kaplan-Meier curves adjusted by ypT stage and ypN stage and stratified by adjuvant therapy for disease-free survival (DFS) (A) and overall survival (OS) (B). *HR*, Hazard ratio; *CI*, confidence interval; *AT*, adjuvant therapy.

In the matched cohort, we found superior pathologic responses (pCR rate, 32.5% vs 6.4%; MPR rate, 57.1% vs 21.7%) and survival outcomes (DFS: HR, 0.50; 95% CI, 0.38-0.68 [$P < .001$]; OS: HR, 0.61; 95% CI, 0.40-0.94 [$P = .024$]) with neoadjuvant immunotherapy plus chemotherapy, further supporting the benefit of treating resectable NSCLC with neoadjuvant immunochemotherapy. Better clinical outcomes with immunochemotherapy compared

to chemotherapy were observed across nearly all key subgroups. Greater benefits were seen in patients with stage III/N2 cancer, consistent with previous studies.[6,17,20] Patients with stage I-II cancer exhibited a significant pathologic response that did not translate into a discernible survival benefit. This raises a critical question regarding the comparative efficacy of neoadjuvant treatment plus surgery versus surgery plus adjuvant treatment for these patients, necessitating further analysis with data from the 2 treatment groups. Females receiving neoadjuvant immunochemotherapy exhibited a significantly higher MPR rate than those receiving chemotherapy alone; however, no survival benefit was observed, possibly due to the relatively small number of females enrolled in the matched cohort.

Although adjuvant therapy is a critical issue for patients undergoing neoadjuvant immunotherapy, rigid adjuvant therapeutic strategies in clinical trials have limited further exploration. Among the 392 patients in our real-world neoadjuvant immunochemotherapy cohort with R0 resection, 82 (20.9%) did not receive adjuvant therapy. Older patients and patients receiving $\geq$4 cycles of neoadjuvant treatment were less likely to receive adjuvant therapy, highlighting the role of patients' physical status and previously received treatment cycles in clinicians' decision making processes in routine clinical practice. Patients receiving adjuvant therapy tended to have longer DFS and had longer OS, and multivariate analyses established adjuvant therapy as an independent prognostic factor for longer DFS and OS. This underscores the consideration of adjuvant treatment for the whole population with neoadjuvant immunochemotherapy. In addition, adjuvant immunotherapy did not exhibit an impact on DFS or OS for the whole population, but a significantly longer DFS with adjuvant immunotherapy was observed in patients with no oncogenic mutations. Considering that adjuvant immunotherapy with atezolizumab compared with best supportive care prolonged OS in patients with stage II-IIIA NSCLC with PD-L1 tumor cell $\geq$1%,[21] further studies are needed to explore stratified factors, such as oncogenic mutation status, PD-L1 expression,[21,22] and ctDNA clearance,[17,23,24] and to refine adjuvant immunotherapy.

From an oncologic perspective, the decision to use adjuvant therapy after neoadjuvant treatment and surgery should be guided by the pathologic response rate of the resected tumor.[25] An exploratory analysis of the Keynote-671 study showed an EFS benefit with perioperative immunotherapy irrespective of the pathologic response status. In our cohort, a significantly longer DFS with adjuvant therapy was observed in non-pCR and non-MPR patients, suggesting that adjuvant treatment potentially could reduce the risk of disease recurrence in patients with a relatively low pathologic response rate. Whether patients with pCR and MPR could benefit from adjuvant therapy requires further investigation, however. Moreover, patients who received 2 cycles of neoadjuvant therapy exhibited a significantly longer DFS with adjuvant therapy, highlighting the importance of perioperative treatment intensity. Therefore, we recommend adjuvant treatment in patients receiving 2 cycles of neoadjuvant therapy.

The application of neoadjuvant immunotherapy in patients with driver gene mutations has remained controversial.[26,27] Owing to the inferior efficacy of immunotherapy for patients with advanced NSCLC harboring an *EGFR*/*ALK* mutation,[28] most clinical trials involving neoadjuvant immunotherapy excluded these patients. The Keynote-671 study showed a potential EFS benefit with neoadjuvant immunotherapy plus chemotherapy in patients with *EGFR* mutations; however, the small numbers of patients and events limit the validity of this finding. In our cohort, a significantly higher MPR rate was observed in the immunochemotherapy group compared to the chemotherapy group among patients with *EGFR* mutations and those with *KRAS* mutations. Zhang and colleagues[29] reported that in their patients with an *EGFR* mutation, MPR and pCR rates were higher in patients receiving neoadjuvant immunotherapy plus chemotherapy compared to those receiving erlotinib plus chemotherapy.[29] Those findings, along with the significant DFS benefit with neoadjuvant immunochemotherapy observed in our patients with *EGFR* mutations, support the potential feasibility of neoadjuvant immunotherapy for resectable oncogene-mutant NSCLC. The LCMC4 study and NeoADAURA study may provide more insight into the treatment of this patient population.[30,31]

Despite our efforts to meticulously collect complete clinical data and address the bias and confounding factors during the analysis, this study is limited by its retrospective nature. In addition, the immunotherapy regimens, clinical staging, surgical techniques, pathologic evaluation, and adjuvant therapy regimens of different centers were subject to local clinical routines, introducing potential confounding factors into the analysis. Furthermore, there was an evolution over time in the use of neoadjuvant immunochemotherapy rather than chemotherapy alone, which might have produced some bias in our survival analysis.

In summary, our results show a pCR rate of 32.8% and a 2-year DFS rate of 82.0% in the neoadjuvant immunochemotherapy setting, and we have validated the superior efficacy of neoadjuvant immunochemotherapy over neoadjuvant chemotherapy alone for NSCLC in our propensity score–matched cohort. Notably, adjuvant therapy could prolong DFS in patients receiving neoadjuvant immunochemotherapy, and patients without pCR and with 2 neoadjuvant cycles appear to be potential beneficiaries of adjuvant therapy.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or

reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: neoadjuvant immunotherapy, pathologic complete response, disease-free survival, resectable NSCLC, real-world study

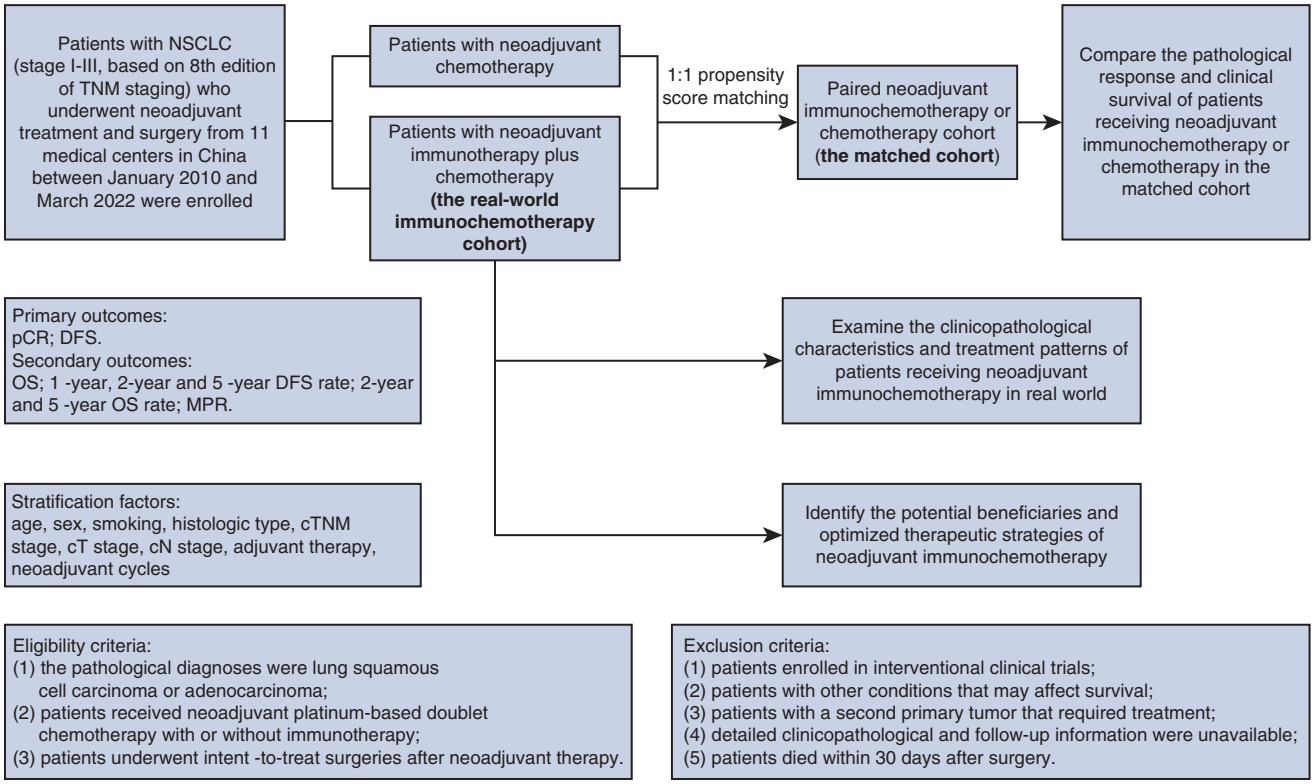


FIGURE E1. Study diagram. *NSCLC*, Non–small cell lung cancer; *cTNM stage*, clinical stage based on 8th edition of TNM staging of lung cancer; *pCR*, pathologic complete response; *DFS*, disease-free survival; *OS*, overall survival; *MPR*, major pathologic response.

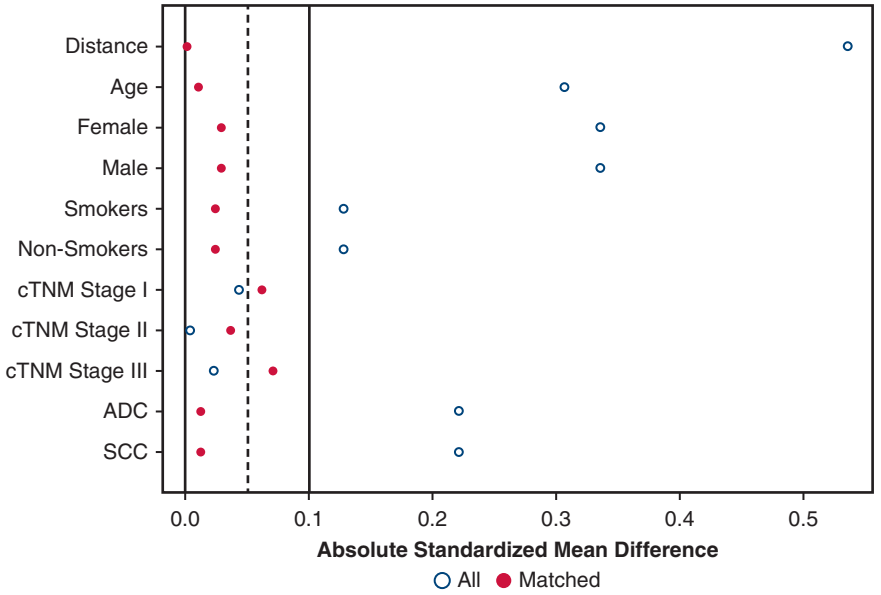


FIGURE E2. Absolute standardized mean difference between neoadjuvant immunochemotherapy group and chemotherapy group in the crude cohort and matched cohort. *cTNM stage*, Clinical stage based on 8th edition of TNM staging of lung cancer; *ADC*, adenocarcinoma; *SCC*, squamous cell carcinoma.

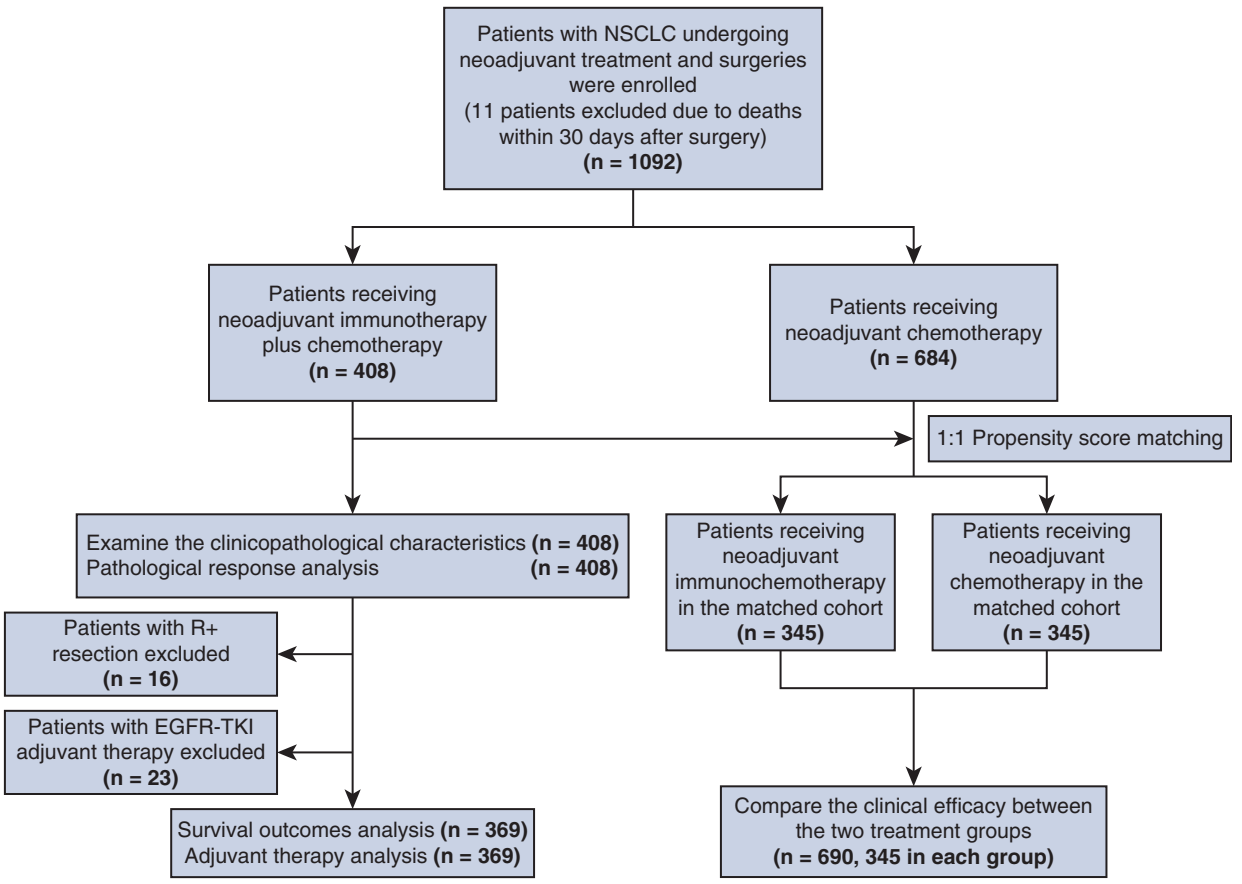
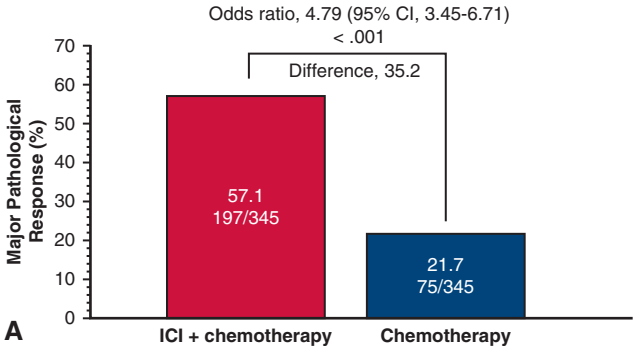


FIGURE E3. CONSORT diagram. *NSCLC*, Non–small cell lung cancer.



Subgroups	N	Chemo	ICI_Chemo	RD% (95% CI)
All patients	690	21.7 (17.5 to 26.5)	57.1 (51.7 to 62.4)	35.4 (26.0 to 44.7)
Age				
< 60	320	23.8 (17.4 to 31.1)	53.8 (45.7 to 61.7)	30.0 (16.4 to 43.6)
≥ 60	400	21.5 (16.0 to 27.8)	59.5 (52.3 to 66.4)	38.0 (25.5 to 50.5)
Sex				
Male	648	23.5 (18.9 to 28.5)	58.3 (52.7 to 63.8)	34.9 (25.0 to 44.7)
Female	76	13.2 (4.4 to 28.1)	42.1 (26.3 to 59.2)	28.9 (5.3 to 52.6)
Smoking				
Yes	566	25.4 (20.5 to 30.9)	60.1 (54.1 to 65.8)	34.6 (23.9 to 45.4)
No	182	13.2 (7.0 to 21.9)	42.9 (32.5 to 53.7)	29.7 (14.3 to 45.1)
Histologic type				
SCC	492	26.8 (21.4 to 32.8)	65.4 (59.1 to 71.4)	38.6 (26.6 to 50.6)
ADC	228	13.2 (7.6 to 20.8)	36.8 (28.0 to 46.4)	23.7 (10.7 to 36.7)
cTNM stage				
I	60	30.0 (14.7 to 49.4)	53.3 (34.3 to 71.7)	23.3 (–9.3 to 56.0)
II	150	18.7 (10.6 to 29.3)	53.3 (41.4 to 64.9)	34.7 (15.5 to 53.9)
III	510	22.7 (17.7 to 28.4)	58.0 (51.7 to 64.2)	35.3 (24.3 to 46.3)
cT stage				
T1-2	402	21.4 (15.9 to 27.7)	54.7 (47.6 to 61.7)	33.3 (21.3 to 45.4)
T3-4	288	22.2 (15.7 to 29.9)	61.1 (52.6 to 69.1)	38.9 (24.0 to 53.8)
cN stage				
N0-N1	296	23.0 (16.5 to 30.6)	52.7 (44.3 to 61.0)	29.7 (15.7 to 43.7)
N2	384	20.3 (14.9 to 26.7)	59.4 (52.1 to 66.4)	39.1 (26.4 to 51.7)
Radiological response				
CR	14	71.4 (29.0 to 96.3)	100.0 (59.0 to 100.0)	28.6 (–68.4 to 125.6)
PR	448	24.6 (19.1 to 30.7)	62.9 (56.3 to 69.3)	38.4 (26.1 to 50.6)
SD	212	6.6 (2.7 to 13.1)	41.5 (32.0 to 51.5)	34.9 (21.7 to 48.1)
PD	-			
EGFR				
Yes	42	0.0 (0.0 to 16.1)	28.6 (11.3 to 52.2)	28.6 (5.7 to 51.4)
No	120	10.0 (3.8 to 20.5)	58.3 (44.9 to 70.9)	48.3 (27.4 to 69.2)
Unknown	488	28.3 (22.7 to 34.4)	63.5 (57.1 to 69.6)	35.2 (23.2 to 47.3)
ALK				
No	242	8.3 (4.0 to 14.7)	44.6 (35.6 to 53.9)	36.4 (23.4 to 49.3)
Unknown	458	29.7 (23.9 to 36.1)	66.8 (60.3 to 72.9)	37.1 (24.4 to 49.8)
Year of diagnosis				
2018~2022	390	16.9 (11.9 to 22.9)	52.8 (45.6 to 60.0)	35.9 (24.2 to 47.6)

FIGURE E4. Major pathologic response (MPR) in the matched cohort. A, Barplots showing the MPR rate of immunochemotherapy group and chemotherapy group in the primary matched cohort. B, MPR in patient subgroups of the matched cohort. *CI*, Confidence interval; *ICI*, immune checkpoint inhibitor; *RD*, rate difference; *SCC*, squamous cell carcinoma; *ADC*, adenocarcinoma; *CR*, complete response; *PR*, partial response; *SD*, stable disease; *PD*, progressive disease.

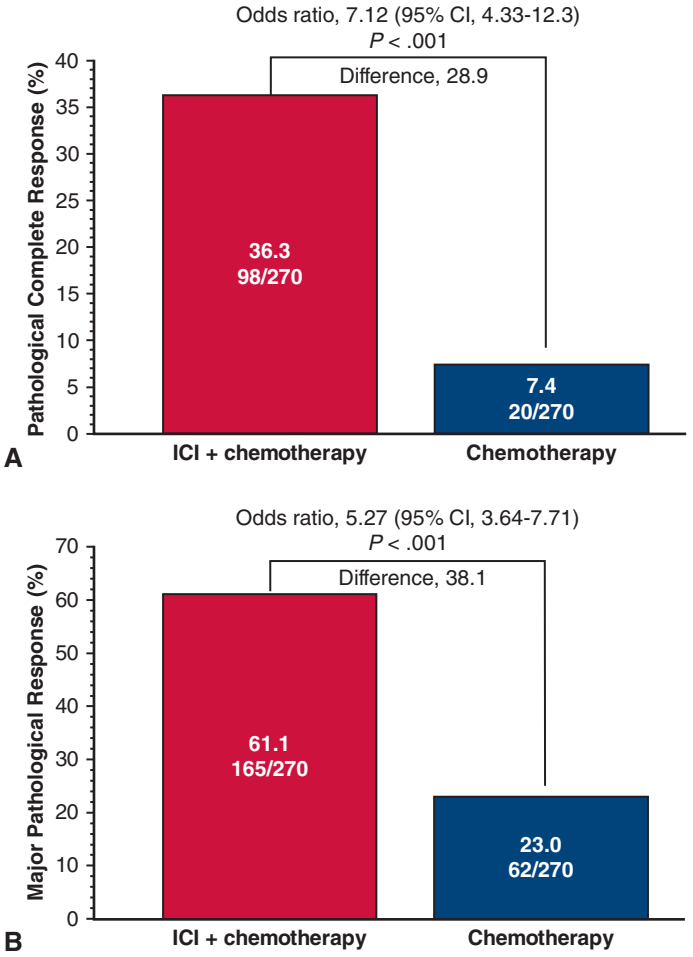


FIGURE E5. Barplots showing pathologic complete response (pCR) (A) and major pathologic response (MPR) (B) in patients without oncogenic mutations after propensity score matching. N = 540, with 270 in each treatment group. Patients with adenocarcinoma with oncogenic mutations or no molecular testing results were excluded from the analysis. *CI*, Confidence interval; *ICI*, immune checkpoint inhibitor.

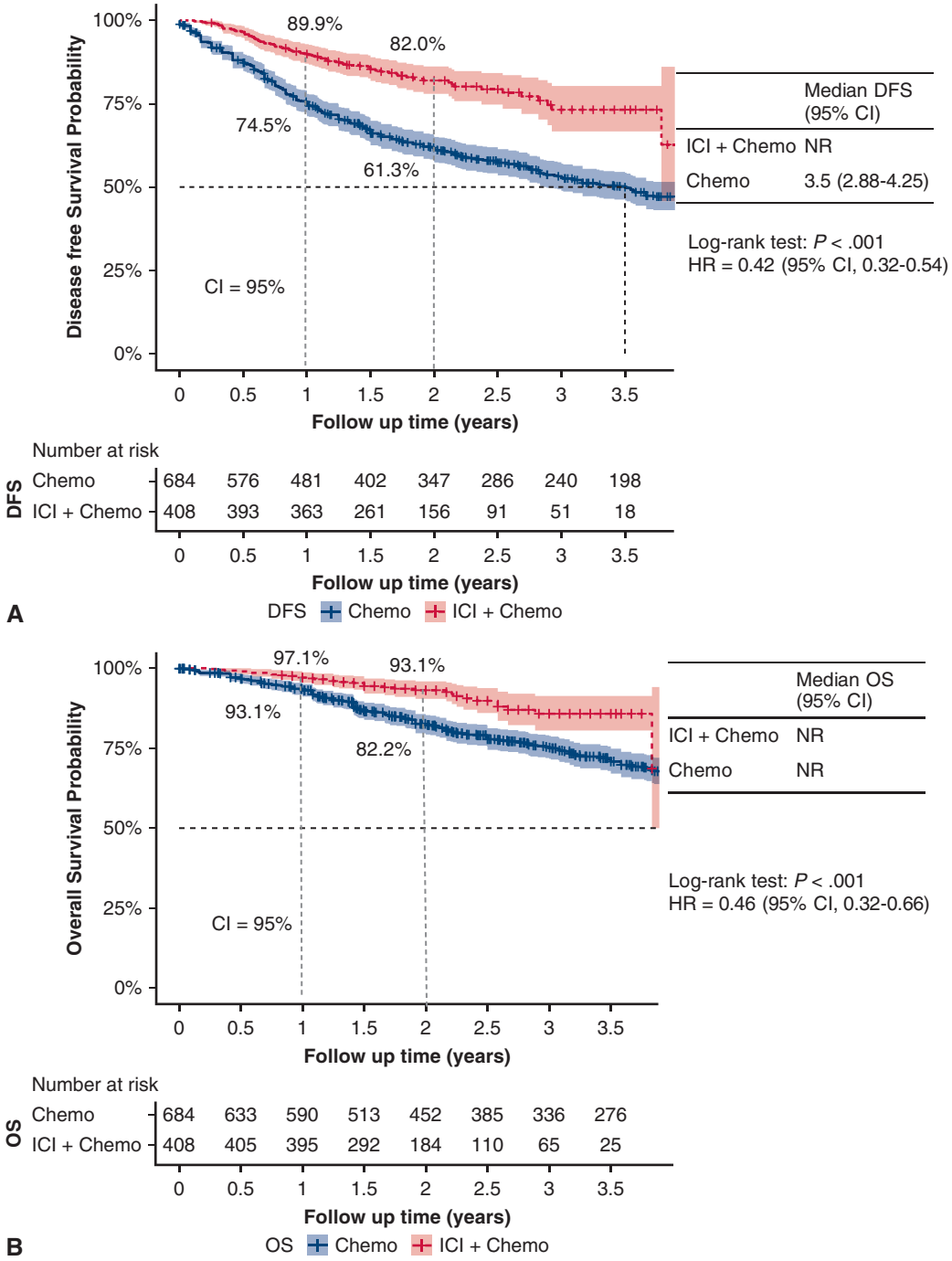
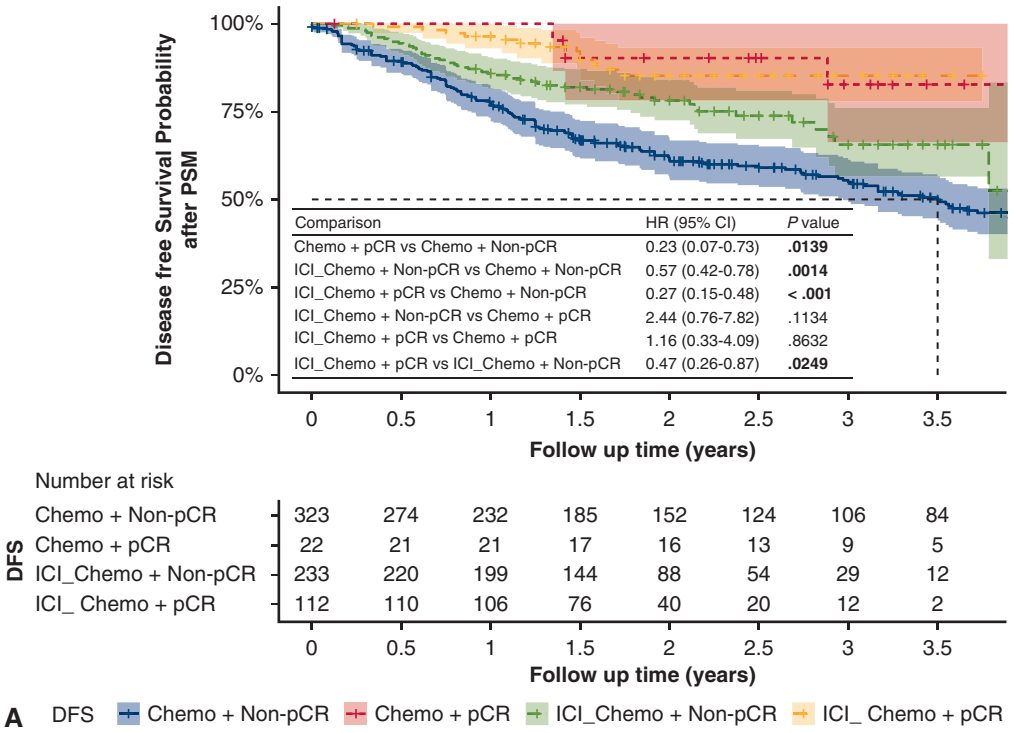


FIGURE E6. Survival outcomes of the crude real-world cohort, with Kaplan-Meier curves showing disease-free survival (*DFS*) (A) and overall survival (*OS*) (B). *CI*, Confidence interval; *ICI*, immune checkpoint inhibitor; *HR*, hazard ratio; *NR*, not reached.



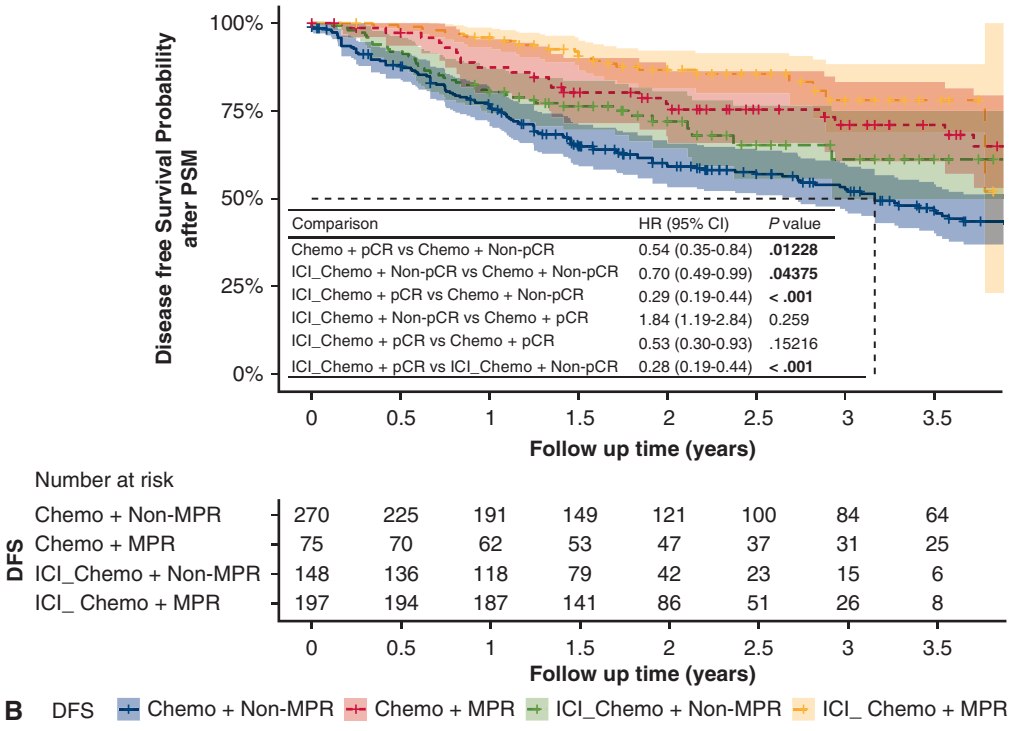


FIGURE E7. Kaplan-Meier curves showing the disease-free survival (*DFS*) of the matched cohort stratified by treatment and pathologic complete response (*pCR*) (A) or major pathologic response (*MPR*) (B). *ICI*, Immune checkpoint inhibitor; *HR*, hazard ratio; *CI*, confidence interval; *PSM*, propensity score matching.

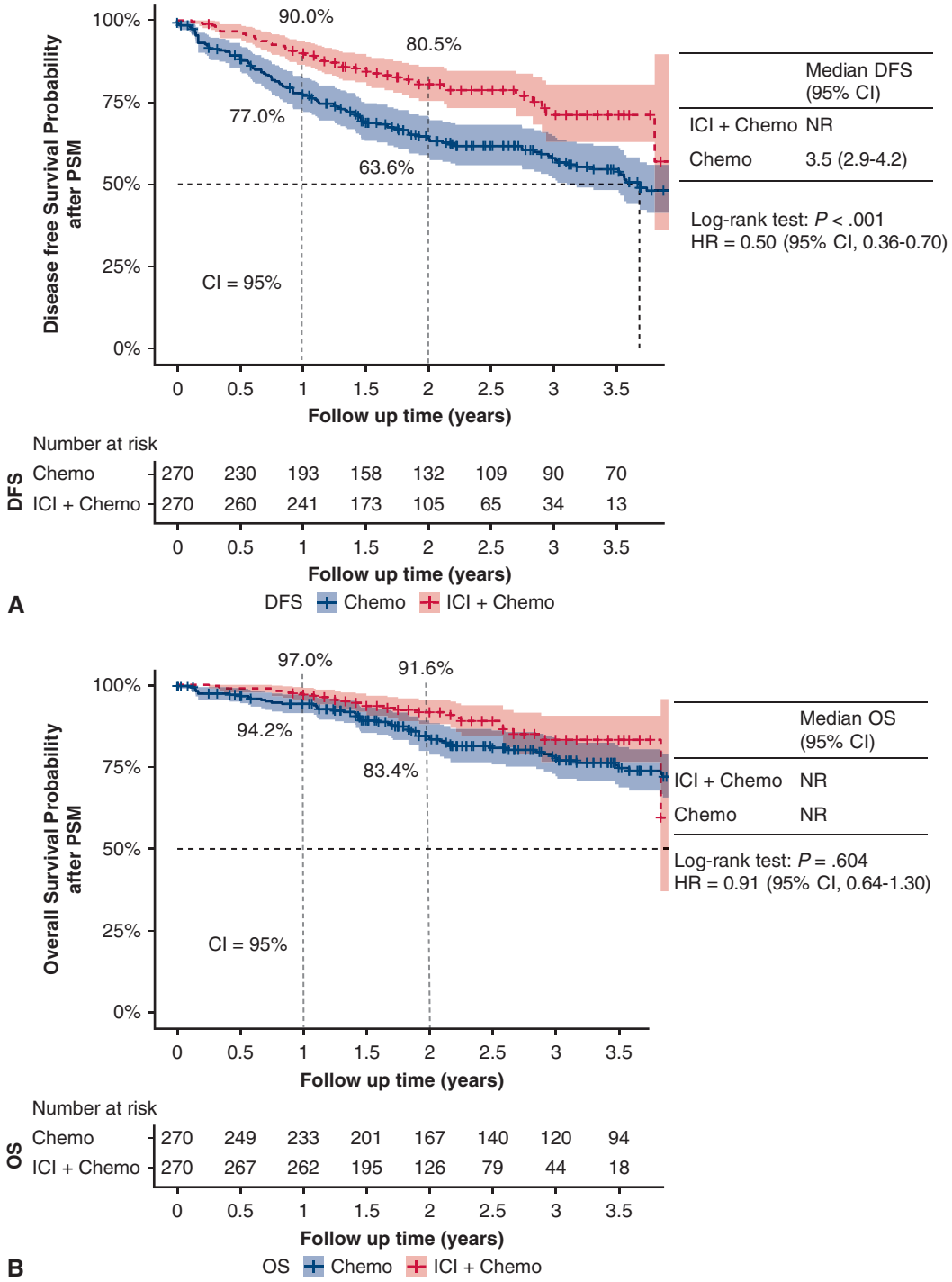
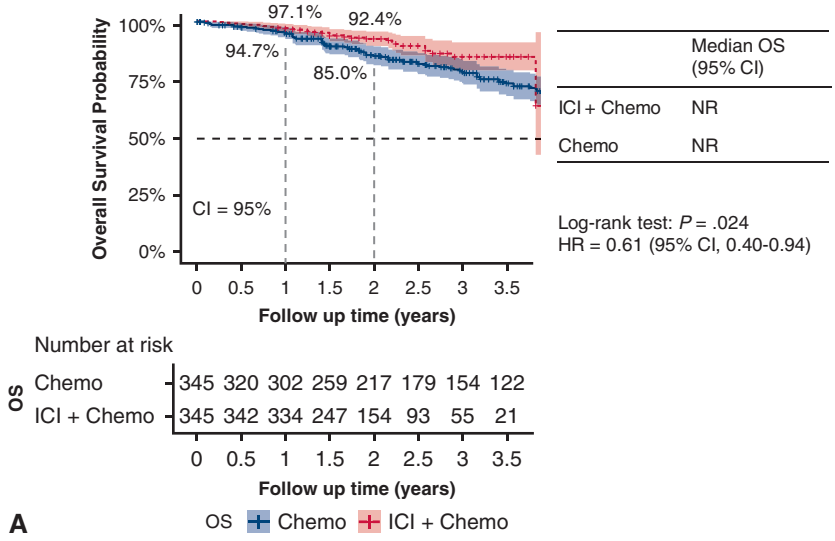


FIGURE E8. Kaplan-Meier curves showing disease-free survival (*DFS*) (A) and overall survival (*OS*) (B) of patients without oncogenic mutations after propensity score matching. N = 540, with 270 in each treatment group. Patients with adenocarcinoma with oncogenic mutations or no molecular testing results were excluded from the analysis. *PSM*, Propensity score matching; *CI*, confidence interval; *ICI*, immune checkpoint inhibitor; *NR*, not reached; *HR*, hazard ratio.



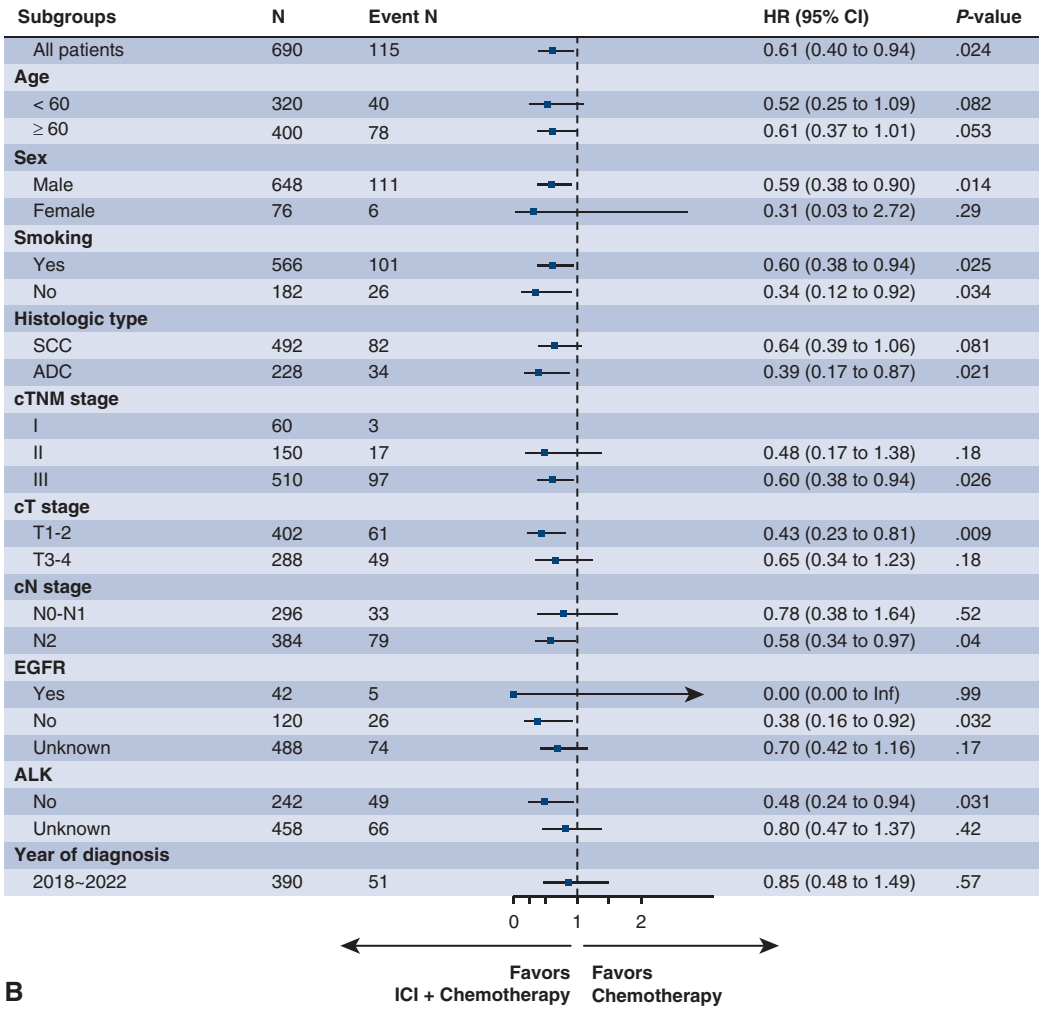


FIGURE E9. Overall survival (*OS*) in the matched cohort. A, Kaplan-Meier curves showing the OS of immunochemotherapy group and chemotherapy group in the primary matched cohort. B, OS in patient subgroups of the matched cohort. *ICI*, Immune checkpoint inhibitor; *NR*, not reached; *HR*, hazard ratio; *cTNM stage*, clinical stage based on 8th edition of TNM staging of lung cancer; *SCC*, squamous cell carcinoma; *ADC*, adenocarcinoma.

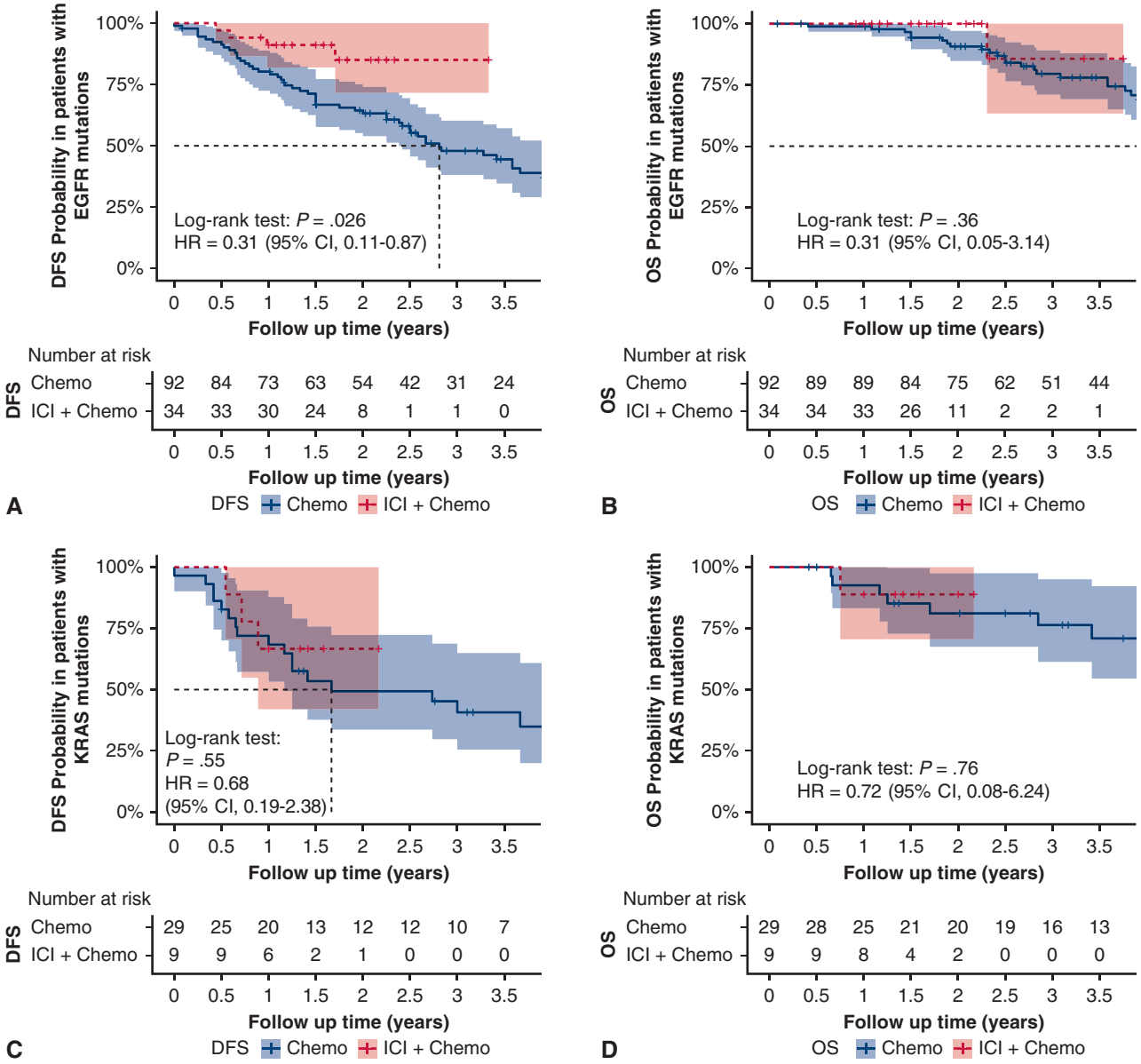


FIGURE E10. Survival outcomes of patients with driver gene mutations. Kaplan-Meier curves stratified by treatment showing disease-free survival (*DFS*) (A) and overall survival (*OS*) (B) of patients with *EGFR* mutations and DFS (C) and OS (D) of patients with *KRAS* mutations. *HR*, Hazard ratio; *CI*, confidence interval.

TABLE E1. NeoR-World study collaboration: participating institutions and investigators

Institution	Location	Investigators
Department of Thoracic Surgery, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College	Beijing, China	Jie He
Department of Thoracic Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine	Hangzhou, Zhejiang, China	Jian Hu
Department of Thoracic Surgery, The First Affiliated Hospital of Xi'an Jiaotong University	Xi'an, Shanxi, China	Guangjian Zhang
Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University	Shanghai, China	Feng Yao
Department of Thoracic Surgery, The Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine	Fuzhou, Fujian, China	Chun Chen
Department of Thoracic Surgery, Jining First People's Hospital	Jining, Shandong, China	Honghao Fu
Department of thoracic surgery, Affiliated Hospital of Zunyi Medical University	Zunyi, Guizhou, China	Yongxiang Song
Department of Thoracic Oncology, Chongqing University Cancer Hospital	Chongqing, China	Yuequan Jiang
Department of Thoracic Surgery, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University	Jinan, Shandong, China	Hounai Xie
Department of Thoracic Surgery, Peking University Third Hospital	Beijing, China	Jingdi Wang
Department of thoracic surgery, Fujian Medical University Union Hospital	Fuzhou, China	Yangtian Chen

TABLE E2. Postoperative surgical outcomes by number of neoadjuvant cycles

Characteristic	Overall (N = 408)	≤2 cycles (N = 239)	3 cycles (N = 103)	≥4 cycles (N = 66)	*P* value
Approach, n (%)					.002
Conversion	31 (7.6)	16 (6.7)	6 (5.8)	9 (13.6)	
Open	130 (31.9)	89 (37.2)	19 (18.4)	22 (33.3)	
VATS/RATS	247 (60.5)	134 (56.1)	78 (75.7)	35 (53.0)	
Operative time, min					.4
Median (IQR)	148 (119-181)	145 (118-180)	150 (120-190)	146 (118-180)	
Range	48-440	53-360	48-375	60-440	
Estimated blood loss, mL, n (%)					NA
<100	310 (76.0)	183 (76.6)	76 (73.8)	51 (77.3)	
100-200	70 (17.2)	41 (17.2)	22 (21.4)	7 (10.6)	
>200	28 (6.9)	15 (6.3)	5 (4.9)	8 (12.1)	
Chest tube duration, d					<.001
Median (IQR)	6.0 (4.0-10.0)	6.0 (4.0-11.0)	5.0 (3.0-8.0)	7.0 (4.0-9.0)	
Range	1.0-30.0	2.0-30.0	1.0-29.0	1.0-30.0	
Length of stay, d					.091
Median (IQR)	9.0 (7.0-14.0)	9.0 (7.0-14.0)	8.0 (7.0-12.5)	10.0 (8.0-15.0)	
Range	2.0-35.0	3.0-31.0	2.0-35.0	4.0-24.0	
Readmission rate, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	NA

VATS, Video-assisted thoracoscopic surgery; *RATS*, robotic-assisted thoracic surgery; *IQR*, interquartile range; *NA*, not applicable.

TABLE E3. pCR and MPR rates before and after PSM

Variable	Before PSM			After PSM		
	Chemo (N = 684)	ICI + Chemo (N = 408)	*P* value	Chemo (N = 345)	ICI + Chemo (N = 345)	*P* value
pCR, n (%)			<.001			<.001
Non-pCR	654 (95.6)	274 (67.2)		323 (93.6)	233 (67.5)	
pCR	30 (4.4)	134 (32.8)		22 (6.4)	112 (32.5)	
MPR, n (%)			<.001			<.001
Non-MPR	553 (80.8)	171 (41.9)		270 (78.3)	148 (42.9)	
MPR	131 (19.2)	237 (58.1)		75 (21.7)	197 (57.1)	

PSM, Propensity score matching; *ICI*, immune checkpoint inhibitor; *pCR*, pathologic complete response; *MPR*, major pathologic response.

TABLE E4. Univariate analysis for DFS and OS in the real-world neoadjuvant immunochemotherapy cohort

Clinicopathologic characteristic (N = 392)	DFS, HR (95% CI)	*P* value	OS, HR (95% CI)	*P* value
Age	1.0 (0.97-1.02)	.71	1.04 (1.00-1.09)	.058
Sex				
Female	1 [Reference]		1 [Reference]	
Male	0.98 (0.45-2.14)	.96	3.29 (0.45-24.1)	.24
Smoking				
No	1 [Reference]		1 [Reference]	
Yes/ever	1.36 (0.81-2.29)	.25	2.18 (0.91-5.27)	.082
Histologic type				
ADC	1 [Reference]		1 [Reference]	
SCC	0.70 (0.44-1.13)	.15	1.32 (0.60-2.91)	.50
Neoadjuvant cycles				
≤2	1 [Reference]		1 [Reference]	
3	0.72 (0.41-1.29)	.27	0.23 (0.05-0.98)	.047
≥4	0.90 (0.48-1.70)	.75	2.03 (0.98-4.20)	.056
pCR				
Non-pCR	1 [Reference]		1 [Reference]	
pCR	0.46 (0.26-0.83)	.010	0.47 (0.20-1.14)	.10
MPR				
Non-MPR	1 [Reference]		1 [Reference]	
MPR	0.40 (0.25-0.63)	<.001	0.28 (0.14-0.57)	<.001
ypT stage				
T0	1 [Reference]		1 [Reference]	
T1-2	1.76 (1.02-3.04)	.042	1.72 (0.76-3.86)	.19
T3-4	3.72 (1.75-7.89)	<.001	3.09 (1.01-9.48)	.048
ypN stage				
N0	1 [Reference]		1 [Reference]	
N1	2.48 (1.38-4.45)	.002	3.52 (1.42-8.72)	.006
N2	2.92 (1.73-4.92)	<.001	5.67 (2.57-12.5)	<.001
ypTNM stage				
0	1 [Reference]		1 [Reference]	
I	0.99 (0.47-2.12)	.99	0.33 (0.07-1.66)	.18
II	3.05 (1.53-6.09)	.002	2.73 (0.97-7.70)	.058
III	3.43 (1.81-6.49)	<.001	4.35 (1.72-11.0)	.002
Adjuvant therapy*				
No	1 [Reference]		1 [Reference]	
Yes	0.61 (0.35-1.05)	.075	0.37 (0.18-0.75)	.006

(Continued)

TABLE E4. Continued

Clinicopathologic characteristic (N = 392)	DFS, HR (95% CI)	*P* value	OS, HR (95% CI)	*P* value
Adjuvant immunotherapy*				
No	1 [Reference]		1 [Reference]	
Yes	0.66 (0.40, 1.08)	.10	0.52 (0.26, 1.04)	.065
PD-L1, n (%)				
<1%	1 [Reference]		1 [Reference]	
≥1%	1.36 (0.45-4.17)	.70	0.75 (0.11-5.36)	.78
Unknown	1.86 (0.74-4.66)	.29	2.12 (0.50-8.93)	.30

DFS, Disease-free survival; *HR*, hazard ratio; *CI*, confidence interval; *OS*, overall survival; *ADC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *pCR*, pathologic complete response; *MPR*, major pathologic response. *N = 369 (patients with R+ resection and EGFR-TKI adjuvant therapy were excluded).

THOR

TABLE E5. Association between clinicopathologic characteristics and adjuvant therapy in the real-world neoadjuvant immunochemotherapy cohort with R0 resection

Clinicopathologic characteristic	Total N	Adjuvant N	OR (95% CI)	*P* value
Age	392	310	0.96 (0.93-0.99)	**.008**
Sex	392	310		.10
Female			1 [Reference]	
Male			0.45 (0.13-1.17)	
Smoking	392	310		.69
No			1 [Reference]	
Yes/ever			0.90 (0.51-1.52)	
Histologic type	392	310		.053
ADC			1 [Reference]	
SCC			0.57 (0.30-1.01)	
Neoadjuvant cycles	392	310		**.002**
≤2			1 [Reference]	
3			1.18 (0.64-2.27)	
≥4			0.36 (0.20-0.67)	
ypT stage	392	310		.52
T0			1 [Reference]	
T1-2			1.32 (0.79-2.19)	
T3-4			0.96 (0.39-2.59)	
ypN stage	392	310		.12
N0			1 [Reference]	
N1			1.87 (0.88-4.46)	
N2			1.70 (0.87-3.59)	
ypTNM stage	392	310		.49
0			1 [Reference]	
I			1.24 (0.68-2.28)	
II			1.22 (0.60-2.60)	
III			1.74 (0.87-3.66)	
pCR	392	310		.23
Non-pCR			1 [Reference]	
pCR			0.73 (0.44-1.22)	
MPR	392	310		.56
Non-MPR			1 [Reference]	
MPR			1.16 (0.71-1.89)	

(Continued)

TABLE E5. Continued

Clinicopathologic characteristic	Total N	Adjuvant N	OR (95% CI)	*P* value
Surgery	392	310		.42
Bilobectomy			1 [Reference]	
Lobectomy			0.65 (0.18-1.76)	
Lobectomy-sleeve			0.72 (0.18-2.40)	
Pneumonectomy			0.40 (0.10-1.29)	
PD-L1	392	310		.64
<1%			1 [Reference]	
≥1%			1.56 (0.62-4.02)	
Unknown			1.22 (0.60-2.38)	

Bold indicates statistical significance. *OR*, Odds ratio; *CI*, confidence interval; *ADC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *pCR*, pathologic complete response; *MPR*, major complete response.

TABLE E6. Subgroup analysis of adjuvant therapy after multivariate adjustment*

Characteristic	DFS			OS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
ALL	0.51	0.29-0.89	.018	0.28	0.13-0.58	<.001
Age						
<60 y	0.52	0.25-1.08	.079	0.31	0.13-0.71	.006
≥60 y	0.47	0.19-1.15	.1	0.24	0.05-1.10	.066
Sex						
Male	0.45	0.25-0.79	.006	0.27	0.13-0.57	<.001
Female	-	-	-	-	-	-
Smoking						
No	2.26	0.27-18.8	.4	0.42	0.03-5.42	.5
Yes/ever	0.32	0.18-0.59	<.001	0.18	0.08-0.41	<.001
Histologic type						
SCC	0.57	0.29-1.12	.1	0.36	0.15-0.85	.02
ADC	0.42	0.16-1.13	.086	0.11	0.02-0.53	.006
Oncogenic mutation						
Yes (*EGFRm/ALK+*)	1.00	0.00-∞	>.99	-	-	-
No	0.44	0.24-0.80	.007	0.27	0.12-0.59	.001
Unknown	0.43	0.24-0.78	.006	0.27	0.12-0.58	<.001
Neoadjuvant cycles						
≤2	0.33	0.16-0.71	.004	0.27	0.10-0.71	.008
3	2.49	0.31-19.8	.4	0.08	0.00-2.39	.14
≥4	0.55	0.16-1.90	.3	0.42	0.11-1.58	.2
pCR						
pCR	0.56	0.17-1.86	.3	0.17	0.03-0.95	.044
non-pCR	0.49	0.26-0.92	.025	0.33	0.14-0.77	.01
MPR						
MPR	0.88	0.32-2.37	.8	0.36	0.10-1.32	.12
non-MPR	0.38	0.19-0.77	.007	0.27	0.10-0.68	.006
PD-L1						
<1%	0.80	0.08-8.18	.85	0.58	0.03-10.3	.71
≥1%	0.20	0.03-1.29	.09	0.00	0-∞	>.99
Unknown	0.53	0.28-1.00	.051	0.31	0.14-0.68	.004

DFS, Disease-free survival; *OS*, overall survival; *HR*, hazard ratio; *CI*, confidence interval; *ADC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *pCR*, pathologic complete response; *MPR*, major pathologic response. *Subgroups (n = 369): adjuvant therapy, yes versus no. Patients with EGFR-TKI adjuvant therapy were excluded (n = 23).

TABLE E7. Subgroup analysis of adjuvant immunotherapy after multivariate adjustment*

Characteristic	DFS			OS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
ALL	0.69	0.41-1.15	.15	0.56	0.27-1.16	.12
Age						
<60 y	0.66	0.29-1.46	.3	0.44	0.11-1.79	.3
≥60 y	0.75	0.37-1.52	.4	0.71	0.30-1.71	.4
Sex						
Male	0.65	0.38-1.11	.12	0.55	0.27-1.12	.1
Female	1.28	0.20-8.30	.8	-	-	-
Smoking						
No	1.41	0.39-5.11	.6	1.35	0.13-14.5	.8
Yes/ever	0.58	0.33-1.03	.063	0.43	0.20-0.93	.033
Histologic type						
SCC	0.58	0.32-1.08	.089	0.64	0.28-1.44	.3
ADC	1.11	0.43-2.89	.8	0.41	0.09-1.93	.3
Oncogenic mutation						
Yes (*EGFRm/ALK*+)	∞	0-∞	>.99	-	-	-
No	0.53	0.30-0.92	.026	0.53	0.25-1.14	.10
Unknown	0.55	0.31-0.95	.032	0.51	0.24-1.09	.083
Neoadjuvant cycles						
≤2	0.53	0.27-1.06	.073	0.61	0.24-1.57	.3
3	1.64	0.41-6.52	.5	0.39	0.02-7.90	.5
≥4	0.86	0.23-3.18	.8	0.7	0.18-2.70	.6
pCR						
pCR	0.71	0.22-2.23	.6	0.3	0.05-1.64	.2
non-pCR	0.67	0.38-1.19	.2	0.7	0.31-1.57	.4
MPR						
MPR	0.93	0.41-2.10	.9	1.05	0.30-3.70	>.9
non-MPR	0.6	0.30-1.18	.14	0.46	0.19-1.14	.093
PD-L1						
<1%	0.73	0.04-12.9	.83	0.61	0-∞	>.99
≥1%	1.06	0.22-5.08	.94	0.48	0.02-10.9	.65
Unknown	0.65	0.36-1.16	.15	0.58	0.27-1.25	.17

DFS, Disease-free survival; *OS*, overall survival; *HR*, hazard ratio; *CI*, confidence interval; *SCC*, squamous cell carcinoma; *ADC*, adenocarcinoma; *pCR*, pathologic complete response; *MPR*, major pathologic response. *Subgroups (n = 369): adjuvant immunotherapy (yes vs no). Patients with EGFR-TKI adjuvant therapy were excluded (n = 23).

TABLE E8. Clinicopathologic characteristics of patients with driver gene mutations receiving neoadjuvant immunochemotherapy or chemotherapy

Characteristic	*EGFR* mutation			*KRAS* mutation		
	Chemo (N = 92)	ICI + Chemo (N = 34)	*P* value	Chemo (N = 29)	ICI + Chemo (N = 14)	*P* value
Age, y, mean (SD)	58.4 (8.07)	55.4 (10.7)	.147	58.2 (10.6)	58.4 (5.68)	.929
Sex, n (%)			.393			.396
Female	53 (57.6)	16 (47.1)		6 (20.7)	1 (7.14)	
Male	39 (42.4)	18 (52.9)		23 (79.3)	13 (92.9)	
Smoking, n (%)			.943			1
No	62 (67.4)	22 (64.7)		7 (24.1)	3 (21.4)	
Yes/ever	30 (32.6)	12 (35.3)		22 (75.9)	11 (78.6)	
cTNM stage			.317			.615
I	12 (13.0)	3 (8.82)		5 (17.2)	2 (14.3)	
II	20 (21.7)	12 (35.3)		3 (10.3)	3 (21.4)	
III	60 (65.2)	19 (55.9)		21 (72.4)	9 (64.3)	
ypTNM stage			**.006**			**.003**
0	1 (1.10)	1 (3.03)		0 (0.0)	5 (38.5)	
I	16 (17.6)	15 (45.5)		7 (24.1)	3 (23.1)	
II	16 (17.6)	2 (6.06)		5 (17.2)	0 (0.0)	
III	58 (63.7)	15 (45.5)		17 (58.6)	5 (38.5)	
pCR			.468			**.002**
Non-pCR	91 (98.9)	33 (97.1)		29 (100)	9 (64.3)	
pCR	1 (1.09)	1 (2.94)		0 (0.0)	5 (35.7)	
MPR			**.003**			**.003**
Non-MPR	88 (95.7)	26 (76.5)		27 (93.1)	7 (50.0)	
MPR	4 (4.35)	8 (23.5)		2 (6.90)	7 (50.0)	

Bold indicates statistical significance. *ICI*, Immune checkpoint inhibitor; *IQR*, interquartile range; *SD*, standard deviation; *cTNM stage*, clinical stage based on 8th edition of TNM staging of lung cancer; *pCR*, pathologic complete response; *MPR*, major pathologic response.

TABLE E9. Summary of research on neoadjuvant immunotherapy for resectable NSCLC

Parameter	CheckMate-816	Keynote-671	AEGEAN	Neotorch	NeoR-World	
Study type	Phase III RCT	Phase III RCT	Phase III RCT	Phase III RCT	Real-world study, matched cohort	Real-world study, crude cohort
ICI regimen	Nivolumab + chemo vs chemo	Pembrolizumab + chemo vs chemo	Durvalumab + chemo vs chemo	Toripalimab + chemo vs chemo	Multiple anti-PD-1/ PD-L1 regimens + chemo vs chemo	
Neoadjuvant cycles	3	4	4	3	2-4*	
No. of patients enrolled	179 vs 179	397 vs 400	366 vs 374	202 vs 202	345 vs 345	408 vs 684
Age, y, median, (range)	64 (41-82) vs 65 (34-84)	63 (26-83) vs 64 (35-81)	65 (30-88) vs 65 (38-85)	<65: 69.3% vs 68.3%	60 (55-66) vs 60 (55-65)	61 (56-66) vs 59 (53-64)
Sex, %	M: 71.5 vs 70.9	M: 70.3 vs 71.0	M: 68.9 vs 74.3	M: 89.6 vs 93.6	M: 88.7 vs 89.6	M: 90.4 vs 80.4
Smoking, %	Smokers: 89.4 vs 88.3	Smokers: 86.4 vs 88.3	Smokers: 86.1 vs 85	Smokers: 86.2 vs 89.6	Smokers: 77.1 vs 78.3	Smokers: 69.4 vs 75.3
Stage, %	IB-IIIA based on AJCC 7th IB-II: 36.3 vs 36.6 IIIA: 63.1 vs 64.2	II-IIIB based on AJCC 8th II: 29.7 vs 30.2 III: 70.3 vs 69.8	II-IIIB based on AJCC 8th II: 28.4 vs 29.4 III: 71.3 vs 70.3	III based on AJCC 8th NR NR	IB-III based on AJCC 8th IB-II: 29.9 vs 26.6 III: 70.1 vs 73.3	 IB-II: 28.2 vs 29.2 III: 71.8 vs 70.8
SCC/non-SCC, % (ICI + Chemo vs Chemo, %)	48.6/51.4 vs 53.1/46.9	56.9/43.1 vs 56.8/43.2	46.2/53.6 vs 51.1/47.9	77.7/22.3 vs 77.7/22.3	69.9/30.1 vs 70.4/29.6	71.8/28.2 vs 61.8/38.2
PD-L1 in ICI + Chemo group (<1%/ 1%-49%/≥50%/ unknown), n (%)	78 (43.6)/51 (28.5)/ 38 (21.2)/12 (6.7)	138 (34.8)/127 (32.0)/ 132 (33)/0 (0)	133 (33.3)/151 (37.8)/ 116 (29.0)/0 (0)	<1% or unevaluable: 69 (34.2); ≥1%: 133 (65.8)		53/35/28/292 12.9%/8.6%/6.9%/71.6
EGFR/*KARS*/others (ICI + Chemo vs Chemo, %)	Inclusion not permitted	*EGFR*: 3.5 vs 4.8 *KRAS*: NR *ALK*: 3.0 vs 2.2	Excluded from modified intention-to-treat population	Inclusion not permitted	*EGFR*: 21 pairs	*EGFR*: 8.3 vs 14.3 *KRAS*: 3.4 vs 5.0 Others: 2.7 vs 1.6
pCR (%)	24.0 vs 2.2	18.1 vs 4.0	17.2 vs 4.3	28.2 vs 1 (by local pathologist) 24.8 vs 1 (by BIPR)	32.5 vs 6.4	32.8 vs 4.4
pCR benefit subgroups	All except never smoking	NR	All except never smoking/ PD-L1 <1%	NR	All except female; cTNM stage I	
MPR, %	36.9 vs 8.9	30.2 vs 11.0	33.3 vs 12.3	48.5 vs 8.4	57.1 vs 21.7	58.1 vs 19.2
MPR benefit subgroups	All except ECOG 1/ never smoking	NR	NR	NR	All except cTNM stage I	
Follow-up	Minimum 21 mo	Median 25.2 mo	Median 11.7 mo	Median 18.25 mo	Median 24 mo	Median 24 mo
2-y EFS rate, %	63.8 vs 45.3	62.4 vs 40.6	63.3 vs 52.4	66.7 vs 46.1	DFS: 80.4 vs 63.1	DFS: 82.0 vs 61.3
EFS HR (95% CI)	0.63 (0.48-0.87)	0.58 (0.46-0.72)	0.68 (0.53-0.88)	0.40 (0.27-0.52)	DFS: 0.50 (0.38-0.68)	DFS: 0.42 (0.32-0.54)

(Continued)

TABLE E9. Continued

Parameter	CheckMate-816	Keynote-671	AEGEAN	Neotorch	NeoR-World	
EFS benefit subgroups	Age <65 y; M/F; Asia; ECOG 0; stage IIIA; nonsquamous; all smoking status; PD-L1 ≥1%/≥50%; carboplatin	All ages; M/F; all races; all regions; current/former smokers; stage III; all histologic features; PD-L1 ≥1%	Age >65 y; M; ECOG 0; Asia; current smoker; nonsquamous; stage IIIA; cisplatin	All age; M; all ECOG; smoker and former smoker; IIIA/IIIB; squamous; PD-L1≥1%	DFS: All age; M; all smoking status; all histologic subtype; cTNM stage III; cT1-4; cN2	-
2-y OS rate, %	87.7 vs 70.6	80.9 vs 77.6	NR	80.1 vs 74.3	92.4 vs 85.0	93.1 vs 82.4
OS HR (95% CI)	0.57 (0.30-1.07)	0.73 (0.54-0.99)	NR	0.62 (0.38-0.99)	0.61 (0.40-0.94)	0.46 (0.32-0.66)
OS benefit subgroups	NR	NR	NR	NR	M; all smoking status; cTNM stage III; cT1-2; cN2	-
Patients undergoing surgery	149 vs 135	325 vs 317	295 vs 302	166 vs 148	345 vs 345	408 vs 684
R0 resection, %	83.2 vs 77.8	92.0 vs 84.2	94.7 vs 91.3	95.8 vs 92.6	96.5 vs 96.5	96.1 vs 97.7
Patients receiving adjuvant therapy, n	19.9 vs 31.8	NR	NR	NR	-	78.0 vs 64.6
Adjuvant therapeutic strategies in treatment arms	NR	Pembrolizumab for 1 y	Durvalumab for 1 y	Toripalimab for 1 y	-	No/Chemo/EGFR-TKI/ICI/ICI + Chemo

RCT, Randomized controlled trial; *M*, males; *F*, females; *NR*, not reported; *SCC*, squamous cell carcinoma; *ICI*, immune checkpoint inhibitor; *HR*, hazard ratio; *CI*, confidence interval; *pCR*, pathologic complete response; *cTNM stage*, clinical stage based on 8th edition of TNM staging of lung cancer; *MPR*, major pathologic response; *RD*, rate difference; *EFS*, event-free survival; *DFS*, disease-free survival; *OS*, overall survival. *93.1% (380 of 408) of patients with neoadjuvant therapy had 2 to 4 cycles.