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Osimertinib With or Without Chemotherapy in Advanced Non–Small Cell Lung Cancer With *EGFR* and Concurrent *TP53* Mutations
A Randomized Clinical Trial

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IMPORTANCE Combination therapy has emerged as a promising therapeutic approach for patients with epidermal growth factor receptor (*EGFR*)–mutated non–small cell lung cancer (NSCLC). However, its clinical benefit-risk profile remains a focus of ongoing debate. Identifying patients most likely to derive benefit from such regimens remains an unmet clinical need.

OBJECTIVE To prospectively compare the efficacy and safety of first-line osimertinib plus chemotherapy with osimertinib monotherapy for patients with *EGFR*-mutated advanced NSCLC harboring concurrent *TP53* mutations.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, randomized, open-label, phase 3 study conducted at 17 sites in China. Between March 25, 2021, and July 11, 2024, a total of 294 eligible patients with treatment-naive, stage IV or recurrent nonsquamous NSCLC harboring concurrent *TP53* and *EGFR*-sensitizing mutations were enrolled.

INTERVENTIONS Patients were randomized (1:1) to receive osimertinib plus chemotherapy (pemetrexed and carboplatin every 3 weeks for 4 cycles, followed by maintenance therapy of osimertinib plus pemetrexed; n = 146) or osimertinib monotherapy (n = 148).

MAIN OUTCOMES AND MEASURES The primary end point was investigator-assessed progression-free survival. Secondary end points included overall survival, response, safety, and quality of life.

RESULTS Among 294 enrolled patients, the median age was 57 years (range, 26-79 years), and 159 (54.1%) were female. The data cutoff date was November 11, 2025. At a median follow-up of 25.1 months for the osimertinib-chemotherapy group and 26.1 months for the osimertinib monotherapy group, median progression-free survival was significantly longer with osimertinib plus chemotherapy than with osimertinib monotherapy (34.0 vs 15.6 months; difference, 18.4 months [95% CI, 9.9-22.3]; hazard ratio, 0.44 [95% CI, 0.32-0.60]; $P < .001$). This benefit was consistent across prespecified subgroups, including those with brain metastases and *L858R* mutations. The overall survival data remained immature (30.6% maturity); however, a trend toward overall survival benefit with combination therapy was observed. The incidence of grade 3 or higher treatment-related adverse events was higher in the combination group, with no new safety signal identified.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, osimertinib plus chemotherapy significantly increased progression-free survival among patients with *EGFR*-mutated advanced NSCLC harboring concurrent *TP53* mutations. These findings provided a clinical rationale for individualized combination strategies in the management of patients with *EGFR*-mutated NSCLC.

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Supplemental content

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Lung cancer remains the leading cause of cancer-related mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all cases.[1] Epidermal growth factor receptor (*EGFR*) mutations are the most common actionable driver of alterations, occurring in up to 40% to 50% of patients in Asian populations and approximately 10% to 15% of patients in Western populations.[2,3]

Third-generation EGFR-tyrosine kinase inhibitor (EGFR-TKI) osimertinib has become the global standard first-line treatment for patients with advanced NSCLC harboring *EGFR*-sensitizing mutations.[4-8] Despite this clinical advancement, acquired resistance remains a significant challenge, particularly in a patient population with high-risk factors.[9-11] As the most commonly acknowledged risk factors, concurrent *TP53* mutations are found in about 50% of *EGFR*-mutated NSCLC cases[12] and are associated with poor treatment response and shorter progression-free survival by promoting genomic instability, lineage plasticity, and evasion of apoptosis.[13-15]

Combination strategies have emerged as a promising therapeutic approach to delay EGFR-TKI resistance and optimize clinical outcomes in *EGFR*-mutated advanced NSCLC. In the FLAURA2 study,[16,17] osimertinib plus pemetrexed-platinum-based chemotherapy improved progression-free survival (hazard ratio [HR], 0.62; 95% CI, 0.49-0.79) and overall survival (HR, 0.77; 95% CI, 0.61-0.96) compared with osimertinib alone. In the MARIPOSA study,[18,19] amivantamab plus lazertinib also improved progression-free survival (HR, 0.70; 95% CI, 0.58-0.85) and overall survival (HR, 0.75; 95% CI, 0.61-0.92) compared with osimertinib monotherapy, but patients with wild-type *TP53* derived no significant benefit from the combination therapy.[20] In addition, combination therapies are inevitably associated with a higher burden of toxicities and costs, as well as less convenience. Whether such regimens should be universally considered for all patients with *EGFR*-mutated NSCLC remains a highly debated question. There is a need to identify patients who are most likely to benefit from combination therapies.

This randomized, phase 3 study was specifically designed to prospectively evaluate the efficacy and safety of first-line osimertinib plus chemotherapy vs osimertinib monotherapy in *EGFR*-mutated advanced NSCLC harboring concurrent *TP53* mutations.

Key Points

Question Which patient populations with non–small cell lung cancer (NSCLC) with a mutation in the epidermal growth factor receptor (*EGFR*) would benefit from a first-line treatment of an intensified combination therapy?

Findings In this randomized phase 3 study including 294 patients with advanced NSCLC and an *EGFR* mutation and concurrent *TP53* mutations, first-line osimertinib plus chemotherapy significantly improved median progression-free survival compared with osimertinib alone (34.0 months vs 15.6 months; hazard ratio for disease progression or death, 0.44).

Meaning This study provides evidence for incorporating *TP53*-based molecular risk stratification into first-line clinical decision-making because the efficacy of intensified combination therapy justifies the added treatment-related burden in this high-risk population.

Methods

Study Design and Patients

This was a multicenter, randomized, open-label, phase 3 study conducted across 17 centers in China. Eligible patients for this study were 18 years or older with histologically or cytologically confirmed stage IV or recurrent nonsquamous NSCLC harboring concurrent *TP53* and *EGFR*-sensitizing mutations (*Ex19del* or *L858R*). *EGFR* and *TP53* alteration status was determined either locally at participating centers or at the central laboratory using next-generation sequencing testing. No prior systemic therapy for advanced disease was allowed. All patients were required to have at least one measurable lesion and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients with asymptomatic, stable brain metastases were eligible. Full inclusion and exclusion criteria are provided in the protocol (Supplement 1).

The study was conducted in compliance with relevant local regulatory requirements and the principles of Declaration of Helsinki.[21] The trial protocol and statistical analysis plan are in Supplement 1 and Supplement 2, respectively. Ethics approval for the protocol was obtained from the ethics committee of the Sun Yat-sen University Cancer Center (approval number B2020-355-01) and each participating center (eTable 2 in Supplement 3). All patients provided written informed consent before enrollment. Patients and the public were not involved in the study's design, conduct, reporting, or dissemination plans. This study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Randomization

Eligible patients were randomly assigned (1:1) to receive either osimertinib plus pemetrexed-carboplatin-based chemotherapy or osimertinib monotherapy. Randomization was performed using a stratified block method with a fixed block size of 6. Stratification factors including ECOG performance status score (0 vs 1), brain metastases (yes vs no), and *EGFR* mutation types (*Ex19del* vs *L858R*). The randomization sequence was generated by an independent statistician and centrally administered via a central randomization system at the Clinical Trials Centre of Sun Yat-sen University Cancer Center. Following informed consent from eligible patients, site investigators contacted the study coordinator to obtain patients' treatment assignment.

Procedures

In the osimertinib-chemotherapy group, patients received osimertinib (80 mg once daily) plus pemetrexed (500 mg/m^2 of body-surface area) and carboplatin (area under the concentration-time curve of 5 mg/mL/min) intravenously every 3 weeks for 4 cycles, followed by maintenance osimertinib plus pemetrexed. Patients in the monotherapy group received osimertinib (80 mg orally once daily) continuously. Study treatment was continued until the onset of any of the following

events: disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, withdrawal of informed consent, intolerable toxic effects, symptomatic progression necessitating urgent medical intervention, or other discontinuation events specified in the study protocol, whichever occurred first.

Baseline tumor assessments were performed within 28 days before randomization. In accordance with RECIST 1.1, required imaging modalities included contrast-enhanced computed tomography (CT) of the chest and abdomen, contrast-enhanced magnetic resonance imaging (MRI) for the brain, and bone imaging when clinically indicated. Subsequent tumor assessments were repeated every 6 weeks (±7 days) until disease progression. For patients with brain metastases, brain imaging was repeated at the same frequency as extracranial scans until disease progression.

Survival status was evaluated every 12 weeks after treatment discontinuation or disease progression until death or withdrawal of consent, whichever occurred first. Adverse events (AEs) were assessed at each visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 for up to 30 days after the last dose of any protocol treatment. Quality of life was evaluated every 6 weeks with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core and its lung module.

Outcomes

The primary end point was investigator-assessed progression-free survival in accordance with RECIST version 1.1. Progression-free survival was defined as the time from randomization to disease progression or death from any cause, whichever occurred first. Secondary end points included overall survival, objective response rate, duration of response, disease control rate, safety, and quality of life. The analyses of the association of other concurrent genetic alterations with efficacy, as well as potential resistance mechanisms, were exploratory end points. (Full definitions of the end points are presented in Supplement 3.)

Statistical Analysis

We calculated that a sample size of 292 patients, with an approximate 170 progression-free survival events anticipated, would provide 80% statistical power to detect an HR of 0.65 for progression or death by the log-rank test, at a 2-sided significance level of .05. This sample size estimation corresponded to a median progression-free survival extension of at least 7 months (20 vs 13 months, respectively), assuming a 0.36% monthly dropout rate in each treatment group.

The full analysis set, defined according to the intention-to-treat principle, included all patients who had undergone randomization and was used for summarizing demographic and clinical characteristics at baseline, as well as for the efficacy analyses. The safety analysis set included all the patients who had received at least 1 dose of any study treatment, with analyses based on actual treatment received.

The primary analysis of progression-free survival was planned to be conducted when approximately 170 events had been observed. A stratified log-rank test was conducted based on prespecified randomization stratified factors. Median progression-free survival and corresponding 95% CIs were estimated using the Kaplan-Meier method. The median duration of follow-up for progression-free survival was estimated with the use of the reverse Kaplan-Meier method.[22] The HRs and 95% CIs were calculated using a stratified Cox proportional hazards model. The proportional hazard assumption for progression-free and overall survival was validated based on Schoenfeld residuals, and no violation was observed. Two preplanned analyses of overall survival were scheduled: an interim analysis at the primary analysis of progression-free survival and a final analysis at approximately 60% overall survival maturity. Both interim and final analysis of overall survival were performed without formal adjustment of α.

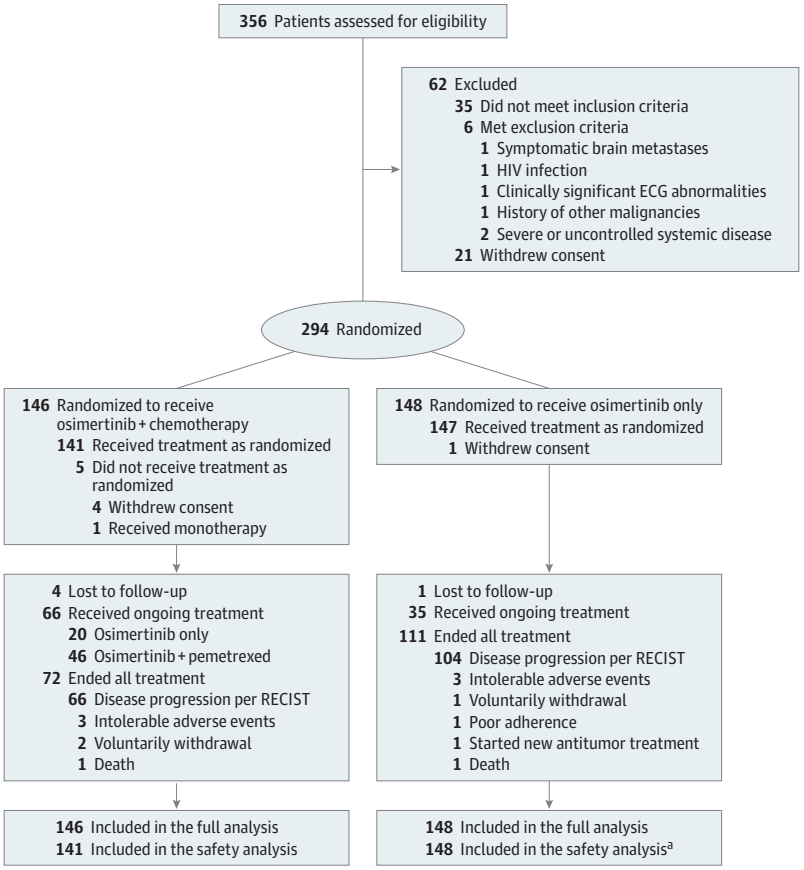
The objective response and disease control rates were summarized as point estimates, with 2-sided 95% CIs calculated using the Clopper-Pearson method. For other time-to-event end points (ie, duration of response), median values and 2-sided 95% CIs were estimated using the Kaplan-Meier method. Safety analyses were performed on the safety analysis set. Time to deterioration was defined as the time from randomization to the first clinically meaningful deterioration (a decrease of ≥10 points for global health status and quality of life or an increase of ≥10 points for symptom scores from baseline), confirmed at a subsequent assessment or followed by death. Changes in quality-of-life scores from baseline were analyzed using a mixed model for repeated measures, including treatment group, scheduled assessment, treatment-by-assessment interaction, and baseline scores as fixed effects, and patient as a random effect. Full statistical details can be found in the statistical analysis plan (Supplement 2). All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Patients and Treatment

Between March 25, 2021, and July 11, 2024, a total of 356 patients were screened, of whom 294 (median age, 57 years [range, 26-79 years]; 159 [54.1%] were female) were enrolled and randomly assigned to receive osimertinib-chemotherapy (n = 146) or osimertinib monotherapy (n = 148). Among them, 181 were enrolled based on central next-generation sequencing testing, and 113 based on local institutional testing. Of these, 289 patients received at least 1 dose of the study treatment (141 patients received osimertinib-chemotherapy, 148 received osimertinib monotherapy), and 5 patients did not receive any study treatment. The one patient who had been randomized to the osimertinib-chemotherapy group but only received osimertinib was included in the osimertinib monotherapy group for the safety analyses (**Figure 1**). The majority of patients had an ECOG performance status score of 1, and 48.6% had brain metastases at baseline. Baseline demographic and clinical characteristics were well balanced between the 2 groups (**Table 1**).

Figure 1. Flow of Patients in the Study (Cutoff Date, November 11, 2025)



[a]One patient in the osimertinib-chemotherapy group received only osimertinib so is analyzed in the osimertinib-monotherapy group.

ECG indicates electrocardiogram; RECIST, Response Evaluation Criteria in Solid Tumors.

As of the data cutoff date on November 11, 2025, the median duration of exposure to osimertinib was 20.3 months (range, 1.1-53.6) in the osimertinib-chemotherapy group and 15.4 months (range, 0.5-53.9) in the osimertinib monotherapy group. In the osimertinib-chemotherapy group, 84.4% of patients (n = 119) completed the planned 4 cycles of carboplatin plus pemetrexed, and the median number of pemetrexed cycles received was 17 (range, 1-52). A total of 66 patients (46.8%) in the osimertinib-chemotherapy group (46 receiving osimertinib plus pemetrexed and 20 receiving osimertinib alone) and 35 patients (23.6%) in the osimertinib monotherapy group remained receiving the study treatment. The most common reasons for osimertinib discontinuation were disease progression (86.7% in the osimertinib-chemotherapy group vs 92.9% in the osimertinib monotherapy group) and adverse events (5.3% vs 2.7%, respectively). For pemetrexed, 44.2% of discontinuations were attributable to disease progression and 37.9% to adverse events.

Efficacy

The median follow-up time for progression-free survival in the osimertinib-chemotherapy group was 25.1 months, compared with 26.1 months in the osimertinib monotherapy group. At the data cutoff date, 174 patients had experienced disease progression or death (59.2% maturity), with 67 (45.9%) in the osimertinib-chemotherapy group and 107 (72.3%) in the osimertinib monotherapy group. The median progression-free survival was 34.0 months (95% CI, 24.9-36.4) in the osimertinib-chemotherapy group and 15.6 months (95% CI, 13.0-18.3) in the osimertinib monotherapy group (difference, 18.4 months [95% CI, 9.9-22.3]). The HR for disease progression or death was 0.44 (95% CI, 0.32-0.60), indicating a significant progression-free survival benefit in the osimertinib-chemotherapy group ($P < .001$; **Table 2**). The Kaplan-Meier curves for progression-free survival showed early separation from the start between the 2 groups and maintained consistently throughout the follow-up period (**Figure 2**A). A consistent progression-free survival benefit with osimertinib plus chemotherapy was observed across all prespecified subgroups, including subgroups defined by *EGFR* mutation types and the history of brain metastases at baseline (**Figure 3**).

The objective response rate was 82.9% (95% CI, 75.8%-88.6%) in the osimertinib-chemotherapy group and 71.6% (95% CI, 63.6%-78.7%) in the osimertinib monotherapy group. The median duration of response was more than twice as long in the osimertinib-chemotherapy group as in the osimertinib monotherapy group (32.7 months [95% CI, 26.0-35.6] vs 15.3 months [95% CI, 13.3-18.4]; eFigure 1 in Supplement 3; Table 2). The disease control rate was similar between the 2 groups: 91.8% (95% CI, 86.1%-95.7%) with osimertinib

Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Full Analysis Set)[a]

Characteristic	No. (%) of patients	
	Osimertinib-chemotherapy (n = 146)	Osimertinib monotherapy (n = 148)
Age		
Median age (range), y	57 (29-79)	57 (26-79)
≥65 y	32 (21.9)	33 (22.3)
Sex		
Male	70 (47.9)	65 (43.9)
Female	76 (52.1)	83 (56.1)
ECOG performance-status score[b]		
0 (Fully active)	43 (29.5)	43 (29.1)
1 (Ambulatory, restricted in strenuous activity)	103 (70.5)	105 (70.9)
History of smoking	37 (25.3)	35 (23.6)
EGFR mutation at randomization[c]		
Exon 19 deletion	80 (54.8)	83 (56.1)
L858R	66 (45.2)	65 (43.9)
Brain metastases present	72 (49.3)	71 (48.0)
Extrathoracic metastases present	128 (87.7)	135 (91.2)
Liver metastases present	23 (15.8)	30 (20.3)
Baseline tumor size, median (range), mm[d]	47.0 (11.2-151.0)	40.7 (11.3-140.6)

[a] The full analysis set included all the patients who had undergone randomization. *EGFR* denotes epidermal growth factor receptor; *L858R*, exon 21 codon p.Leu858Arg.

[b] Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

[c] The presence of *EGFR* mutations was determined by central or local testing.

[d] The baseline tumor size was defined as the sum of the longest diameters of the target lesions.

Table 2. Efficacy End Points (Full Analysis Set)[a]

End point	Osimertinib-chemotherapy (n = 146)	Osimertinib monotherapy (n = 148)
Primary outcome		
Progression-free survival, median (95% CI), mo	34.0 (24.9-36.4)	15.6 (13.0-18.3)
Disease progression or death, hazard ratio (95% CI)	0.44 (0.32-0.60)	
Secondary outcomes		
Progression-free survival (95% CI), %		
12 mo	78.5 (70.6-84.6)	60.7 (52.2-68.2)
18 mo	69.9 (61.3-76.9)	42.2 (33.8-50.2)
24 mo	60.8 (51.4-69.0)	26.7 (19.0-35.0)
Best objective response, No. (%)		
Partial response	121 (82.9)	106 (71.6)
Stable disease	13 (8.9)	19 (12.8)
Disease progression	5 (3.4)	18 (12.2)
Could not be evaluated[b]	7 (4.8)	5 (3.4)
Median duration of response (95% CI), mo[c]	32.7 (26.0-35.6)	15.3 (13.3-18.4)

[a] Tumor response was evaluated by investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The data cutoff date was November 11, 2025. The full analysis set included all the patients who underwent randomization.

[b] Seven patients in the osimertinib-chemotherapy group and 5 patients in the osimertinib monotherapy group had no postbaseline tumor imaging assessments. Among them, 4 patients in the osimertinib-chemotherapy group and 1 patient in the osimertinib monotherapy group did not receive treatment and therefore had no posttreatment tumor evaluations.

[c] Duration of response was defined as the time from first documented response to the documented progression or death, whichever occurred first; the median duration was estimated using the Kaplan-Meier method.

plus chemotherapy and 84.5% (95% CI, 77.6%-89.9%) with osimertinib monotherapy. Data regarding the depth of response are provided in eFigure 2 in Supplement 3.

At the prespecified interim analysis for overall survival, 90 of 294 patients (30.6% maturity) had died, of whom 36 (24.7%) were in the osimertinib-chemotherapy group and 54 (36.5%) were in the osimertinib monotherapy group. The median overall survival was 48.4 months (95% CI, 42.7-nonestimable [NE]) in the osimertinib-chemotherapy group and 36.5 months (95% CI, 28.1-NE) in the osimertinib monotherapy group (HR for death, 0.57; 95% CI, 0.38-0.88; Nominal P = .01; Figure 2B). Subsequent anticancer therapies after discontinuation of study treatment are summarized in eTable 5 in Supplement 3. These therapies were administered at the investigator's discretion.

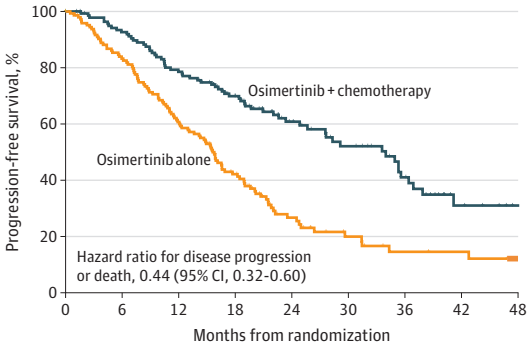
Safety

The safety analysis set included 289 patients: 141 patients in the osimertinib-chemotherapy group and 148 patients in the

Figure 2. Kaplan-Meier Survival Curves for Progression-Free Survival and Overall Survival

A Progression-free survival

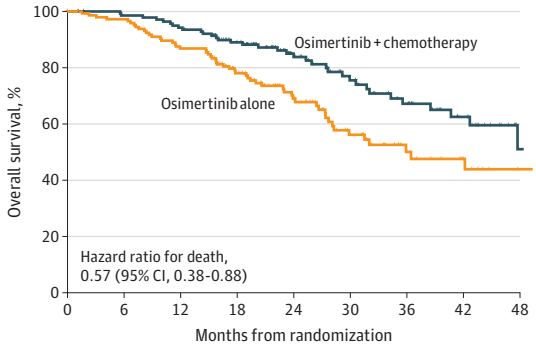
	No. of events/ patients (%)	Median No. of mo of progression-free survival (95% CI)
Osimertinib + chemotherapy	67/146 (45.9)	34.0 (24.9-36.4)
Osimertinib alone	107/148 (72.3)	15.6 (13.0-18.3)



No. at risk									
Osimertinib + chemotherapy	146	126	105	82	47	33	21	8	3
Osimertinib alone	148	119	86	51	22	12	7	6	4

B Overall survival

	No. of events/ patients (%)	Median No. of mo of overall survival (95% CI)
Osimertinib + chemotherapy	36/146 (24.7)	48.4 (42.7–NE)
Osimertinib alone	54/148 (36.5)	36.5 (28.1–NE)



No. at risk									
Osimertinib + chemotherapy	146	137	131	109	70	50	36	22	6
Osimertinib alone	148	141	125	94	58	35	20	13	7

A, Progression-free survival was assessed by investigators using Response Evaluation Criteria in Solid Tumors, version 1.1. The median duration of follow-up was 25.1 months (IQR, 19.1-39.6) for the osimertinib-chemotherapy group and 26.1 months (IQR, 19.9-46.9) for the osimertinib monotherapy group. CIs have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

B, Overall survival in the interim analysis (data cutoff: November 11, 2025). The median duration of follow-up was 27.7 months (IQR, 19.7-41.4) for the osimertinib-chemotherapy group and 26.3 months (IQR, 19.8-38.6) for the osimertinib monotherapy group.

NE indicates nonestimable.

osimertinib monotherapy group. Treatment-emerged adverse events occurring during the treatment period are summarized in eTable 6 in Supplement 3. Treatment-related AEs (TRAEs) of any grade and the TRAEs with an incidence of at least 15% are shown in **Table 3**. The highest percentage of TRAEs were in the osimertinib-chemotherapy group: 129 patients (91.5%) experienced anemia; 115 (81.6%), neutrophil count decreased; 110 (78.0%), leukopenia; and 89 (63.1%) platelet count decreased. In the osimertinib monotherapy group, 79 patients (53.4%) experienced lymphocyte count decreased; 73 (49.3%), diarrhea; 72 (48.6%), blood creatine phosphokinase increased; and 69 (46.6%), rash. Grade 3 or higher TRAEs occurred more frequently with the osimertinib-chemotherapy group than in the osimertinib monotherapy group (88 [62.4%] vs 22 [14.9%]), including neutrophil count decrease (54 [38.3%] vs 6 [4.1%]), leukopenia (34 [24.1%] vs 0), platelet count decrease (33 [23.4%] vs 0), and anemia (13 [9.2%] vs 1 [0.7%]). Serious TRAEs were also more common in the osimertinib-chemotherapy group than in the osimertinib monotherapy group (10.6% vs 1.4%), including platelet count decreased (7 [5.0%] vs 0), neutrophil count decreased (4 [2.8%] vs 0), and white blood cell count decreased (4 [2.8%] vs 0; eTable 7 in Supplement 3). One patient in the osimertinib-chemotherapy group died of treatment-related severe thrombocytopenia (platelet nadir, 14 × 10^9/L) leading to pulmonary hemorrhage (eTable 8 in Supplement 3).

AEs of special interest are summarized in eTable 9 in Supplement 3. Interstitial lung disease or pneumonitis occurred in 7 patients (5.0%) in the osimertinib-chemotherapy group, and 10 patients (6.8%) in the osimertinib monotherapy group. Cardiac failure was reported in 3 patients (2.1%) and 1 patient (0.7%), respectively.

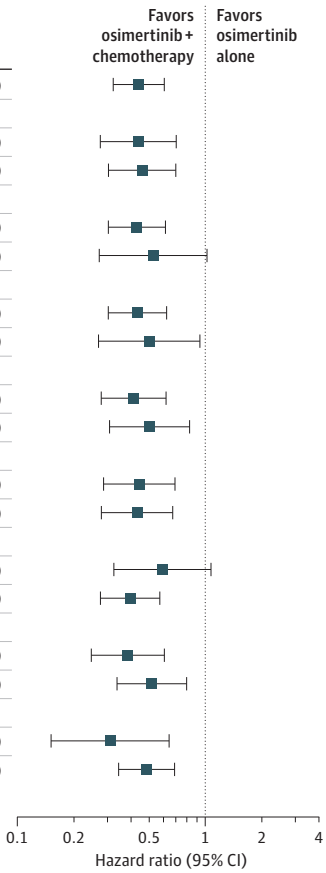
In the osimertinib-chemotherapy group, TRAEs led to dose interruption of any study treatment in 58 patients (41.1%), dose reduction in 28 (19.9%), and discontinuation of study treatment in 37 (26.2%). Specifically, TRAEs led to interruption of osimertinib in 44 patients (31.2%), dose reduction in 1 (0.7%), and discontinuation in 4 (2.8%). In the osimertinib monotherapy group, the corresponding rates were 8.8% (n = 13) for dose interruption, 0% for dose reduction, and 1.4% (n = 2) for discontinuation. Stomatitis was the most frequent event leading to discontinuation of osimertinib, whereas blood creatinine increased was the most common cause for discontinuation of pemetrexed.

Quality of Life

Overall, 131 of 146 patients (89.7%) in the osimertinib-chemotherapy group and 124 of 148 patients (83.8%) in the osimertinib monotherapy group were evaluable for quality of life analysis. The time to deterioration of global health status favored osimertinib monotherapy (difference of restricted mean survival time, −7.8; 95% CI, −15.6 to 0), with a more rapid decline observed in the osimertinib-chemotherapy group during the induction phase. After this initial separation during induction phase, the curves were generally parallel (eFigure 3A in Supplement 3). For other key lung cancer-related symptoms,

Figure 3. Dot Plot Subgroup Analysis of Progression-Free Survival

	Osimertinib + chemotherapy		Osimertinib alone		
	Events/No. of patients	Median progression-free survival, mo	Events/No. of patients	Median progression-free survival, mo	Hazard ratio (95% CI)
Overall population	67/146	34.00	107/148	15.64	0.44 (0.32-0.60)
Sex					
Male	30/70	34.96	45/65	15.90	0.44 (0.28-0.70)
Female	37/76	29.17	62/83	15.44	0.46 (0.30-0.69)
Age, y					
<65	52/114	34.00	85/115	16.16	0.43 (0.30-0.61)
≥65	15/32	27.66	22/33	12.01	0.53 (0.27-1.02)
History of smoking					
Never	49/109	29.17	84/113	15.44	0.43 (0.30-0.62)
Current or former	18/37	35.35	23/35	16.92	0.50 (0.27-0.93)
Method used for tissue testing					
Central	41/94	35.35	63/87	14.88	0.41 (0.28-0.62)
Local	26/52	28.35	44/61	16.62	0.50 (0.31-0.82)
EGFR mutation					
Exon 19 deletion	32/80	34.00	56/83	16.62	0.44 (0.29-0.69)
L858R	35/66	23.39	51/65	12.35	0.43 (0.28-0.67)
ECOG performance-status score					
0	19/43	35.35	26/43	20.21	0.59 (0.33-1.07)
1	48/103	28.35	81/105	14.32	0.40 (0.28-0.57)
Brain metastases at baseline					
Yes	31/72	35.35	54/71	15.38	0.39 (0.25-0.60)
No	36/74	27.60	53/77	16.62	0.52 (0.34-0.79)
Liver metastases at baseline					
Yes	11/23	27.66	24/30	11.47	0.31 (0.15-0.64)
No	56/123	34.00	83/118	16.16	0.49 (0.35-0.68)



Shown is the progression-free survival as assessed by investigator in prespecified subgroups. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. *EGFR* indicates epidermal growth factor receptor, and *L858R*, exon 21 codon p.Leu858Arg.

including dyspnea, cough, and chest pain, similar time to deterioration were observed between the 2 groups (eFigure 3 B-D and eTable 10 in Supplement 3).

Regarding individual symptoms, appetite loss scores were higher in the osimertinib-chemotherapy group than in the osimertinib monotherapy group, with an estimated between-group difference of 7.6 points (95% CI, 5.0-10.1; eFigure 4 C and eTable 11 in Supplement 3). For fatigue, the osimertinib-chemotherapy group showed less improvement from baseline compared with the osimertinib monotherapy group (difference, 3.0 points; 95% CI, 0.0-6.0) (eFigure 4 D and eTable 11 in Supplement 3).

Discussion

To our knowledge, this is the first prospective, randomized phase 3 study specifically designed to evaluate the efficacy and safety of first-line osimertinib combined with pemetrexed and carboplatin in patients with advanced NSCLC harboring concurrent *EGFR* and *TP53* mutations. The study demonstrated a progression-free survival benefit with the combination therapy compared with osimertinib monotherapy.

Although first-line EGFR-TKI–based combination regimens have reshaped the therapeutic landscape by significantly improving progression-free survival and overall survival in unselected *EGFR*-mutated NSCLC, their universal application is limited by increased toxicity, health care costs, and reduced convenience.[23-27] The FLAURA2 and MARIPOSA studies both reported high incidences of grade 3 or higher AEs (64% and 75% in the combination groups, respectively).[16,18] Furthermore, post hoc analyses from the MARIPOSA study showed that patients with wild-type *TP53* achieved no significant progression-free survival benefit from combination therapy compared with osimertinib monotherapy (HR, 0.75; 95% CI, 0.52-1.07; $P = .11$).[20] These results highlight the need to identify patients who would benefit most from intensified first-line therapy. This study addresses this gap by prospectively selecting a high-risk population with concurrent *TP53* mutations. The study results demonstrated a progression-free survival benefit with combination therapy compared with monotherapy, and this benefit was consistent across all prespecified subgroups. The Kaplan-Meier curves for progression-free survival showed early separation and remained divergent throughout the follow-up period. Of note, despite the inclusion of a high-risk population with concurrent *TP53*

Table 3. Treatment-Related Adverse Events (Safety Analysis Set)[a]

	Patients who experienced treatment-related adverse events, No. (%)[b]			
	Osimertinib-chemotherapy group (n = 141)[c]		Osimertinib monotherapy group (n = 148)[c]	
	Grade ≥3	Any grade	Grade ≥3	Any grade
Any treatment-related adverse event leading to death[d]	1 (0.7)	1 (0.7)	0	0
Any treatment-related serious adverse event	11 (7.8)	15 (10.6)	0	2 (1.4)
Any treatment-related adverse event	88 (62.4)	138 (97.9)	22 (14.9)	140 (94.6)
Leading to dose reduction	20 (14.2)	28 (19.9)	0	0
Leading to dose interruption	31 (22.0)	58 (41.1)	3 (2.0)	13 (8.8)
Leading to treatment discontinuation	18 (12.8)	37 (26.2)	0	2 (1.4)
Treatment-related adverse event with an incidence of ≥15% in either group				
Neutrophil count decrease	54 (38.3)	115 (81.6)	6 (4.1)	42 (28.4)
Leukopenia	34 (24.1)	110 (78.0)	0	48 (32.4)
Platelet count decrease	33 (23.4)	89 (63.1)	0	28 (18.9)
Anemia	13 (9.2)	129 (91.5)	1 (0.7)	63 (42.6)
Lymphocyte count decrease	11 (7.8)	85 (60.3)	2 (1.4)	79 (53.4)
Blood creatine phosphokinase increased	7 (5.0)	84 (59.6)	4 (2.7)	72 (48.6)
Diarrhea	5 (3.5)	84 (59.6)	3 (2.0)	73 (49.3)
Stomatitis	4 (2.8)	88 (62.4)	4 (2.7)	64 (43.2)
Decreased appetite	3 (2.1)	75 (53.2)	0	31 (20.9)
Fatigue	3 (2.1)	59 (41.8)	2 (1.4)	26 (17.6)
Nausea	3 (2.1)	50 (35.5)	0	21 (14.2)
Aspartate aminotransferase increase	1 (0.7)	89 (63.1)	0	42 (28.4)
Blood creatinine increased	1 (0.7)	83 (58.9)	1 (0.7)	67 (45.3)
Alanine aminotransferase increase	1 (0.7)	78 (55.3)	0	43 (29.1)
Vomiting	1 (0.7)	37 (26.2)	0	19 (12.8)
Rash	0	84 (59.6)	1 (0.7)	69 (46.6)
Hyponatremia	0	68 (48.2)	0	58 (39.2)
Hypoalbuminemia	0	63 (44.7)	0	32 (21.6)
Constipation	0	53 (37.6)	0	15 (10.1)
Paronychia	0	46 (32.6)	0	34 (23.0)
Insomnia	0	32 (22.7)	1 (0.7)	14 (9.5)
Alopecia	0	28 (19.9)	0	16 (10.8)
Hypoaesthesia	0	28 (19.9)	0	15 (10.1)
Blood cholesterol increased	0	24 (17.0)	0	7 (4.7)
Electrocardiogram ST-T segment abnormal	0	23 (16.3)	0	17 (11.5)
Pain	0	22 (15.6)	0	11 (7.4)

[a] Safety analysis set included all the patients who had received at least 1 dose of any study treatment, with analyses based on actual treatment received. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Adverse events that emerged during treatment were defined as all adverse medical events that occurred or worsened from the time the patient first received the study treatment until 30 days after treatment discontinuation.

[b] Adverse events related to osimertinib, pemetrexed, or carboplatin. The relationship between an adverse event and the study treatment was assessed by the investigators based on the temporal relationship, known drug safety profile, and potential alternative causes.

[c] One patient randomized to the osimertinib-chemotherapy group but received only osimertinib, then was included in the osimertinib monotherapy group for the safety analyses.

[d] One patient (0.7%) in the osimertinib-chemotherapy group died because of a treatment-related adverse event (severe thrombocytopenia).

mutations, the progression-free survival in the combination group was comparable with the results reported in the FLAURA2 study.[16] This might be explained by the higher median number of pemetrexed exposure in this study (17 cycles) than that in the FLAURA2 study (12 cycles).[28]

TP53 mutations represent a major mechanism of intrinsic resistance to targeted therapies, promoting genomic instability, lineage plasticity, and evasion of apoptosis across various malignancies.[14,29,30] As the most frequent concurrent genetic alteration in *EGFR*-mutated advanced NSCLC, *TP53* mutations are identified in approximately 50% of patients and are associated with shorter progression-free survival than with EGFR-TKI monotherapy.[12,31,32] Furthermore, *TP53* mutations often overlap with other clinical high-risk features, such as liver metastases and brain metastases, which are also established factors for a poor prognosis.[33-35] Collectively, concurrent *TP53* mutations may serve as a marker for identifying a high-risk population that is most likely to benefit from first-line combination therapy. This patient selection strategy may also be applicable to other emerging therapeutic regimens, such as antibody-drug conjugate–based combination therapies.

The combination therapy was associated with a higher incidence of grade 3 or higher TRAEs, which were largely attributable to toxic effects associated with chemotherapy. Hematologic grade 3 or higher TRAEs were more frequent in the osimertinib-chemotherapy group, particularly neutrophil count decrease, leukopenia, and platelet count decrease. Similarly, gastrointestinal AEs were also typically observed in the osimertinib-chemotherapy group, including decreased appetite, constipation, nausea, and vomiting. TRAEs led to treatment interruption, dose reduction, or discontinuation in patients receiving osimertinib plus chemotherapy. Regarding

quality of life, although time to deterioration in lung cancer-related symptoms were comparable between both groups, global health status declined more rapidly in the combination group, particularly during the induction phase. Specifically, appetite loss was more pronounced in the combination group, with scores remaining consistently above baseline and exceeding those in the monotherapy group throughout the treatment period. These findings reinforce the rationale for a molecularly guided patient selection strategy, demonstrating that nearly half of the patients with wild-type *TP53* may achieve comparable clinical outcomes through monotherapy, thereby being spared the incremental toxicity of chemotherapy without compromising overall efficacy.

Limitations

Several limitations of this study should be noted. First, this study had a relatively short follow-up duration for overall survival. At the data cutoff, the number of overall survival events was insufficient to support a conclusive assessment. Although overall survival data remained immature, a trend favoring osimertinib-chemotherapy over osimertinib monotherapy was observed. Continued follow-up is warranted to confirm the long-term survival benefit. Second, the study was conducted within one region, so further validation in other populations is warranted. Third, biomarker analyses, including the association of other concurrent genetic alterations with efficacy, and potential resistance mechanisms were not included in the current report. These analyses are currently in progress but will be reported separately. Fourth, this study was an open-label design that may have introduced assessment bias in investigator-assessed outcomes. To minimize these biases, all radiological assessments were performed at the same prespecified intervals in both groups and assessed according to RECIST, version 1.1. AEs were graded according to the NCI-CTCAE, version 5.0, and dose-modification procedures were prespecified in the protocol.

Conclusions

In summary, osimertinib plus pemetrexed and carboplatin significantly improved progression-free survival in patients with *EGFR*-mutated advanced NSCLC with concurrent *TP53* mutations. These findings provide key evidence to support a molecular risk-guided, individualized treatment strategy for *EGFR*-mutated advanced NSCLC.

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REFERENCES

1. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin*. 2025;75(1):10-45. doi:10.3322/caac.21871

2. Chen J, Yang H, Teo ASM, et al. Genomic landscape of lung adenocarcinoma in East Asians. *Nat Genet*. 2020;52(2):177-186. doi:10.1038/s41588-019-0569-6

3. Melosky B, Kambartel K, Häntschel M, et al. Worldwide prevalence of epidermal growth factor receptor mutations in non–small cell lung cancer: a meta-analysis. *Mol Diagn Ther*. 2022;26(1):7-18. doi:10.1007/s40291-021-00563-1

4. Soria JC, Ohe Y, Vansteenkiste J, et al; FLAURA Investigators. Osimertinib in untreated *EGFR*-mutated advanced non–small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125. doi:10.1056/NEJMoa1713137

5. Ramalingam SS, Vansteenkiste J, Planchard D, et al; FLAURA Investigators. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50. doi:10.1056/NEJMoa1913662

6. Hendriks LE, Kerr KM, Menis J, et al; ESMO Guidelines Committee. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(4):339-357. doi:10.1016/j.annonc.2022.12.009

7. Jaiyesimi IA, Leighl NB, Ismaila N, et al. Therapy for stage IV non-small cell lung cancer with driver alterations: ASCO living guideline, version 2023.3. *J Clin Oncol*. 2024;42(11):e1-e22. doi:10.1200/JCO.23.02744

8. Riely GJ, Wood DE, Ettinger DS, et al. Non-small cell lung cancer, version 4.2024, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2024;22(4):249-274. doi:10.6004/jnccn.2204.0023

9. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in *EGFR*-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121(9):725-737. doi:10.1038/s41416-019-0573-8

10. Roper N, Brown AL, Wei JS, et al. clonal evolution and heterogeneity of osimertinib acquired resistance mechanisms in *EGFR* mutant lung cancer. *Cell Rep Med*. 2020;1(1):100007. doi:10.1016/j.xcrm.2020.100007

11. Choudhury NJ, Marra A, Sui JSY, et al. Molecular biomarkers of disease outcomes and mechanisms of acquired resistance to first-line osimertinib in advanced *EGFR*-mutant lung cancers. *J Thorac Oncol*. 2023;18(4):463-475. doi:10.1016/j.jtho.2022.11.022

12. Blakely CM, Watkins TBK, Wu W, et al. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage *EGFR*-mutant lung cancers. *Nat Genet*. 2017;49(12):1693-1704. doi:10.1038/ng.3990

13. Ibusuki R, Iwama E, Shimauchi A, et al. *TP53* gain-of-function mutations promote osimertinib resistance via TNF-α-NF-κB signaling in *EGFR*-mutated lung cancer. *NPJ Precis Oncol*. 2024;8(1):60. doi:10.1038/s41698-024-00557-2

14. Hobor S, Al Bakir M, Hiley CT, et al; TRACERx consortium. Mixed responses to targeted therapy driven by chromosomal instability through p53 dysfunction and genome doubling. *Nat Commun*. 2024;15(1):4871. doi:10.1038/s41467-024-47606-9

15. Vokes NI, Chambers E, Nguyen T, et al. Concurrent *TP53* mutations facilitate resistance evolution in *EGFR*-mutant lung adenocarcinoma. *J Thorac Oncol*. 2022;17(6):779-792. doi:10.1016/j.jtho.2022.02.011

16. Planchard D, Jänne PA, Cheng Y, et al; FLAURA2 Investigators. Osimertinib with or without chemotherapy in *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2023;389(21):1935-1948. doi:10.1056/NEJMoa2306434

17. Jänne PA, Planchard D, Kobayashi K, et al; FLAURA2 Investigators. Survival with osimertinib plus chemotherapy in *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2026;394(1):27-38. doi:10.1056/NEJMoa2510308

18. Cho BC, Lu S, Felip E, et al; MARIPOSA Investigators. Amivantamab plus lazertinib in previously untreated *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2024;391(16):1486-1498. doi:10.1056/NEJMoa2403614

19. Yang JC, Lu S, Hayashi H, et al; MARIPOSA Investigators. Overall survival with amivantamab-lazertinib in *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2025;393(17):1681-1693. doi:10.1056/NEJMoa2503001

20. Felip E, Cho BC, Gutiérrez V, et al. Amivantamab plus lazertinib versus osimertinib in first-line *EGFR*-mutant advanced non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. *Ann Oncol*. 2024;35(9):805-816. doi:10.1016/j.annonc.2024.05.541

21. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human participants. *JAMA*. 2025;333(1):71-74. doi:10.1001/jama.2024.21972

22. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343-346. doi:10.1016/0197-2456(96)00075-X

23. Wu YL, Zhou Q. Combination therapy for *EGFR*-mutated lung cancer. *N Engl J Med*. 2023;389(21):2005-2007. doi:10.1056/NEJMe2311559

24. Chen LN, Lee ATM, Nagasaka M, Ou SI. Chemotherapy and osimertinib combination should be the first-line treatment for all advanced *EGFR*+ NSCLC. *J Thorac Oncol*. 2024;19(3):380-384. doi:10.1016/j.jtho.2023.12.018

25. Lim SM, Lee JB, Cho BC. Chemotherapy and osimertinib combination should not be the first-line treatment for all advanced *EGFR*+ NSCLC. *J Thorac Oncol*. 2024;19(3):376-379. doi:10.1016/j.jtho.2023.12.007

26. Zheng MM, Wu YL. "Tumor-free survival" does not outweigh the adverse effects of anti-*EGFR* therapy and chemotherapy in patients with NSCLC. *J Thorac Oncol*. 2024;19(8):1146-1150. doi:10.1016/j.jtho.2024.04.009

27. Zheng Y, Cao WM, Shao X, et al. Pyrotinib plus docetaxel as first-line treatment for HER2-positive metastatic breast cancer: the PANDORA phase II trial. *Nat Commun*. 2023;14(1):8314. doi:10.1038/s41467-023-44140-y

28. Planchard D, Cheng Y, Kobayashi K, Mann H, et al. 53P: characterisation of benefit-risk by pemetrexed (pem) exposure in patients (pts) with *EGFR* aNSCLC treated with 1L osimertinib (osi) + platinum-pem in FLAURA2. *J Thorac Oncol*. 2025;20(suppl):S43-S44. Abstract 53P. Accessed July 20, 2026. https://www.jto.org/action/showPdf?pii=S1556-0864%2825%2900248-5

29. Kruer TL, Quintana A, Newman H, et al. XPO1 drives resistance to eprenetapopt and azacitidine and can be targeted in *TP53*-mutated myeloid malignancies. *Blood*. 2025;146(18):2244-2258. doi:10.1182/blood.2025028803

30. Kudo R, Safonov A, Jones C, et al. Long-term breast cancer response to CDK4/6 inhibition defined by TP53-mediated geroconversion. *Cancer Cell*. 2024;42(11):1919-1935.e9. doi:10.1016/j.ccell.2024.09.009

31. Aisner DL, Sholl LM, Berry LD, et al; LCMC2 investigators. The impact of smoking and *TP53* mutations in lung adenocarcinoma patients with targetable mutations—the Lung Cancer Mutation Consortium (LCMC2). *Clin Cancer Res*. 2018;24(5):1038-1047. doi:10.1158/1078-0432.CCR-17-2289

32. Roeper J, Christopoulos P, Falk M, et al. *TP53* co-mutations as an independent prognostic factor in 2nd and further line therapy-*EGFR* mutated non-small cell lung cancer IV patients treated with osimertinib. *Transl Lung Cancer Res*. 2022;11(1):4-13. doi:10.21037/tlcr-21-754

33. Skakodub A, Walch H, Tringale KR, et al. Genomic analysis and clinical correlations of non-small cell lung cancer brain metastasis. *Nat Commun*. 2023;14(1):4980. doi:10.1038/s41467-023-40793-x

34. Liu M, Jagodinsky JC, Callahan SC, et al. Genomic and immune landscape of non-small cell lung cancer brain metastases. *JCO Precis Oncol*. 2025;9:e2400690. doi:10.1200/PO-24-00690

35. Liao R, Yi G, Shen L, et al. Characterization of the genomic landscape in liver oligometastatic NSCLC. *BMC Cancer*. 2025;25(1):93. doi:10.1186/s12885-025-13478-5