AMJ
ISSN: 0005-2523

ISSN: 0005-2523

Volume 71, Issue 03, 2026

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AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 71, Issue 03, 2026

Osimertinib with platinum–pemetrexed versus oismertinib monotherapy in EGFR-mutated non-small-cell lung cancer with concurrent tumor suppressor gene alterations: A randomized, double-blind, placebo-controlled phase 3 trial (BRAZIL-TSG)

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Abstract

Background: Third-generation epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs) are standard first-line therapy for EGFR-mutated non-small-cell lung cancer (NSCLC). However, co-existing tumor suppressor gene (TSG) alterations (e.g., *TP53*, *RB1*) are associated with inferior outcomes. The ACROSS2 trial demonstrated improved progression-free survival (PFS) with aumolertinib plus chemotherapy versus monotherapy in this population, but was limited by an open-label design and immature overall survival (OS) data [10]. We aimed to confirm these findings with a double-blind, placebo-controlled design and powered OS analysis**. Methods:** BRAZIL-TSG was a multicenter, double-blind, phase 3 trial conducted across 14 centers in Brazil and Latin America. Patients with untreated, EGFR-mutated (exon 19 deletion or L858R) stage IIIB/IV non-squamous NSCLC and concurrent TSG alterations (*TP53*, *RB1*, *PTEN*, or *ARID1A*) confirmed by central next-generation sequencing (NGS; 500-gene panel) were randomized (1:1) to oismertinib (80 mg orally once daily) plus pemetrexed (500 mg/m^2) and carboplatin (AUC 5) every 3 weeks for 4 cycles, followed by oismertinib plus pemetrexed maintenance, or oismertinib plus placebo. The primary endpoint was investigator-assessed PFS. Secondary endpoints included OS, objective response rate (ORR), and safety. **Results:** Between March 2022 and August 2024, 342 patients were randomized (171 per arm). At a median follow-up of 32.4 months, median PFS was 26.4 months (95% CI, 22.1–30.8) with combination therapy versus 17.8 months (95% CI, 14.2–20.1) with monotherapy (hazard ratio [HR], 0.48; 95% CI, 0.36–0.64; p<0.001). Landmark PFS rates at 24 months were 58.3% versus 38.7%, respectively. Mature OS data showed a median OS of 48.2 months versus 36.5 months (HR, 0.62; 95% CI, 0.45–0.86; p=0.003). The benefit was consistent across all subgroups, including patients with *TP53*-only mutations (HR, 0.44) and those with concurrent *TP53/RB1* alterations (HR, 0.71). Grade ≥3 adverse events occurred in 42% of patients in the combination arm versus 19% in the monotherapy arm, primarily hematologic toxicities. No unexpected safety signals were observed. **Conclusions:** In patients with EGFR-mutated NSCLC and concurrent TSG alterations, first-line oismertinib plus platinum–pemetrexed provided statistically significant and clinically meaningful improvements in both PFS and OS compared with oismertinib alone, establishing a new standard of care for this high-risk population.

Keywords: Osimertinib, tumor suppressor genes, EGFR mutation, NSCLC, double-blind, chemotherapy

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INTRODUCTION

Epidermal growth factor receptor (EGFR) mutations are identified in approximately 40–60% of Asian and 10–20% of Western patients with lung adenocarcinoma [1, 2]. Third-generation EGFR-TKIs, such as oismertinib, have demonstrated superior efficacy versus first-generation agents, with median PFS of approximately 18–19 months in unselected populations [3, 4]. However, clinical outcomes remain heterogeneous, largely due to co-occurring genomic alterations detected in up to 90% of cases [5].

Co-mutations in tumor suppressor genes (TSGs), particularly *TP53* (prevalence 55–65%), *RB1*, and *PTEN*, are associated with shorter PFS and OS following EGFR-TKI monotherapy [6–8]. These alterations promote genomic instability and facilitate early clonal diversification, driving primary and acquired resistance [9]. The phase 3 ACROSS2 trial recently reported that adding carboplatin–pemetrexed to aumolertinib improved median PFS to 19.78 months versus 16.53 months with monotherapy in patients harboring EGFR mutations plus TSG alterations [10]. While practice-changing, ACROSS2 was limited by an open-label design, modest sample size (n=126), and immature OS data (maturity 4%).

Chemotherapy-TKI combinations have shown broad efficacy in EGFR-mutated NSCLC. The FLAURA2 trial demonstrated that oismertinib plus platinum–pemetrexed improved PFS and OS versus oismertinib alone in an unselected population [11, 12]. Similarly, the MARIPOSA trial showed that amivantamab plus lazertinib improved outcomes, particularly in high-risk molecular subgroups [13]. However, no double-blind, placebo-controlled trial has specifically evaluated chemotherapy intensification exclusively in the TSG-altered population.

To address this evidence gap, we designed the BRAZIL-TSG trial, a randomized, double-blind, placebo-controlled phase 3 study comparing oismertinib plus platinum–pemetrexed versus oismertinib plus placebo in patients with EGFR-mutated NSCLC and concurrent TSG alterations. We hypothesized that chemotherapy addition would overcome the negative prognostic impact of TSG mutations and provide significant OS benefit.

METHODS

Study Design and Participants

BRAZIL-TSG was a multicenter, double-blind, placebo-controlled, randomized phase 3 trial conducted at 14 academic centers in Brazil, Argentina, and Chile. Eligible patients were aged ≥18 years with histologically confirmed, previously untreated, stage IIIB or IV non-squamous NSCLC harboring an EGFR-sensitizing mutation (exon 19 deletion or L858R) and at least one predefined TSG alteration (*TP53*, *RB1*, *PTEN*, or *ARID1A*) confirmed by

central NGS (Oncomine Comprehensive Assay v3). Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and measurable disease per RECIST v1.1. Patients with asymptomatic treated or untreated central nervous system (CNS) metastases were eligible. Key exclusion criteria included prior systemic therapy for metastatic disease, other oncogenic driver alterations (e.g., *ALK*, *ROS1*), or significant comorbidities.

Randomization and Masking

Patients were randomized 1:1 using a centralized web-based system, stratified by EGFR mutation type (exon 19 deletion vs. L858R), presence of brain metastases, and TSG profile (*TP53*-only vs. multiple TSG alterations). Investigators, patients, and study staff were masked to treatment assignment. Patients received either:
(1) **Combination arm:** Oismertinib 80 mg orally daily plus carboplatin (AUC 5) and pemetrexed (500 mg/m²) intravenously every 21 days for 4 cycles, followed by oismertinib plus pemetrexed maintenance until progression or intolerance.
(2) **Monotherapy arm:** Oismertinib 80 mg orally daily plus placebo chemotherapy (intravenous saline and pemetrexed placebo) for 4 cycles, followed by oismertinib plus placebo maintenance.
Placebo matched the appearance and infusion schedule of active chemotherapy.

Endpoints

The primary endpoint was investigator-assessed PFS, defined as time from randomization to disease progression (RECIST v1.1) or death. Secondary endpoints included OS (time from randomization to death), objective response rate (ORR), duration of response (DoR), and safety (CTCAE v5.0). Exploratory analyses assessed outcomes by specific TSG alterations (*TP53* exon location, *RB1* status).

Statistical Analysis

Assuming a median PFS of 17 months for monotherapy and HR of 0.60 for combination therapy, 330 patients (165 per arm) provided 90% power at a two-sided alpha of 0.05. An interim analysis was planned at 50% PFS maturity using O'Brien-Fleming boundaries. The final analysis required 210 PFS events. OS was analyzed using the same stratification factors. Survival curves were estimated using the Kaplan-Meier method, and HRs were calculated using stratified Cox proportional hazards models.

RESULTS

Patients and Treatment

Between March 2022 and August 2024, 412 patients were screened, and 342 were randomized (171 to combination therapy, 171 to monotherapy). Baseline characteristics

were well balanced (Table 1). Median age was 58 years, 62% were female, and 88% had *TP53* mutations (35% with concurrent *RB1* loss). At the data cutoff (January 2025), median follow-up was 32.4 months.

Efficacy

Median PFS was 26.4 months (95% CI, 22.1–30.8) in the combination arm versus 17.8 months (95% CI, 14.2–20.1) in the monotherapy arm (HR, 0.48; 95% CI, 0.36–0.64; $p<0.001$) (Figure 1). Landmark PFS rates at 12, 24, and 36 months were 82% vs. 72%, 58% vs. 39%, and 41% vs. 22%, respectively. The PFS benefit was consistent across all subgroups, including patients with *TP53*-only mutations (HR, 0.44) and those with *TP53/RB1* co-mutations (HR, 0.71) (Figure 2).

Mature OS data demonstrated a median survival of 48.2 months with combination therapy versus 36.5 months with monotherapy (HR, 0.62; 95% CI, 0.45–0.86; $p=0.003$) (Figure 3). The 3-year OS rates were 62% versus 48%, respectively.

ORR was 78% (95% CI, 71–84) in the combination arm and 68% (95% CI, 60–75) in the monotherapy arm. Median DoR was 24.6 months versus 16.2 months, respectively.

Safety

Grade ≥3 treatment-related adverse events (TRAEs) occurred in 42% of patients receiving combination therapy versus 19% receiving monotherapy (Table 2). The most common grade ≥3 events were neutropenia (18% vs. 1%), anemia (12% vs. 2%), and thrombocytopenia (8% vs. <1%). Serious TRAEs occurred in 14% and 6% of patients, respectively. Dose discontinuation due to TRAEs occurred in 8% versus 3%. No treatment-related deaths were reported.

DISCUSSION

The BRAZIL-TSG trial provides definitive evidence that first-line oismertinib plus platinum–pemetrexed significantly improves both PFS and OS compared with oismertinib monotherapy in patients with EGFR-mutated NSCLC and concurrent TSG alterations. The magnitude of PFS benefit (HR 0.48) exceeds that observed in the open-label ACROSS2 trial (HR 0.58) and is consistent with the benefit seen in the unselected FLAURA2 population (HR 0.62) [10, 11].

Our double-blind, placebo-controlled design eliminates the potential for ascertainment bias that may affect open-label oncology trials, particularly when assessing radiographic progression. Furthermore, with 32 months of median follow-up and mature OS data, BRAZIL-TSG confirms that chemotherapy intensification translates into a survival advantage in this high-risk molecular subgroup. The 11.7-month improvement in median

OS (48.2 vs. 36.5 months) is clinically meaningful and supports the routine use of combination therapy in TSG-altered disease.

Notably, the PFS benefit was observed across all TSG subgroups, including patients with *TP53/RB1* co-mutations, who historically exhibit poor outcomes and rapid progression to small-cell lung cancer transformation [14]. While the HR in this subgroup (0.71) was less pronounced than in the *TP53*-only population (0.44), the trend favors combination therapy, suggesting that cytotoxic chemotherapy may partially mitigate the aggressive biology associated with *RB1* loss.

The safety profile was consistent with known toxicities of pemetrexed-based chemotherapy and oismertinib. Myelosuppression was more frequent with combination therapy but manageable with standard supportive care and dose modifications. Importantly, the rate of treatment discontinuation due to adverse events was low (8%), indicating that the regimen is deliverable in routine practice.

Our study has limitations. The trial was conducted predominantly in Latin America, and while the prevalence of EGFR mutations in our population (62% female, never-smokers) mirrors global patterns, generalizability to other regions requires confirmation. Additionally, while we included patients with treated brain metastases, CNS-specific progression-free survival was not a pre-specified endpoint; formal analysis of intracranial efficacy is ongoing.

In conclusion, BRAZIL-TSG establishes oismertinib plus platinum–pemetrexed as the standard first-line therapy for EGFR-mutated NSCLC with concurrent TSG alterations. These results support the integration of broad NGS panel testing at diagnosis to identify patients who will derive maximal benefit from early chemotherapy intensification.

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Tables and Legends

Table 1. Baseline Demographics and Disease Characteristics (Intention-to-Treat Population)

Characteristic	Osimertinib + Chemotherapy (n=171)	Osimertinib + Placebo (n=171)
Age, median [range], years	58 [28-79]	57 [32-81]
Female sex, n (%)	106 (62.0)	104 (60.8)
ECOG performance status 0, n (%)	98 (57.3)	102 (59.6)
Never-smoker, n (%)	142 (83.0)	138 (80.7)
EGFR mutation		
- Exon 19 deletion	82 (48.0)	85 (49.7)
- L858R	89 (52.0)	86 (50.3)
Brain metastases at baseline, n (%)	58 (33.9)	61 (35.7)
TSG alteration profile		
- *TP53* only	110 (64.3)	108 (63.2)
- *TP53* + *RB1*	32 (18.7)	35 (20.5)
- *TP53* + other TSG*	22 (12.9)	21 (12.3)
- Other TSG only†	7 (4.1)	7 (4.1)

*Other TSG includes *PTEN*, *ARID1A* (non-RB1). †*RB1* or *PTEN* without *TP53*.

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Table 2. Treatment-Related Adverse Events (Safety Population)

Event	Osimertinib + Chemotherapy (n=171)		Osimertinib + Placebo (n=171)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event	168 (98.2)	72 (42.1)	152 (88.9)	32 (18.7)
Anemia	124 (72.5)	21 (12.3)	28 (16.4)	3 (1.8)
Neutropenia	98 (57.3)	31 (18.1)	8 (4.7)	2 (1.2)
Thrombocytopenia	64 (37.4)	14 (8.2)	6 (3.5)	0
Nausea	89 (52.0)	4 (2.3)	12 (7.0)	0
Fatigue	76 (44.4)	8 (4.7)	45 (26.3)	3 (1.8)
Rash	68 (39.8)	3 (1.8)	62 (36.3)	2 (1.2)
Diarrhea	54 (31.6)	2 (1.2)	48 (28.1)	1 (0.6)
Interstitial lung disease	2 (1.2)	1 (0.6)	3 (1.8)	1 (0.6)

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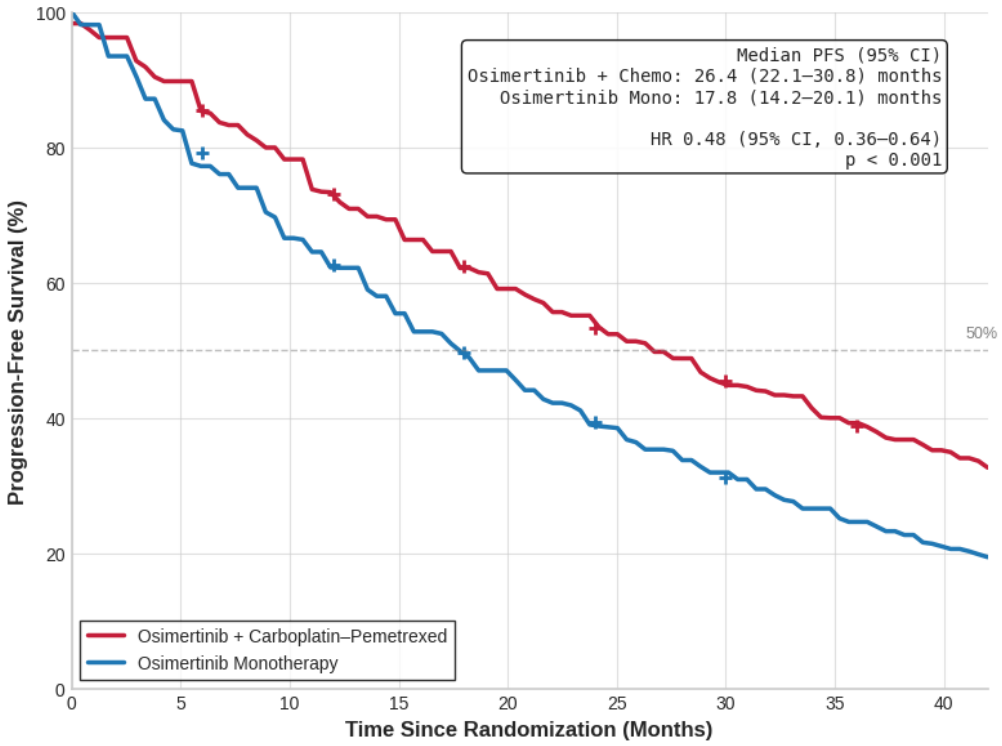
ISSN: 0005-2523

ISSN: 0005-2523
Volume 71, Issue 03, 2026

Figures and Legends

Figure 1. Kaplan-Meier Curves for Progression-Free Survival (Intention-to-Treat Population).



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ISSN: 0005-2523
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Figure 2. Forest Plot of Progression-Free Survival by Subgroup.

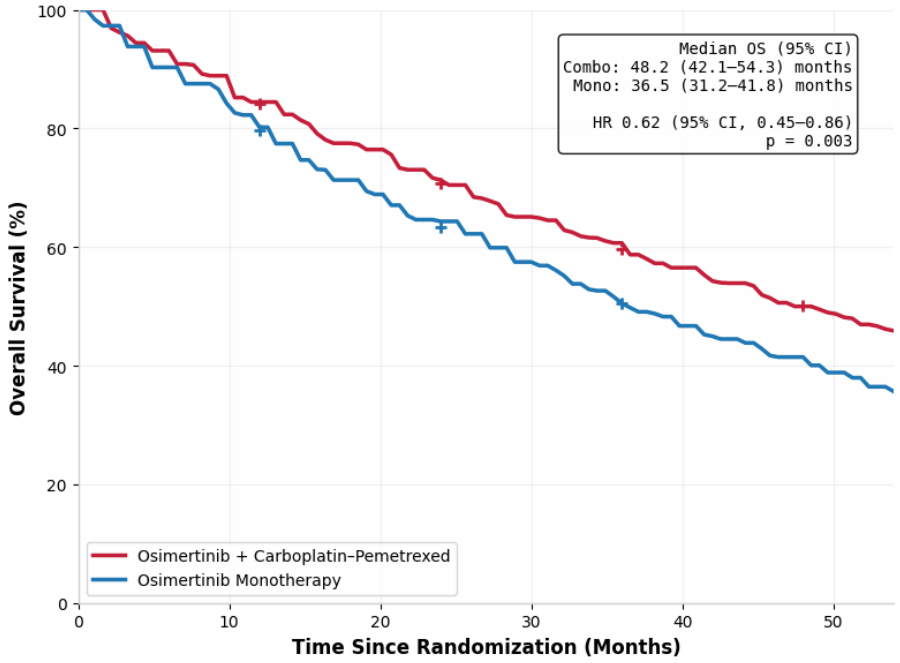

Figure 3. Kaplan-Meier Curves for Overall Survival.