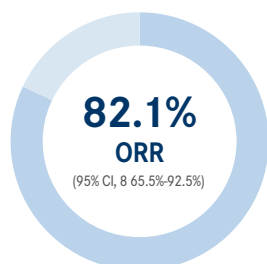


Osimertinib Plus Gefitinib Suppresses Acquired *EGFR* Resistance Mutations in First-Line NSCLC

Phase 1/2—study presented at IASLC 2026 World Conference on Lung Cancer (WCLC), September 12-15, 2026, Seoul, South Korea

Top-Line Finding



ZERO known second-site *EGFR* resistance mutations detected among 29 profiled patients at progression

Osimertinib 80 mg + gefitinib 250 mg daily, first-line, treatment-naïve *EGFR*-mutated NSCLC

Efficacy

Finding	Result
Partial response	82.1%
Stable disease	15.4%
Progressive disease	2.6%
Median PFS	18.4 months (95% CI, 14.6-32.0)
PFS rate: 12-months/24 months	71.1%/46.5%
Median OS	44.4 months (95% CI, 29.3-53.7)
OS rate: 12-months/24 months	89.7%/76.3%

High response rate, but median PFS (18.4 mo) tracked with historical osimertinib monotherapy despite the added agent

Trial Snapshot



Population

Newly diagnosed stage IV NSCLC, *EGFR* exon 19 deletion or L858R, ECOG 0-1, treatment-naïve



CNS Metastases

Asymptomatic untreated CNS metastases permitted



Dose Escalation

Osimertinib 80 mg + gefitinib 250 mg daily
42 patients in safety set; 39 efficacy-evaluable



Follow-Up

Median 60.8 months (PFS), 72.4 months (OS)
Primary endpoint: safety and feasibility

Resistance Profiling at Progression

Finding	Rate
Known <i>EGFR</i> second-site mutations	0%
Mechanism unknown	56%
<i>PIK3CA</i> alterations	8%
<i>KRAS</i> amplification	8%
<i>EGFR</i> amplification	8%
<i>BRAF</i> alterations	8%
<i>MET</i> amplification	8%
Small cell transformation	5%
β -Catenin or <i>ERBB4</i> alterations	4%

The combination fully suppressed classic second-site *EGFR* resistance mutations—but bypass-pathway mechanisms still emerged, and over half of resistant cases had no identified driver.

Safety

Most common treatment-related adverse events (TRAEs)



92.9%
Diarrhea



69.0%
Dry skin



50.0%
Acneiform rash



47.6%
Paronychia

- 54.8% of patients** had a grade 3 treatment-related AE; 16.7% grade 4
- One grade 5 event** (pulmonary embolism), deemed unrelated to study drugs
- Only 56% of patients** met the prespecified feasibility threshold; investigators still judged it manageable with dose modification

Why It Matters

Dual *EGFR*-targeted strategies remain an active area of investigation in frontline *EGFR*-mutated NSCLC. Although osimertinib plus gefitinib suppressed second-site *EGFR* resistance mutations entirely, the lack of a corresponding PFS improvement over historical monotherapy data—combined with a demanding tolerability profile—raises the question of whether resistance suppression alone translates to durable clinical benefit. At the same meeting, an exploratory FLAURA2 (NCT04035486) analysis showed *TP53* comutation status remains prognostic for PFS/OS regardless of treatment arm.