

# Combination Osimertinib plus Gefitinib for First-Line Treatment of EGFR-Mutated Non-Small Cell Lung Cancer

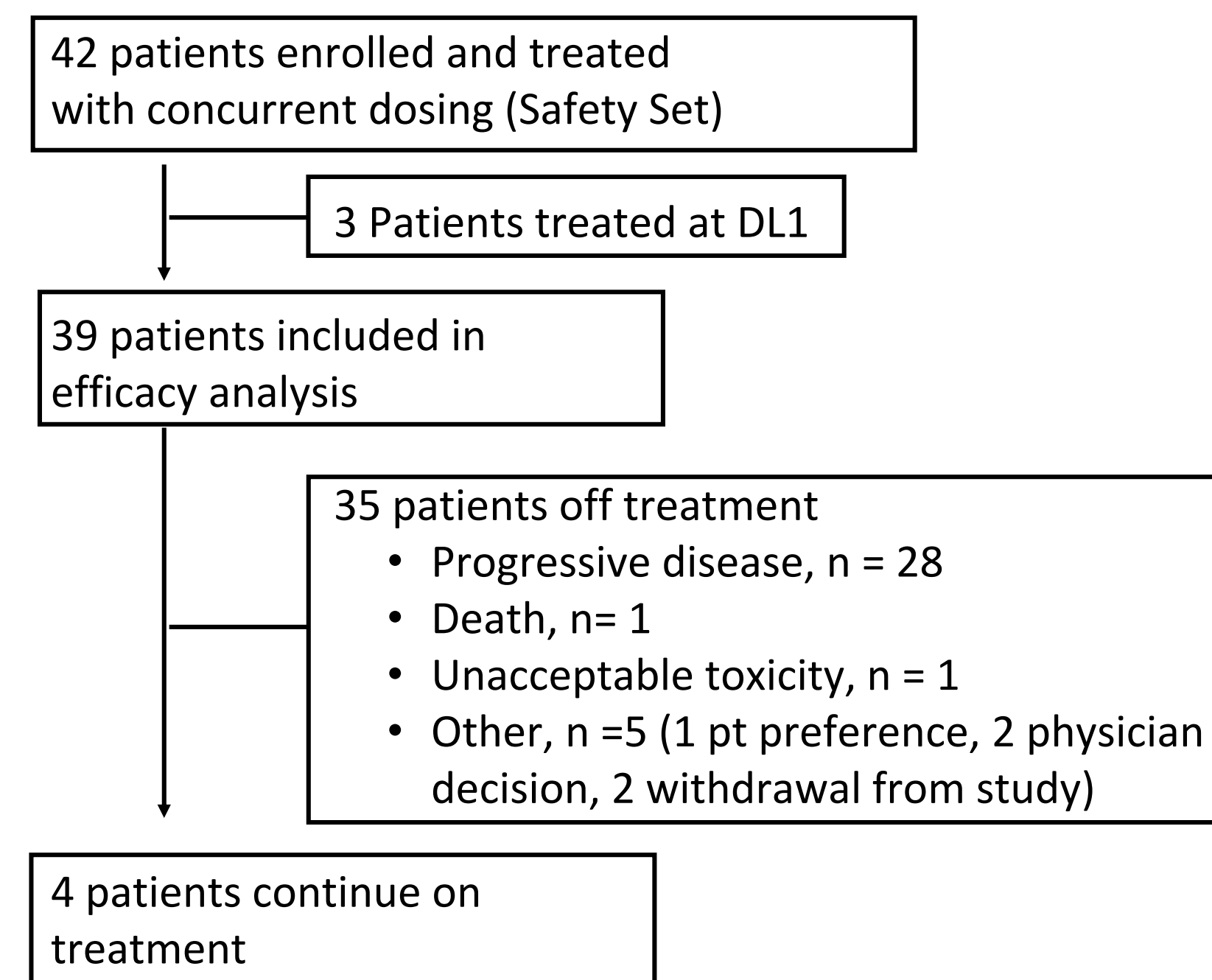
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## Introduction

- The standard-of-care for metastatic NSCLC with a classical EGFR mutation is a third-generation EGFR TKI either as osimertinib monotherapy or in combination with chemotherapy or amivantamab.
- Third-generation EGFR TKIs overcome the EGFR T790M first-generation TKI resistance mutation but are vulnerable to first-generation TKI-sensitive EGFR C797S mutations.
- Sequential acquisition of both mutations as triple-mutant disease produces resistance to all currently approved classes of EGFR TKIs. Combination rather than sequential therapy may be able to prevent the development of compound resistance mutations.
- Here we evaluate whether dual EGFR-targeted therapy with the third-generation EGFR TKI osimertinib and the first-generation EGFR TKI gefitinib is feasible, prevents acquired EGFR resistance mutations, and improves outcomes in newly diagnosed EGFR-mutated NSCLC.

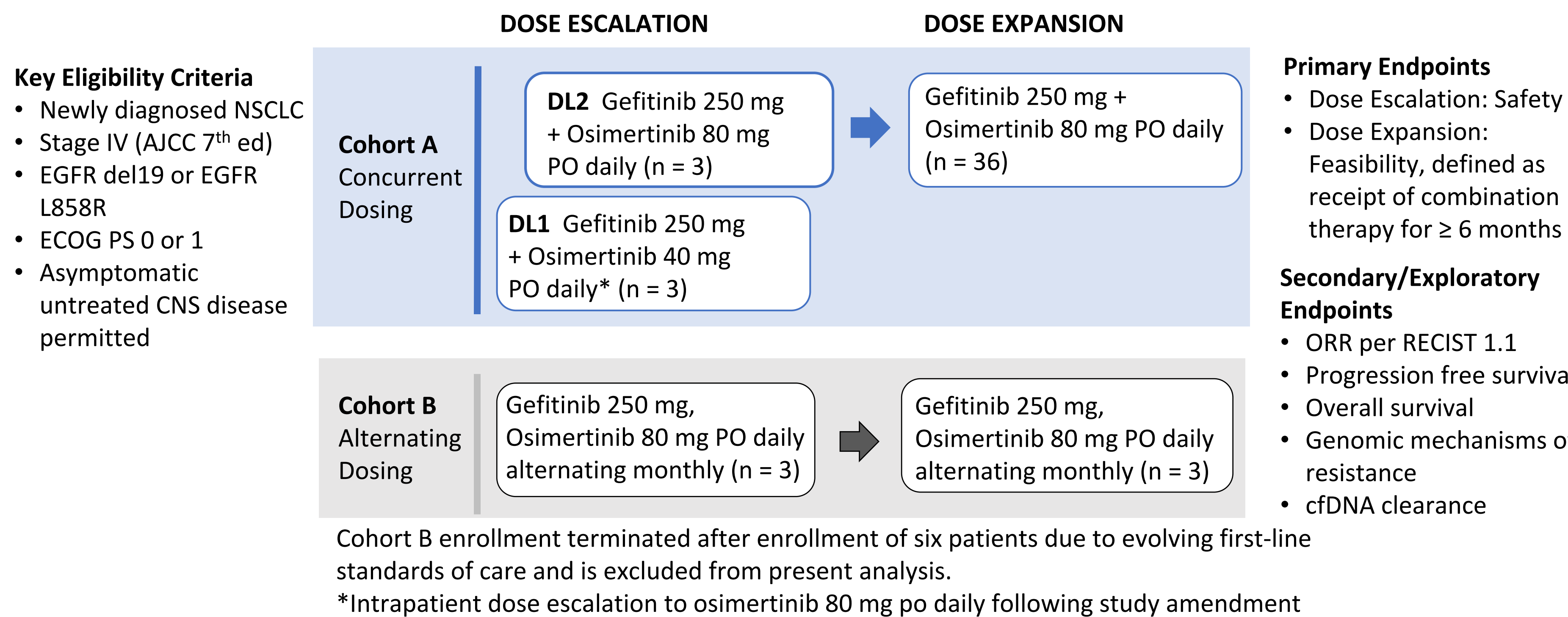
## Figure 1 Patient Disposition



## Table 1. Baseline Characteristics

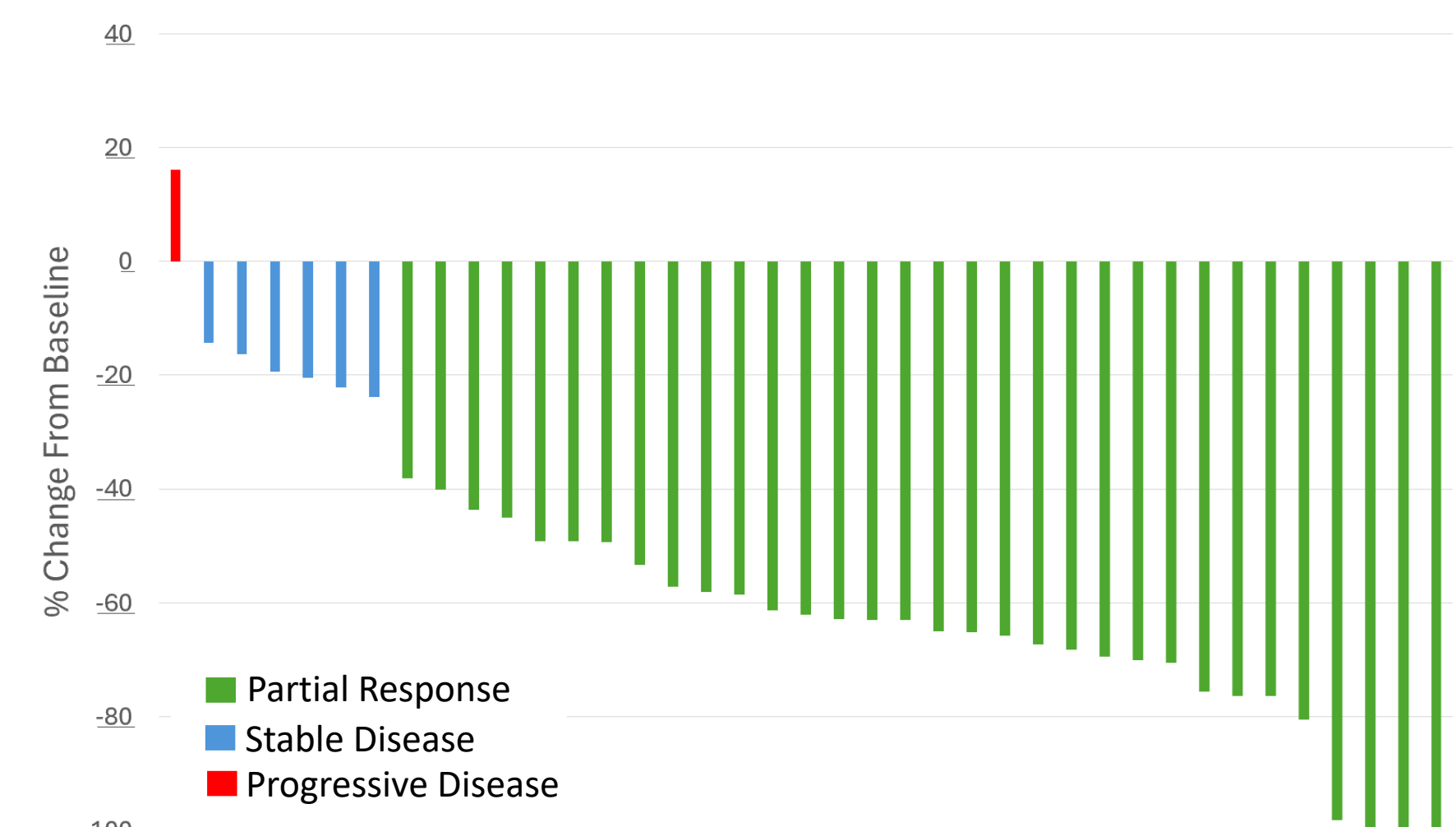
| Characteristic                | Safety Set<br>N = 42 | Characteristic                        | Safety Set<br>N = 42 |
|-------------------------------|----------------------|---------------------------------------|----------------------|
| <b>Median age (range), yr</b> | 62 (39, 79)          | <b>Histology</b>                      |                      |
| <b>Site, n(%)</b>             |                      | Adenocarcinoma                        | 39 (92.9%)           |
| DFCI                          | 30 (71.4%)           | Squamous                              | 2 (4.8%)             |
| BIDMC                         | 12 (28.6%)           | NSCLC NOS                             | 1 (2.3%)             |
| <b>Sex, n(%)</b>              |                      | <b>EGFR Mutation</b>                  |                      |
| Female                        | 28 (66.7%)           | Exon 19 del                           | 24 (57.1%)           |
| Male                          | 14 (33.3%)           | L858R                                 | 18 (42.9%)           |
| <b>Race, n(%)</b>             |                      | <b>Baseline CNS Metastases, n (%)</b> |                      |
| White                         | 35 (83.3%)           | Present                               | 20 (47.6%)           |
| Asian                         | 5 (11.9%)            | Untreated                             | 8 (19.0%)            |
| Black                         | 1 (2.4%)             | <b>TP53, n(%)</b>                     |                      |
| Other                         | 1 (2.4%)             | Mutated                               | 20 (47.6%)           |
| <b>ECOG PS, n(%)</b>          |                      | Wildtype                              | 9 (21.4%)            |
| 1                             | 28 (66.7%)           | Unknown                               | 13 (31%)             |
| 0                             | 14 (33.3%)           |                                       |                      |
| <b>Tobacco Use, n(%)</b>      |                      |                                       |                      |
| Never                         | 26 (61.9%)           |                                       |                      |
| Former                        | 15 (35.7%)           |                                       |                      |
| Current                       | 1 (2.3%)             |                                       |                      |

## Study Design



## Results

### Figure 2. Objective response to treatment

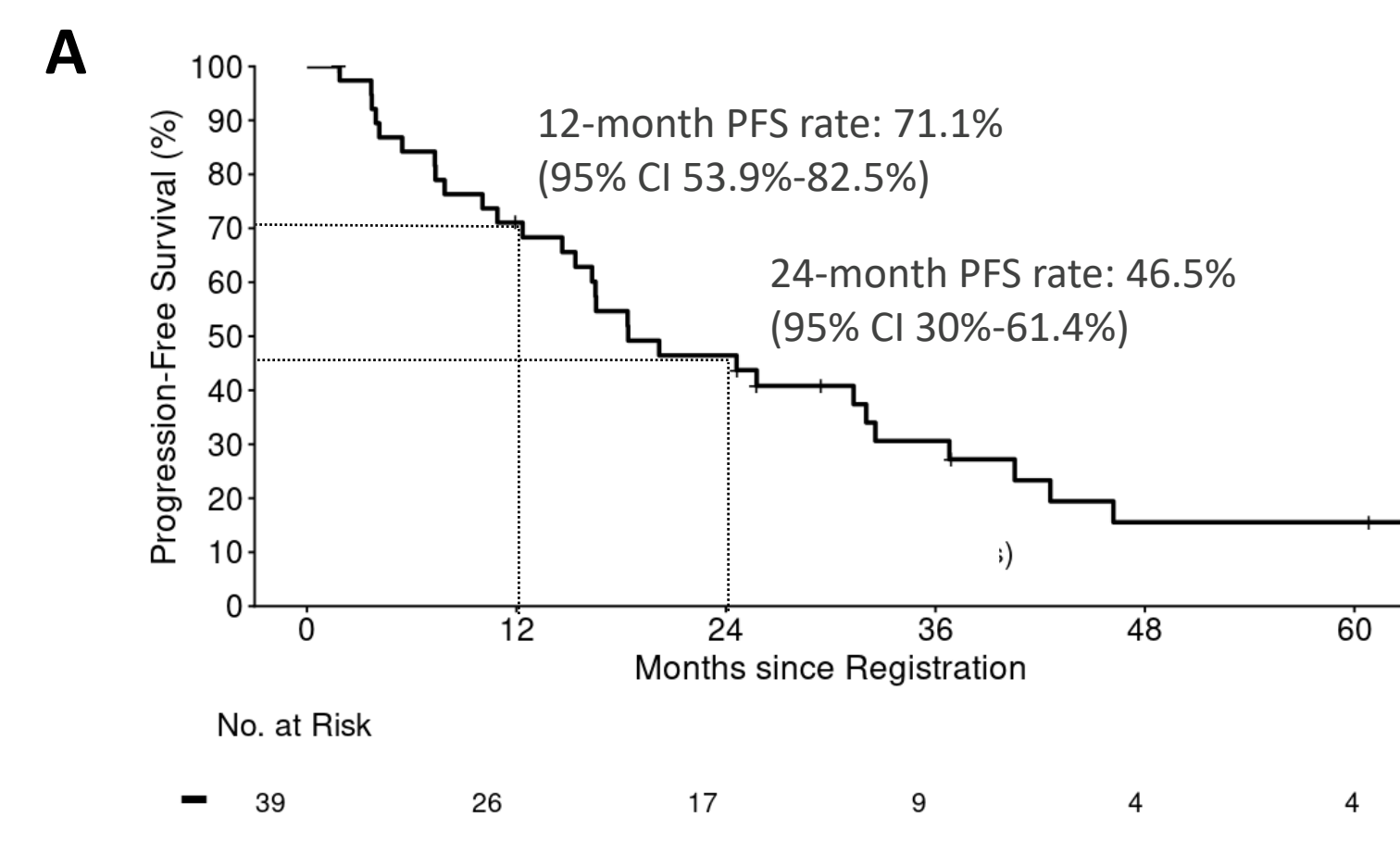


|                                            |                    |
|--------------------------------------------|--------------------|
| <b>Objective response rate, % (95% CI)</b> | 82.1 (65.5 – 92.5) |
| <b>Best objective response, n(%)</b>       |                    |
| Partial response                           | 32 (82.1%)         |
| Stable disease                             | 6 (15.4%)          |
| Progressive disease                        | 1 (2.6%)           |

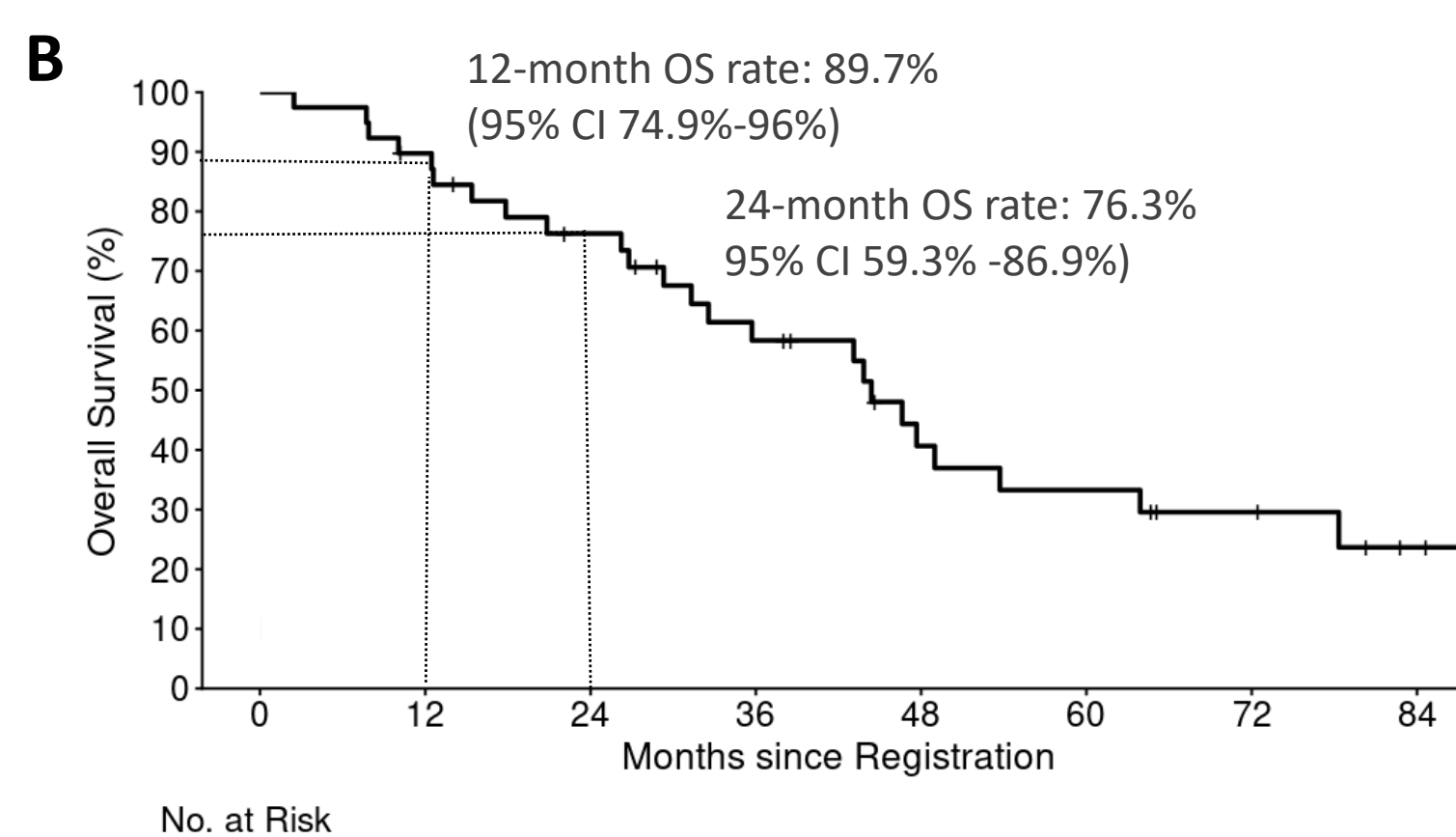
### Feasibility of treatment

- Patients received a median 13 cycles of gefitinib and 23 cycles of osimertinib
- The protocol defined feasibility as completion of six cycles on study with ≤2 doses held per cycle in at least 80% of patients
- While 56% of patients met this criteria, which did not meet the prespecified study feasibility threshold, clinically treatment was manageable with most patients receiving a prolonged period of combination therapy with appropriate dose modification and supportive care

### Figure 3. Progression-free survival (A) and overall survival (B) on osimertinib plus gefitinib



The median duration of follow-up for PFS was 60.8 months (95% CI 14.6-32.0 months). **The median PFS was 18.4 months** (95% CI 14.6-32.0 months).



The median duration of follow-up for OS was 72.4 months (90% CI: 64.6 – 82.8). **The median OS was 44.4 months** (95% CI 29.3-53.7 months)

## Safety

### Table 3. Most common TRAEs

| Event, n(%)          | Any Grade | Grade 1   | Grade 2   | Grade 3  |
|----------------------|-----------|-----------|-----------|----------|
| Diarrhea             | 39 (92.9) | 24 (57.1) | 9 (21.4)  | 6 (14.3) |
| Dry skin             | 29 (69)   | 27 (64.3) | 2 (4.8)   | 0        |
| Rash acneiform       | 21 (50)   | 13 (31)   | 7 (16.7)  | 1 (2.4)  |
| Paronychia           | 20 (47.6) | 9 (21.4)  | 11 (26.2) | 0        |
| Skin/subcutaneous    | 20 (47.6) | 14 (33.3) | 6 (14.3)  | 0        |
| Fatigue              | 18 (42.9) | 10 (23.8) | 8 (19)    | 0        |
| Anorexia             | 16 (38.1) | 4 (9.5)   | 12 (28.6) | 0        |
| AST increased        | 16 (38.1) | 14 (33.3) | 0         | 2 (4.8)  |
| Nausea               | 16 (38.1) | 11 (26.2) | 4 (9.5)   | 1 (2.4)  |
| Alopecia             | 13 (31)   | 7 (16.7)  | 6 (14.3)  | 0        |
| QT prolonged         | 13 (31)   | 9 (21.4)  | 4 (9.5)   | 0        |
| Platelet decreased   | 13 (31)   | 12 (28.6) | 1 (2.4)   | 0        |
| ALT increased        | 12 (28.6) | 9 (21.4)  | 0         | 3 (7.1)  |
| Rash maculopapular   | 12 (28.6) | 7 (16.7)  | 2 (4.8)   | 3 (7.1)  |
| Weight loss          | 11 (26.2) | 7 (16.7)  | 4 (9.5)   | 0        |
| Papulopustular rash  | 10 (23.8) | 6 (14.3)  | 3 (7.1)   | 1 (2.4)  |
| WBC decreased        | 10 (23.8) | 7 (16.7)  | 3 (7.1)   | 0        |
| Anemia               | 9 (21.4)  | 6 (14.3)  | 3 (7.1)   | 0        |
| Creatinine increased | 9 (21.4)  | 8 (19)    | 1 (2.4)   | 0        |
| ANC decreased        | 7 (16.7)  | 6 (14.3)  | 1 (2.4)   | 0        |
| Dysgeusia            | 6 (14.3)  | 5 (11.9)  | 1 (2.4)   | 0        |
| GI disorders         | 6 (14.3)  | 6 (14.3)  | 0         | 0        |
| Mucositis oral       | 6 (14.3)  | 4 (9.5)   | 2 (4.8)   | 0        |
| Vomiting             | 6 (14.3)  | 4 (9.5)   | 1 (2.4)   | 1 (2.4)  |

### Table 4. Adverse events by attribution

| N (%)                                      | Grade 1  | Grade 2   | Grade 3   | Grade 4  | Grade 5  |
|--------------------------------------------|----------|-----------|-----------|----------|----------|
| <b>Any attribution</b>                     | 0        | 11 (26.2) | 23 (54.8) | 7 (16.7) | 1 (2.4)* |
| <b>At least possibly related to either</b> | 4 (9.5)  | 22 (52.4) | 15 (35.7) | 1 (2.4)† | 0        |
| To osimertinib                             | 5 (11.9) | 23 (54.8) | 13 (31.0) | 1 (2.4)† | 0        |
| To gefitinib                               | 4 (9.5)  | 23 (54.8) | 14 (33.3) | 1 (2.4)† | 0        |

†Optic neuropathy  
\*Pulmonary embolism, attributed as unrelated to treatment

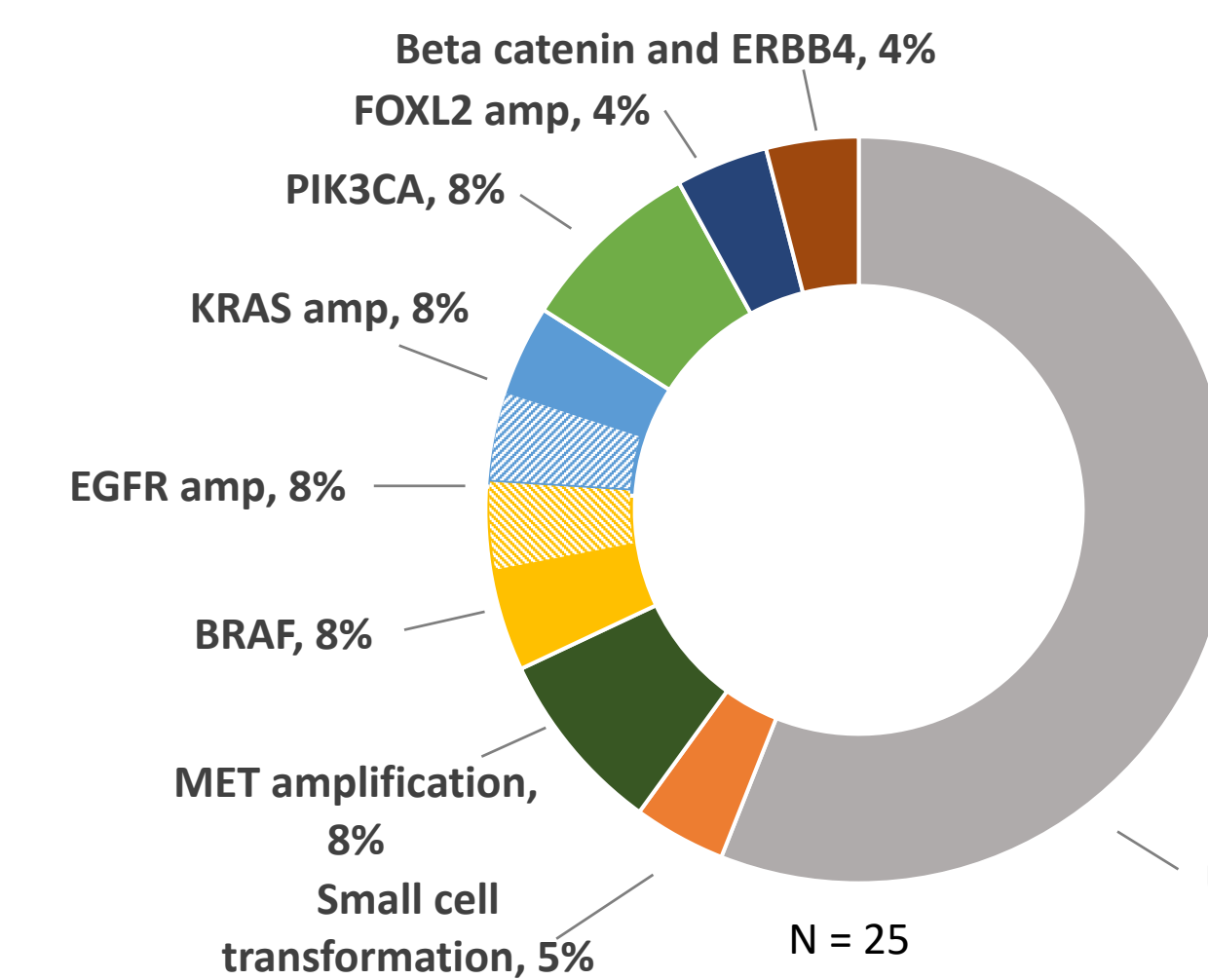
### Table 5. Dose modification rates

| N=39                                   | Osimertinib n(%) | Gefitinib n(%) |
|----------------------------------------|------------------|----------------|
| <b>Dose interruption rate for TRAE</b> | 13 (33.3%)       | 18 (46.2%)     |
| <b>Dose reduction rate for TRAE</b>    | 5 (12.8%)        | 11 (28.2%)     |
| <b>Discontinuation Rate for TRAE</b>   | 3 (7.7%)         | 14 (35.9%)     |

Two patients (4.8%) experienced drug-induced pneumonitis (2.4% G1, 2.4% G2)  
Five patients (11.9%) had reduced LVEF attributed to study drugs (9.5% G2, 2.4% G3). Treatment held transiently in two patients, both of whom subsequently resumed and tolerated osimertinib monotherapy

## Mechanisms of Acquired Resistance

### Figure 4. Post-treatment genomics



32 patients with acquired treatment resistance  
29 (90.6%) Resistance profiling completed  
11 Tissue-based NGS  
9 Both tissue and ctDNA-based  
9 ctDNA profiling (4 nondiagnostic/EGFRm not detected)

- No known EGFR second-site acquired resistance mutations detected.
- One EGFR VUS (V1047M) which is not known to be oncogenic was identified in a post-treatment sample
- EGFR amplifications (11X, 6X CNG) were found in 2 patients (8%), both co-occurring with other bypass pathway alterations in KRAS (6X CNG) and BRAF (16X CNG)

## Conclusions

- First-line combination osimertinib plus gefitinib suppressed emergence of second-site EGFR resistance mutations and produced a manageable adverse effect profile.
- Despite preventing EGFR resistance mutations, combination therapy produced a median PFS of 18.4 months, which is comparable to historical data on osimertinib monotherapy.

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**References:** Soria et al. NEJM. 2018. 378:113-25, Ramalingam et al. NEJM. 2020. 382(1):41, Yang et al. 2018. Clin Can Res. 2018. 24(13):3097-107, Oxnard et al. JAMA Oncol. 2018. 4(11), Arulananda et al. JTO. 2017. 12(11):1728-32, 1723-27, Janne et al. NEJM. 2015. 372:1689-99, Leonetti et al. British J Cancer 2019. 121:725-37, Maemondo et al. NEJM. 2010. 362:2380-8; Planchard et al NEJM 2023; Cho et al NEJM 2024.

**Abbreviations:** CNG, copy number gain; CNS, central nervous system; EGFR, epidermal growth factor receptor; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; TKI, tyrosine kinase inhibitor; TREA, treatment-related adverse event.

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