

Lazertinib with Pemetrexed/Carboplatin After First-/Second-Generation TKI: Efficacy Across T790M status and Leptomeningeal Disease

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INTRODUCTION

- Third-generation EGFR tyrosine kinase inhibitors (TKIs) demonstrated superior progression-free survival (PFS) in the first-line setting, regardless of T790M mutation status.
 - In the FLAURA2 trial, osimertinib combined with pemetrexed and carboplatin significantly improved survival outcomes compared with osimertinib alone.
- The purpose of this study is to evaluate the efficacy of lazertinib in combination with pemetrexed/carboplatin after progression on first- or second-generation EGFR TKIs, irrespective of T790M mutation status, with the hypothesis that combination therapy would provide clinical benefit beyond TKI monotherapy.

METHODS

Study design and Population

- A prospective, single-center exploratory study
- Enrolled between Sep 2022 and Sep 2025
- Eligibility : Patients progressed on first- or second-generation EGFR TKIs and had not received prior third-generation EGFR TKIs
- The data cutoff date was March 7, 2026.

Patient assignment

- Patients were assigned to three cohorts
- 1) cohort 1 : T790M-negative
- 2) cohort 2 : T790M-positive
- 3) cohort 3 : Leptomeningeal seeding (LMS), regardless of T790M status
- T790M assessed using tissue or plasma PCR.

Outcomes

Primary endpoint: Progression-free survival
Secondary endpoint: Safety, cell-free DNA (ctDNA) dynamics.

* ctDNA was analyzed using Guardant360 at baseline, cycle 2, and at end of treatment.

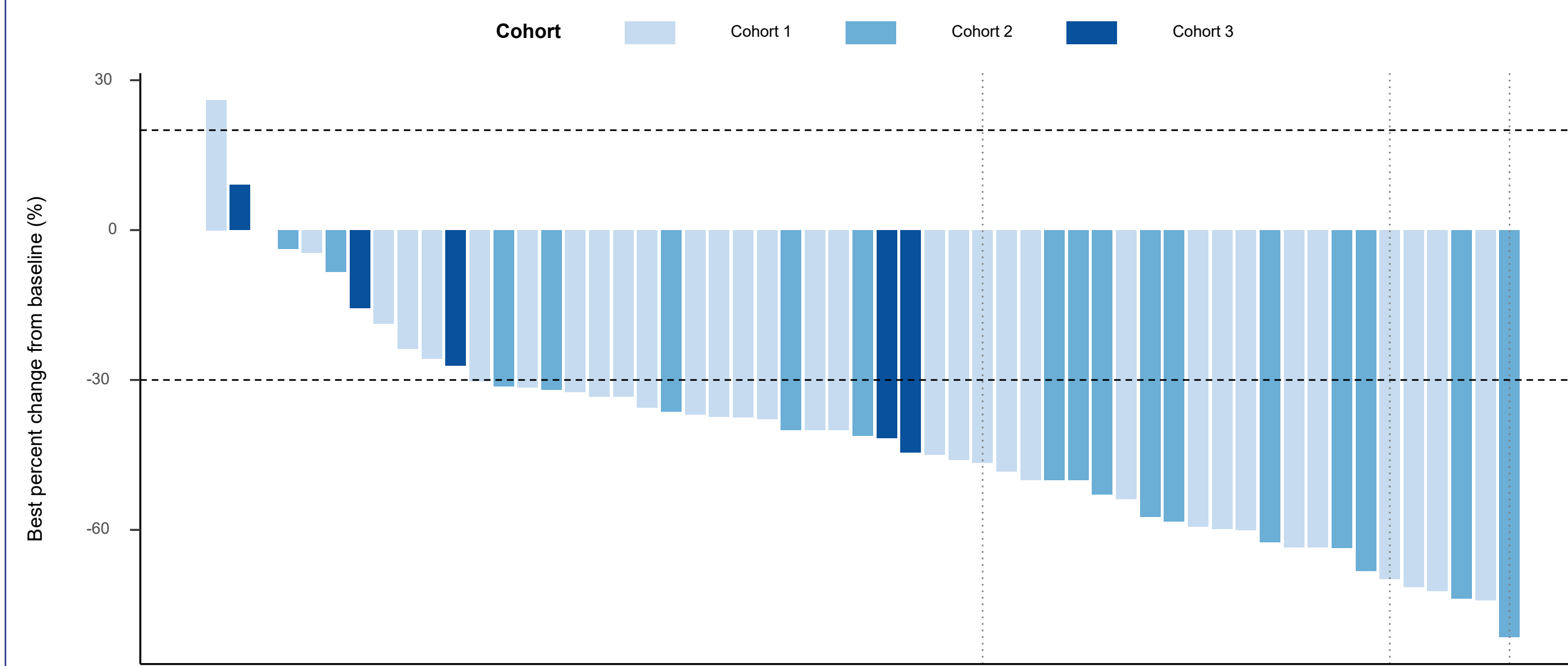
RESULTS

Table 1. Baseline characteristics of the study & Figure 1. Consort diagram

Characteristic	Cohort 1: T790M negative (N = 36)	Cohort 2: T790M positive (N = 18)	Cohort 3: LMS positive (N = 7)	p-value
Male	16/36 (44%)	5/18 (28%)	3/7 (43%)	0.5
Age, yr	67.5 (57.0, 73.5)	62.5 (55.0, 68.0)	68.0 (63.0, 71.0)	0.2
Smoking history	15/36 (42%)	3/18 (17%)	1/7 (14%)	0.11
Lung metastasis	23/36 (64%)	7/18 (39%)	1/7 (14%)	0.030
Brain metastasis	20/36 (56%)	4/18 (22%)	4/7 (57%)	0.051
Pleural metastasis	14/36 (39%)	6/18 (33%)	2/7 (29%)	0.9
Liver metastasis	3/36 (8.3%)	2/18 (11%)	0/7 (0%)	>0.9
Lymph node metastasis	22/36 (61%)	8/18 (44%)	3/7 (43%)	0.5
Bone metastasis	14/36 (39%)	7/18 (39%)	1/7 (14%)	0.5
Line of treatment at study entry				0.6
1L	0/36 (0%)	0/18 (0%)	0/7 (0%)	
2L	34/36 (94%)	17/18 (94%)	6/7 (86%)	
3L	2/36 (5.6%)	1/18 (5.6%)	1/7 (14%)	
Duration of prior 1L treatment, months	281.2 (273.4, 283.6)	279.8 (267.4, 318.0)	274.0 (274.0, 274.0)	>0.9

* IP : Investigational product / ¹n/N (%); Median (Q1, Q3)

Figure 2. Waterfall plot of response



- The overall response rate (ORR) was 76.8% across all cohorts (82%, 82%, and 33% in cohorts 1, 2, and 3, respectively).

Figure 3. Survival curves for progression-free survival and overall survival

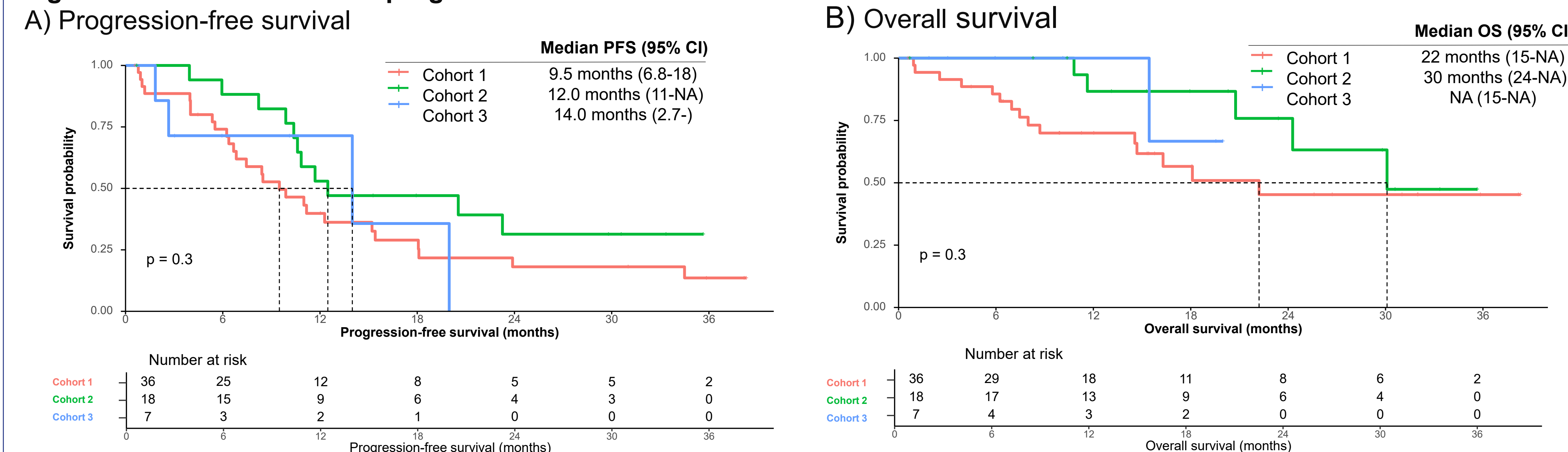
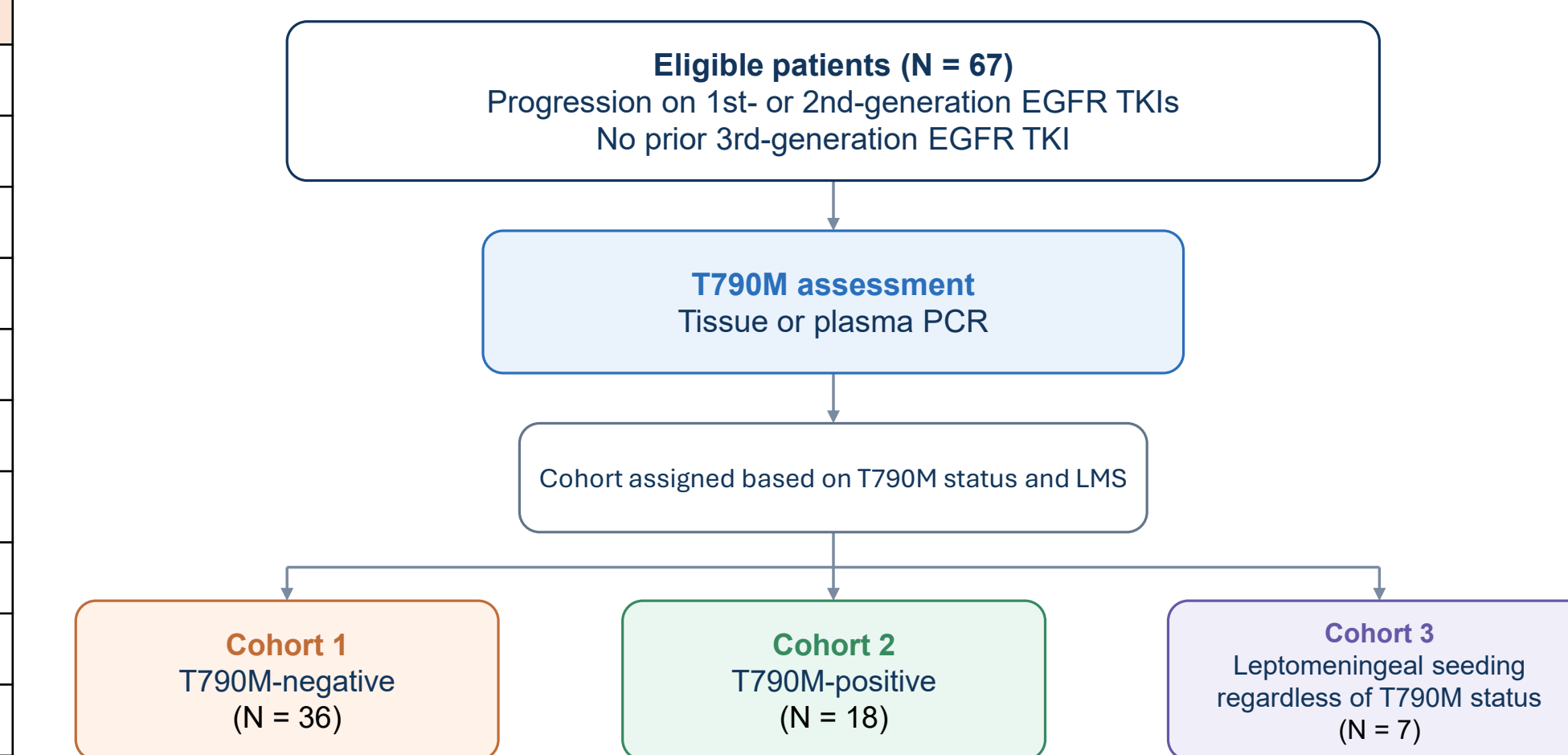


Table 2. Dose reduction & discontinuation of treatment by cohort

	Cohort 1: T790M negative (N = 36)	Cohort 2: T790M positive (N = 18)	Cohort 3: LMS positive (N = 7)	p-value
Dose reduction of IP*	21/35 (60%)	10/17 (59%)	4/5 (80%)	0.8
Discontinuation of IP*	6/35 (17%)	10/17 (59%)	1/5 (20%)	0.008

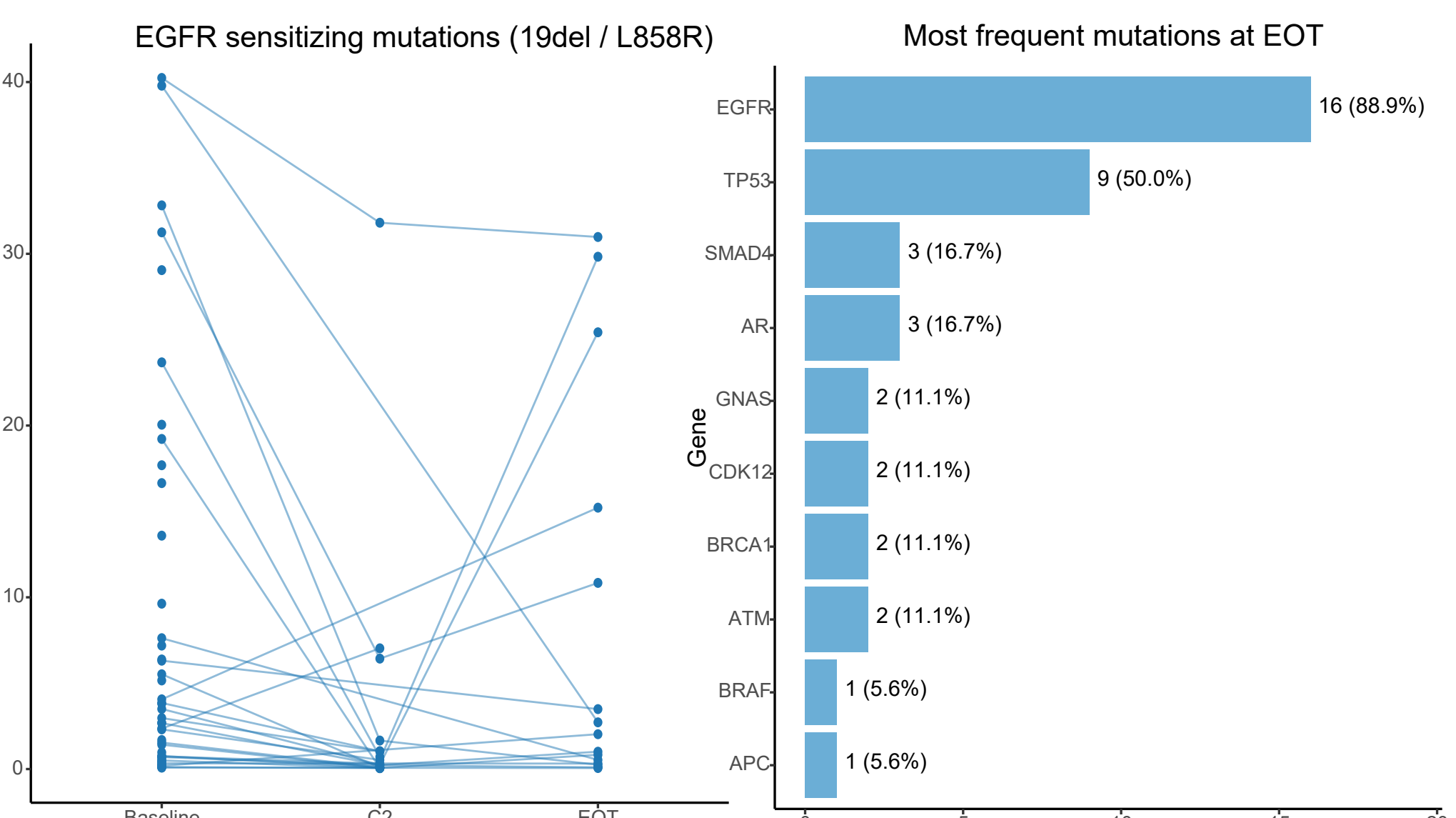
* IP : Investigational product

Consort diagram :



- Median follow-up: 14.7 months
- Most patients received the study treatment after progression on first-line TKIs (94%, 94%, and 84% in cohorts 1, 2, and 3, respectively)

Figure 4. Longitudinal dynamics of EGFR ctDNA & co-mutation at EOT



- At cycle 2, ctDNA clearance was observed in 56.7% (17/30) of patients in cohort 1 and 64.3%(9/14) in cohort 2.

DISCUSSION & CONCLUSION

- ✓ Lazertinib combined with pemetrexed/carboplatin demonstrated durable clinical activity with a manageable safety profile.
 - ✓ Patients without T790M mutations also showed meaningful responses, suggesting potential benefit beyond T790M-positive populations.
 - ✓ Promising outcomes were observed in patients with LMS, a population often excluded from clinical trials.
- These findings support the use of lazertinib-based combination therapy as a treatment option for patients with disease progression after first- or second-generation EGFR TKIs.

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