

P3.220: Clinical Efficacy and Plasma-Based Genomic Profiling of First-Line Lazertinib in EGFR-Mutant NSCLC: Interim Analysis

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INTRODUCTION

- Lazertinib** is a third-generation EGFR tyrosine kinase inhibitor that selectively targets both sensitizing EGFR mutations (EGFRm) and T790M.
- In this study, we evaluated the clinical efficacy of Lazertinib in treatment-naïve EGFRm non-small cell lung cancer (NSCLC) patients along with genomic analysis based on co-alteration profile and acquired mutations.

METHODS

- This single-arm phase II prospective study recruited a total of 150 treatment-naïve, tissue-based EGFRm confirmed patients in the palliative setting between January 2nd, 2023, and February 27th, 2024, at Samsung Medical Center, and 149 patients were available for the analysis.
- Patients were treated with once daily 240 mg of Lazertinib until disease progression or loss of clinical benefit.
- In addition to clinical efficacy, **plasma-based genomic profiling** was performed using the **Guardant360 assay** at baseline and after disease progression (n=61). The data cutoff for this analysis was March 17th, 2026.

CONCLUSIONS

- In this study, first-line lazertinib demonstrated meaningful clinical efficacy in treatment-naïve EGFRm NSCLC patients in a real-world setting.
- Plasma-based genomic profiling revealed that baseline co-alterations — particularly concurrent TP53 mutations and additional EGFR alterations — were significantly associated with shorter PFS, highlighting their potential role as prognostic biomarkers in the lazertinib-treated setting.
- Acquired resistance mechanisms were diverse and heterogeneous across patients, and further analyses with a larger post-progression cohort are planned as more patients experience disease progression over time.
- Paired tissue-based whole-genome sequencing analysis for detailed genomic profiling of acquired mutation will be conducted.

Clinical Characteristics and Efficacy of First-Line Lazertinib

Table 1. Patient Demographics and Baseline Characteristics of the Analysis Population

Characteristic	Overall (N = 149)
Age, years, median (range)	63 (32–86)
Age group, years, No. (%)	
<65	84 (56.4)
≥65	65 (43.6)
Sex, No. (%)	
Male	55 (36.9)
Female	94 (63.1)
Smoking history, No. (%)	
Never	105 (70.5)
Ex or current	44 (29.5)
ECOG performance status score, No. (%)	
0	37 (24.8)
1	108 (72.5)
2	4 (2.7)
Baseline EGFR mutation, No. (%)	
Exon 19 deletion	84 (56.4)
L858R	65 (43.6)
Baseline brain metastasis, No. (%)	
Yes	66 (44.3)
No	83 (55.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Median duration of follow-up was 30.4 months (95% CI, 30.3–32.2) and at the timepoint of analysis 64 patients (43%) were still on the treatment, and 85 patients (57%) were discontinued the treatment due to the following reasons: disease progression or death (n=73, 49%); adverse events (n=4, 2.7%); withdrawal of consent (n=6, 4%) or clinical decision (n=2, 1.3%).

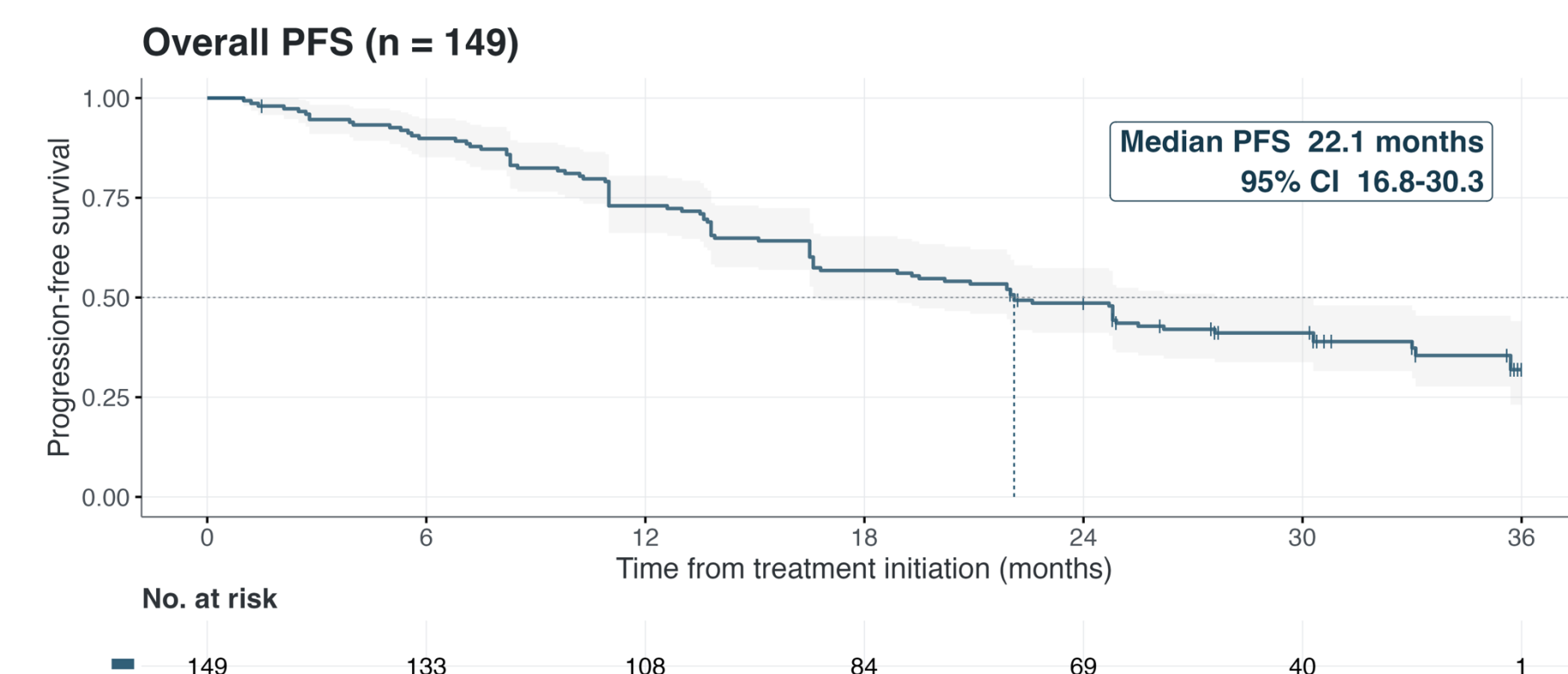


Figure 1. Overall Progression-Free Survival in 149 Patients Treated with First-Line Lazertinib

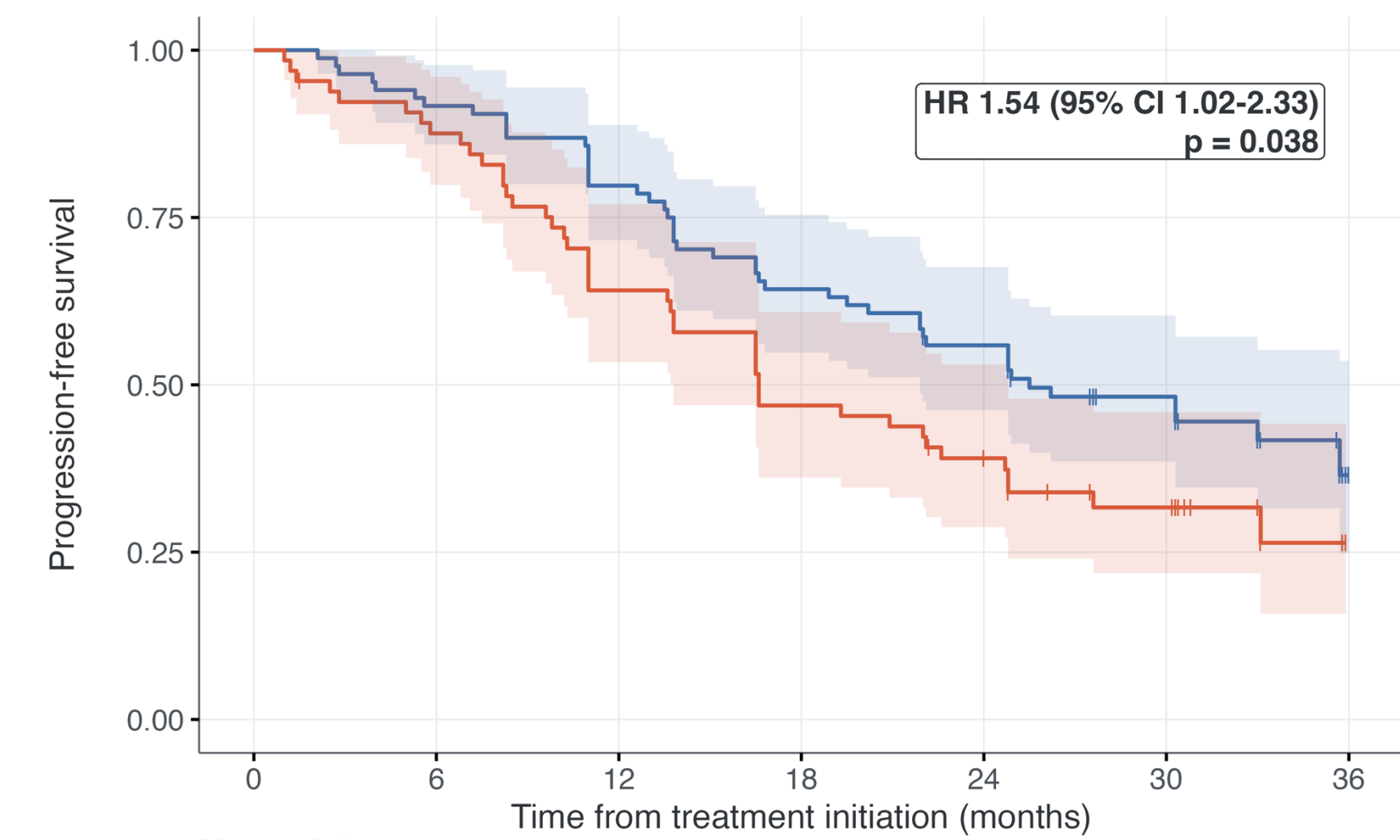


Figure 2. PFS according to tissue-based EGFR Driver Mutation Type

Overall median progression-free survival (PFS) was 22.1 months (95% CI, 16.8–30.3). Median PFS for Del 19 and L858R subgroup was 25.5 (95% CI, 21.9–NA) vs 16.6 (95% CI, 13.8–24.8) months, respectively (HR 1.54, 95% CI [1.02–2.33], p=0.038).

RESULTS

Baseline Genomic Alterations Associated with Clinical Outcomes

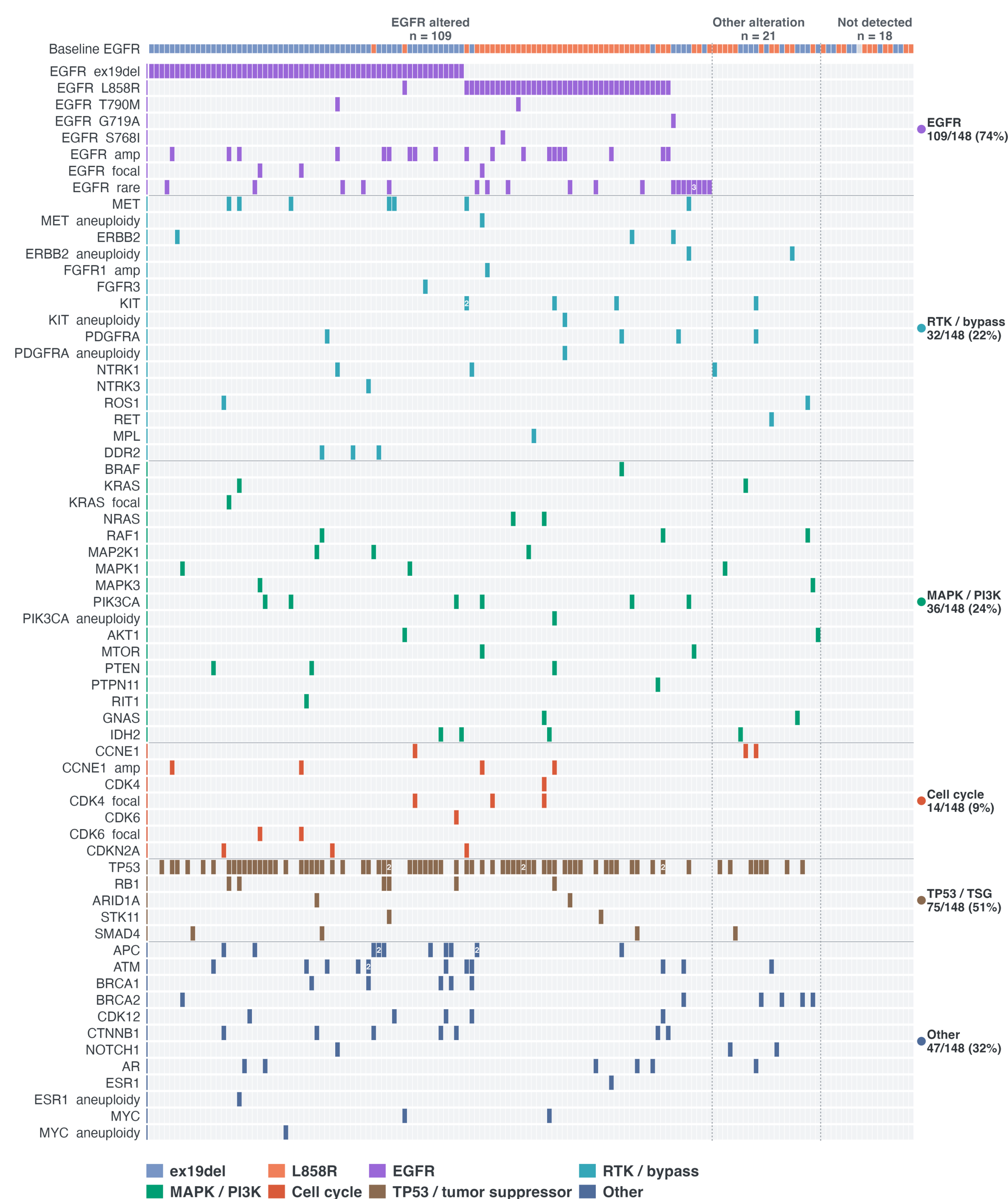


Figure 3. Baseline Plasma-Based Genomic Alteration Profiling Using Guardant360

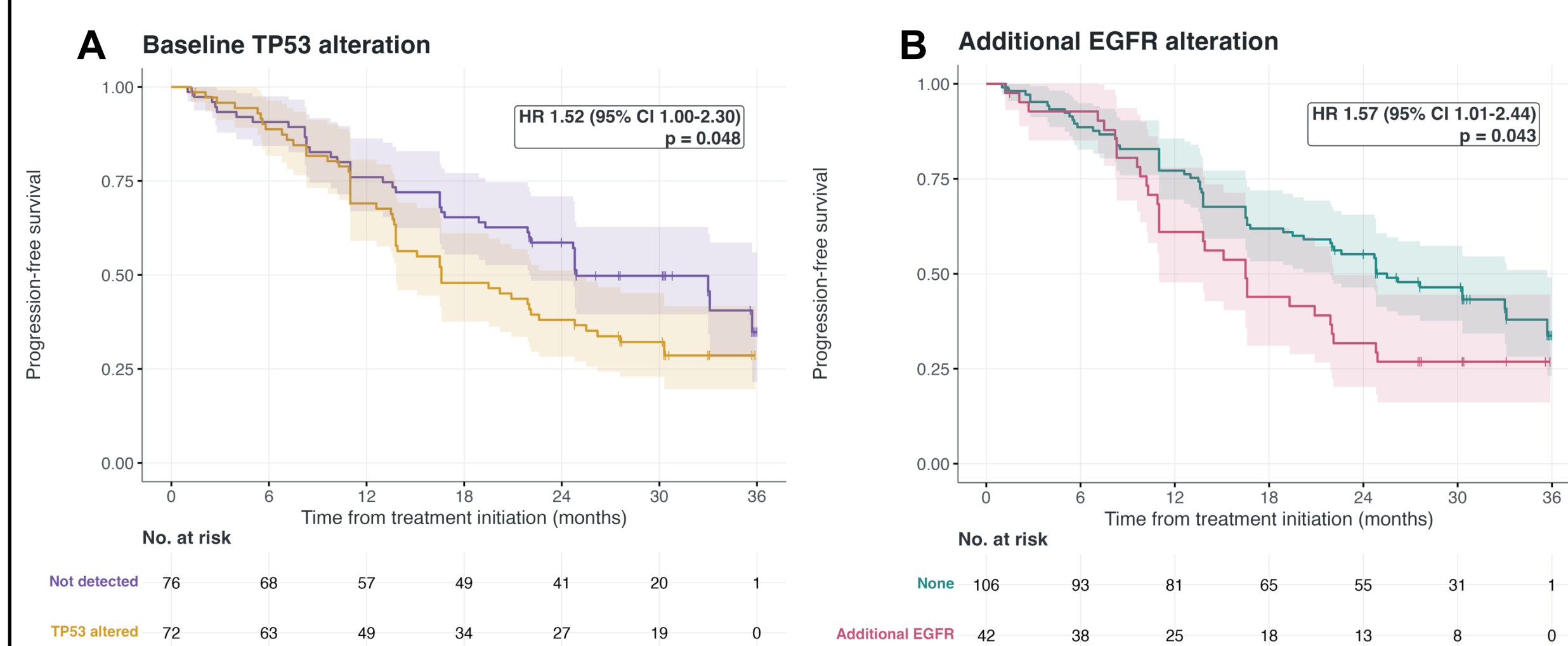


Figure 4. Association of Baseline Plasma Genomic Alterations with PFS

Patients with **TP53 alterations** (n=72, 48.3%) were significantly associated with an increased risk of progression (HR 1.52, 95% CI [1.00–2.30], p=0.048). Among patients with ex19del or L858R, the presence of an additional EGFR alteration—such as EGFR amplification, focal gain, or an uncommon EGFR variant—was associated with an increased risk of progression (n=42, 28.2%; HR 1.57, 95% CI [1.01–2.44], p = 0.043).

Landscape of Acquired Resistance Alterations

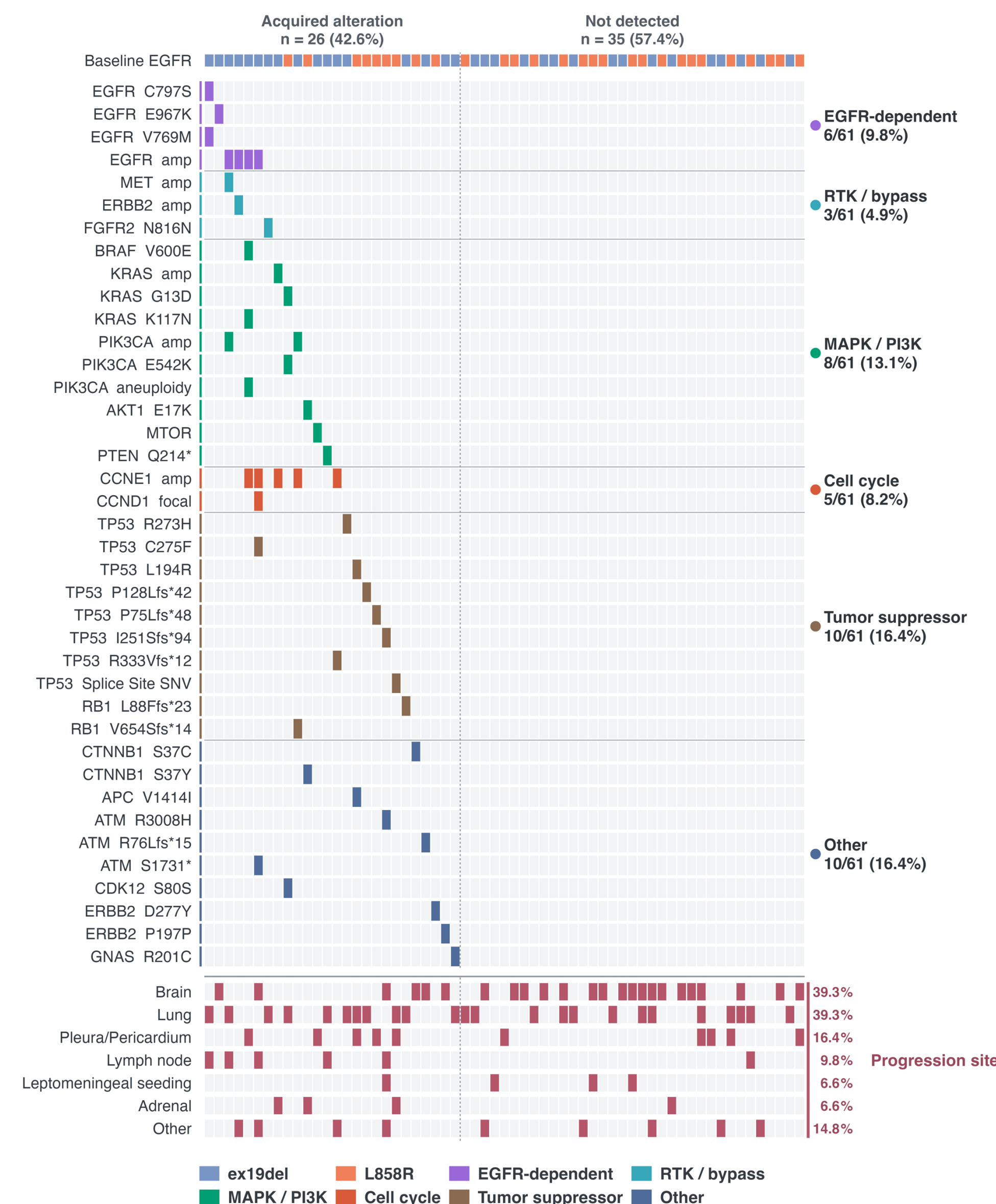


Figure 5. Acquired Plasma-Based Genomic Alterations Identified After Disease Progression in 61 Patients

Acquired alterations were identified in 26 of 61 patients (42.6%). EGFR-dependent resistance alterations were observed in 6 patients (9.8%), most commonly EGFR amplification in 4 patients (6.6%), followed by EGFR C797S, V769M, and E967K in 1 patient each (1.6% each). Notably, these resistance mechanisms were detected exclusively in patients with baseline EGFR exon 19 deletion. EGFR-independent acquired alterations were observed in 20 patients (32.8%).

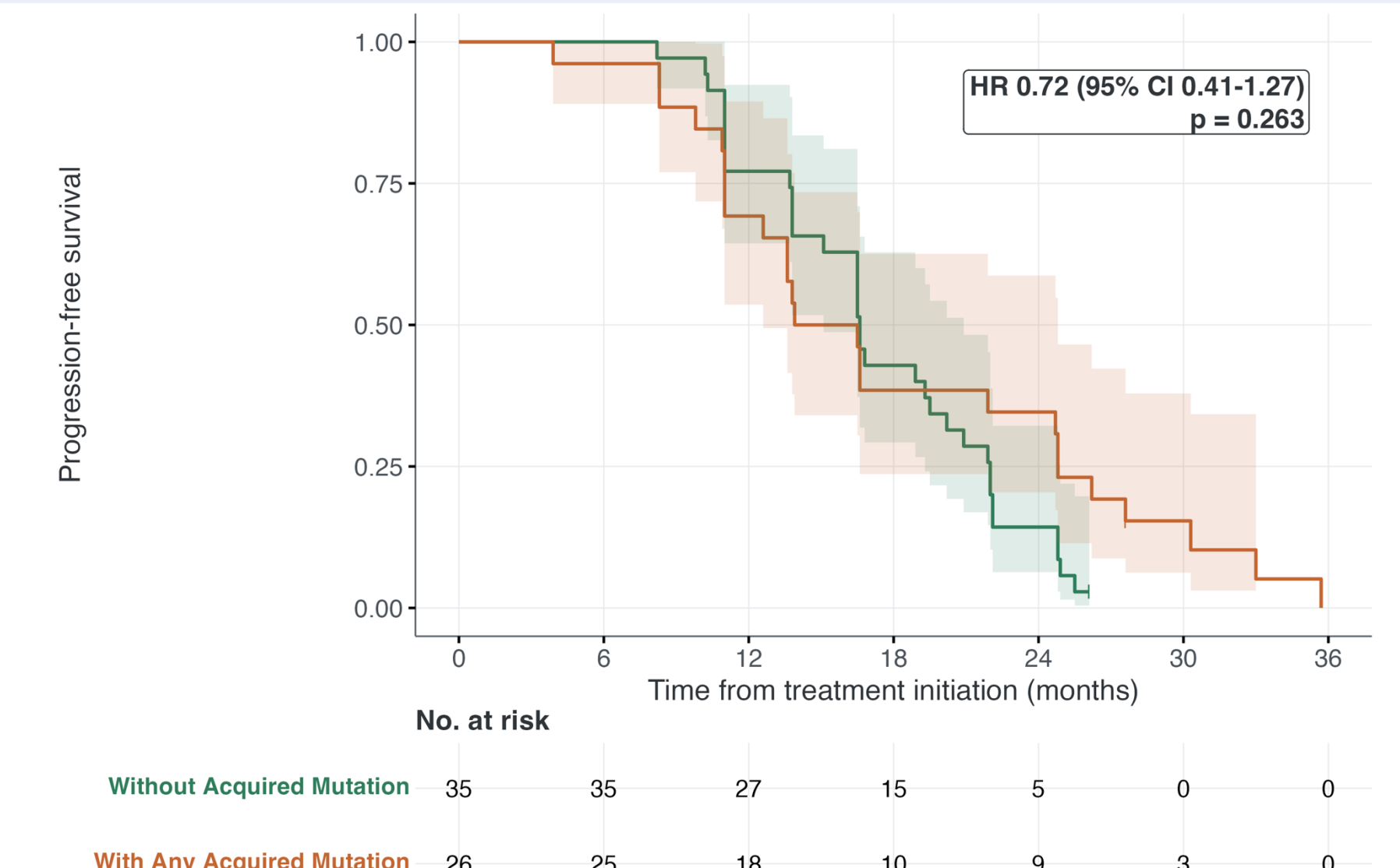


Figure 6. PFS According to the Presence of Acquired Genomic Alterations

The presence of acquired mutations was not significantly associated with PFS (HR 0.72, 95% CI [0.41–1.27], p=0.263).

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Artificial Intelligence (AI) Use Disclaimer

ChatGPT (OpenAI) was used to assist with figure preparation and visualization. All scientific content and interpretations were independently reviewed and verified by the authors.

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