

EP03.03: Impact of CTNNB1 Co-mutations on Clinical Outcomes and Response to Targeted Therapy in EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC): A Multicenter International Real-World Study

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INTRODUCTION

Co-occurring genomic alterations in EGFR-mutant NSCLC contribute to molecular heterogeneity and variable clinical outcomes.

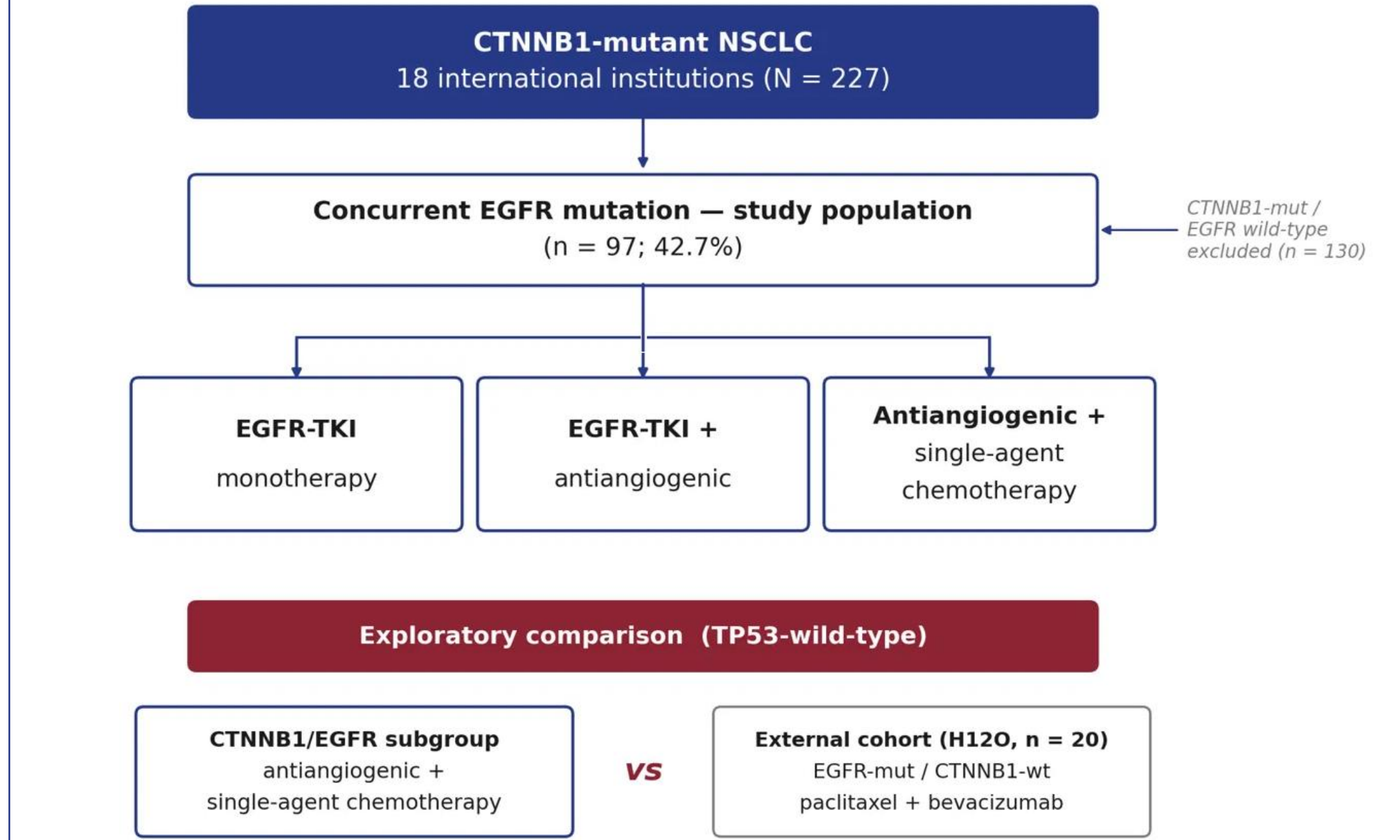
CTNNB1 mutations have been proposed as a mechanism of primary and acquired resistance to EGFR tyrosine kinase inhibitors (TKIs), and linked to sensitivity to **antiangiogenic therapy** in other tumour types.

This study evaluates the clinical impact of **CTNNB1** co-mutations in a large multicenter cohort of EGFR-mutant NSCLC.

METHODS

Retrospective study across **18 international institutions**: 227 CTNNB1-mutant NSCLC patients screened; **97 (42.7%) with concurrent EGFR mutations** formed the study population.

Exploratory comparison with an independent unicentric cohort (Hospital 12 de Octubre) of **20 EGFR-mutant / CTNNB1-wt / TP53-wt** patients treated with paclitaxel plus bevacizumab..



DISCUSSION AND CONCLUSION

Key Findings

- **CTNNB1** co-mutations define a distinct molecular subset of EGFR-mutant NSCLC.
- Wnt/ β -catenin pathway activation may influence response to EGFR-TKIs.
- **Antiangiogenic-based strategies**, particularly combined with chemotherapy, may provide clinical benefit in selected patients.

Conclusion

In CTNNB1/EGFR co-mutant patients without TP53, antiangiogenic plus single-agent chemotherapy nearly **doubled PFS** versus a matched external cohort (10.1 vs 4.1 months; HR 0.44, p=0.04). Prospective validation is warranted.

DESCRIPTIVE STUDY

Table 1. Baseline clinical and demographic characteristics of the study population (N=97).

RESULTS

Population: 74.2% female, 57.7% never-smokers, 80.4% stage IV (Table 1).

EGFR-TKI monotherapy: median PFS 17.3 months (95% CI 12.4–22.1), no differences across TKIs (p=0.185); ORR 75.8% (Figure 1 and 2).

Antiangiogenic therapy (bevacizumab, ramucirumab) in 51.6%. Combined with EGFR-TKIs: median PFS 21.2 months (95% CI 20.8–21.6). With single-agent non-platinum chemotherapy in later lines: PFS 6.6 months, ORR 40.9%, DCR 70.5% (Figure 1 and 2).

Comparative analysis (TP53-wt): CTNNB1/EGFR patients on single-agent chemo + antiangiogenic had longer PFS than the external EGFR-mutant cohort on paclitaxel + bevacizumab: **10.1 vs 4.1 months (HR 0.44, 95% CI 0.17-0.97, p=0.04)** (Figure 3).

Median OS (metastatic/relapsed): 58.5 months (95% CI 42.6–74.5).

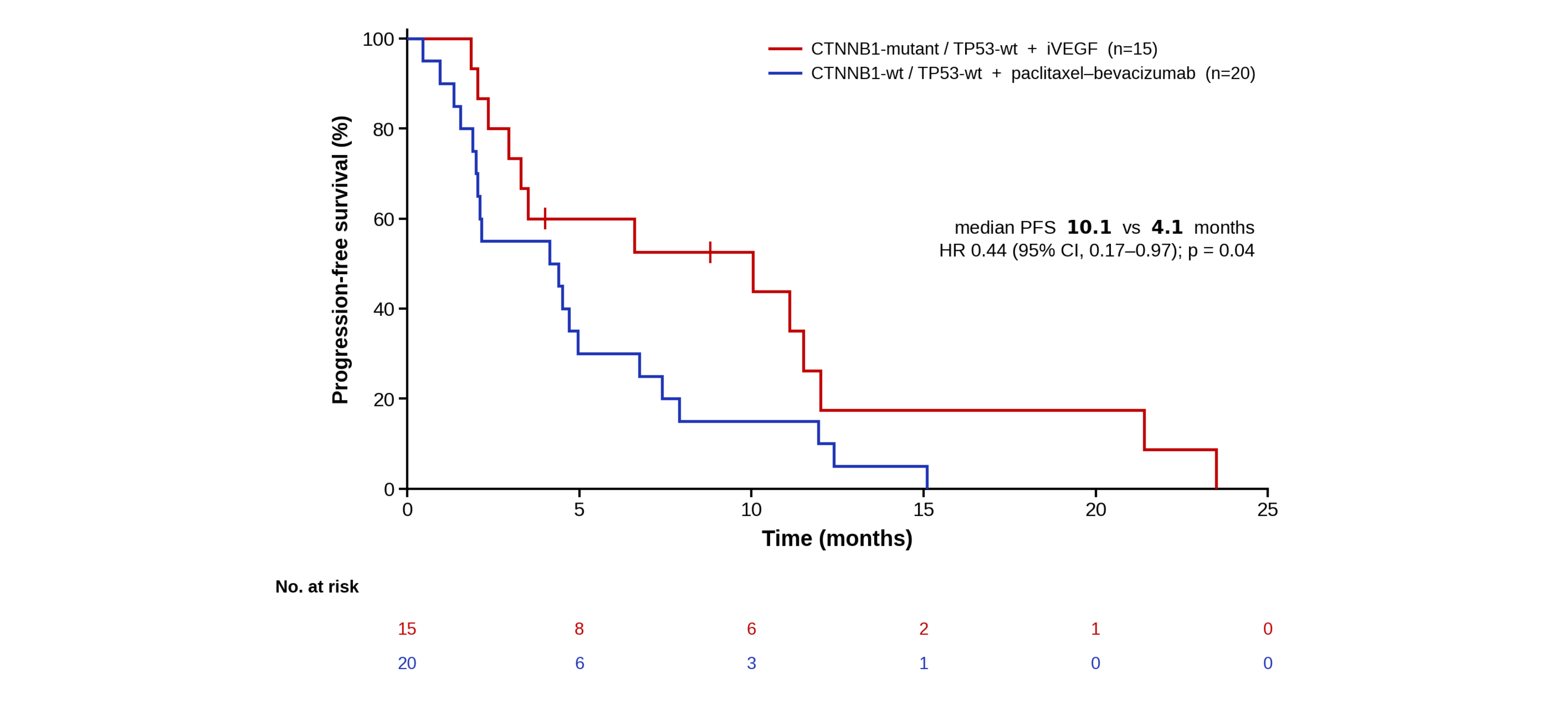
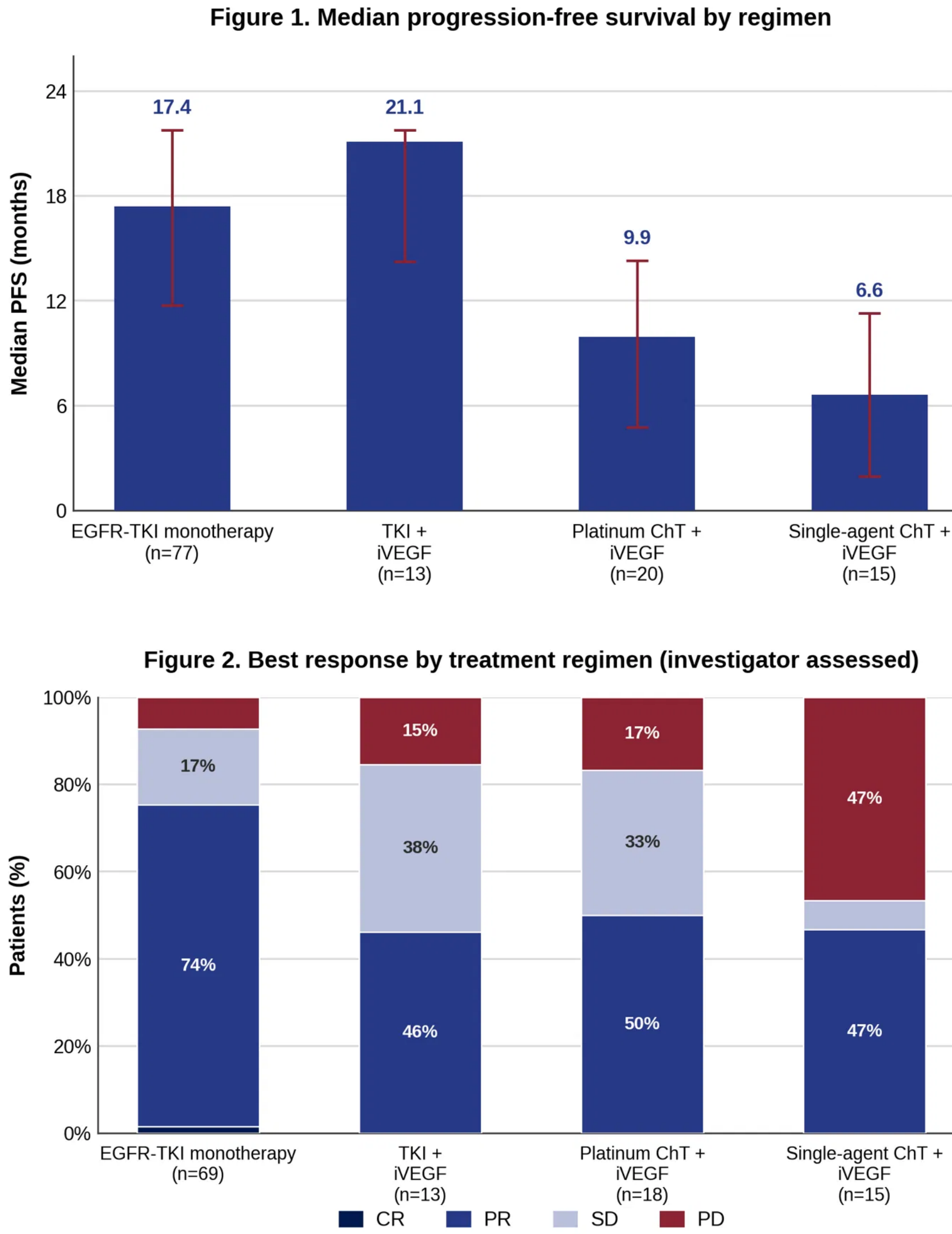


Figure 3. PFS with antiangiogenic + single-agent chemotherapy: CTNNB1/EGFR co-mutant vs external CTNNB1-wt/TP53-wt cohort (10.1 vs 4.1 months; HR 0.44, p=0.04).