



EP08.13: Comparative Efficacy of Subsequent Therapies After Progression on Third-Generation EGFR-TKIs: A Systematic Review and IPD Meta-Analysis

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INTRODUCTION

Clinical need

Acquired resistance to third-generation EGFR-TKIs is inevitable, yet the optimal subsequent systemic therapy remains undefined.

Evidence gap

Biomarker-guided and biomarker-agnostic strategies have rapidly expanded, but evidence remains fragmented across heterogeneous randomised and single-arm trials, with few direct class-level comparisons.

Study aim

We reconstructed IPD from published Kaplan–Meier curves to synthesise PFS and OS, evaluate 12-month milestone survival, explore clinically relevant subgroups, and describe treatment-related toxicity.

METHODS

Systematic review and reconstructed-IPD meta-analysis

23,458 records screened	15 trials included	1,999 patients analysed
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Treatment classes

TROP2-ADC | MET-TKI + osimertinib | ICI-based | amivantamab-based | TKI beyond progression

Design: systematic review + one-stage IPD meta-analysis (PRISMA-IPD; PROSPERO CRD420261391304).

Search: PubMed, Embase, CENTRAL, Scopus (Jan 2000–Jun 2026) + ASCO/ESMO/WCLC 2020–2026; phase 2/3 trials.

Eligibility: Prospective phase 2/3 trials in advanced EGFR-mutant NSCLC after third-generation EGFR-TKI progression; KM curves or IPD available.

IPD: Reconstructed from published Kaplan–Meier curves (Guyot method; WebPlotDigitizer).

Analysis: One-stage IPD meta-analysis; HR with 95% CI; 12-month PFS/OS by Kaplan–Meier and random-effects meta-analysis of proportions; RMST when proportional hazards violated.

Quality: RoB 2 (RCTs) / JBI (single-arm); sensitivity, leave-one-out and Egger/trim-and-fill.

DISCUSSION AND CONCLUSION

Actionable take-away

TROP2-ADCs may be preferred for the broader post-3G EGFR-TKI population, whereas MET-TKI+Osi remains relevant for selected MET-amplified disease.

Interpretation

MET-directed therapy showed a PFS signal but no OS translation. In SACHI, 52% crossover in the chemotherapy arm may have attenuated OS separation.

TROP2-ADCs may better address heterogeneous post-EGFR-TKI resistance through payload delivery and bystander killing.

Evidence boundary

Most class-level comparisons were indirect; reconstructed IPD, single-arm studies, crossover and heterogeneous MET definitions limit causal interpretation.

Treatment choice should integrate biology, clinical features, tolerability and next-line options.

REFERENCES & ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

None declared.

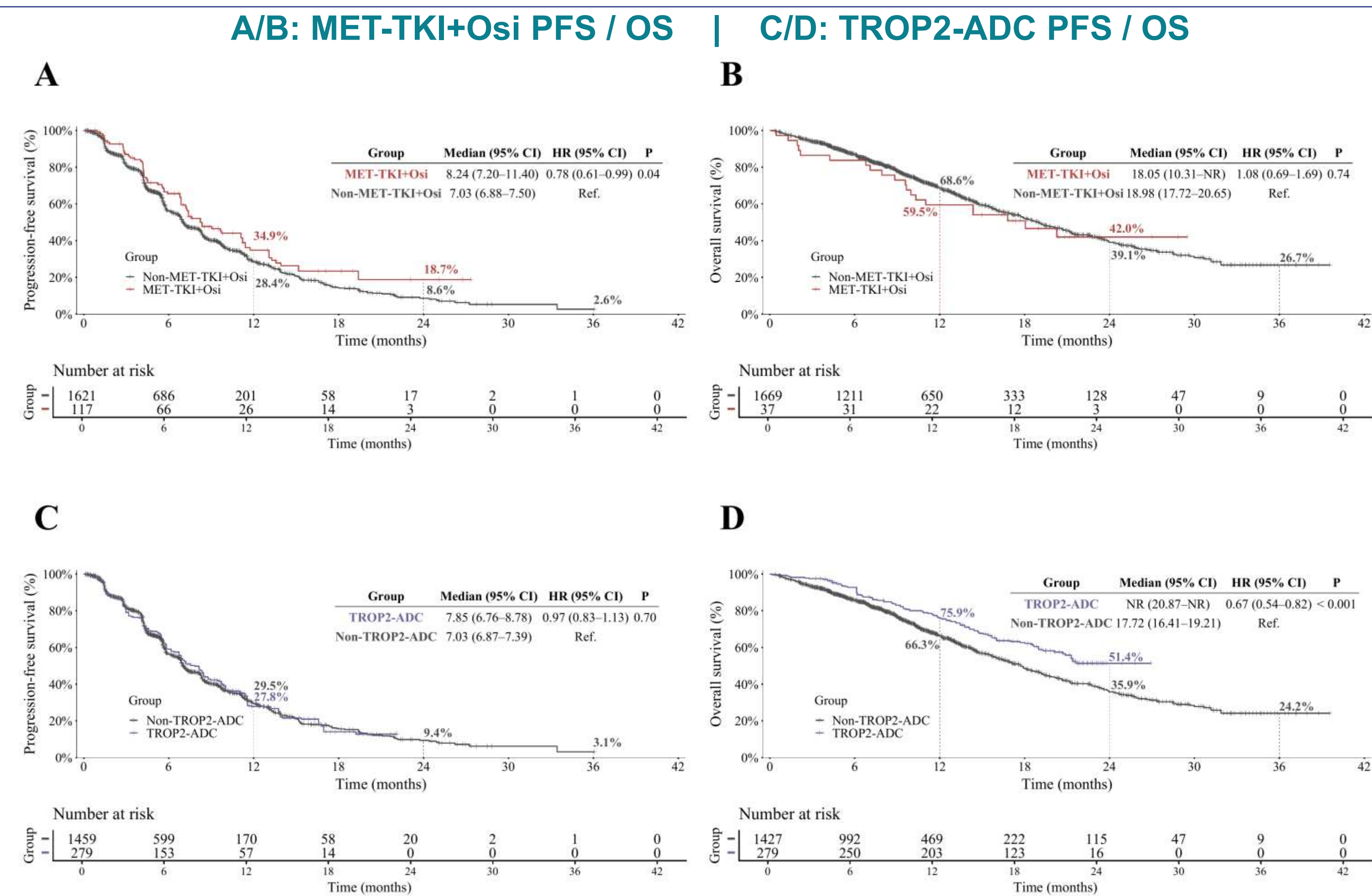
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None.

ARTIFICIAL INTELLIGENCE (AI) USE DISCLOSURE

OpenAI Codex was used to support language editing, poster formatting, and consistency checks. The authors reviewed and edited all output, independently verified the underlying data and analyses, and take full responsibility for the scientific content. AI was not used to generate study data or conduct the survival analyses.

RESULTS



Among 15 trials (1,999 patients), MET-directed therapy improved PFS (HR 0.78, 95% CI 0.61–0.99) but not OS (HR 1.08, 95% CI 0.69–1.69). TROP2-ADCs improved OS (HR 0.67, 95% CI 0.54–0.82) but not PFS. ICI-based and TKI-beyond-progression regimens showed no clear benefit; amivantamab-based therapy had inferior PFS and OS. Pooled 12-month PFS and OS were 31% (27–36%) and 68% (63–73%). TROP2-ADC subgroup findings warrant prospective validation.

Head-to-head efficacy and 12-month milestone survival

Relative treatment effects

Treatment class	PFS HR, estimate (95% CI)	OS HR, estimate (95% CI)
TROP2-ADC	0.97 (0.83–1.13)	0.67 (0.54–0.82)
MET-TKI+Osi	0.78 (0.61–0.99)	1.08 (0.69–1.69)
ICI-based	0.88 (0.78–1.01)	0.98 (0.84–1.15)
Ami-based	1.27 (1.12–1.44)	1.47 (1.22–1.77)
TKI-BP	0.92 (0.65–1.31)	1.13 (0.75–1.72)

Absolute milestone rates

Treatment class	12-month PFS, estimate (95% CI)	12-month OS, estimate (95% CI)
TROP2-ADC	24% (0–99)	75% (11–99)
MET-TKI+Osi	35% (7–78)	59%* (42–75)
ICI-based	31% (20–45)	70% (47–86)
Ami-based	30% (17–48)	65% (52–76)
TKI-BP	26%* (13–46)	67%* (49–81)

Comparison framework: each HR compares the named treatment class with all other treatment classes combined (head-to-head trial subset). HR < 1 favors the named treatment class. Milestone rates are descriptive absolute estimates; *single contributing study. Head-to-head overall: 12-month PFS 31% (27–36); OS 68% (63–73). All-study estimates: PFS 31% (28–35); OS 68% (64–72).

Exploratory TROP2-ADC subgroup estimates

PFS HR with 95% CI	
EGFR exon 19 del	0.40 (0.31–0.52)
EGFR L858R	0.44 (0.25–0.78)
Age <65 years	0.42 (0.32–0.55)
Never-smokers	0.41 (0.32–0.52)
No brain metastases	0.41 (0.32–0.51)
Brain metastases	0.37 (0.08–1.61)

Grade >=3 TRAEs by class

Crude pooled proportions; no indirect statistical comparisons.	
MET-TKI+Osi	48.0%
ICI-based	48.6%
TKI-BP	55.4%
TROP2-ADC	58.3%
Ami-based	61.4%