

INTRODUCTION

- EGFR-mutant Stage IV lung adenocarcinoma has a rapidly expanding set of first- and second-line targeted therapies, but head-to-head trials comparing these regimens remain scarce.
- Cross-trial comparison using reconstructed individual patient-level data (IPD) offers a rigorous alternative when randomized head-to-head data are unavailable.
- Validating control-arm concordance provides an internal calibration step that strengthens confidence in experimental-arm comparisons.
- We applied this framework, developed with LARVOL's Onco Data AI platform, across landmark first- and second-line EGFR-mutant NSCLC trials.
- Subgroup analyses examined CNS metastasis status and EGFR exon 19 deletion — both established prognostic and predictive factors.

Objectives

- Compare EGFR-directed regimens (MARIPOSA, FLAURA2, MARIPOSA-2, TROPION-Lung, OptiTROP-Lung04, HARMONi-A) using reconstructed IPD.
- Validate cross-trial comparability by testing control-arm concordance before comparing experimental arms.
- Evaluate results by CNS metastasis status and EGFR exon 19 deletion subgroup.

METHODS

Data source

- Published Kaplan-Meier curves and at-risk tables from first- and second-line EGFR-mutant Stage IV NSCLC trials (MARIPOSA, FLAURA2, MARIPOSA-2, TROPION-Lung01/05, OptiTROP-Lung04, HARMONi-A).
- Curves reconstructed into IPD via the Guyot algorithm using LARVOL's Onco Data AI platform.

Trial comparisons

- First-line: MARIPOSA vs. FLAURA2 (OS; PFS overall and by CNS-metastasis status).
- Second-line: MARIPOSA-2, OptiTROP-Lung04, HARMONi-A, and pooled TROPION-Lung01/05, compared pairwise for OS and PFS, including an EGFR exon 19 deletion subgroup.

Statistical analysis

- Hazard ratios (HR) computed using Cox proportional hazards models.
- Between-group differences assessed by Fleming-Harrington weighted log-rank tests.

Control-arm validity check

- Control-arm concordance was evaluated first, as an internal validity check, before interpreting experimental-arm comparisons.

Endpoints & subgroups

- OS and PFS compared overall and within CNS-metastasis and EGFR exon 19 deletion subgroups, wherever data were reported.

Software & Validation

- Analyses performed using LARVOL's Onco Data AI survival-reconstruction platform (Guyot algorithm implementation).

DISCUSSION AND CONCLUSION

Actionable Takeaway

CNS metastasis status may meaningfully inform the choice between FLAURA2 and MARIPOSA in the first line, while OptiTROP-Lung04 shows a consistent OS signal across multiple second-line comparators.

- FLAURA2's overall PFS advantage over MARIPOSA (HR 0.70) was driven entirely by patients with CNS metastases (HR 0.63) — no PFS advantage was seen without brain metastases (HR 0.96).
- OptiTROP-Lung04 showed significant OS advantages over all three second-line comparators tested (MARIPOSA-2, TROPION pooled, HARMONi-A), HRs 0.47–0.66.
- MARIPOSA-2 and HARMONi-A performed comparably in OS and in the exon 19 deletion PFS subgroup, with concordant control arms.

Why This Matters

- With no randomized trials directly comparing these regimens, clinicians currently rely on informal, visual cross-trial comparisons to guide sequencing decisions.
- Reconstructed IPD enables patient-level statistical modeling — Cox regression and weighted log-rank tests — rather than simple visual overlay of published curves.
- A pre-specified control-arm concordance check helps distinguish genuine treatment effects from differences driven by disparate trial populations, eras, or designs.

Conclusion

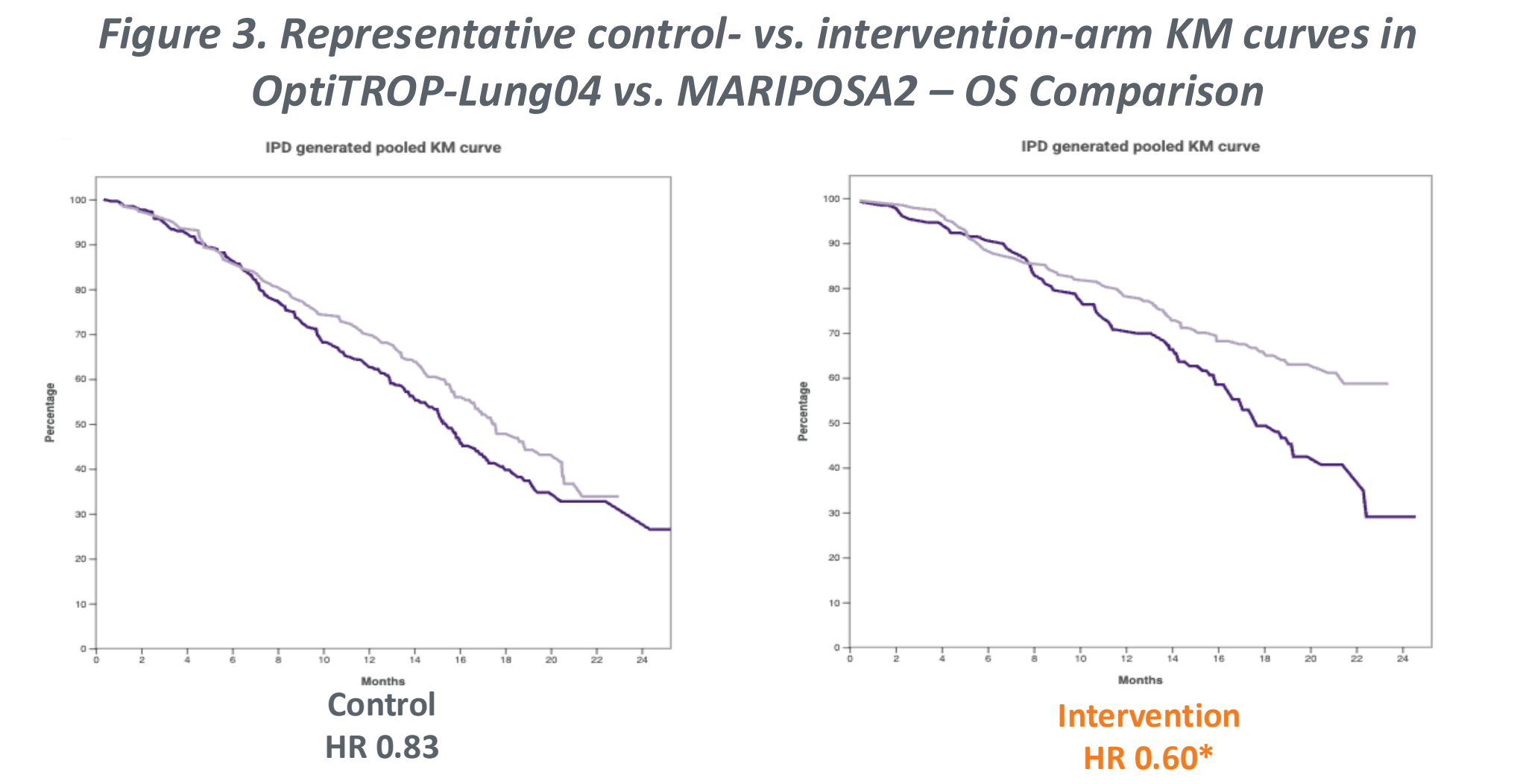
- Statistical IPD reconstruction enables rigorous indirect treatment comparisons where head-to-head trial data are unavailable.
- Control-arm concordance was observed in all 9 comparisons with available control-arm data, supporting cross-trial population comparability.
- This methodology generates actionable comparative evidence to inform treatment sequencing where randomized head-to-head trials are lacking.

Future Directions

- Prospectively validate the CNS-metastasis PFS signal and the OptiTROP-Lung04 OS signal in head-to-head or larger pooled analyses.
- Apply the control-arm concordance check as a standard validity gate in future cross-trial IPD comparisons.

Limitations

- Cross-trial comparisons rely on published aggregate KM curves rather than true patient-level trial data, and cannot fully account for differences in trial design, era, or unmeasured confounders.
- Control-arm data were unavailable for 5 of 14 comparisons, all involving pooled TROPION-Lung01/05 data.



AI-Use Disclosure

Claude (Anthropic) was used to assist with grammar and vocabulary review during abstract preparation. All analytic outputs and figures were reviewed and verified by the authors prior to this final version.

Abbreviations: IPD, individual patient-level data; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CNS, central nervous system; KM, Kaplan-Meier; 1L/2L, first-/second-line.

RESULTS

- Control arms were concordant in all 9 comparisons with available control-arm data (100%), supporting cross-trial population comparability.
- OS was similar between MARIPOSA and FLAURA2 (HR 1.02, p=0.632); FLAURA2 showed a significant overall PFS advantage over MARIPOSA (HR 0.70, p=0.003), driven entirely by patients with CNS metastases (HR 0.63, p=0.005).
- In the second line, OptiTROP-Lung04 showed significant OS advantages over MARIPOSA-2 (HR 0.60), TROPION pooled (HR 0.47), and HARMONi-A (HR 0.66).
- MARIPOSA-2 and HARMONi-A were broadly comparable in OS (HR 1.04) and in the exon 19 deletion PFS subgroup (HR 1.14), both with concordant control arms.

Table 1. Cross-trial comparisons of first- and second-line EGFR-directed therapies using statistical IPD reconstruction.

Comparison	Endpoint	Experimental HR (95% CI; p)	Control HR (95% CI; p)	Concordant?
MARIPOSA vs. FLAURA2	OS	1.02 (0.81–1.28; p=0.632)	1.06 (0.86–1.30; p=0.481)	Yes
FLAURA2 vs. MARIPOSA	PFS — overall	0.70 (0.55–0.89; p=0.003)*	0.80 (0.65–0.99; p=0.094)	Yes
FLAURA2 vs. MARIPOSA	PFS — no CNS mets	0.96 (0.71–1.29; p=0.478)	0.87 (0.67–1.13; p=0.254)	Yes
FLAURA2 vs. MARIPOSA	PFS — CNS mets	0.63 (0.45–0.89; p=0.005)*	1.03 (0.77–1.37; p=0.572)	Yes
MARIPOSA-2 vs. TROPION pooled	OS	0.74 (0.53–1.05; p=0.074)	N/A	—
MARIPOSA-2 vs. TROPION pooled	PFS	0.73 (0.53–1.00; p=0.044)*	N/A	—
OptiTROP-Lung04 vs. MARIPOSA-2	OS	0.60 (0.43–0.84; p=0.010)*	0.83 (0.64–1.06; p=0.126)	Yes
OptiTROP-Lung04 vs. MARIPOSA-2	PFS	0.98 (0.73–1.31; p=0.805)	0.89 (0.73–1.09; p=0.048)	Yes
MARIPOSA-2 vs. HARMONi-A	OS	1.04 (0.75–1.44; p=0.842)	1.02 (0.79–1.33; p=0.962)	Yes
MARIPOSA-2 vs. HARMONi-A	PFS — ex19del	1.14 (0.77–1.69; p=0.329)	1.12 (0.81–1.55; p=0.285)	Yes
OptiTROP-Lung04 vs. TROPION pooled	OS	0.47 (0.33–0.66; p<0.001)*	N/A	—
OptiTROP-Lung04 vs. TROPION pooled	PFS	0.71 (0.53–0.93; p=0.023)*	N/A	—
HARMONi-A vs. TROPION pooled	OS	0.74 (0.53–1.03; p=0.113)	N/A	—
OptiTROP-Lung04 vs. HARMONi-A	OS	0.66 (0.48–0.91; p=0.013)*	0.85 (0.64–1.13; p=0.173)	Yes

* p<0.05 (statistically significant). HR <1.0 favors first-named trial. N/A: control-arm data unavailable for concordance assessment.

Figure 2. Representative control- vs. intervention-arm KM curves in FLAURA 2 vs. MARIPOSA 2 – PFS Comparison in CNS Metastases

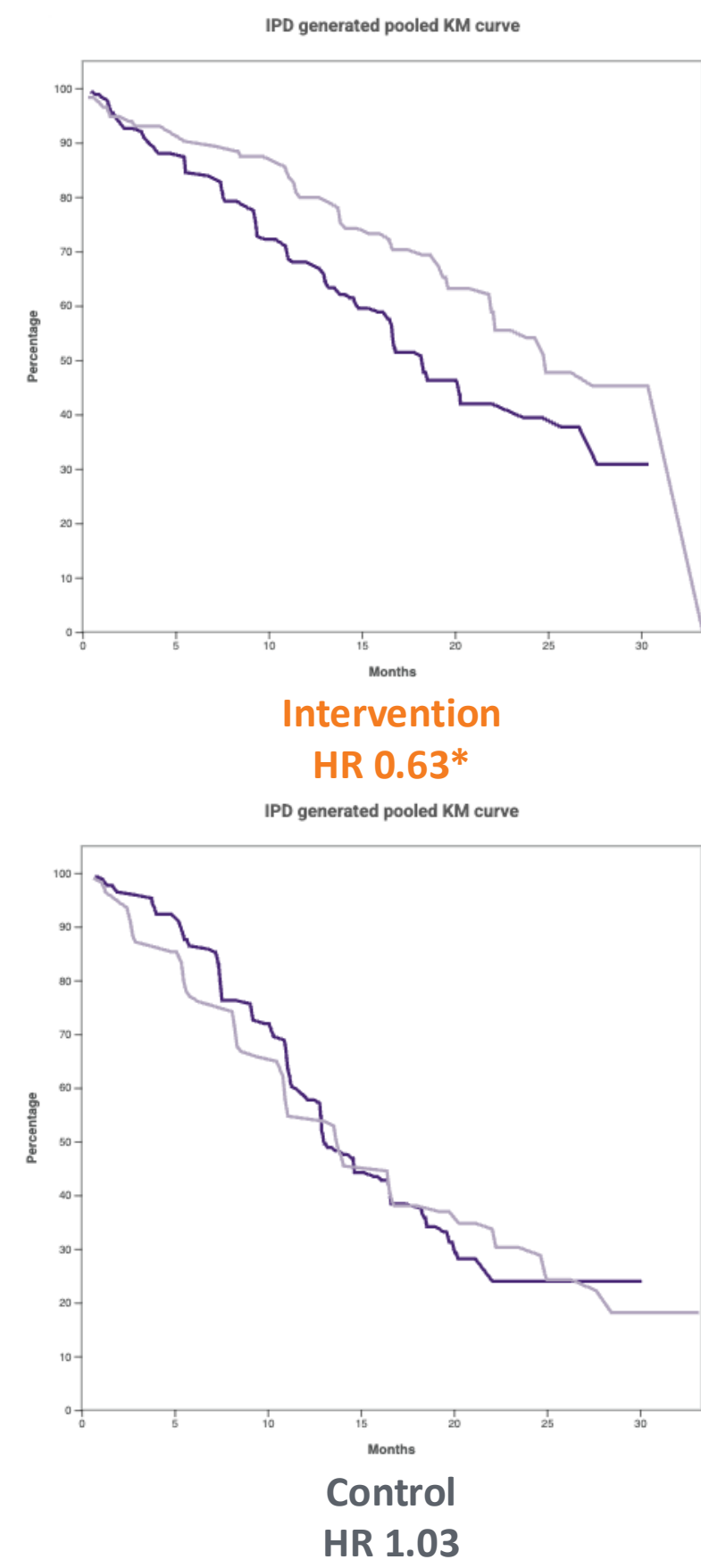
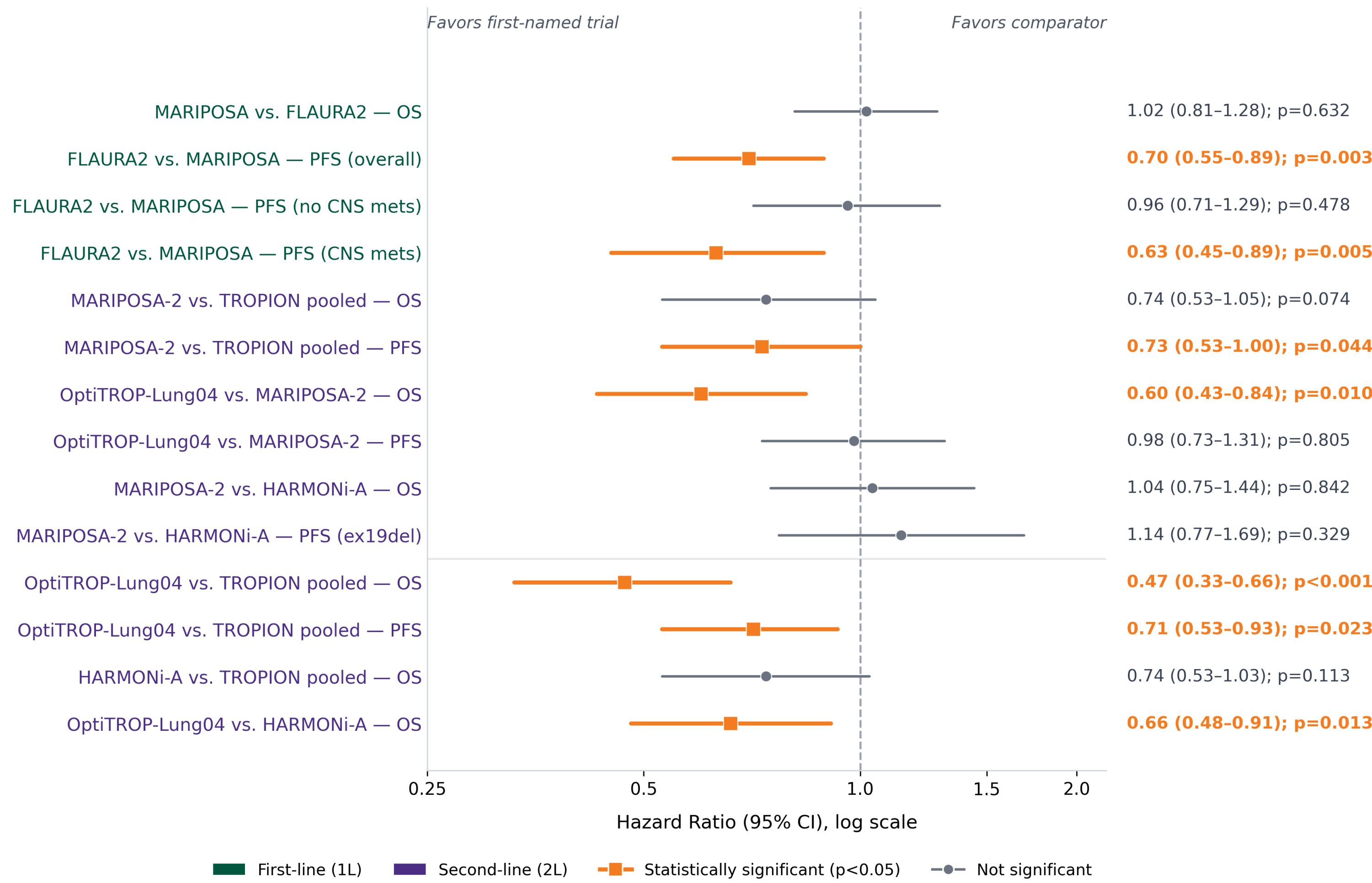


Figure 1. Forest plot of hazard ratios across all 14 cross-trial comparisons, grouped by treatment line.



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