

Restricted Mean Survival Time-Based Interpretable Treatment Sequencing for Initial Management of EGFR-Mutated Stage III NSCLC

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IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 - 15, 2026
SEOUL, REPUBLIC OF KOREA

INTRODUCTION

- Optimal initial treatment selection among surgery, chemoradiotherapy (CRT) and upfront EGFR-TKI in EGFR-mutated stage III NSCLC remains uncertain.
- Stage III disease is heterogeneous and dedicated evidence in EGFR-mutated subsets is limited, so sequencing decisions are largely extrapolated.
- Restricted mean survival time (RMST) summarises cumulative event-free time over a fixed horizon and does not rely on proportional hazards.

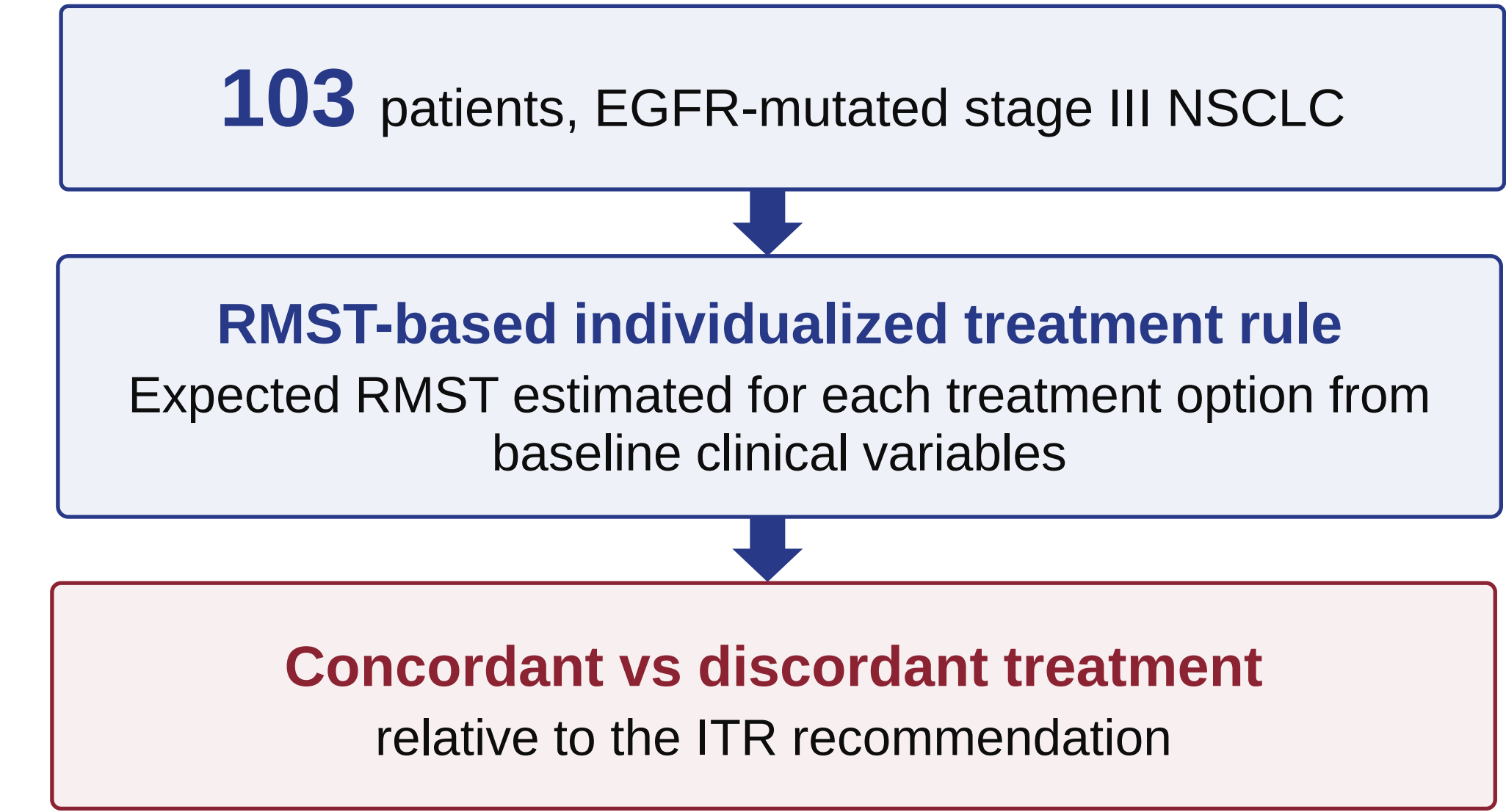
Knowledge gap: no interpretable, patient-level rule exists to guide the choice of initial treatment modality.

Objective: to develop and evaluate an interpretable RMST-based individualized treatment rule (ITR) for initial treatment sequencing.

METHODS

Design

Retrospective analysis of 103 patients with EGFR-mutated stage III NSCLC treated with surgery, definitive CRT or upfront EGFR-TKI as the initial strategy.



Endpoints

PFS2 and OS. RMST estimated at 36 and 48 months, overall and by stage subgroup.

ITR Development & Concordance Definition

- For each patient, the ITR estimated expected RMST under each treatment option (Surgery / CRT / Upfront EGFR-TKI) using baseline clinical variables
- The treatment with the highest predicted RMST was defined as the ITR-recommended treatment
- Concordant: actual treatment received matched the ITR recommendation**
- Discordant: actual treatment did not match the ITR recommendation
- Model interpretability assessed by quantifying the contribution of each clinical variable to the treatment recommendation

DISCUSSION AND CONCLUSION

Actionable take-away message

- An interpretable RMST-based rule separated patients whose initial strategy matched the model recommendation from those whose did not, with large cumulative PFS2 differences.
- PFS2 effects were consistent across both the 36- and 48-month rules; OS signals were directionally concordant but less certain.

Interpretation and limitations

- Retrospective, multi-institution cohort of 103 patients with unbalanced groups (CRT n = 13); confounding by indication cannot be excluded.
- The rule was developed and evaluated in the same cohort, so the concordance effect is likely optimistic and requires external validation.
- Under the 48-month rule the OS hazard ratio was not significant, although the OS RMST difference remained positive — a reminder that RMST and HR answer different questions.

Future direction for research

- Prospective, multicentre validation with pre-specified rules, and extension of the covariate set to molecular and imaging features.

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Acknowledgements, funding and disclosures

The authors thank all patients and the clinical staff at both institutions. No pharmaceutical or biotech funding was received and no industry-sponsored medical writers contributed. The authors declare no relevant conflicts of interest.

Artificial intelligence (AI) use disclosure

The authors disclose that OpenAI ChatGPT assisted with language refinement, organisational clarity and draft coding support for the statistical workflow and data visualisation;
All clinical data, analyses, statistical results and interpretations were generated from the authors' original research and independently verified by the authors. No results or conclusions were generated by AI.

RESULTS

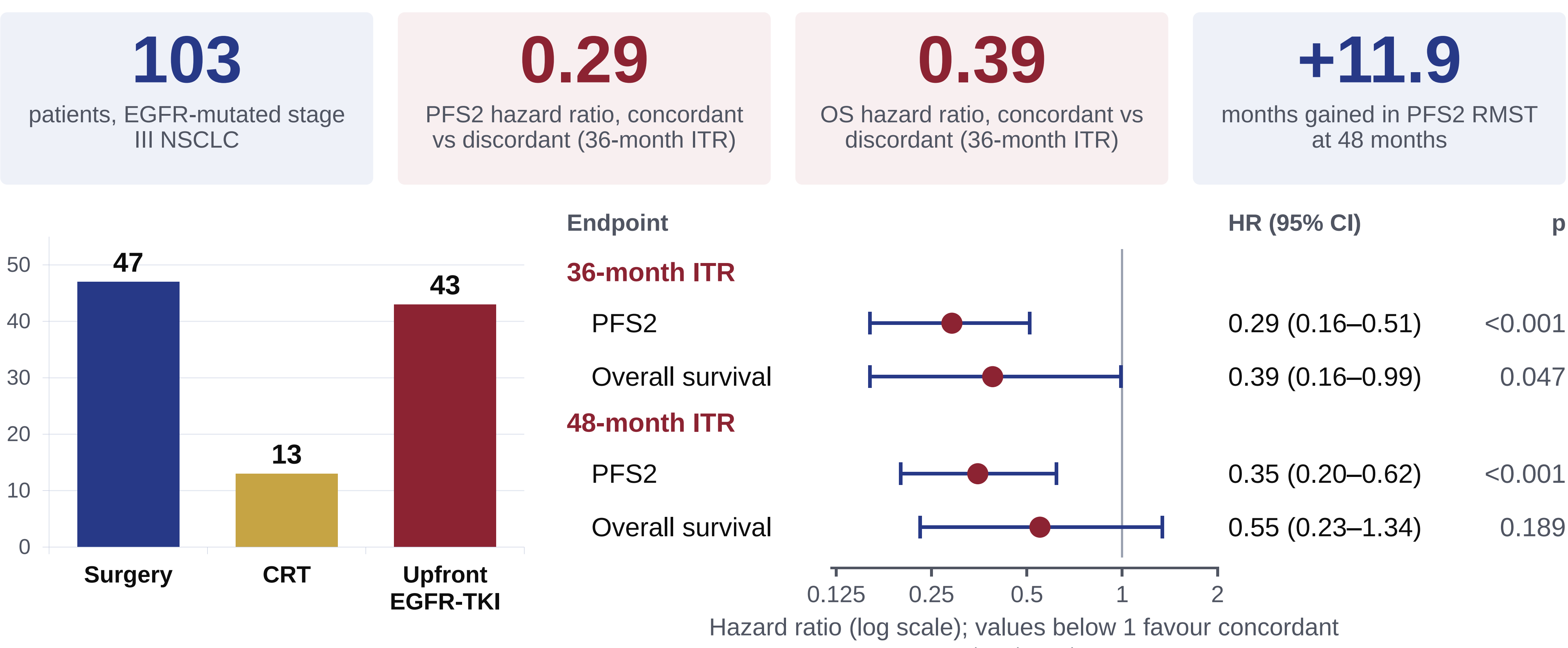


Figure 1. Initial treatment strategy in the 103-patient cohort.

Figure 2. Concordance with the ITR recommendation versus discordant treatment. Squares are hazard ratios, bars are 95% confidence intervals.

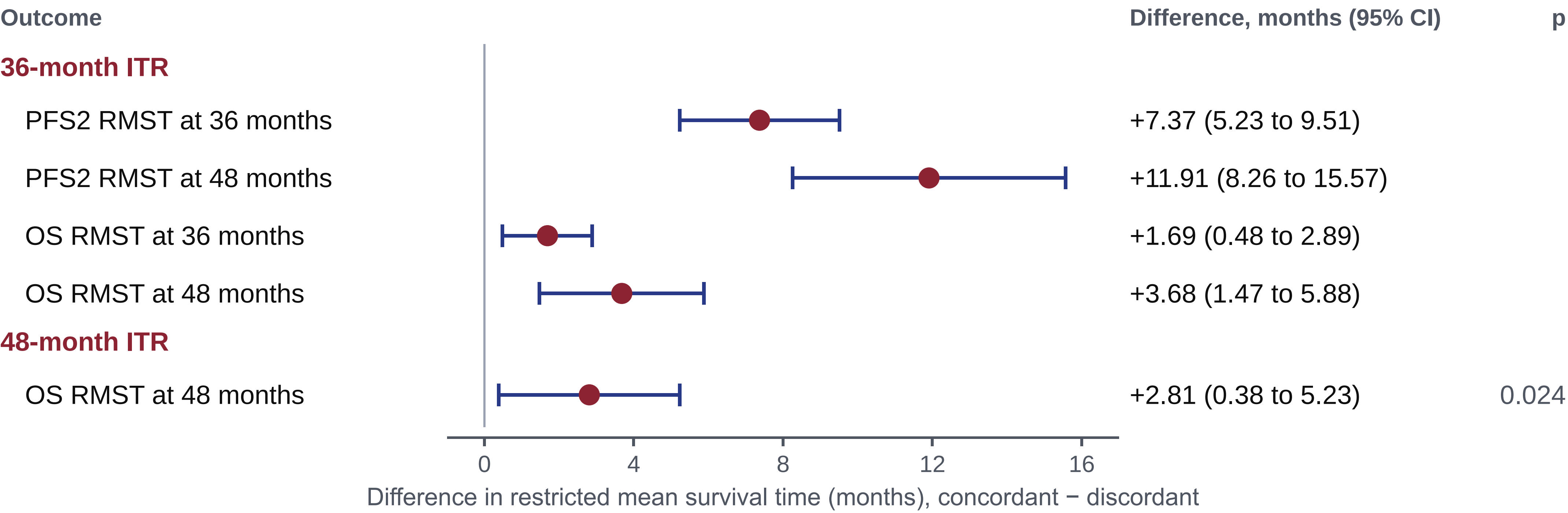


Figure 3. Gains in restricted mean survival time for patients treated concordantly with the ITR recommendation. All intervals exclude zero.

Strongest contributors to predicted cumulative outcome (SHAP-style contribution summaries)



Listed as identified by the model; no ranking of relative magnitude is implied.

Key result: RMST-based interpretable treatment sequencing identified clinically meaningful differences in cumulative outcome across initial strategies. Concordance with model-recommended therapy was associated with substantially better cumulative PFS2 and favourable OS signals.