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Predicting overall survival in EGFR-mutated aNSCLC via *in silico* clinical trials and hybrid joint modeling

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BACKGROUND

Predicting **overall survival (OS)** in EGFR-mutated aNSCLC is challenging: subsequent lines of therapy and prolonged survival loosen the link between progression and death.

In silico clinical trials built on mechanistic disease models accurately predict progression-free survival; our model prospectively predicted the **PFS of FLAURA2 in 2023** [1]. Long-term OS, however, requires integrating complex disease dynamics beyond the simulated horizon.

We therefore extended this validated framework with a **hybrid joint model** designed to predict long-term (5-year) OS.

METHODS

Mechanistic disease model

The EGFR-mutated aNSCLC model [2] that prospectively predicted FLAURA2 PFS in 2023 [1] was upgraded for this study. It integrates treatment models for osimertinib, pemetrexed and cisplatin and returns, for each virtual patient, the time to progression (RECIST 1.1 [3]) simulated up to **36 months**.

Virtual cohorts and trial simulation

Virtual patients were generated from published population characteristics of similar trials [1]; the trial protocols were replicated and simulated on the jinkō platform [1].

Hybrid joint model for OS

A **statistical joint model** links the simulated disease progression (0–36 months) to OS. It was **calibrated on the public data of the FLAURA trial** (first-line osimertinib) [4,5] and then **independently validated on FLAURA2** (osimertinib ± pemetrexed-cisplatin) [6,7], whose OS data were not used for calibration.

Comparison with observed data

Simulated and observed outcomes were compared on median OS (95% CI), on the hazard ratio between arms and on the **log-rank metric**, i.e. the percentage of non-significant bootstrapped weighted log-rank tests comparing simulated and observed Kaplan–Meier curves [8].

RESULTS

The hybrid joint model translated 36 months of simulated progression into **5-year OS predictions** whose curves, median OS and confidence intervals closely aligned with clinical outcomes, both on the calibration trial (FLAURA) and on the independent validation trial (FLAURA2, Figure 2 and Table 1).

In FLAURA2, simulated median OS reached **34.93 months vs 37.6 observed** for osimertinib monotherapy and **52.5 vs 47.5 months** for the osimertinib + chemotherapy doublet; **88.1%** and **99.2%** of the bootstrapped log-rank tests, respectively, found no significant difference between simulated and observed curves.

The simulated hazard ratio for the osimertinib + chemotherapy doublet vs osimertinib monotherapy was **0.705 (95% CI 0.667–0.744)**, consistent with the observed **0.767 (0.614–0.957)**.

CONCLUSION

Combining a mechanistic disease model with a statistical joint model provides a **robust framework** for predicting long-term OS in EGFR-mutated aNSCLC, **confirmed on an independent trial**.

The approach anticipates **mature survival outcomes from a surrogate endpoint** (36-month simulated progression) before OS data mature, with the potential to **accelerate drug development** and **inform trial design**.

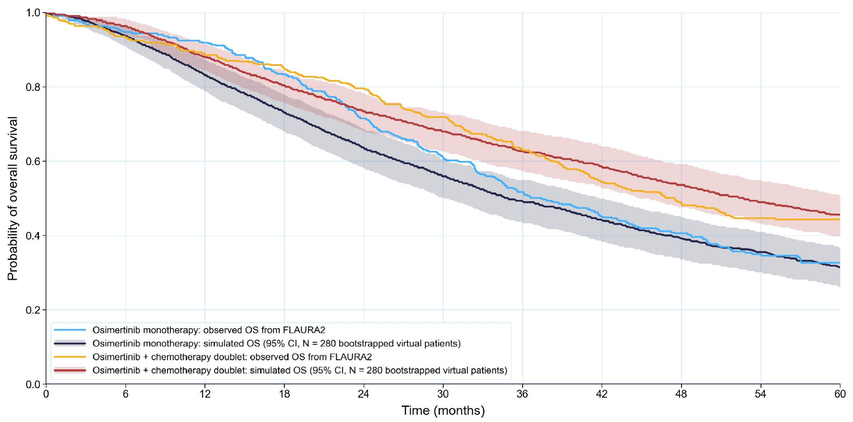
REFERENCES

1. Duruisseaux M, et al. J Clin Oncol 2024;42(16_suppl):8614 (ASCO 2024). 2. Darré H, et al. Biomedicines 2024;12(3):704. 3. Eisenhauer EA, et al. Eur J Cancer 2009;45(2):228-247 (RECIST 1.1). 4. Soria JC, et al. N Engl J Med 2018;378(2):113-125 (FLAURA). 5. Ramalingam SS, et al. N Engl J Med 2020;382(1):41-50 (FLAURA overall survival). 6. Planchard D, et al. N Engl J Med 2023;389(21):1935-1948 (FLAURA2). 7. Jänne PA, et al. N Engl J Med 2026;394(1):27-38 (FLAURA2 final overall survival). 8. Jacob E, et al. BMC Bioinformatics 2023;24:331.

aNSCLC: advanced non-small cell lung cancer; AKT: protein kinase B; CI: confidence interval; EGFR: epidermal growth factor receptor; ERK: extracellular signal-regulated kinases; HR: hazard ratio; KM: Kaplan–Meier; NC: not calculable; OS: overall survival; PBPK: physiologically based pharmacokinetic; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumours; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor. Chemotherapy: pemetrexed + cisplatin.

A mechanistic disease model coupled with a **hybrid joint model** turns 36 months of simulated progression into accurate **5-year overall survival** predictions, validated on **FLAURA2**.

Figure 2 · Validation — FLAURA2: overall survival, observed vs simulated



Independent validation set: observed OS (FLAURA2 final OS analysis [7]) vs simulated OS, osimertinib monotherapy and osimertinib + chemotherapy doublet. Simulated curves: prediction with its 95% CI over N = 280 bootstrapped virtual patients; the joint model was calibrated on public FLAURA data only. Metrics in Table 1.

Table 1 · Comparison of simulated vs observed OS metrics — FLAURA2

Study	Arm	Mean Median OS (95% CI)	Log-rank Test (%) *
FLAURA2 (Observed data)	Osimertinib monotherapy	37.6 (33.2, 43.2)	**88.1**
FLAURA2 (Simulated data)	Osimertinib monotherapy	**34.93 (29.90, 39.60)**	
FLAURA2 (Observed data)	Osimertinib + Chemotherapy	47.5 (41.0, NC)	**99.2**
FLAURA2 (Simulated data)	Osimertinib + Chemotherapy	**52.5 (44.4, 62.60)**	

** compared with observed clinical trial*

88.1%
of bootstrapped weighted log-rank tests found no significant difference between simulated and observed OS curves (osimertinib monotherapy, FLAURA2)

99.2%
of bootstrapped weighted log-rank tests found no significant difference between simulated and observed OS curves (osimertinib + chemotherapy doublet, FLAURA2)

From simulated progression to long-term survival

1. Mechanistic disease model
Virtual EGFR-mutated aNSCLC cohorts simulated on jinkō: tumor dynamics, metastases and resistance under osimertinib ± pemetrexed-cisplatin, up to 36 months.

2. Hybrid joint model
Statistical joint model linking simulated progression (0–36 months) to survival, calibrated on public FLAURA OS data.

3. Long-term OS
Predicted OS curves and median OS per arm, independently validated against FLAURA2 final OS.

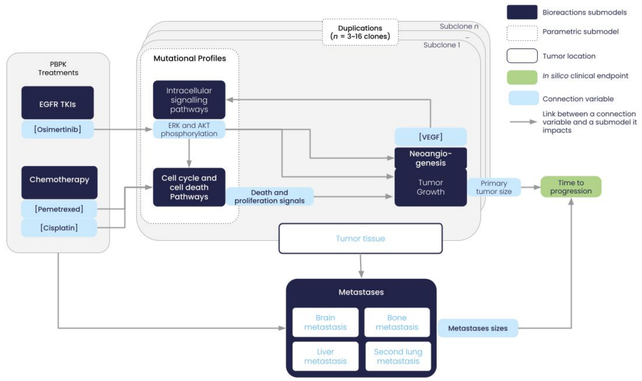


Figure 1. Structure of the mechanistic EGFR-mutated aNSCLC model [2], integrated with three treatment models: osimertinib, pemetrexed and cisplatin (from the ASCO 2024 poster [1]).

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