# In silico validation of MARIPOSA trial outcomes in EGFR-mutated NSCLC using a QSP-based disease model integrated with a newly implemented lazertinib drug model

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**In silico** post-hoc simulations **independently** estimate the PFS outcomes of the **Phase III MARIPOSA** clinical trial

## Mechanistic model

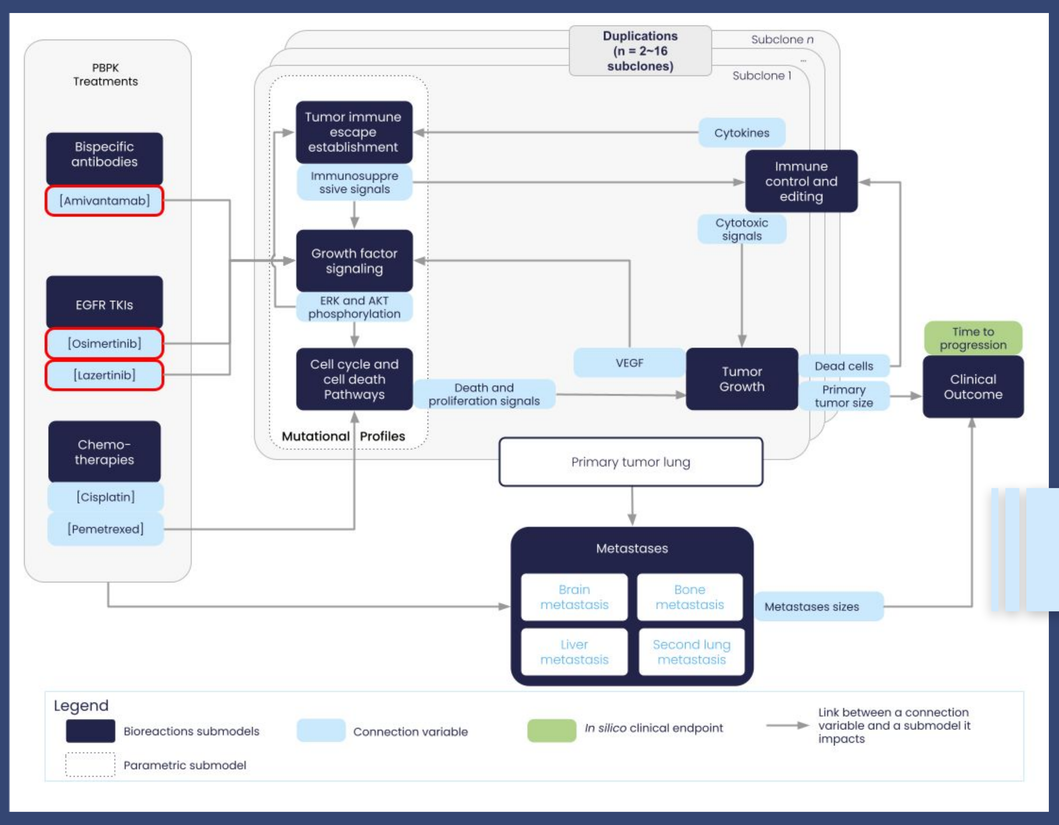
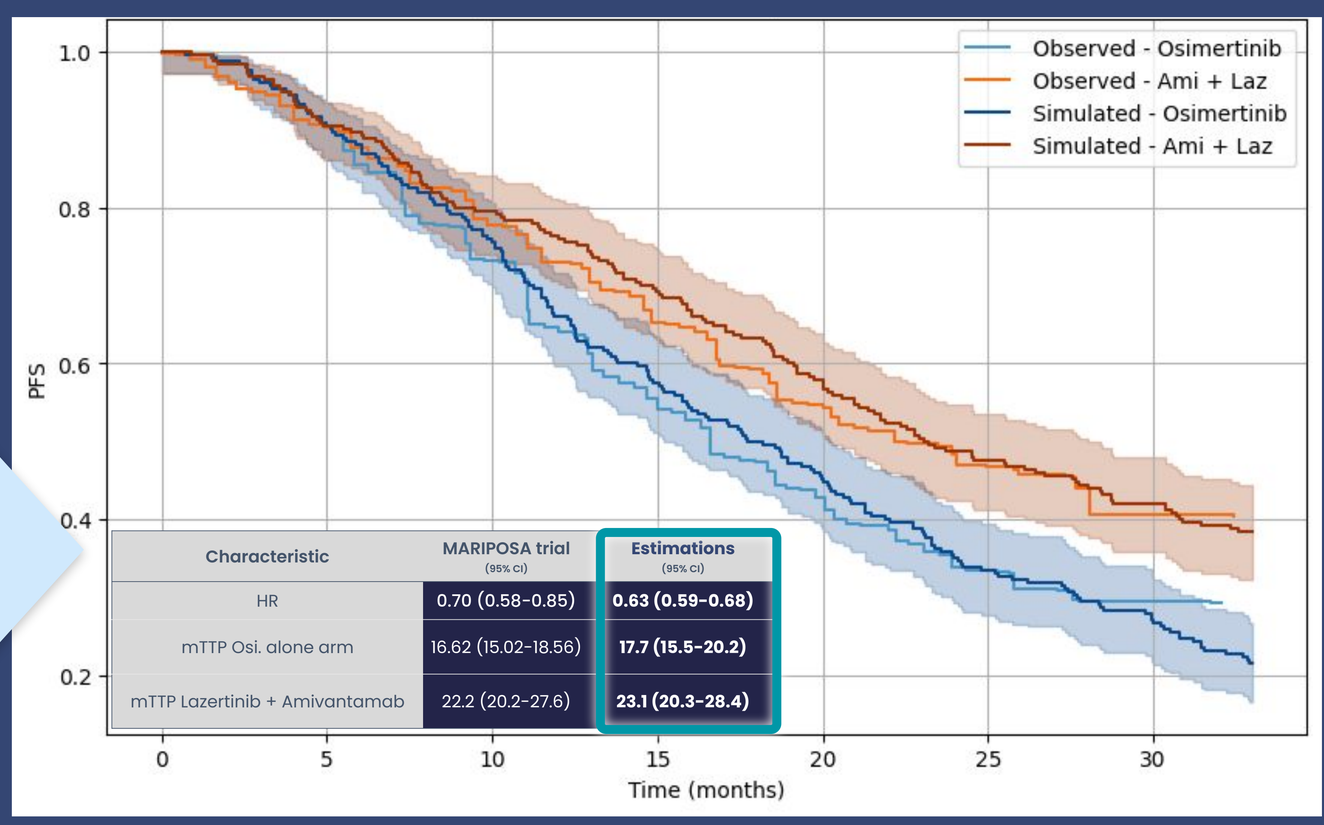



**Figure 1: Structure of the EGFR-mutated NSCLC model**, integrated with 3 treatment models: osimertinib, amivantamab and lazertinib.

## Trial simulation




| Characteristic | MARIPOSA trial (95% CI) | Estimations (95% CI) |
|---|---|---|
| HR | 0.70 (0.58-0.85) | **0.63 (0.59-0.68)** |
| mTTP Osi. alone arm | 16.62 (15.02-18.56) | **17.7 (15.5-20.2)** |
| mTTP Lazertinib + Amivantamab | 22.2 (20.2-27.6) | **23.1 (20.3-28.4)** |

**Figure 2: Simulated TTP vs observed PFS in MARIPOSA**. Blue and red: simulated; Light blue and orange: reported in [9]. The 95% bootstrapped estimation intervals of the simulated curves are represented by the shaded areas. The model reproduces both median PFS separation and overall HR benefit for lazertinib+amivantamab over osimertinib with overlapping confidence bands.

## BACKGROUND

EGFR-mutated advanced NSCLC is commonly treated with first-line osimertinib (EGFR TKI). The phase-3 MARIPOSA trial showed superior PFS with lazertinib (EGFR TKI) + amivantamab (EGFR/MET Bispecific Antibody) vs osimertinib (HR≈0.70). Mechanistic QSP models can run in silico trials to project outcomes and guide design.

We extended a validated NSCLC QSP model with a new lazertinib PK/PD module to reproduce MARIPOSA results and assess model credibility to clinical data in a similar context of use [1-3].

## METHODS

In Jinkō platform [4], we developed and used a pathophysiology-based NSCLC QSP model coupled to treatment models for osimertinib, amivantamab, and lazertinib (Fig. 1). Credibility of the model in the current context of use was assessed by comparing the simulation results with publicly available CHRYSALIS I & II and FLAURA2 clinical trials results [5-7]. MARIPOSA results were reserved for the external validation step only.

### Endpoint & analysis

- **Primary endpoint**: PFS by RECIST 1.1. Kaplan–Meier estimation; median PFS with 95% intervals. Simulated time-to-progression (TTP) served as a proxy for observed PFS.
- **Statistical comparisons**: bootstrapped weighted log-rank tests [8] used to compare simulated and observed Kaplan-Meier curves (α=0.05) (Fig. 1).

## RESULTS

### Quantitative comparisons

The digital-twin simulations estimated a median TTP of approximately 23.1 months for first-line amivantamab + lazertinib, versus 17.7 months for osimertinib. These estimations were consistent with the trial's reported median PFS of 22.2 months and 16.6 months for the two arms, respectively. The corresponding hazard ratio for PFS in the virtual trial (~0.63) was also consistent with the observed hazard ratio (0.70) from MARIPOSA [9].

### Statistical comparisons

No statistically significant differences were detected when comparing the simulated vs. actual PFS distributions: a bootstrapped log-rank test yielded $p > 0.05$, confirming that the model's TTP estimations fell within the variability of the observed outcomes.

## CONCLUSION

- **Successful validation**: digital-twin simulations accurately recapitulated the MARIPOSA trial's PFS outcomes. The simulated and observed Kaplan-Meier PFS curves for the combination and control arms showed consistent shapes and overlapping confidence intervals (Fig. 2), indicating alignment between model estimations and clinical reality.
- **Broader application**: the validated QSP model can potentially be a useful tool to support clinical development in other therapeutic scenarios in EGFR-mutant NSCLC, such as novel combination regimens, sequential therapy strategies, and resistance mutation contexts beyond those tested in MARIPOSA.

## REFERENCES

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