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Prospective validation of *in silico* clinical trials prediction using an EGFR-mutated NSCLC mechanistic computational disease model

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BACKGROUND

Conducting practice-changing and cost-effective randomized trials on lung adenocarcinoma is challenging.

- Advanced lung adenocarcinoma (aLUAD) is divided into multiple molecularly-defined subsets, each with specific biological characteristics and responses to targeted therapy.
- Considering diverse patient populations, numerous drug regimens and sequences of drugs make the design of clinical trials increasingly complex.

In silico clinical trials can provide a precious help to design and enhance trials.

- *In silico* clinical trials, utilizing mechanistic computational models, have the potential to rapidly incorporate past trial data to inform future research, with the capability for endless simulations and explorations.
- Yet, their ability to predict clinical trial results had not been proven until today.

METHODS

Computational model of EGFR-mutated aLUAD and associated drug treatments

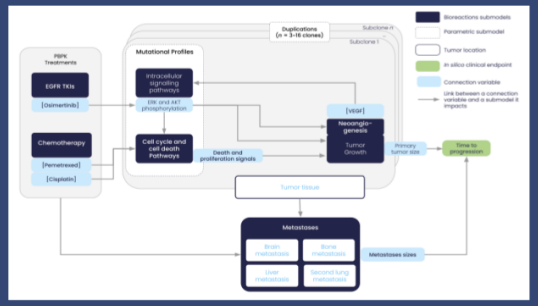


***Figure 1**: Structure of the EGFR-mutated aLUAD model[1], integrated with 3 treatment models: osimertinib, pemetrexed and cisplatin.*

- Mechanistic models are founded on causal connections between biological entities and phenomena, establishing a link between the specific biological behaviors of EGFR-mutated aLUAD and the evolution of tumor size and progression over time.
- **Model output:** time to progression (TTP), computed from the evolution of the primary tumor and metastases over time, according to the RECIST 1.1 criteria[2]
- **Model calibration and validation:** performed using *in vitro* and *in vivo* (mouse and human) published data[1,3,4,5,6,7]

Trial patients

- Cohorts of virtual patients were generated using publicly available population characteristics of similar trials (FLAURA[5] and CHRYSALIS[8]) and safety run-in subset[9].
- The size of the virtual cohorts was at least 7 times the number of patients in a single arm of the corresponding randomized trial.

aLUAD: advanced lung adenocarcinoma; AKT: Protein kinase B; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinases; TKI: tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor

In silico clinical trial simulations prospectively **predict outcomes** of **Phase III** FLAURA2 clinical trial

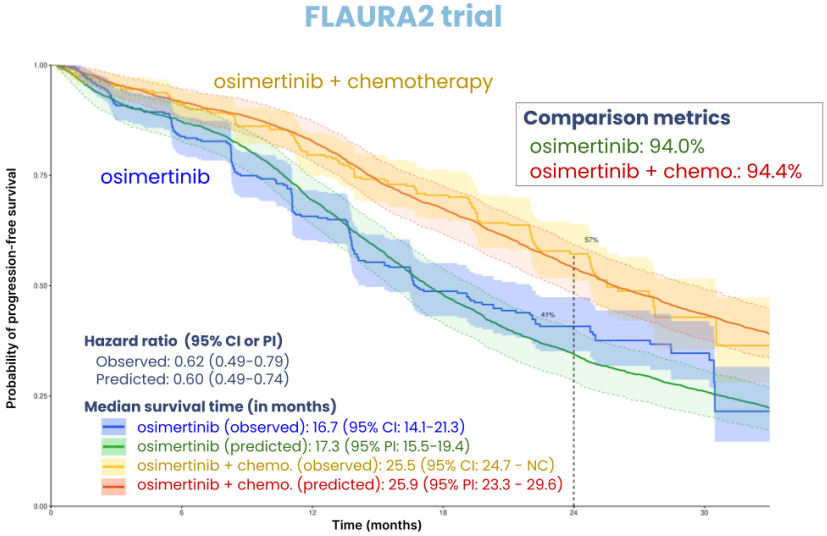
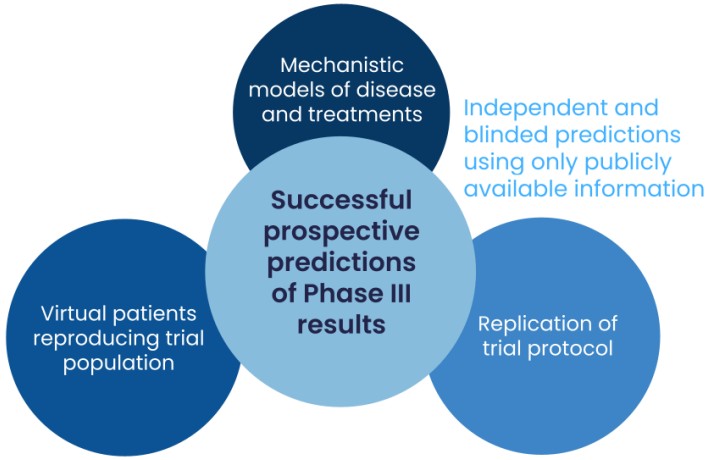


Figure 2: Kaplan-Meier curves of observed PFS and simulated TTP for FLAURA2 trial (both arms).
The comparison metrics is the percentage of non-significant bootstrapped weighted log-rank tests (predicted vs observed data).

PFS: progression free survival; TTP: time to progression; chemo: chemotherapy (pemetrexed+cisplatin/carboplatin); CI: confidence interval; PI: prediction interval



Trial protocols

- Trial protocols were replicated from published trial designs of FLAURA2 and MARIPOSA trials[10,11].

Trial simulations

- Virtual trials were run on the jinkō trial simulation platform, by combining the computational model, the virtual cohort of patients and the trial protocol. For a given trial, the whole cohort of virtual patients was assigned to every arm.
- Virtual trial durations were set at 33 months (FLAURA2) and 32 months (MARIPOSA).

RESULTS

- *In silico* results were released before communication of FLAURA2 results.
- FLAURA2 simulations yielded predictions with overlapping confidence intervals, similar hazard ratios, median survival times, and shapes of curves compared to the actual trial data (Fig 2).
- 94% of the bootstrapped weighted log-rank tests[12] that compared simulated and observed Kaplan-Meier curves were statistically non-significant (α=0.05) (Fig 2), confirming the accuracy of the predictions.
- Excellent accuracy was also obtained for the prospective prediction of the osimertinib arm of MARIPOSA trial (Fig 3).

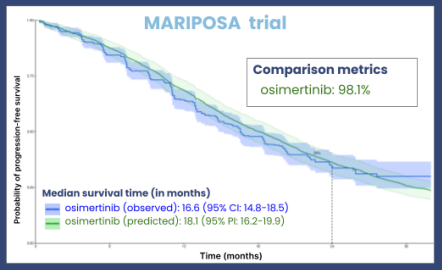


***Figure 3**: Kaplan-Meier curves of observed PFS and simulated TTP for MARIPOSA trial (osimertinib arm only).*

FUTURE DIRECTIONS

- This first-of-its-kind prediction of clinical trial outcomes demonstrates that *in silico* trials, when based on robust mechanistic models, can be a reliable tool for enhancing the design of actual trials, particularly for EGFR-mutated aLUAD.
- They offer a promising avenue for overcoming the challenges of comparator arms in single-arm trials and may serve as a new standard for formulating statistical hypotheses in future studies.

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