

M. Duruisseaux<sup>1,2,3</sup>, P. Masson<sup>4</sup>, A. Nativel<sup>4</sup>, N. Girard<sup>5</sup>, J. Cadranet<sup>6</sup>, A. Swalduz<sup>7</sup>, M. Coudron<sup>4</sup>, G. Bouchard<sup>4</sup>, R. Kahoul<sup>4</sup>, E. Jacob<sup>4</sup>, J. Bosley<sup>4</sup>, JL. Palgen<sup>4</sup>, A. L'Hostis<sup>4</sup>, C. Monteiro<sup>4</sup>

(1) Respiratory Department and Early Phase (EPSILYON), Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, Lyon, France (2) Oncopharmacology Laboratory, Cancer Research Center of Lyon, UMR INSERM 1052 CNRS 5286, Lyon, France (3) Université Claude Bernard, University of Lyon, Lyon, France (4) Novadiscovery, Lyon, France (5) Institut Curie, Institut du Thorax Curie Montsouris, Paris, France (6) AP-HP, Tenon Hospital, Department of Pulmonology and Thoracic Oncology and GRC Theranoscan Sorbonne University, Paris, France (7) Department of Pneumology, Comprehensive Cancer Centre Léon Bérard, Lyon, France.

## BACKGROUND

QSP models represents a good opportunity to improve patients avenues in lung adenocarcinoma.

Advanced lung adenocarcinoma (aLUAD) is divided into multiple molecularly-defined subsets, each with specific biological characteristics and responses to targeted therapy.

QSP models, of which mechanistic computational model, have the potential to integrate this complexity and to enable the exploration of various subtype targeting therapeutics scenario [1].

Exploring the combination of existing treatments is one application where the use of QSP can make a difference.

Drug combinations offer promising therapeutic responses in subtypes of aLUAD. However, conducting clinical trials to assess their precise benefits can be resource-intensive.

Mechanistic computational models built with appropriate granularity enable cost-effective in silico trials to predict the efficacy of combination therapies.

## A mechanistic modeling approach to predict the efficacy of treatment combinations in aLUAD

### Modeling drug combination

In cancer therapy, treatment combination can improve treatments efficacy and overcome potential drug resistance. However, benefit is not always guarantee and drug combination can sometimes be detrimental to the patient. The **synergy, additivity or antagonism** will often depend on the **mechanism of action (MoA)** of each drug and the cancer subtype [2]. For new drug combination, mechanistic modeling integrating these various components and considering their interaction at the good granularity level may provide robust prediction of the outcome of a combination.

In the following, we demonstrate the different steps of the modeling process to evaluate the combination of an **EGFR tyrosine kinase inhibitor (TKI), osimertinib**, with a **platinum-based chemotherapy doublet—cisplatin and pemetrexed**.

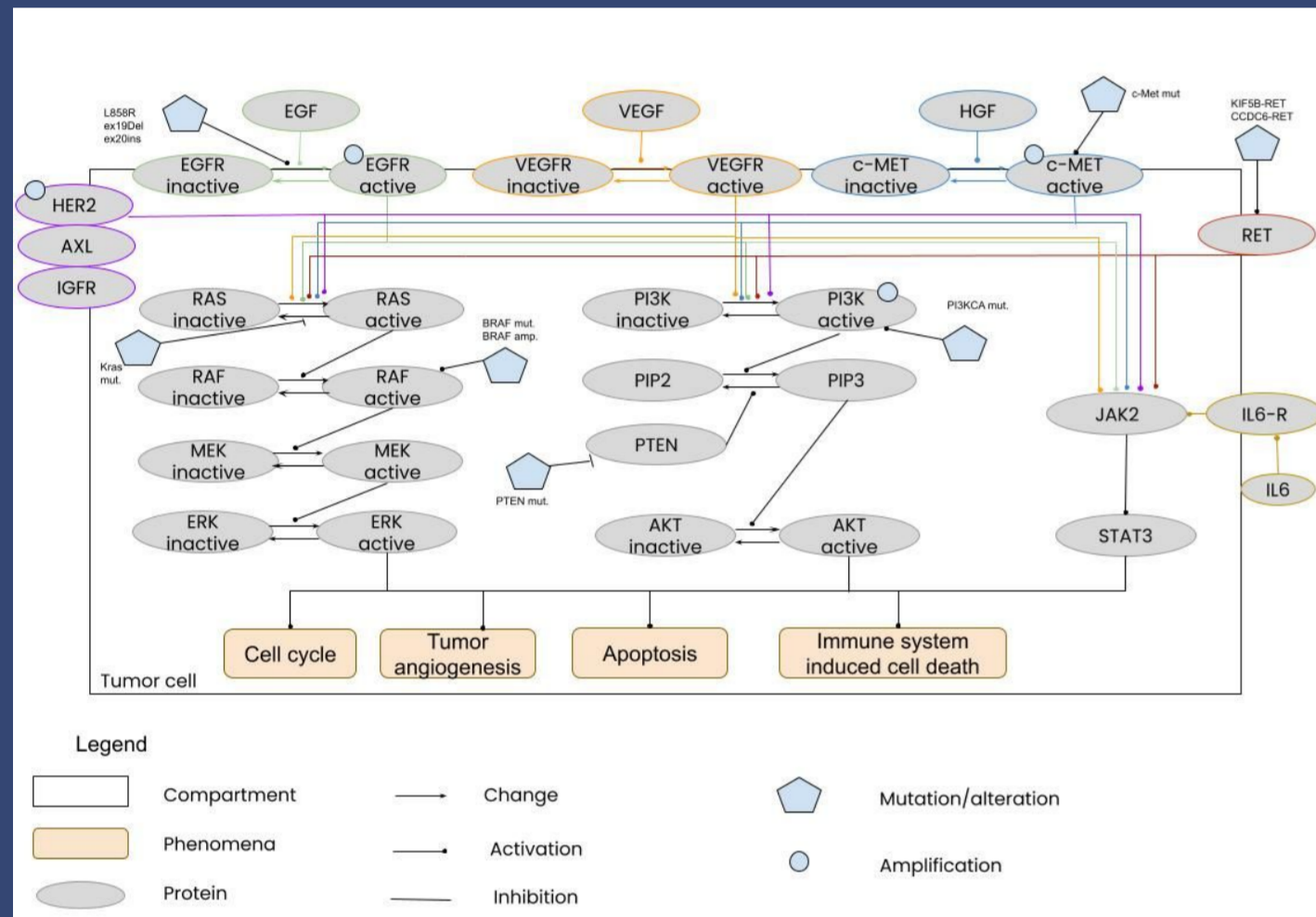


Figure 1: Intracellular signaling pathway model graph. It integrates the effect of Osimertinib. It also contains mechanisms of resistance, appearing in that context

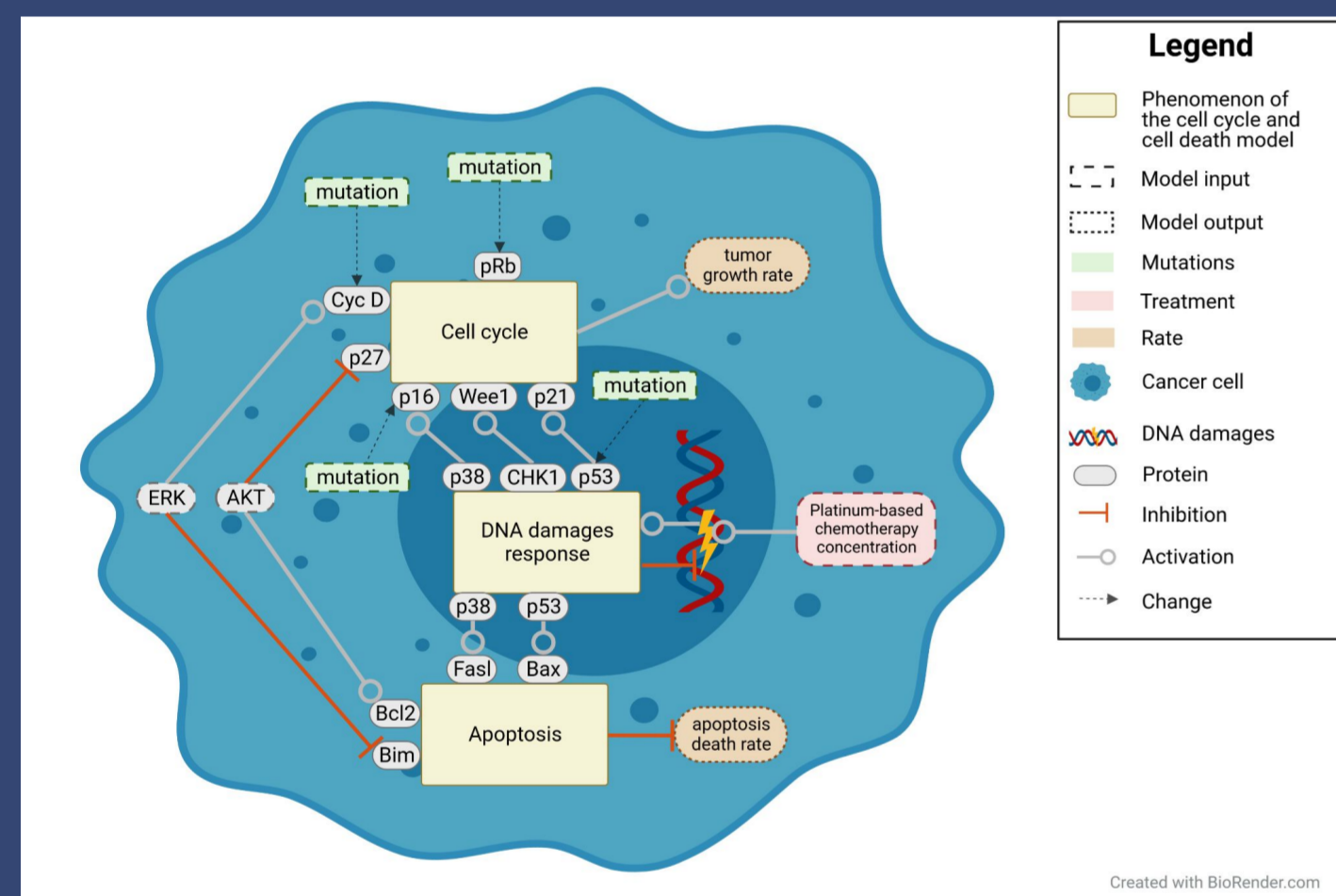


Figure 2: Cell cycle and cell death submodel. It transforms the signal sent by the intracellular signaling pathway into a dynamic growth rate for the tumor cells population. It integrates the effect of cisplatin and pemetrexed

**Osimertinib** is a drug that targets the activation of the EGFR protein, the main driver in this LUAD subtype that induces the activation of MAPK and PI3K/ca pathways, and uncontrolled tumor growth.

**Cisplatin and Pemetrexed** are chemotherapies that will respectively target the DNA and the nucleotide metabolism, impairing the progression of cell division and leading to apoptosis.

### Calibration

Mechanistic models convey a quantitative aspect driven by parameters. Calibration aims to integrate behaviors extracted from various experimental contexts and to constrain parameter values so that these behaviors are faithfully reproduced by the model.

### Preclinical efficacy

Although preclinical models (in vitro, xenograft, etc.) differ from the final context of use, they inform the model's core pathophysiological behaviors and drug efficacy.

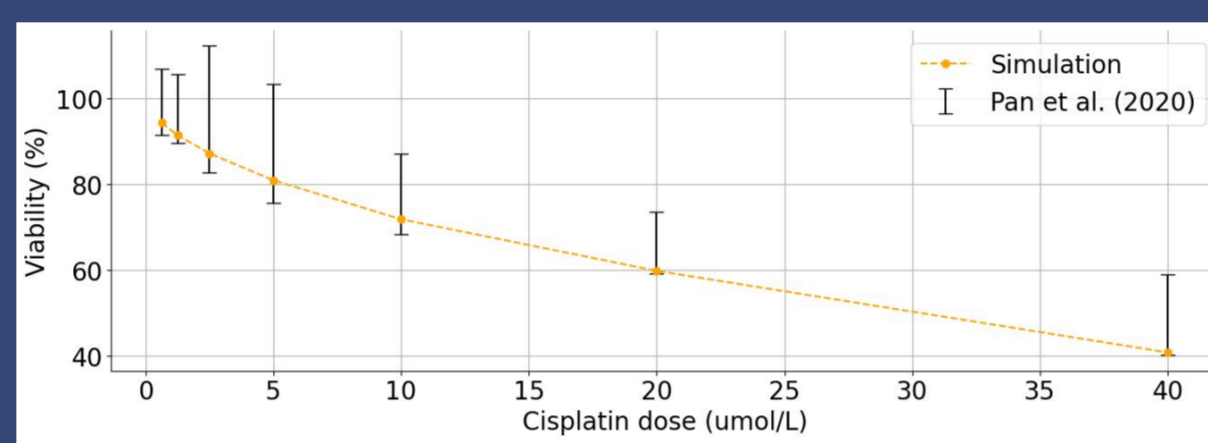


Figure 3: Simulation of in vitro Cisplatin dose-response of the H1975 cell line. Data from Pan et al. (2020)

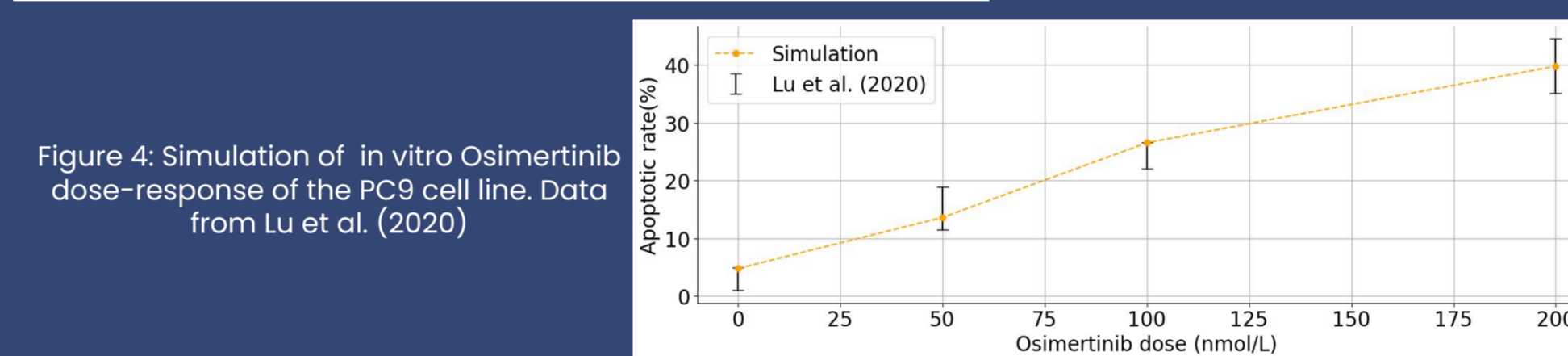


Figure 4: Simulation of in vitro Osimertinib dose-response of the PC9 cell line. Data from Lu et al. (2020)

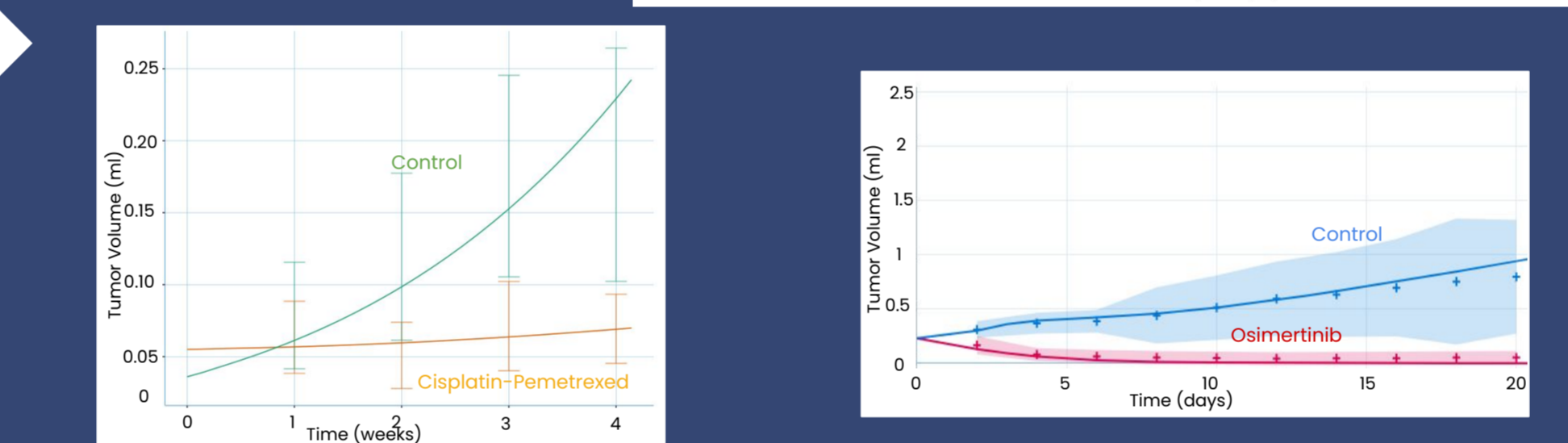


Figure 5: Simulated Growth curves of LCSC-derived xenografts in control mice or mice treated with cisplatin/pemetrexed combination. Experimental points from Setti et al. (2015)

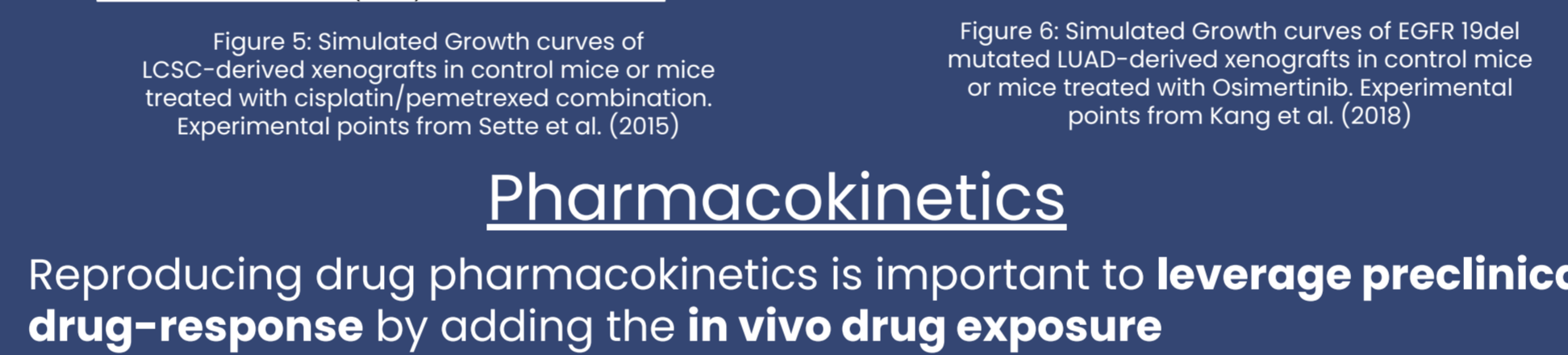


Figure 6: Simulated Growth curves of EGFR 19del mutated LUAD-derived xenografts in control mice or mice treated with Osimertinib. Experimental points from Kang et al. (2018)

### Pharmacokinetics

Reproducing drug pharmacokinetics is important to leverage preclinical drug-response by adding the in vivo drug exposure

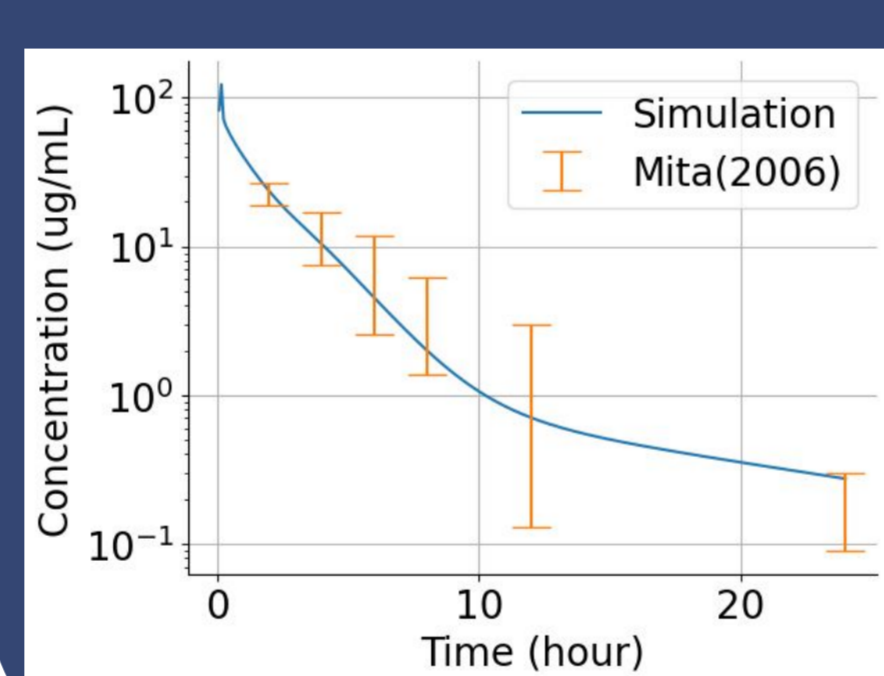


Figure 7: Simulated plasma pemetrexed concentration-time profile, following 500 mg/kg intravenous administration. Experimental points from Mita et al. (2006)

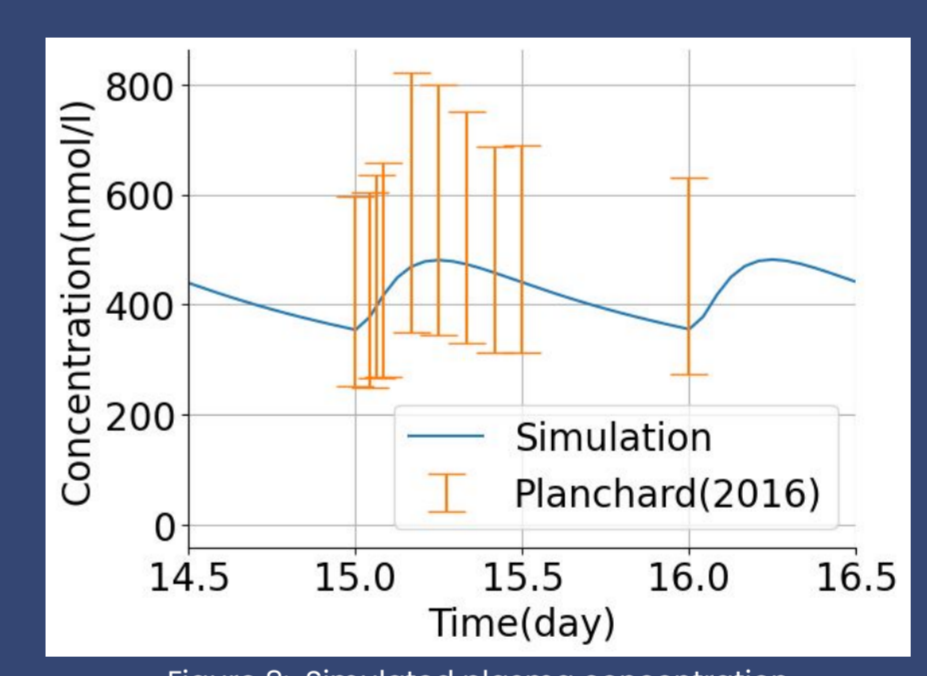


Figure 8: Simulated plasma concentration concentration-time profile, following multi-dose 80 mg oral administration. Experimental points from Planchard et al. (2016)

### Virtual population

The virtual population is designed to capture the variability inherent in biological systems. It comprises individual virtual patients, each defined by a unique set of parameters, and each serves as one simulation of the model. Choosing which parameters to vary and specifying their distributions constitutes the final step.

### Clinical

For EGFR-mutated aLUAD, the primary clinical outcome criteria are PFS and OS, based on RECIST v1.1 [3]. The model mechanistically incorporates both the immediate patient response and the long-term outcome characterized by the **emergence of resistance mechanisms**. By reproducing clinical trials in the target population, we calibrate parameters governing the initial prevalence of resistance pathways and the timing of their appearance.

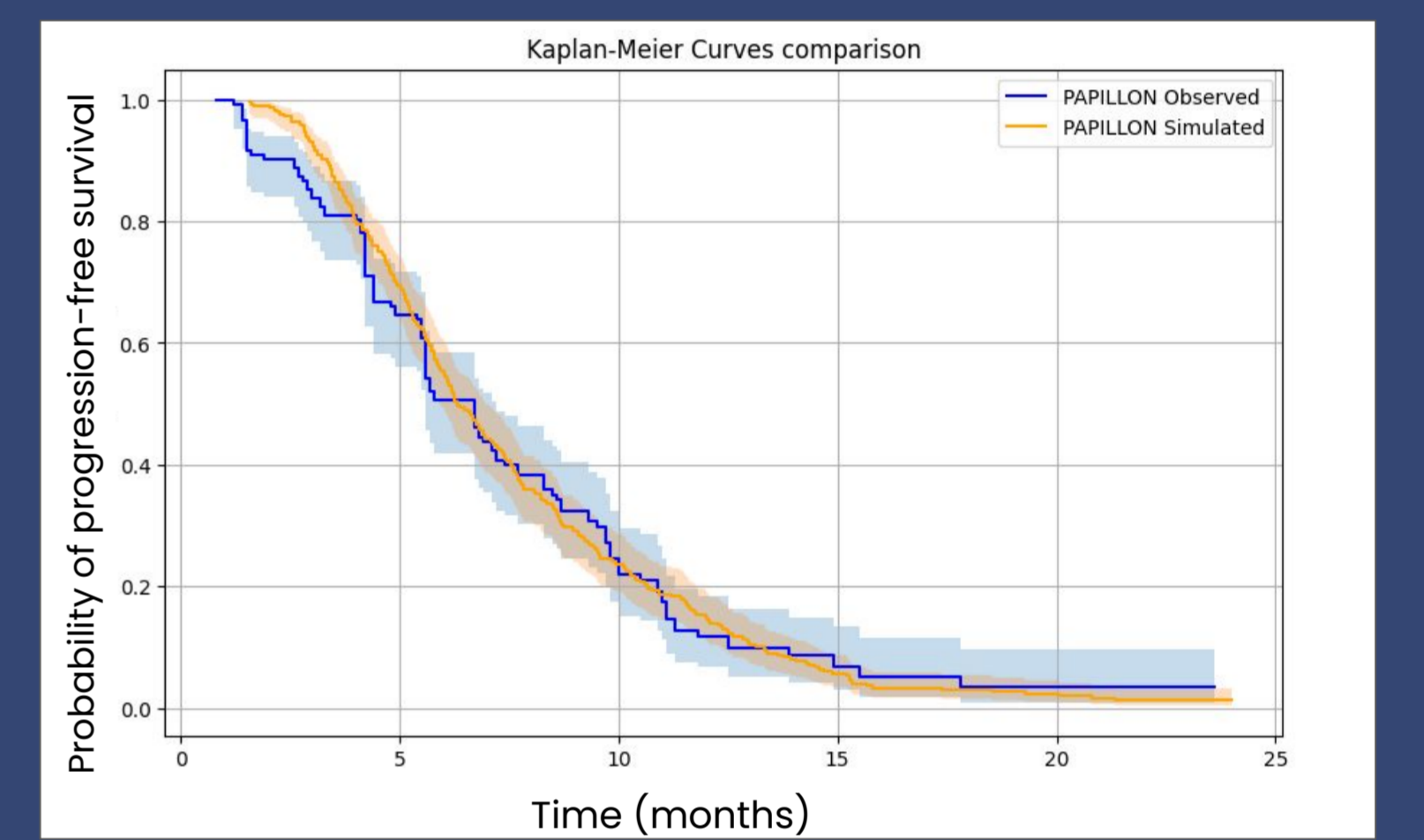


Figure 9: Reproduction of the clinical efficacy of chemotherapies doublet in the target population. Data from PAPILLON clinical trial in aLUAD EGFR mutated patients

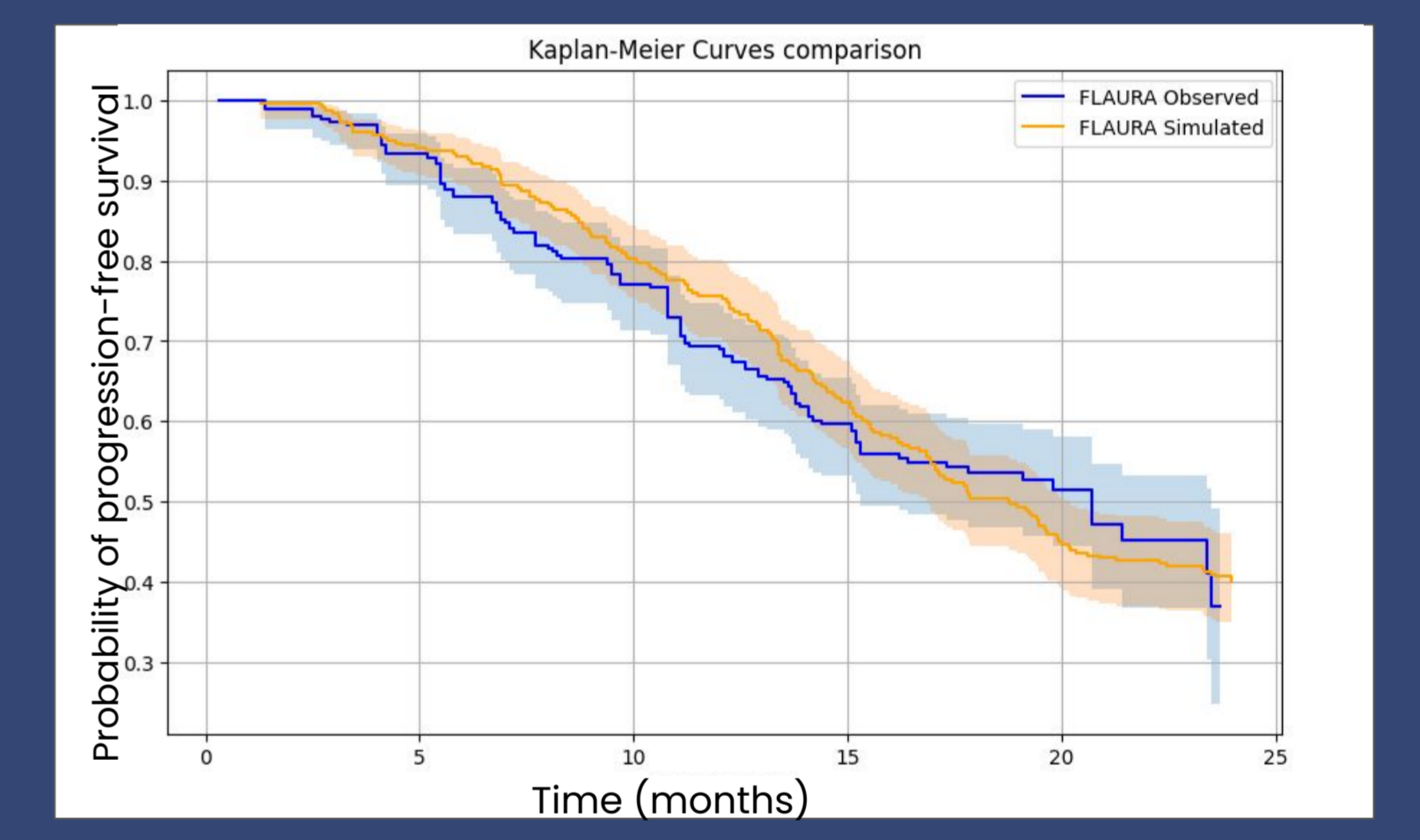


Figure 10: Reproduction of the clinical efficacy of Osimertinib in the target population. Data from PAPILLON clinical trial in aLUAD EGFR mutated patients

## METHODS

We developed a **mechanistic multiscale model of EGFR-mutated aLUAD** that incorporates the most relevant pathophysiological processes [4]. This model reproduces and integrates biological behaviors ranging from EGFR protein activation to tumor growth dynamics and time to progression. It is coupled with three treatment submodels—**Osimertinib, Cisplatin, and Pemetrexed**—each representing their mechanisms of action at the molecular level.

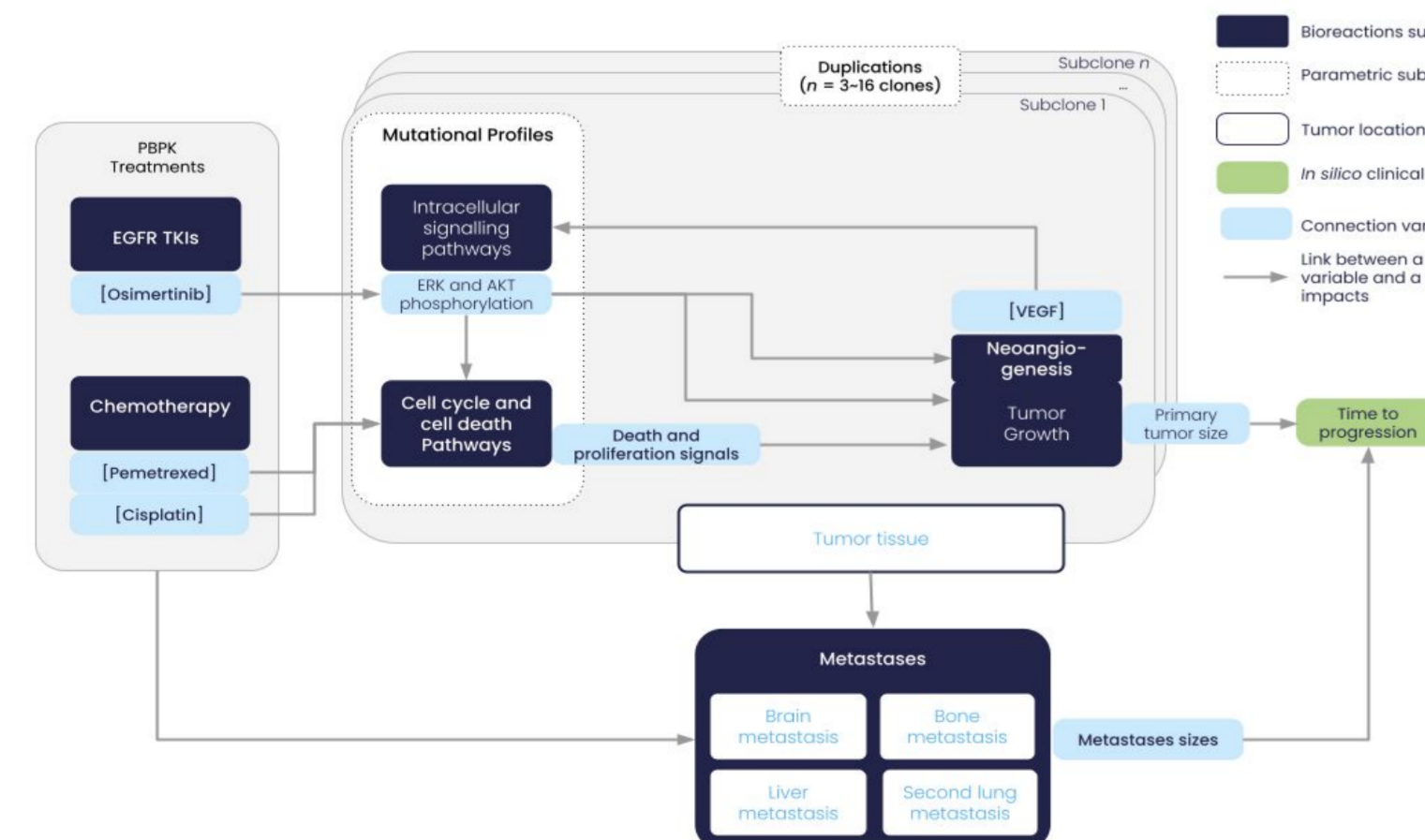


Figure 11: Egfr-mutated aLUAD model graph. It integrates the principal pathophysiological phenomena. It contains duplication layers accounting for tumor heterogeneity and metastases

**Virtual populations** were generated using the joint distribution of trial-specific biomarkers and by constraining variability in key pathophysiological parameters.

**Replication of clinical trials** was performed on the jinkō trial simulation platform, by combining the computational model, the virtual cohort of patients and the trial protocols, from published trial designs.

## RESULTS

This multiscale model of EGFR-mutated NSCLC accurately reproduces quantitative physiological and pathophysiological behaviors derived from multiple real-world contexts (in vitro, in vivo, and clinical data).

The model successfully predicted the exploratory arm of the FLAURA2 clinical trial—osimertinib combined with platinum-based chemotherapy—with overlapping confidence intervals and curve shapes similar to those observed in the actual trial data [5].

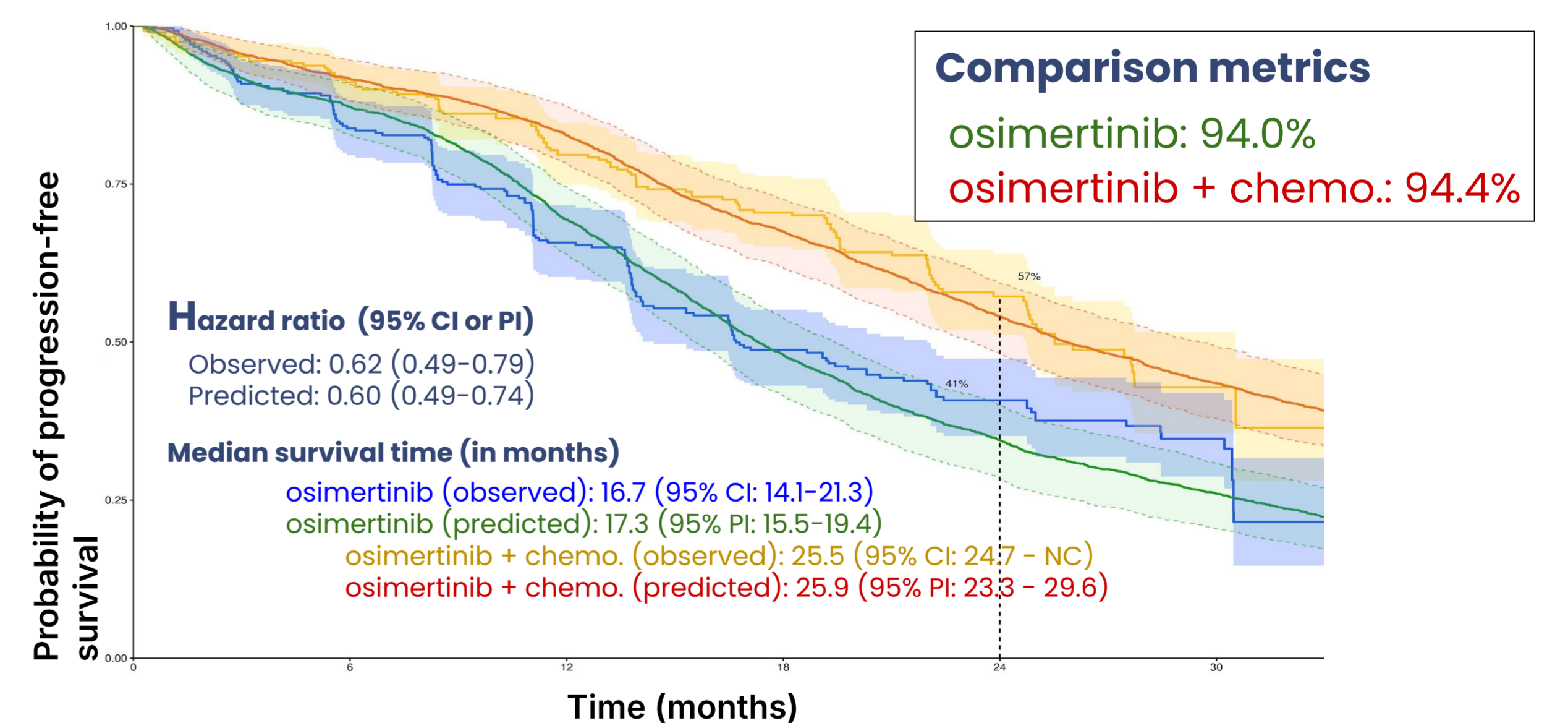


Figure 12: Kaplan-Meier curves of observed PFS and simulated TTP for FLAURA2 trial (both arms).

The comparison metrics is the percentage of non-significant bootstrapped weighted log-rank tests (predicted vs observed data) [6].

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

## CONCLUSION

Building multiscale mechanistic computational models of advanced EGFR-mutated LUAD—by integrating knowledge and data from diverse sources—enables robust and accurate predictions in both similar and novel use contexts.

Such models can provide robust and reliable insights into specific treatment combinations, optimal dosing regimens, patient-stratification strategies, and potential mechanisms of resistance—thereby guiding the design of more efficient clinical trials and personalized therapeutic approaches.

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## REFERENCES

[1] Arsène et al. 2023; [2] Abd El-Hafeez, et al. 2024; [3] Eisenhauer et al. 2009; [4] Darré H et al. 2024; [5] Planchard et al. 2023 [6] Jacob E et al. 2023