Application of Knowledge-based Mechanistic Modeling to Optimize Phase III Clinical Trials of Targeted Therapy

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Background

Clinical trials for targeted therapies are complex due to small population size and cost of trials. Therefore, tools to address these limitations are necessary. We propose here to complement early clinical results with knowledge-based mathematical mechanistic models to derisk and optimize phase III clinical trials of target therapies. We illustrate the construction of the models with examples on the following indication: lung adenocarcinoma.

Project Formulation

Lung adenocarcinoma: most common lung cancer [1]. ⅛ harbor a tumor driver mutation of the **Epidermal Growth Factor Receptor (EGFR)** [2]. Eligible to EGFR-targeted therapies, *e.g.* Standard of Care Gefitinib [3]

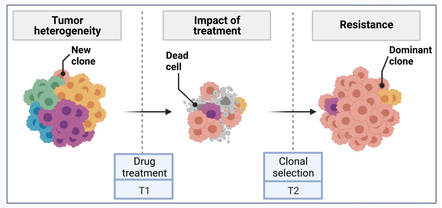
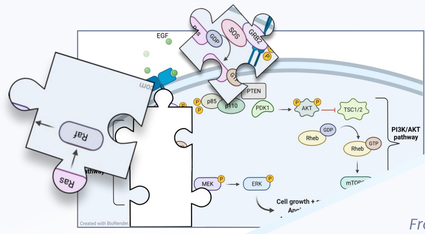


Illustration of the phenomena that drive tumor growth

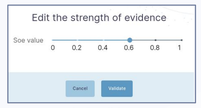
Questions:
1. What is the **natural prognosis** of patients with the rare **EGFR Exon 20 insertion** (EGFR-E20)?
2. What are the clinical differences of **EGFR-E20 patients versus patients with common EGFR mutations**?

Systemic Knowledge Review

300+ scientific papers
- Identify the relevant **biological entities** and their **relationship**
- Define a **Strength of evidence** (SoE) scoring for every piece of knowledge
- Manual curation of pieces of knowledge



We assemble pieces of knowledge



SoE edition

Realized on the **jinkō platform**, a state of the art clinical trial simulation cloud-based SaaS solution

Computational Model Development

From knowledge to mathematical equations, embedded in computer code

Mathematical modeling

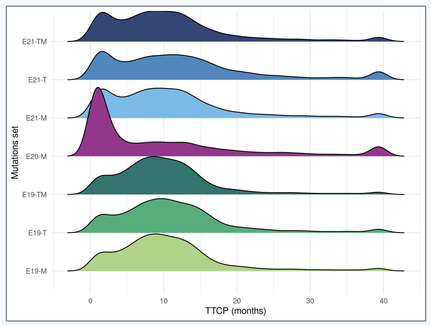
6 biological **models** implemented in parallel & integrated with connecting variables. The model is composed of up to **83 ODEs, 43 variables, and 170 parameters** reflecting the intra-tumor heterogeneity.

Focus on the clonal heterogeneity

Tumor clone: Group of cells that might harbor genotype differences but that share the same phenotype. In the model, we consider:
- **Coexistence of between 2 and 15 clones** [4]
- A **common EGFR+ mutation** across clones
- Clones with **similar behavior** in response to biological signals
- Clones with **distinct properties** derived from sub-clonal (epi) mutations
  - Inter-clonal variability
  - Some might yield a new tumor clone

Simulation & Analysis

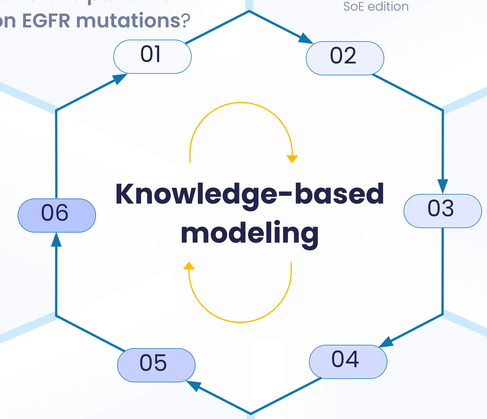
We ran an *in silico* trial following **5000** EGFR+ LUAD patients, treated daily with 250mg of **Gefitinib,** and monitored their TTP according to the RECIST v1.1 criteria [6].

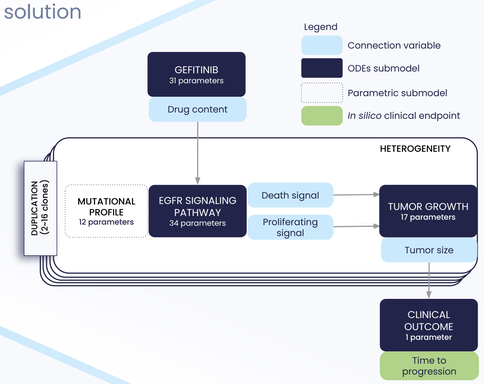


Density plot of TTP distribution over time (in months) for populations with different sets of mutations

Q1. Natural prognosis of EGFR-E20 patients
- Median TTP: **4.9 months**
- 25% of patients have a progression during the 1st month, **<5%** of patients did not progress after 36 months

Q2. EGFR-E20 vs common EGFR mutations
- median TTP of patients with common EGFR mutations is approximately **10 months**
- EGFR-E20 patients' TTP is statistically significantly lower





Graphical representation of the computational model

Model Validation

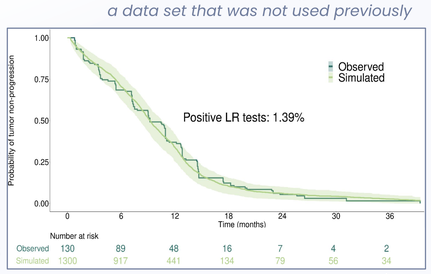
Consists in reproducing the results of a data set that was not used previously

Validation criterion

Percentage of log-rank-test with *p* value >0.05, when comparing bootstrapped samples of VPOP patients to the 130 real patients from the reference paper: **Inferred TTP from Paz-Ares study** [5].

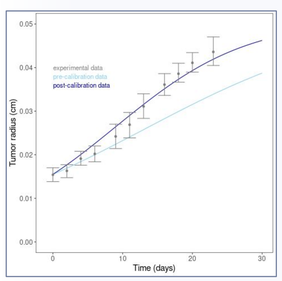
Results

Our model is validated on the **TTP derived from the study by Paz-Ares et al.**



Kaplan-Meier curves of probability of tumor non progression (months) for Lux-Lung7 cohort & its corresponding simulated VPOP. LR=log-rank

Calibration & VPOP



Example of simulation outputs before and after calibration

Protocol

1. Gather **calibration data**
   - **data from 26** published experiments: spheroids, xenografts, clinical results, with relevant mutational profiles
2. Ensure **adequation between data and the model**
3. Define a calibration protocol, composed of **steps with increasingly broad objectives: step-by-step calibration**
4. Create **fitness functions** representative of the calibration data
   - Iterative optimization until minimization is deemed satisfying
5. Create **virtual patients** = vectors of parameter values to generate a **VPOP**

Relevant model endpoints

Time to progression (TTP): duration from the treatment start until disease progression
Tumor radius: Radius in centimeter of the primary tumor, under the assumption that the tumor is spheroid

Next steps?

Due to its **mechanistic** properties, our model can be completed to **study new drugs** and **compare** them to already implemented treatments, to find the **best responders** to a given treatment, the **best posology** and eventually **optimize** late phases of clinical trials.

Conclusion

This *in silico* approach enables more informed clinical trial decisions and more cost-effective Research & Development. Indeed, its use in the context of clinical trials overcomes major limitations in the investigation of current targeted therapies :
- **reproducibility crisis**, as we are able to simulate clinical trials with an **unlimited number of patients**
- ethical and practical difficulties of running control arms: modeling **digital twins** for each patient enrolled in a trial effectively creates a synthetic control arm.

Finally, NOVA's *in silico* approach **complements** *in vitro* and *in vivo* experiments, by allowing to test any relevant hypothesis as early as possible.

References

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[4] Hanjani *et al.*, N Engl J Med, 2017
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[6] Eisenhauer *et al.*, Eur J Cancer, 2009