Poster 856

Comparison of the effect of two EGFR-TKI in patients with EGFR-mutant lung adenocarcinoma using *in silico* clinical trials

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BACKGROUND

16.4% of lung adenocarcinomas (LUADs) are presenting a mutation in the Epidermal Growth Factor Receptor (EGFR), resulting in its constitutive activation and leading to uncontrolled cell proliferation. While some tyrosine kinase inhibitors (TKIs) have been developed to target EGFR mutations, their efficacy is not long-lasting, due to the emergence of resistance mutations [1]. Gefitinib and osimertinib are two EGFR-TKIs (respectively first and third generation) with osimertinib being able to target the T790M EGFR mutation, a resistance mutation that frequently emerges from gefitinib treatment. Based on *in silico* approaches, we can investigate and compare the impact of those two TKIs, on tumor size evolution and clinical outcome, depending on the target population.

METHODS

We developed a mechanistic model of LUAD based on knowledge, focusing on patients harboring an EGFR mutation (mutations on exon 19, 20 and 21 were considered) and that are at an advanced stage of the disease (stage IIIa, IIIb, IIIc or IV). The structure of this model is illustrated in Figure 1.

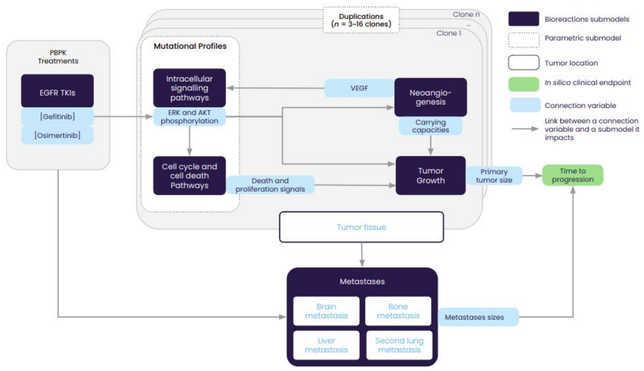

Figure 1: Representation of structure of the LUAD model developed by nova. The final output of the model is the time to progression (TTP) and is dependent on individual parameters as the initial tumor radius or the driver mutations.
PBPK: Physiologically based pharmacokinetics; ERK: Extracellular signal-regulated kinases; AKT: Protein kinase B VEGF: Vascular endothelial growth factor; EGFR: Epidermal growth factor receptor; TKI: Tyrosine kinase inhibitor

The EGFR-TKI physiologically based pharmacokinetics (PBPK) models output the drug concentration in the blood, the main organs and the tumor tissues. The latter is used for the modeling of the drug mechanism of action *i.e.* the inhibition of the EGFR intracellular signaling. The PBPK models were calibrated both in humans and mice using data on plasma concentration after administration in several settings (oral and intravenous for humans and oral for mice). Then, the drugs' mechanisms of action were calibrated using mice data on xenograft models with tumor volume evolution. Finally, the clinical outcome of the treatment was calibrated using two first line TKI clinical trials FLAURA (osimertinib) and NEJ002 (gefitinib).

The model was then used to simulate an *in silico* clinical trial with the arms described in the retrospective study from Li *et al.* [2], that compares the efficacy of gefitinib and osimertinib on first-line patients. We assessed whether the results from the *in silico* clinical trial would lead to the same conclusions as the retrospective study, considering that the two clinical outcomes are different (time to progression (TTP) for the *in silico* trial and progression free survival (PFS) for the retrospective study).

RESULTS

Calibration results in mice xenograft

After calibration with mice data [3-5], the model was able to reproduce both the tumor volume evolution after treatment and the TKIs' pharmacokinetics as confirmed by the visual predictive checks presented in Figure 2. The model was calibrated on multiple EGFR mutations even though only results on exon 19 mutation are shown.

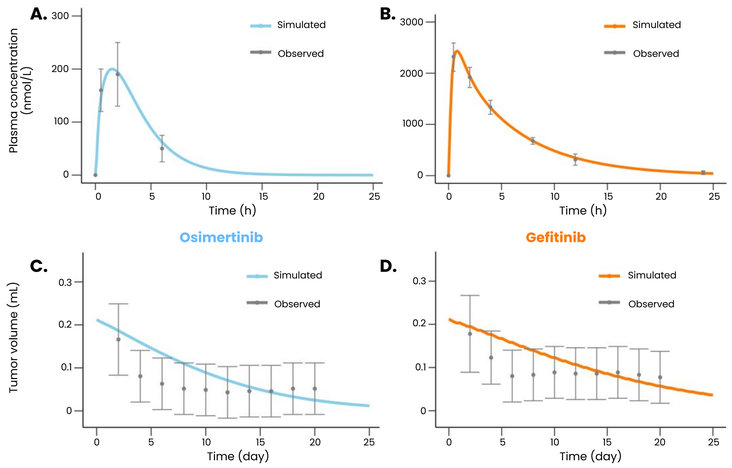

Figure 2: Calibration results in mice xenograft. Plasma concentration of osimertinib (A) and gefitinib (B) in mice after an oral administration of 5 mg/kg and 50 mg/kg respectively. Tumor volume evolution in mice implanted with a tumor carrying an exon 19 mutation and treated with osimertinib (C) and gefitinib (D).

Calibration results in humans

After calibration using the data from the clinical trials FLAURA and AURA3, the model was able to reproduce the time to progression of the studies using two virtual populations that match the baseline characteristics of the real patients. The virtual populations contain ten times more patients than the real studies in order to have a better representation of the dynamics. The results of this calibration are shown in Figure 3.

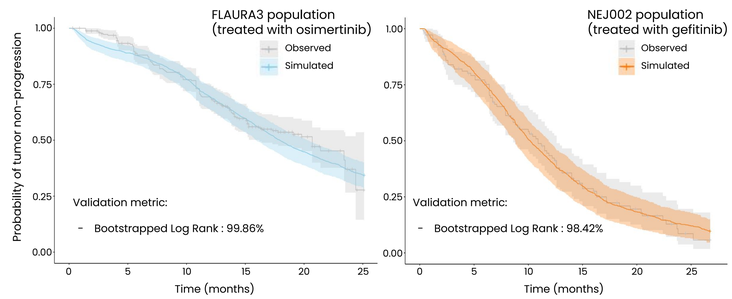

Figure 3: Visualization of the *in silico* clinical trials performed with the LUAD model and compared accordingly with the trials used for the calibration (left: FLAURA3 clinical trial; right: NEJ002 clinical trial). The uncertainty interval of the simulated curve corresponds to the variability obtained from bootstrapping the virtual population while the one of the observed curve stands for the 95% confidence interval.

A combination of weighted bootstrapped log-rank tests (poster 4287) was performed in support of the visual predictive checks to assess whether the model correctly reproduced the reality. The threshold was set at 80% and was largely reached for both trials (above 95%).

Comparison of gefitinib and osimertinib efficacy with an *in silico* trial

We created a virtual population with the same baseline characteristics as the one described in the retrospective study from Li *et al.* [2] and performed an *in silico* clinical trial using the LUAD model. The results are presented in Figure 4.

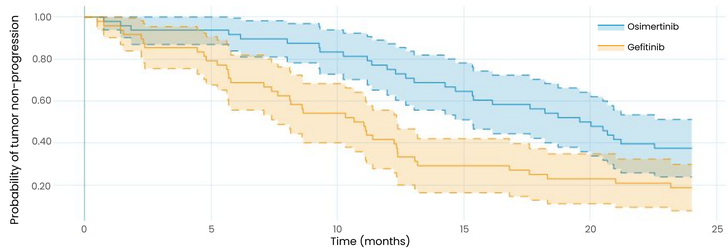

Figure 4: Exploratory *in silico* clinical trial: comparison of gefitinib and osimertinib performed with the LUAD model and with the same patient baseline characteristics as the retrospective study from Li *et al.* The uncertainty intervals stand for the 95% confidence intervals of the progression curves.

The results of the *in silico* clinical trial show that osimertinib is associated with longer TTP than gefitinib for the designed population with a median TTP of 20 months (95%CI: 15-24) for osimertinib and 11 months (95% CI: 7.5-12) for gefitinib. The retrospective study reported a median PFS of 18.1 months (95% CI: 15.4-20.7) for osimertinib and 10.7 months (95% CI: 9.9-11.4) for gefitinib, in coherence with the results of our *in silico* clinical trial, giving that the two studies have different endpoints.

DISCUSSION & CONCLUSION

The model successfully reproduces results from real-world data. The credibility of the model thereby acquired is a first step in the use of the model to:

- Compare an investigational treatment to osimertinib or gefitinib in a first line administration setting
- Provide insights to help the design of future clinical trials

To further increase the credibility of the model, the former should be confronted with data that were not used during the calibration process and validated using statistical tests.

We believe that *in silico* approaches are complementary tools to existing *in vitro*, animal experiments, and clinical trials, that together drive drug development and approval.

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