Poster 859

Simulations of tumor heterogeneity impact on treatment response using a mechanistic model of EGFR-mutant lung adenocarcinoma

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BACKGROUND

- **Epidermal growth factor receptor (EGFR) mutations** occur in about 40% of Asian and 13-25% of Western patients with **lung adenocarcinoma (LUAD)**[1,2], leading to EGFR constitutive activation and uncontrolled cell proliferation.
- **EGFR tyrosine kinase inhibitors (TKIs)** have been developed to target tumors with an EGFR driver mutation, but drug resistance often emerges.
- EGFR-mutated tumors harbor **additional mutations and genotypic alterations**, which contribute to the **variability in treatment response** and **therapeutic resistance**.
- Here, we used a **mechanistic model** of late stage EGFR-mutant LUAD to evaluate the **impact** of tumor **mutational profiles** on **treatment response**.

METHODS

We developed a knowledge-based model of late stage EGFR-mutant LUAD, which combines an EGFR-TKI model and several mechanistic submodels based on ordinary differential equations (Figure 1).

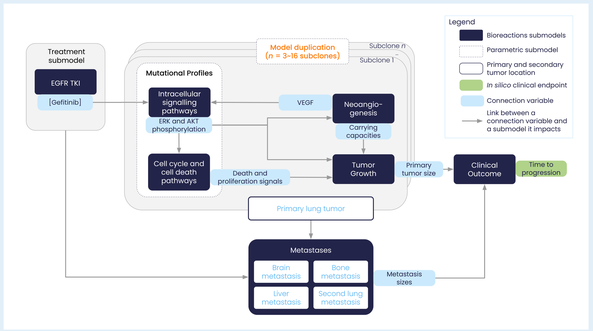

Figure 1: Representation of the structure of the EGFR-mutant LUAD model

- **Modeling of tumor heterogeneity:**
  - The primary tumor and the metastases are composed of subclones. The number of subclones varies between patients and between tumors, ranging from 3 to 16.
  - Subclones are characterized by distinct sets of mutations, leading to distinct proliferating phenotypes and responses to treatment.
  - The equations in the tumor growth, intracellular signaling, cell cycle and death & neoangiogenesis submodels are replicated for each subclone.
  - Mutations can be clonal (shared by all subclones) or subclonal.
  - The mutation frequencies are taken from the literature and their impact has been calibrated using literature data.

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 trial A

In silico trial with 107 virtual EGFR-mutant LUAD patients reproducing the gefitinib arm of NEJ002 study[4]

Dynamics of tumors and subclones

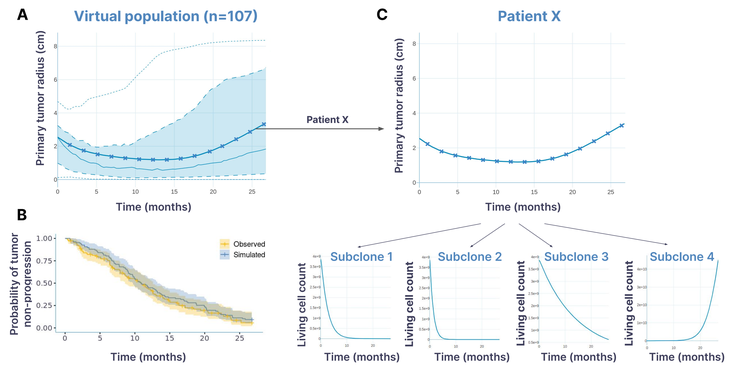

Figure 2: Visualization of *in silico* trial A results

(A) Evolution of primary tumor radius over time in the virtual population treated with gefitinib
[solid line: median; dashed lines: 25-75th percentiles; dotted lines: 2.5-97.5th percentiles]

(B) Kaplan-Meier curves of TTP with 95% confidence interval

(C) Evolution of the primary tumor radius over time for one patient (top), with the evolution of the number of living cells in 4 tumor subclones (bottom)

Impact of tumor mutations on time to progression

Figure 3: Kaplan-Meier curves of TTP for *in silico* trial A according to the presence/absence of specific mutations in the primary tumor
[shaded zones: 95% confidence intervals]

Clinical trial simulations using a computational model of **lung adenocarcinoma** with **EGFR mutation** provide insights on the impact of **tumor heterogeneity** on **clinical outcome**

In silico trial B

In silico trial on 100 virtual EGFR-mutant LUAD patients having no other explicit baseline mutation in their primary tumor, treated with gefitinib (control arm)
4 other arms are simulated, with exactly the same patients except that they harbor an additional mutation

Impact of tumor mutations on time to progression

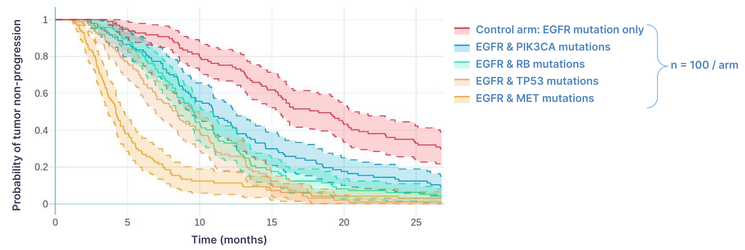

Figure 4: Kaplan-Meier curves of TTP for *in silico* trial B according to study arms
[shaded zones: 95% confidence intervals]

EGFR: Epidermal growth factor receptor; MET: Mesenchymal epithelial transition factor; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TP53: Tumor Protein P53; RB: Retinoblastoma

- **Drug model:** physiologically-based pharmacokinetics (PBPK) and drug effect model of gefitinib (1st generation TKI)
- **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[3]
- **Model calibration:** performed using *in vitro* and *in vivo* (mouse and human) data, as described in poster 856
- ***In silico* clinical trials:** 2 trials with gefitinib (250 mg/day orally) launched on virtual populations reproducing the reported baseline characteristics of the patients in the gefitinib arm of NEJ002 study[4]

RESULTS

In silico trial A

Dynamics of tumors and subclones

Figure 2A: the overall evolution of the primary tumor size in the virtual population shows first a response to treatment, followed by the emergence of treatment resistance

Figure 2B: the simulated Kaplan-Meier TTP curve correctly reproduces the curve generated from the data of the real clinical trial.

Figure 2C: the tumor subclones evolve differently depending on their mutations. Here, subclones 1-3 respond to treatment with diverse dynamics, subclone 4 is resistant.

Impact of tumor mutations on time to progression

Figure 3: Patients with MET mutation (median TTP: 2.3 [95% CI: 0.91-4.3] *vs.* 12 [9.9-14] months) and TP53 mutation (8.4 [6.6-9.7] *vs.* 17 [13-20] months) have significantly lower TTP compared with patients without each of these mutations.

The low frequency of most mutations in the EGFR-mutant population makes result interpretation and comparison challenging.

This can however be overcome by simulating a trial with a different design, as *in silico* trials have the major advantage of making possible to enroll an unlimited number of patients with specific characteristics.

In silico trial B

Impact of tumor mutations on time to progression

Figure 4: EGFR-mutant patients with additional MET (median TTP: 4.2 months [95% CI: 3.6-4.7]), TP53 (8.3 months [6.9-9.7]), RB (9.6 months [8.4-10]) or PIK3CA (11 months [9.2-13]) mutations have significantly lower TTP compared with EGFR-mutant patients with no other mutation (18 months [15-21]) (all $p < 0.001$).

DISCUSSION & CONCLUSION

The implementation of subclones in the tumor model enables taking into account tumor heterogeneity and reproducing the apparition of treatment resistance after initial response. Exploratory *in silico* trials on the EGFR-mutant LUAD model provide insights on the impact of additional mutations on disease progression. The generated results should be further confronted to data from real clinical trials to assess their credibility, although these data are scarce.

Clinical trial simulations using knowledge-based models of disease and treatment provide relevant additional tools to help clinicians in exploring new hypotheses.

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