Cancer Treatment:
In silico model of EGFR+ lung adenocarcinoma

Avicenna Alliance
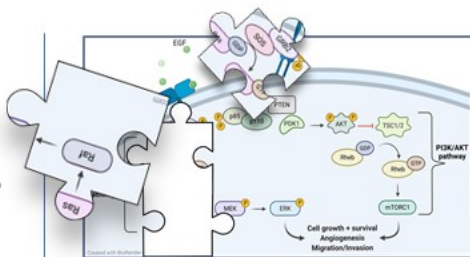Association for Data Driven Medicine

Objectives

- Integrate the effect of EGFR mutations (E19, E20, E21) and treatment on tumor growth using mathematical modeling
- Describe and predict tumor growth variability between patients treated with the same a standard of care: gefitinib
- Run an *in silico* clinical trial that is predictive on a clinical endpoint: time to progression (TTP)
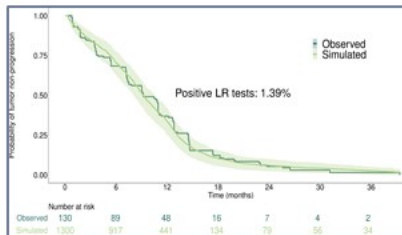
Calibration process

- **Step 1:** Reproduce growth of *in vitro* spheroids [1-[3]
- **Step 2:** Reproduce tumor growth in xenografted mice[4]
- **Step 3:** Reproduce the TTP of an EGFR+ lung adenocarcinoma population[5-11]

Main results

- Model validated on dataset[12] that was not used for calibration
- Median TTP for EGFR-E20 patients treated with gefitinib: 4.9mo. 25% of patients have a progression during the 1st month ; 5% did not progress after 36 months
- Median TTP for patients with common EGFR mutations treated with gefitinib: 10mo. EGFR-E20 patients' TTP is statistically lower
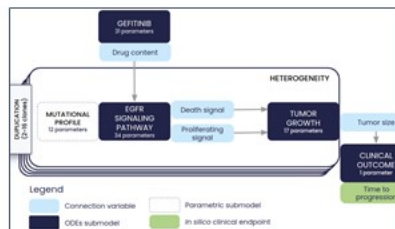
[1] Jagiella et al. (2016)
[2] Ekert et al. (2014)
[3] Freyer (1988)
[4] Kang et al. (2018)
[5] Asahina et al. (2006)
[6] Yang et al. (2008)
[7] Wu et al. (2008)
[8] Vasconcelos et al. (2020)
[9] Yasuda et al. (2013)
[10] Sugio et al. (2018)
[11] Maemondo et al. (2010)
[12] Paz-Ares et al. (2017)

We assemble pieces of knowledge

Implement

Implementation of a computational model

Calibrate

Calibration with CMA-ES algorithm; thanks to constraints extracted from literature

Validation

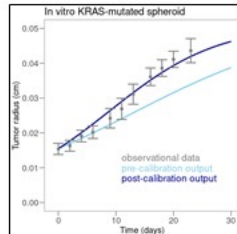Kaplan-Meier curves of probability of tumor non progression (months) for Lux-Lung7 cohort & its corresponding simulated VPOP. LR=log-rank

Model potential

- Can be used as an investigational and control arm for unbiased study of mutational effects
- Can explore
  - the natural history of patients treated with Gefitinib harboring specific mutated tumors
  - complement with an additional treatment, to explore best responders and posology