Leiden University Medical Center

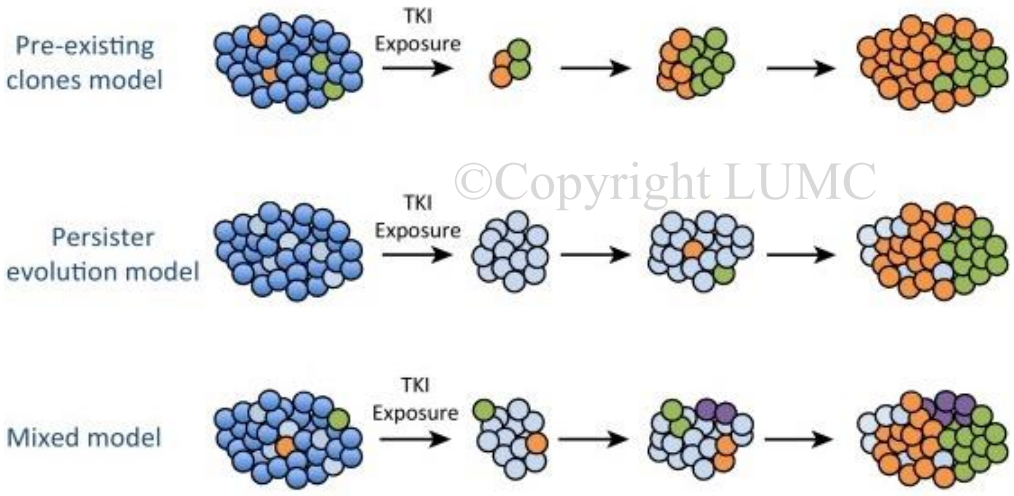
Anti-cancer treatment schedule optimization based on tumor dynamics modelling incorporating evolving resistance

Anyue Yin[1,2], Johan G.C. van Hasselt[3], Henk-Jan Guchelaar[1,2], Lena E. Friberg[4] , Dirk Jan A.R. Moes[1,2]

1. Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands
2. Leiden Network for Personalized Therapeutics, Leiden University Medical Center, Leiden, the Netherlands
3. Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands,
4. Department of Pharmacy, Uppsala University, Uppsala, Sweden.

Background

- **Evolutionary mechanisms and Treatment resistance**
  - Intra-tumor heterogeneity
  - Evolving adaptation



Lin, J.J. and A.T. Shaw, Trends Cancer, 2016. **2**(7): p. 350-364.

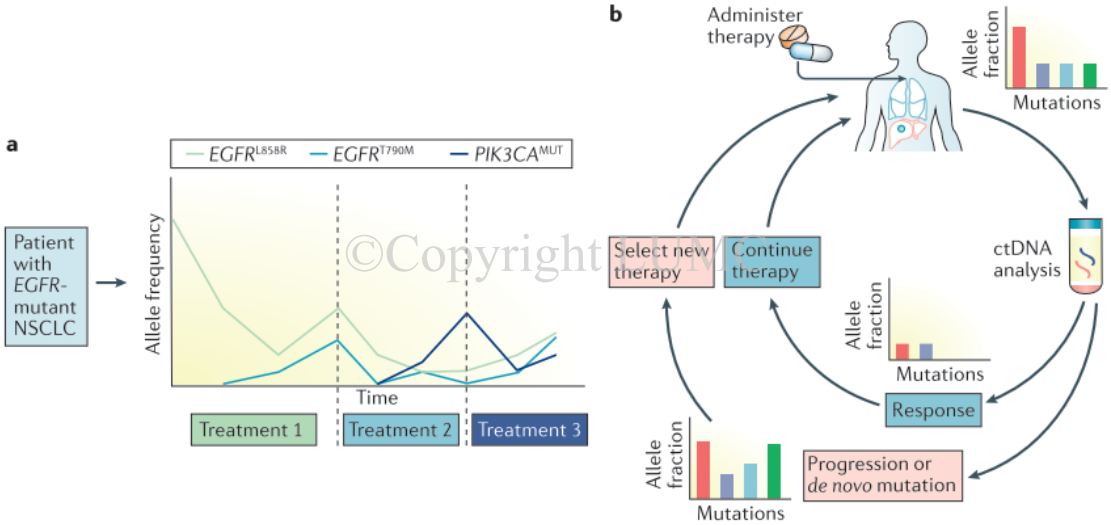
Background

- **Circulating tumor DNA (ctDNA)**
  - Clinical genetic biomarker
  - Capture the tumor heterogeneity
  - Monitor the evolving treatment resistance
  - Correlate with tumor burden and stage

Jiang, T., S. Ren, and C. Zhou, Lung Cancer, 2015. **90**(2): p. 128-34.
Wan, J.C.M., et al., Nat Rev Cancer, 2017. **17**(4): p. 223-238.
Nagano, T., M. Tachihara, and Y. Nishimura, Cells, 2018. **7**(11).

Background

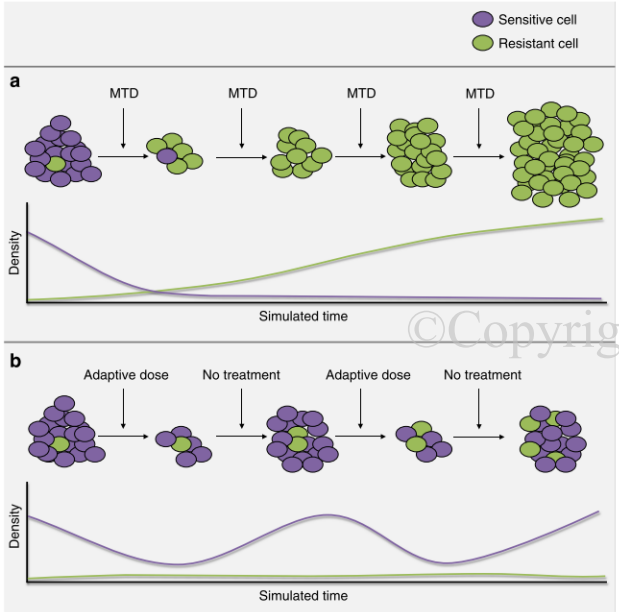
- **Circulating tumor DNA (ctDNA)**
- **Reactive monitoring and adaptive therapy**

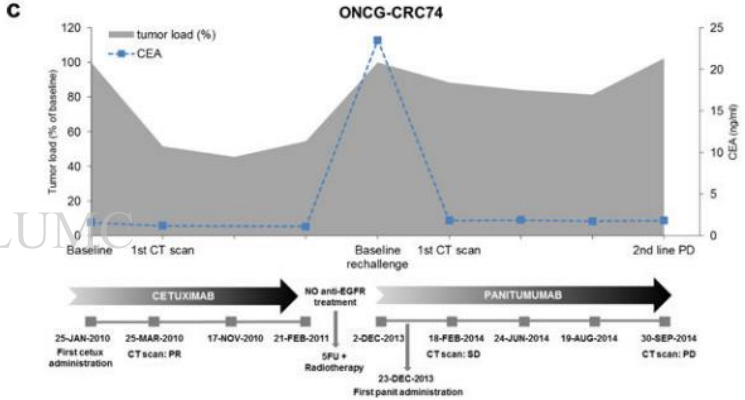


Wan, J.C.M., et al., Nat Rev Cancer, 2017. **17**(4): p. 223-238.
Nagano, T., M. Tachihara, and Y. Nishimura, Cells, 2018. **7**(11).

Background

- **Intermittent therapy with treatment holiday**





Zhang, J., et al., Nature Communications, 2017. **8**(1).
Siravegna, G., et al., Nat Med, 2015. **21**(7): p. 795-801.

Aims

- To develop a model incorporating evolving treatment resistance to characterize treatment response.

- To evaluate the proposed adaptive and intermittent therapy using simulations

Data

- Longitudinal tumor sizes and mutant *KRAS* levels in ctDNA

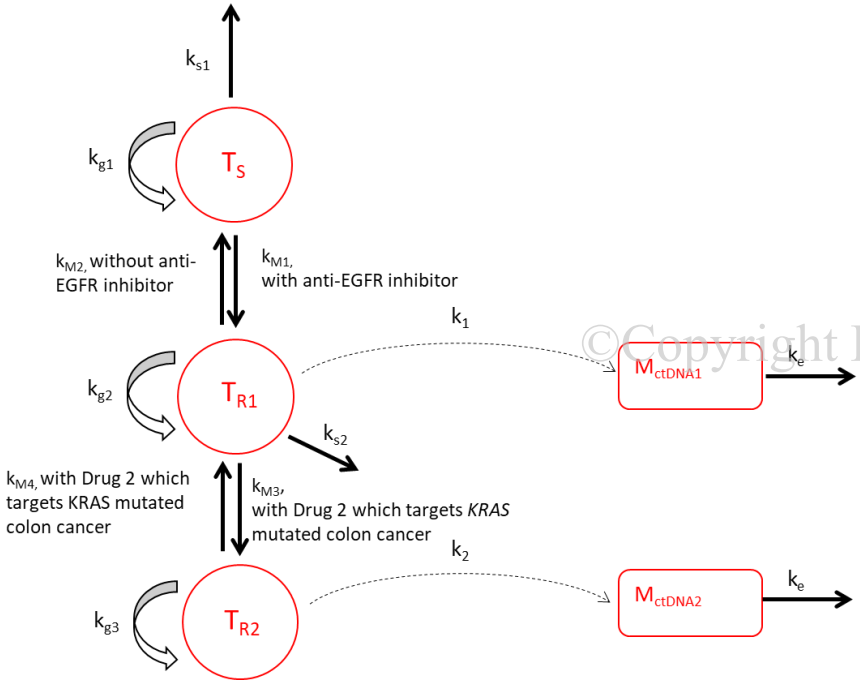
- 28 metastatic colorectal cancer (mCRC) patients
  - 25 WT(wild-type)-KRAS patients
    - 9 developed detectable KRAS mutation during treatment
  - 3 M(mutant)-KRAS patients

- Treated with the anti-EGFR antibody panitumumab

Diaz, L.A., Jr., et al., Nature, 2012. **486**(7404): p. 537-40.

Model development

- **Model structure**

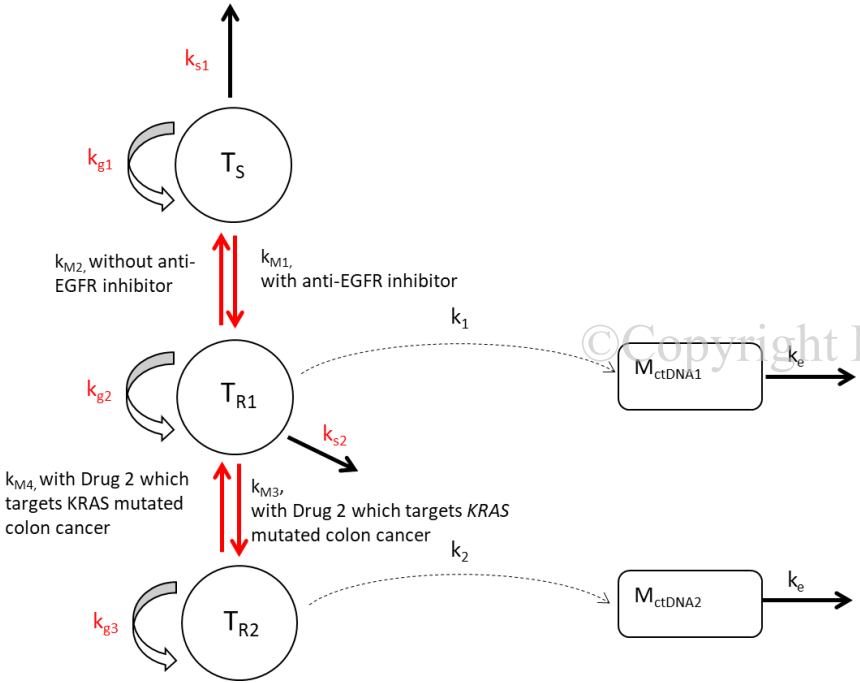


- T_S: sensitive to anti-EGFR treatment (D_1)
- T_{R1}: harbors KRAS mutation (M_{ctDNA1})
  resistant to D_1
  sensitive to a hypothetical treatment D_2
- T_{R2}: harbors a hypothetical mutation (M_{ctDNA2})
  resistant to both D_1 and D_2

$$TS = T_S + T_{R1} + T_{R2}$$

Model development

- **Model structure**

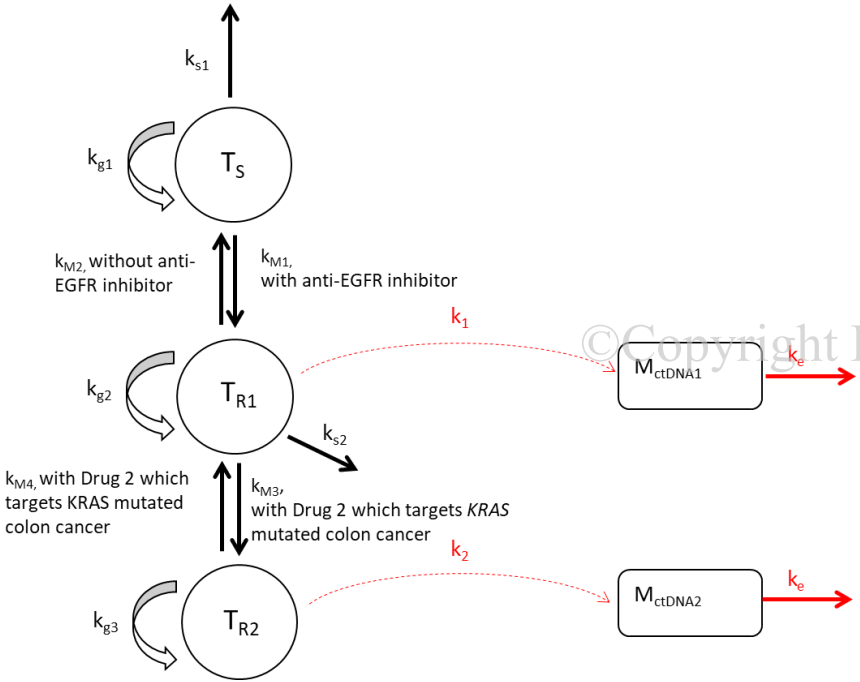


- k_g, net growth rate constant, exponential growth
- k_s, tumor shrinkage rate
- k_M, mutation rate constant, acquired mutation
- Upon drug suspension, a back transfer process was incorporated
- IIV on k_g and baselines

Parseghian, C.M., et al., Ann Oncol, 2019. **30**(2): p. 243-249. Siravegna, G., et al., Nat Med, 2015. **21**(7): p. 795-801.

Model development

- **Model structure**



- ctDNA with the target mutations: from T_R
- The shedding rate: $k_1 \sim T_{R1}, k_2 \sim T_{R2}$,

$$k_1 = k_{\max\_1} \cdot {T_{R1}}^H / ({T_{R1}}^H + K{T_{50}}^H)$$

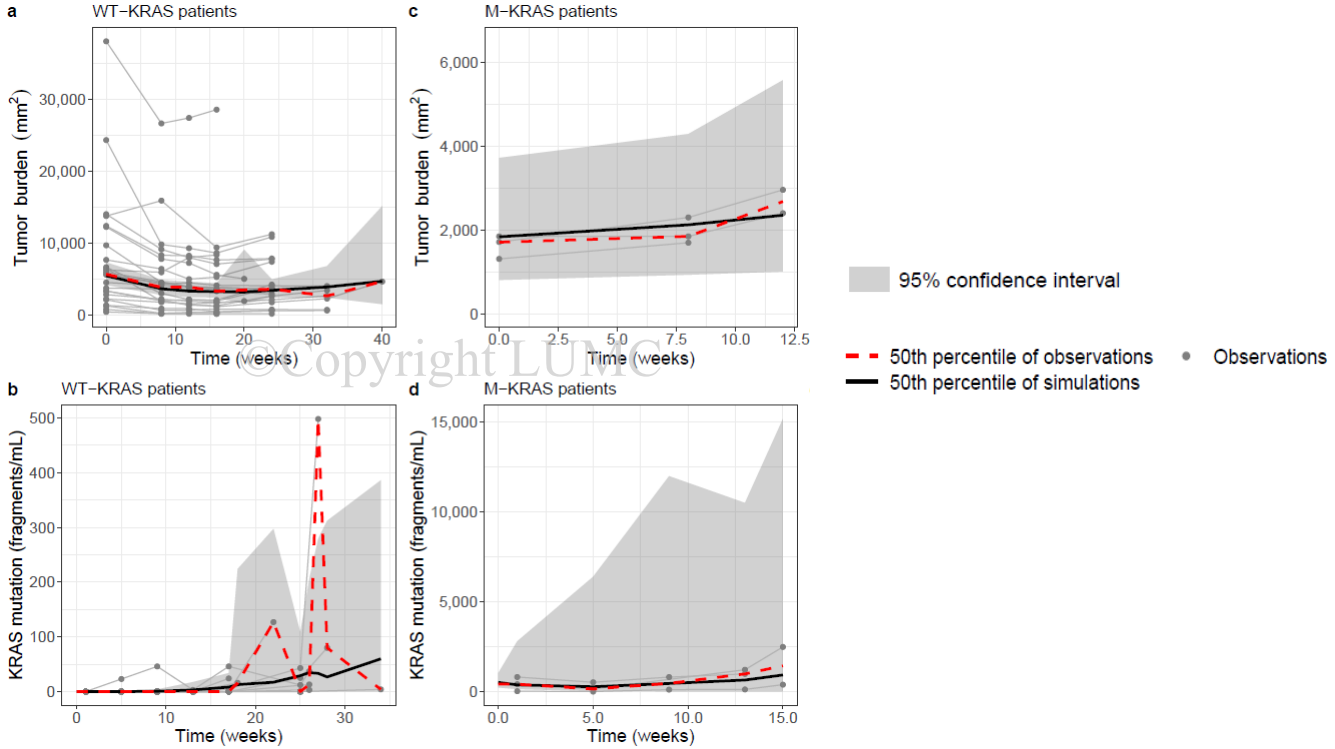
$$\frac{dM_{ctDNA1}}{dt} = k_1 \cdot T_{R1} - k_e \cdot M_{ctDNA1}$$

- k_e, the elimination rate constant of ctDNA

Parseghian, C.M., et al., Ann Oncol, 2019. **30**(2): p. 243-249. Siravegna, G., et al., Nat Med, 2015. **21**(7): p. 795-801.

Model evaluation

- **Model evaluation**



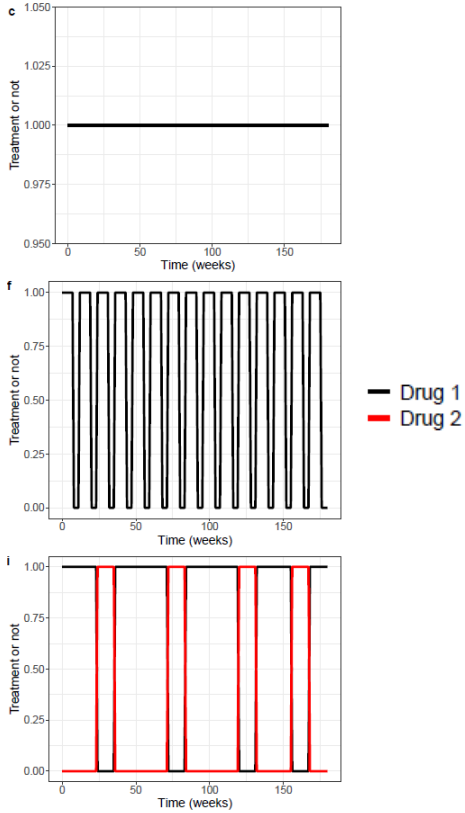
Treatment regimen evaluation

- **100 virtual WT-KRAS patients**

- **Evaluated regimens**
- Continuous schedule

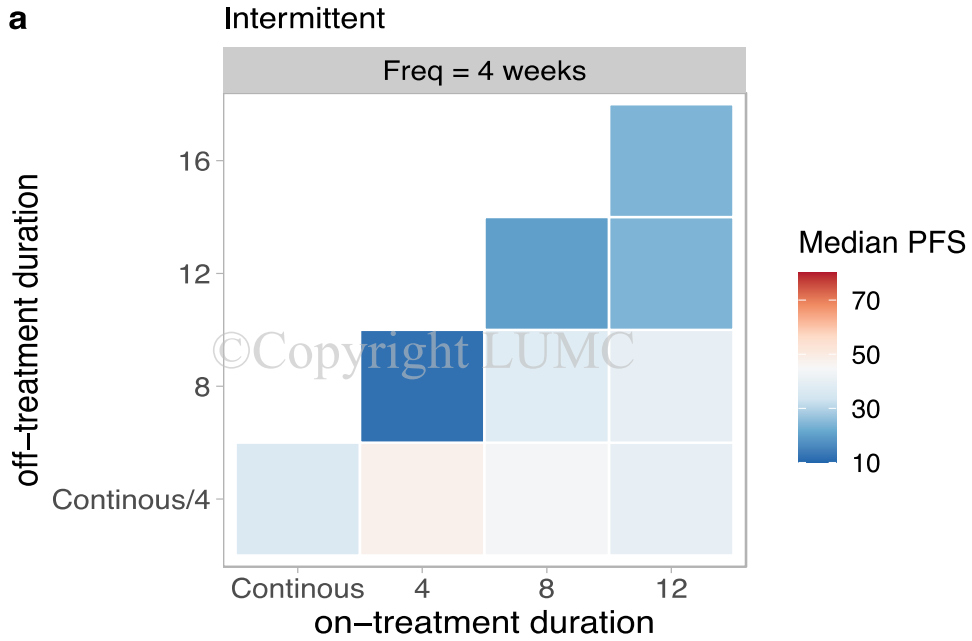
- Intermittent schedule
  - Different on- and off-dosing durations

- Adaptive schedule
  - D_1 and D_2 was guided by individual ctDNA measurements
  - Different ctDNA limits for drug adjustment and monitoring frequency



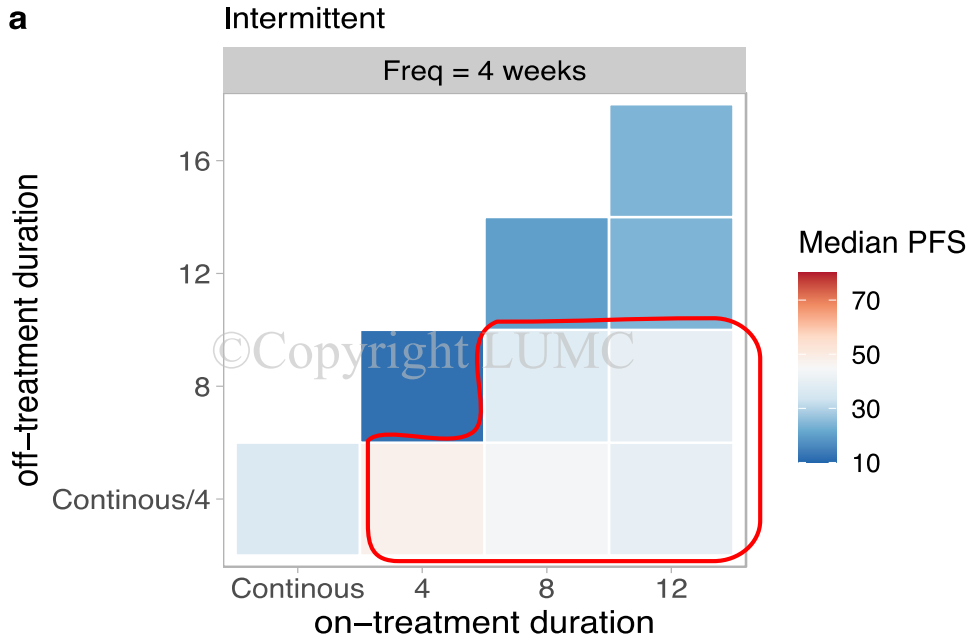
Treatment regimen evaluation - Intermittent

- **Median PFS**



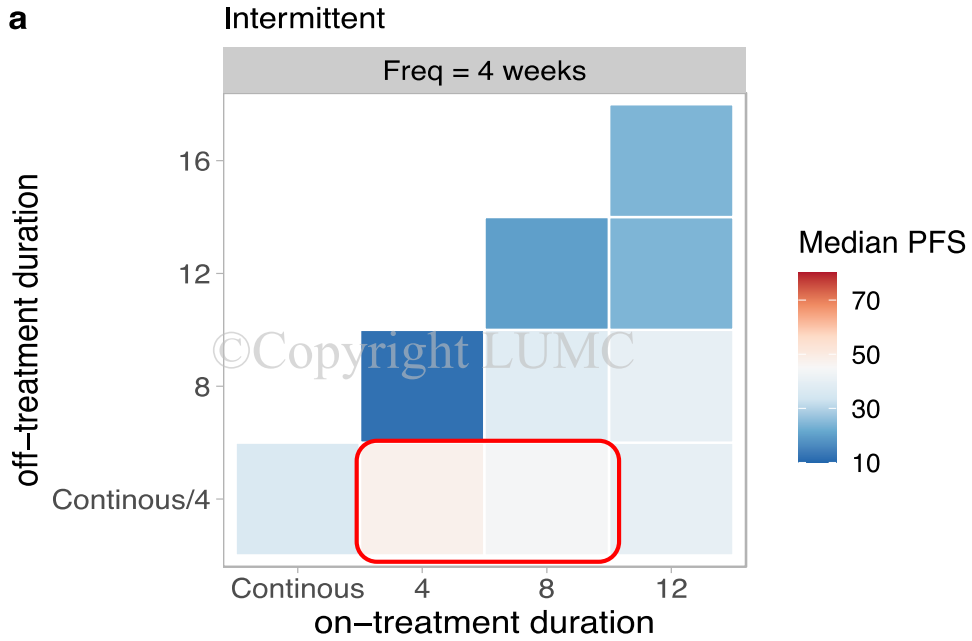
Treatment regimen evaluation - Intermittent

- **Median PFS**



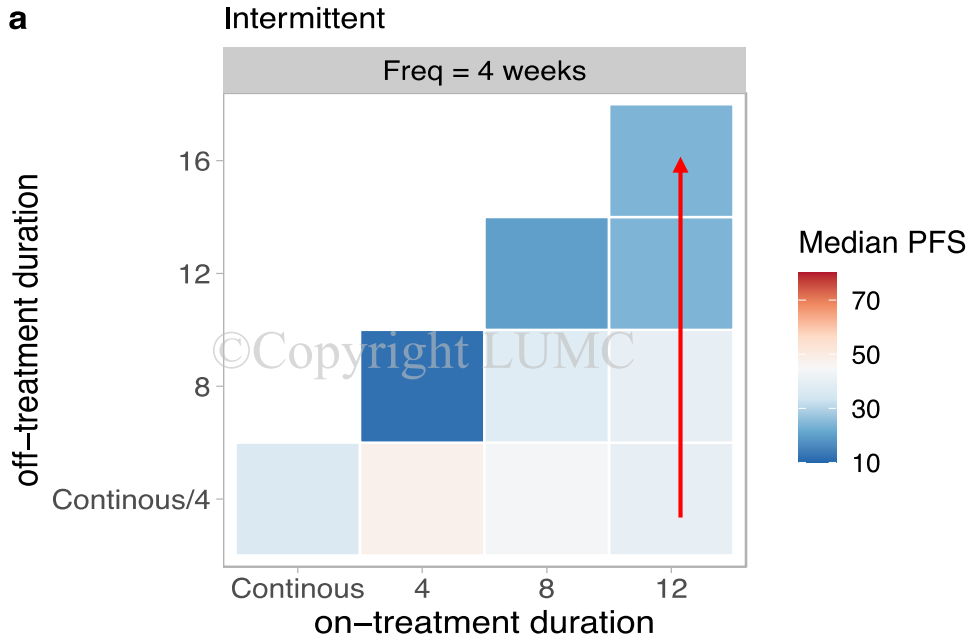
Treatment regimen evaluation - Intermittent

- **Median PFS**



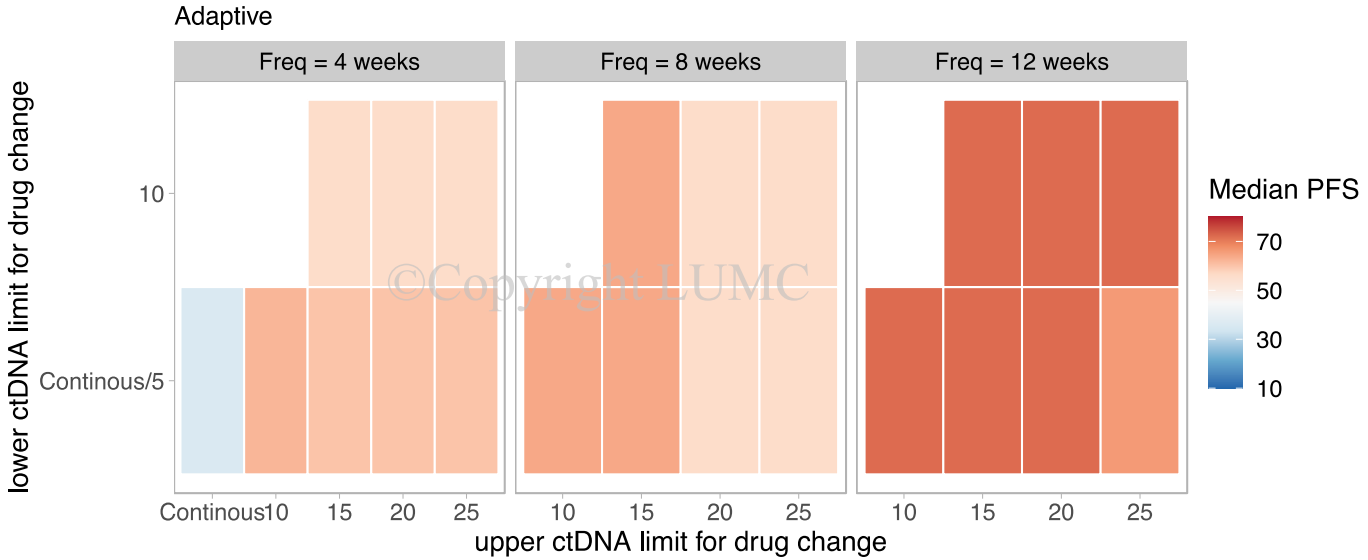
Treatment regimen evaluation - Intermittent

- **Median PFS**



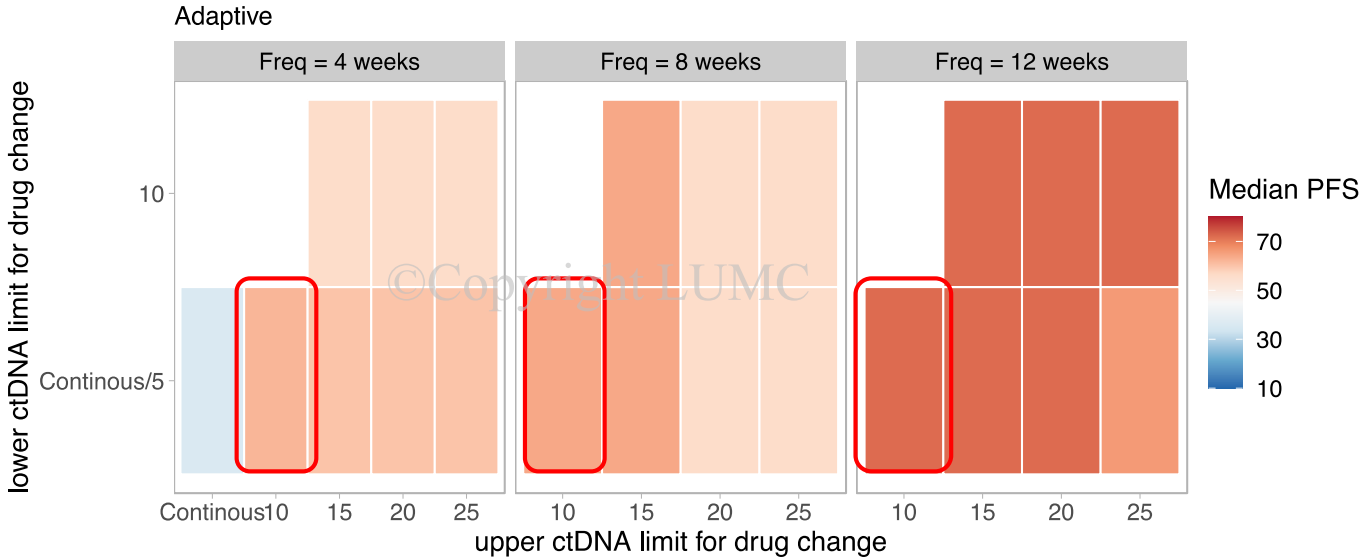
Treatment regimen evaluation - Adaptive

- **Median PFS**



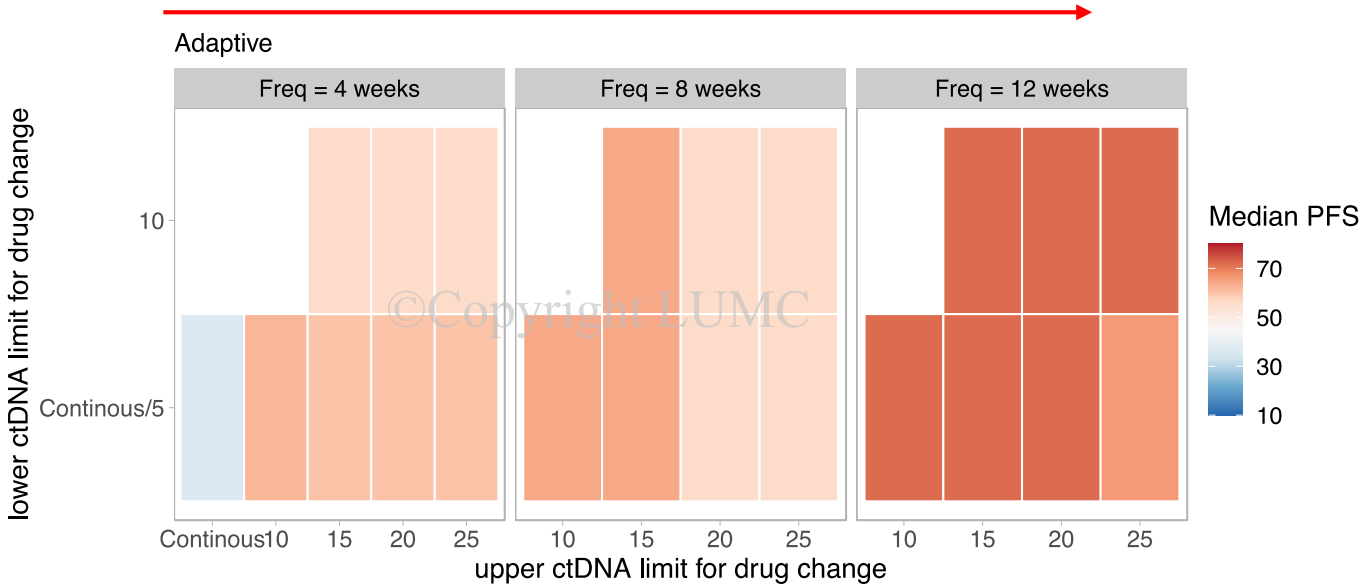
Treatment regimen evaluation - Adaptive

- **Median PFS**



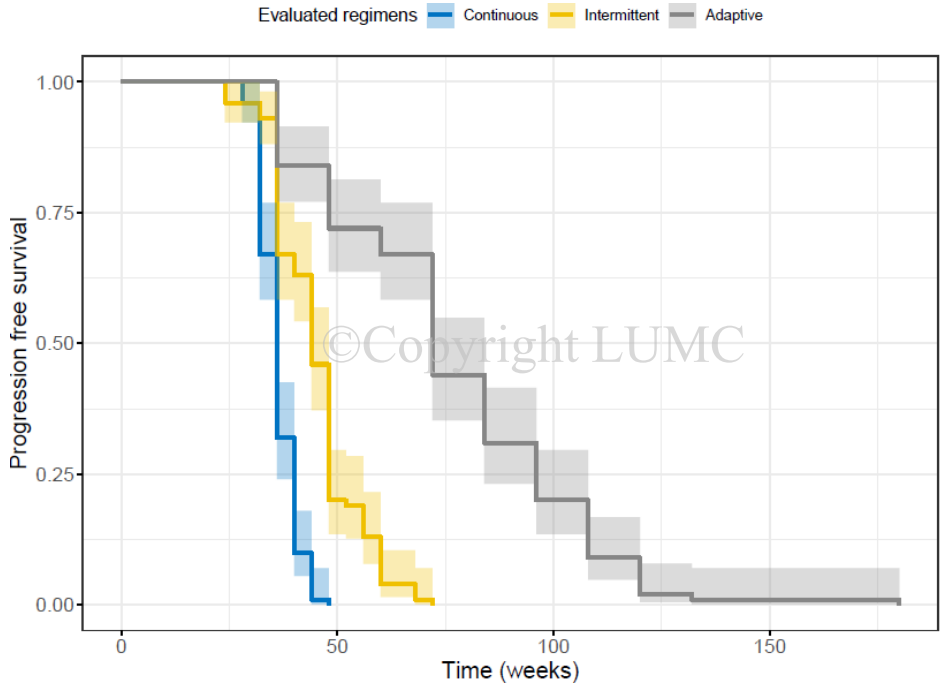
Treatment regimen evaluation - Adaptive

- **Median PFS**



Treatment regimen evaluation

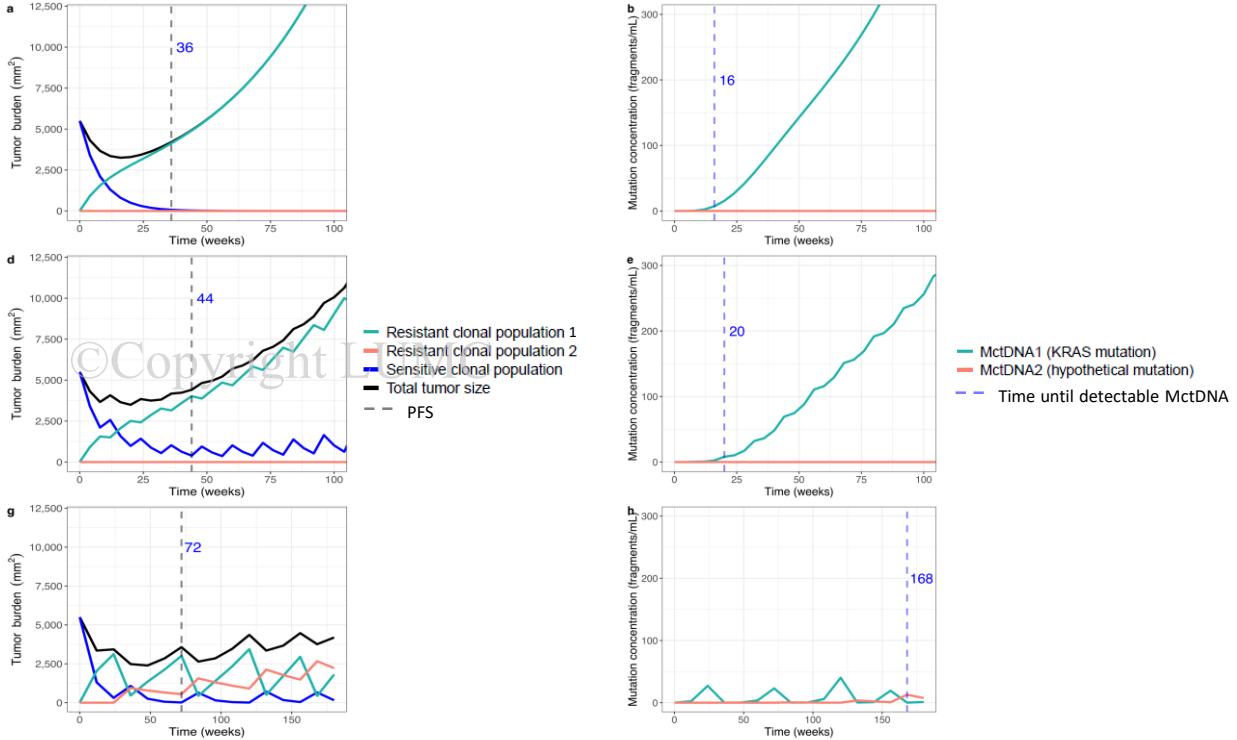
- **Survival plot**



- Continuous schedule
- $S_{intermittent(8on\_4off)}$
- $S_{adaptive(5\_10\_Freq12)}$

Treatment regimen evaluation

- **Time-curves of each clonal population and ctDNA measurement**
  - Continuous schedule
  - $S_{intermittent(8on\_4off)}$
  - $S_{adaptive(5\_10\_Freq12)}$

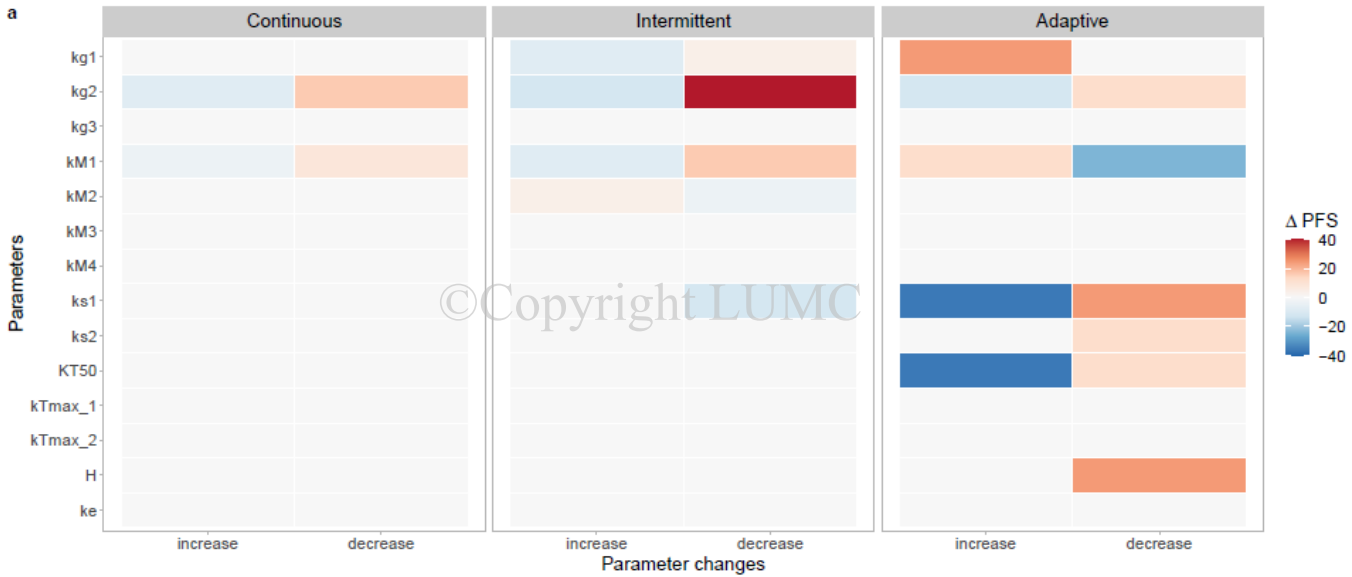


Sensitivity analysis

- The parameter values were altered by increasing or decreasing by 50%
- Continuous schedule, $S_{intermitent(8on\_4off)}$, $S_{adaptive(5\_10\_Freq12)}$

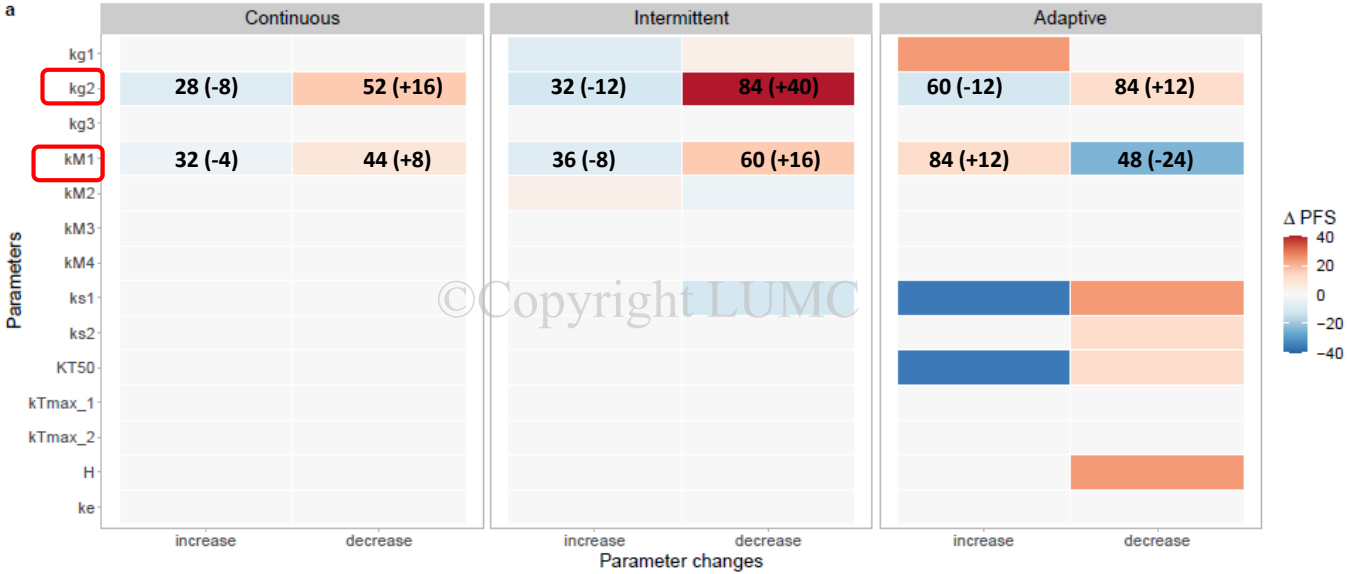
Sensitivity analysis

- **Relative change (Δ) of predicted PFS (tumor dynamics)**



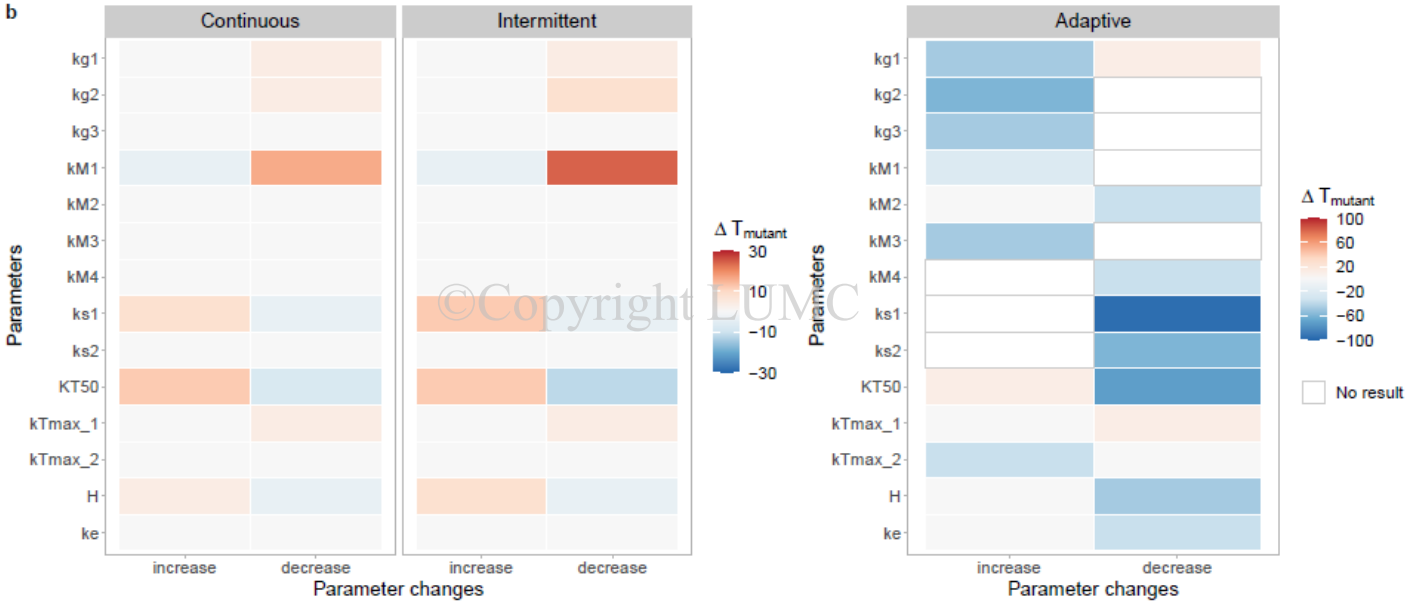
Sensitivity analysis

- **Relative change (Δ) of predicted PFS (tumor dynamics)**



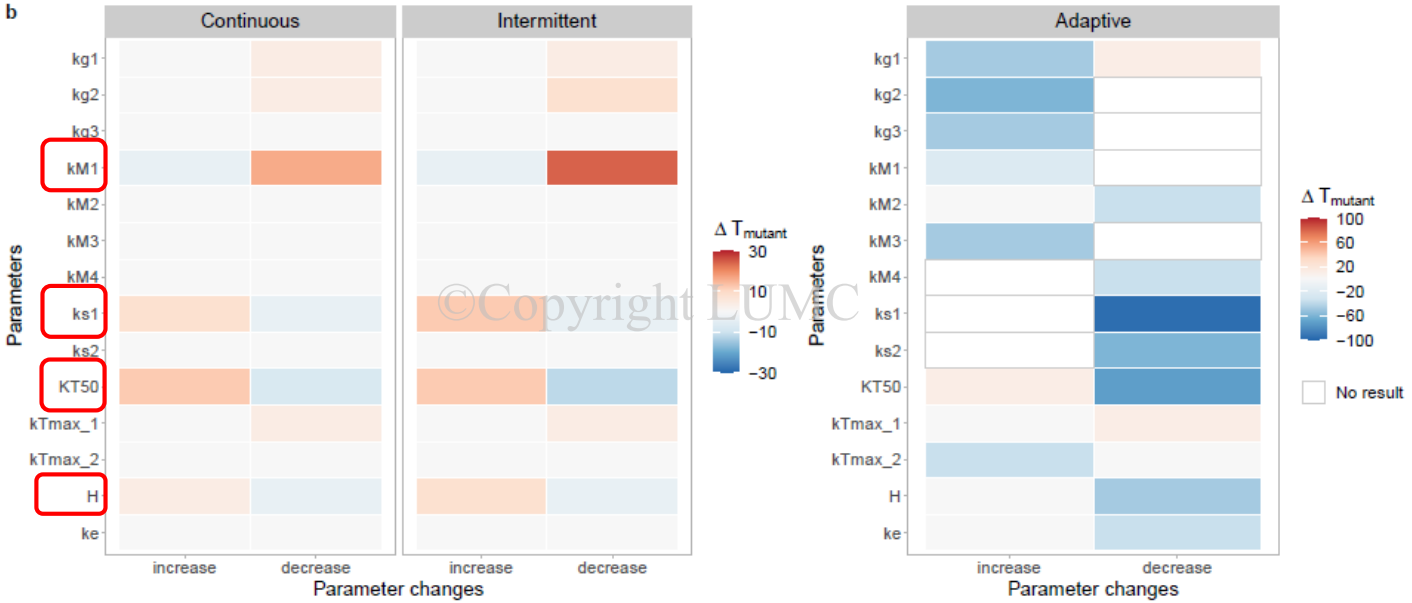
Sensitivity analysis

- **Relative change (Δ) of predicted time until detectable mutation (ctDNA dynamics)**



Sensitivity analysis

- **Relative change (Δ) of predicted time until detectable mutation (ctDNA dynamics)**



Challenges and limitations

- Identification of the mutations that are associated with the resistance (or sensitivity)
- Intermittent therapy is not suitable for M-KRAS patients
- Adaptive therapy may not be feasible for all WT-KRAS patients
- Data for parameter estimation in modelling studies

Take home message

- Tumor dynamics model incorporating evolving cancer resistance may support the optimization of anti-cancer treatment schedules

- Intermittent and adaptive schedules, with certain designs: better suppress the evolving resistance, suggest potential improved clinical outcome, need to be validated

Acknowledgement

Department of Clinical Pharmacy and Toxicology,
Leiden University Medical Center
Prof. Henk-Jan Guchelaar
Dr. Dirk Jan A.R. Moes

Department of Pharmacy, Uppsala University
Prof. Lena E. Friberg

Division of Systems Biomedicine and Pharmacology,
LACDR, Leiden University
Associate Prof. Coen van Hasselt

Leiden University
Medical Center

Thank you for your attention!