Optimization of chemotherapy delivery protocols, to treat low-grade glioma patients

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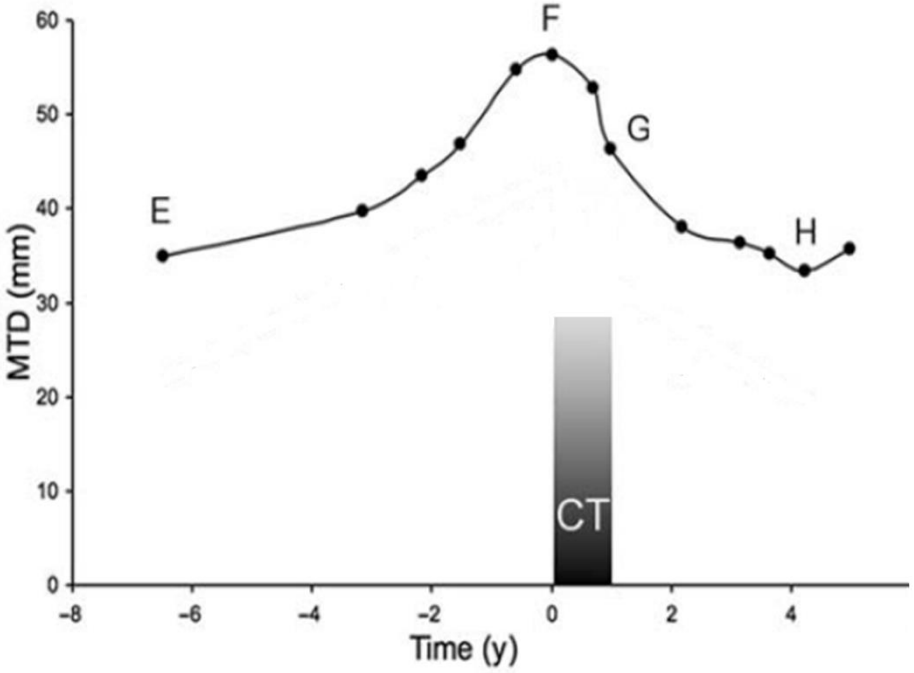
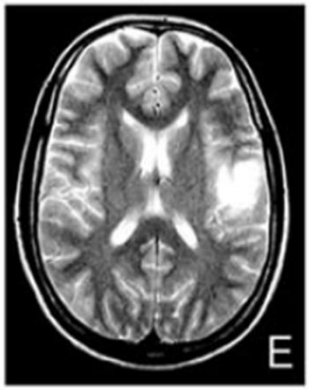
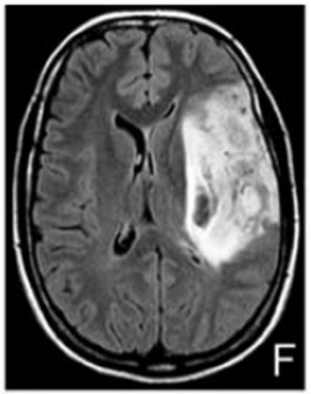
Context

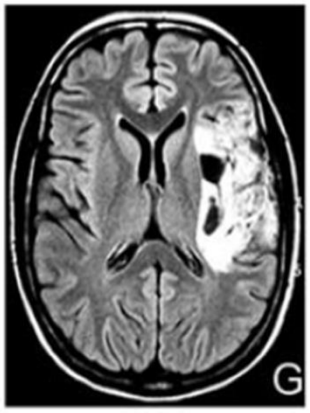
- Low-grade glioma: brain tumor with slow and continuous growth
- Different treatments

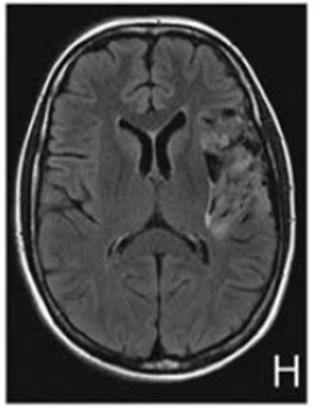
Prolonged response with PCV[1]





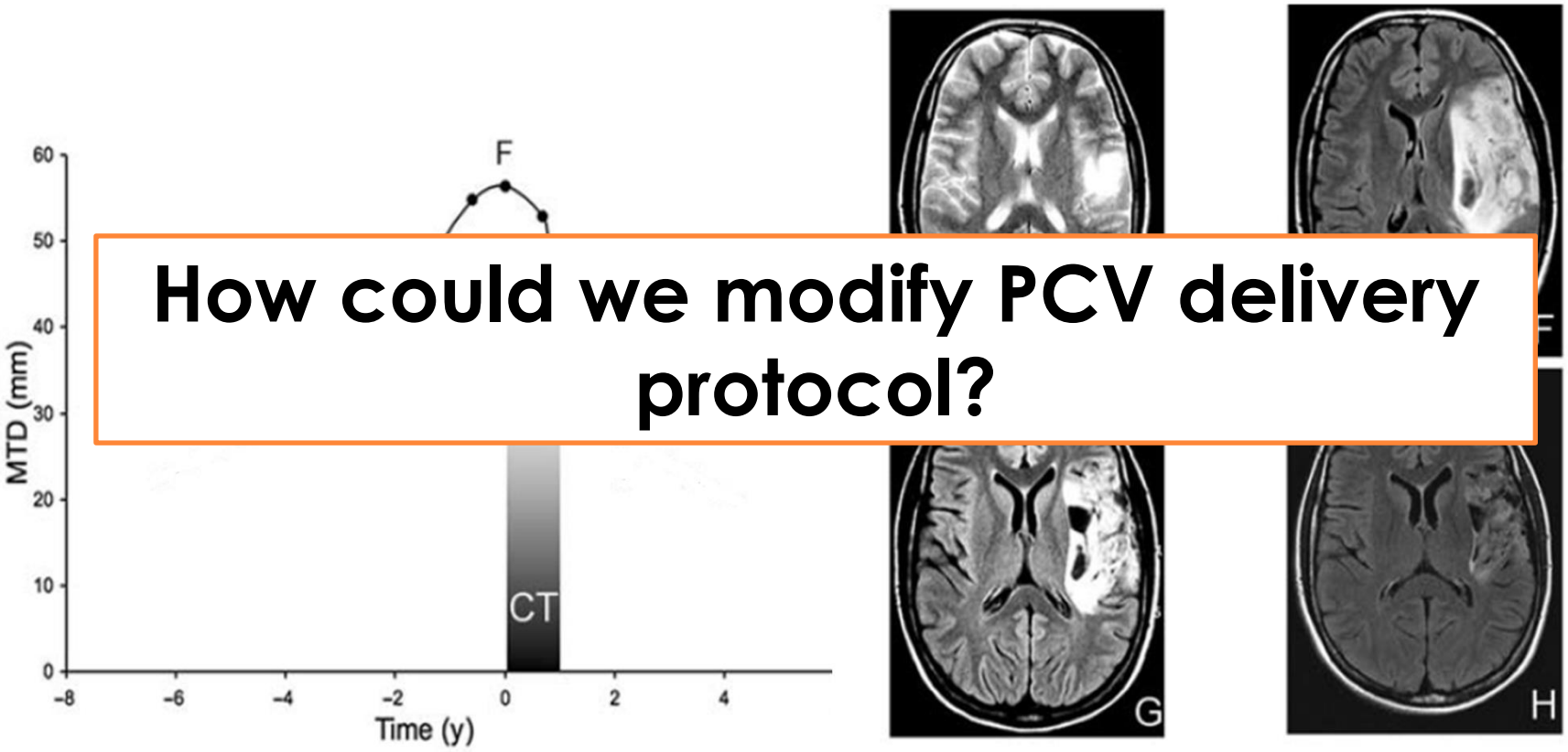






[1] Peyre, M. et al., 2010. Prolonged response without prolonged chemotherapy: a lesson from PCV chemotherpy in low-grade gliomas. *Neuro-Oncology*, 82, pp.281-288

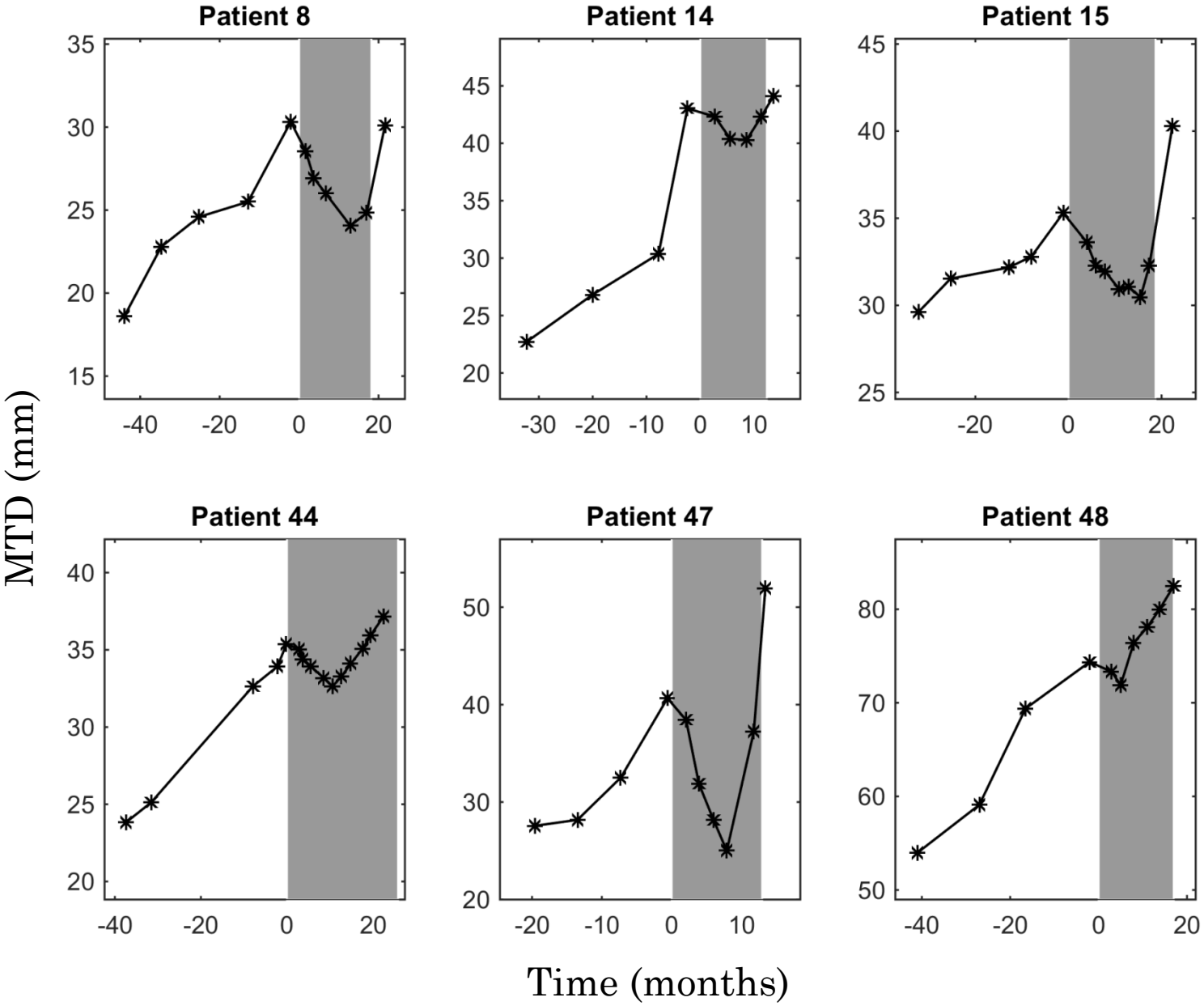
Prolonged response with PCV[1]



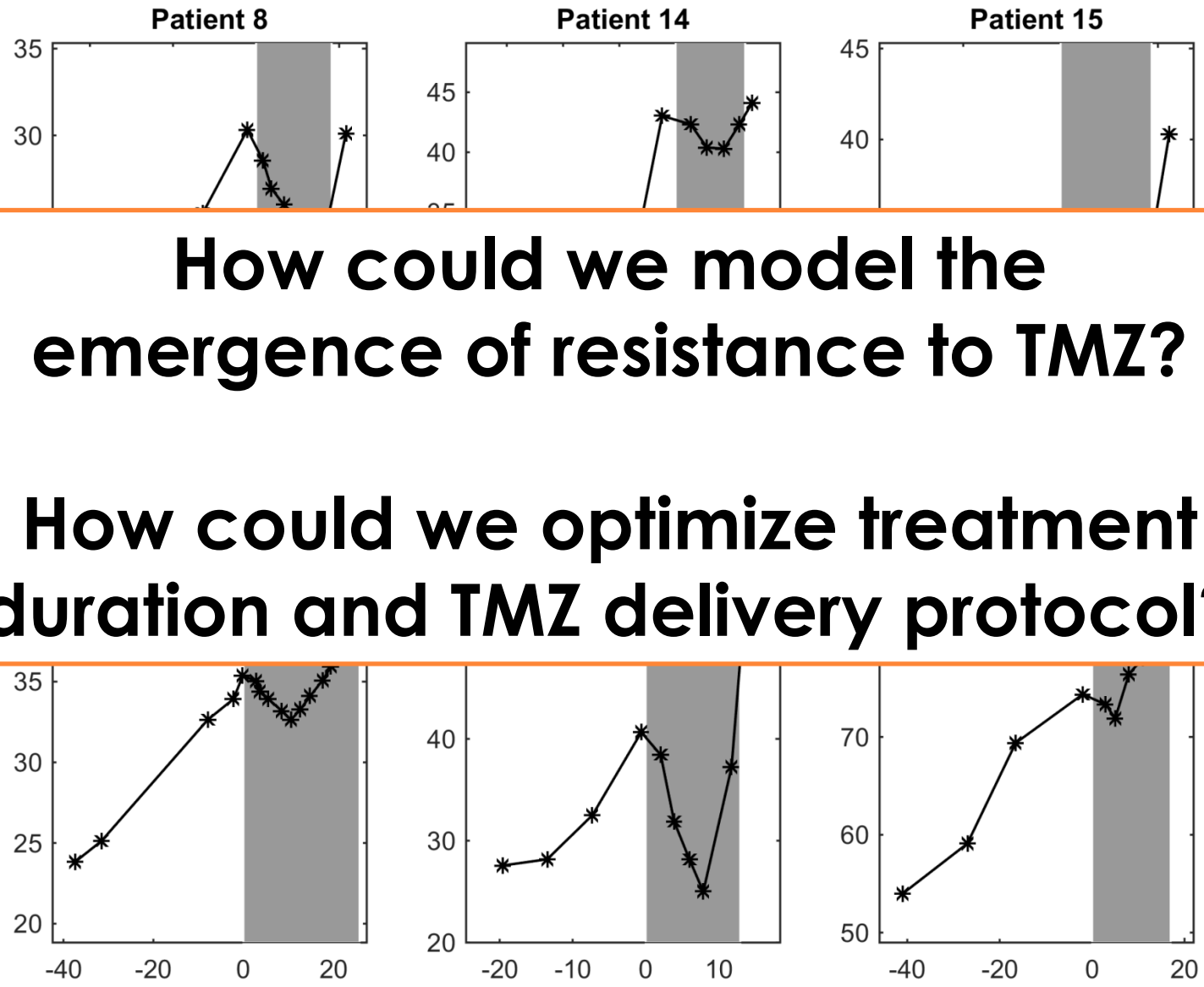
How could we modify PCV delivery protocol?

[1] Peyre, M. et al., 2010. Prolonged response without prolonged chemotherapy: a lesson from PCV chemotherpy in low-grade gliomas. *Neuro-Oncology*, 82, pp.281-288

Resistance to TMZ



Resistance to TMZ



How could we model the emergence of resistance to TMZ?

How could we optimize treatment duration and TMZ delivery protocol?

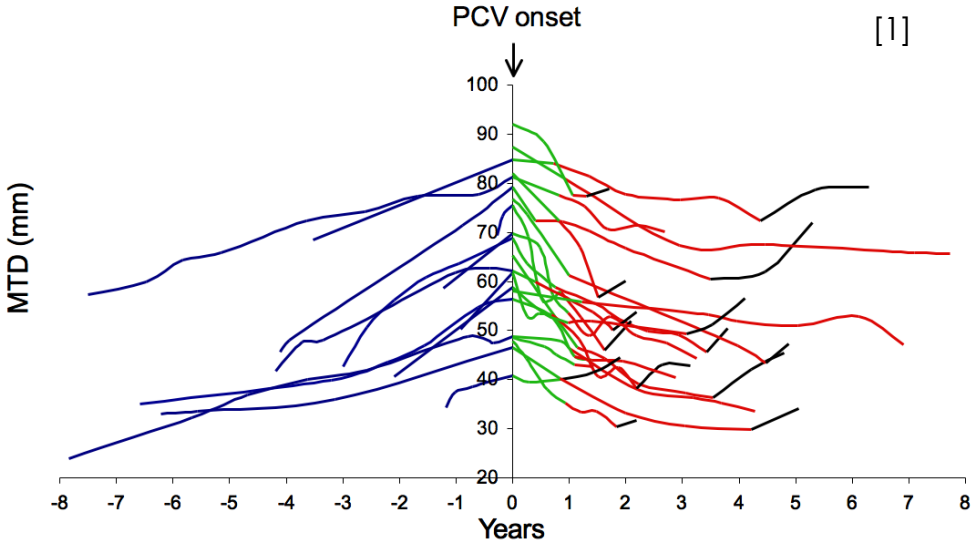
Objectives

To use mathematical modeling to

- Propose modifications of therapeutic protocols on a population level
- Optimize the treatment delivery on an individual level

LGG DYNAMICS MODELING

[1]



[2]

$$\frac{dC}{dt} = -KDE \times C$$

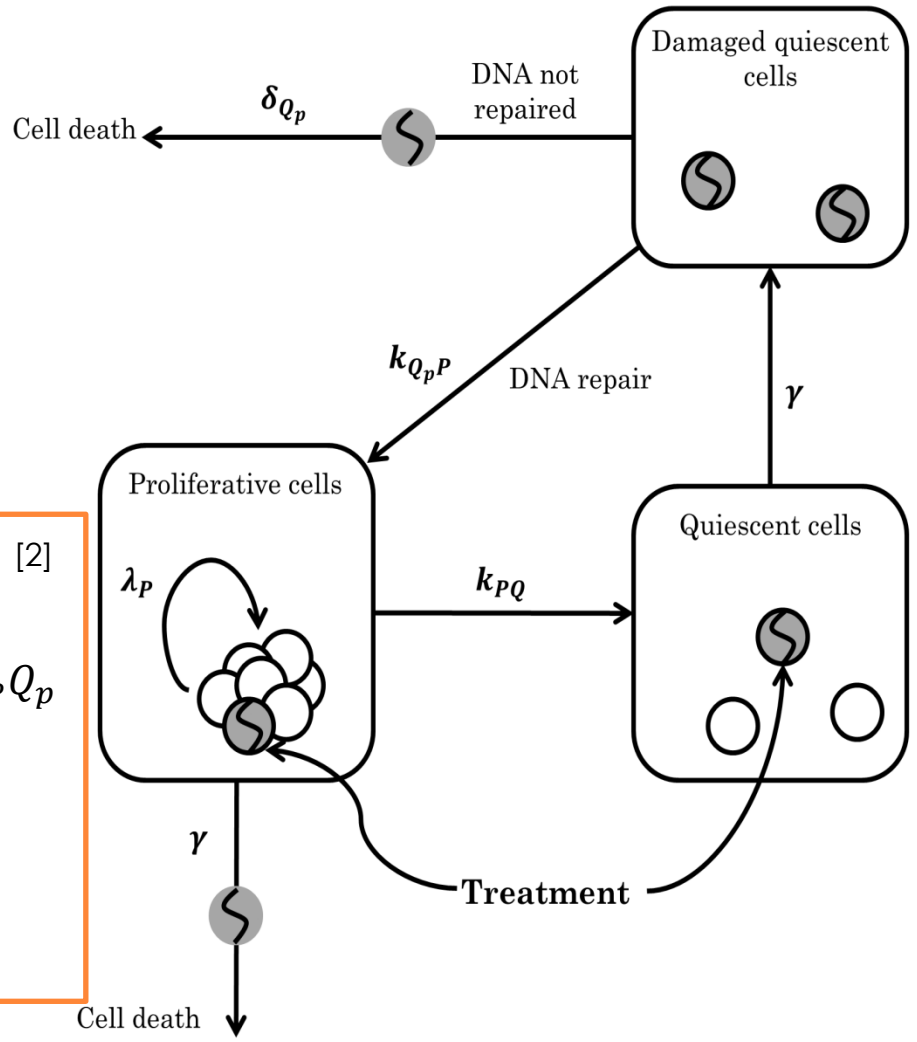
$$\frac{dP}{dt} = \lambda_P P\left(1 - \frac{P^*}{K}\right) - k_{PQ}P - \gamma C \times KDE \times P + k_{Q_pP}Q_p$$

$$\frac{dQ}{dt} = k_{PQ}P - \gamma C \times KDE \times Q$$

$$\frac{dQ_p}{dt} = \gamma C \times KDE \times Q - k_{Q_pP}Q_p - \delta_{Q_pQ_p}$$

$$P^* = P + Q + Q_p$$

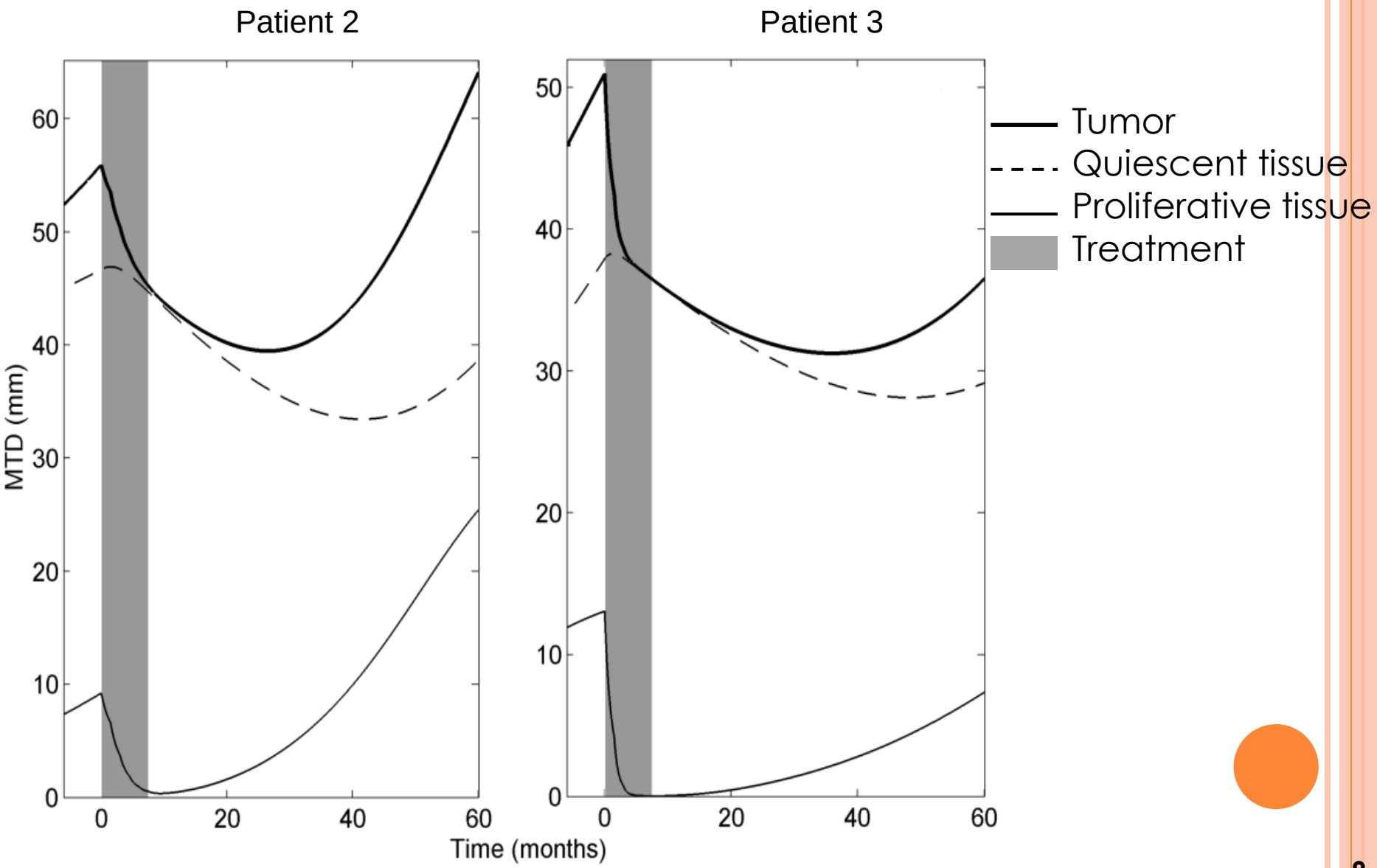
[2]



[2] Ribba, B., et al., 2012. A tumor growth inhibition model for low-grade glioma treated with chemotherapy or radiotherapy. *Clinical Cancer Research,* 18(18), pp.5071-80.

Modification of PCV delivery protocol

Individual fits



Modification of PCV administration for a population[3]

- Modification of therapeutic protocol:

$$\frac{dC}{dt} = -KDE \times C$$

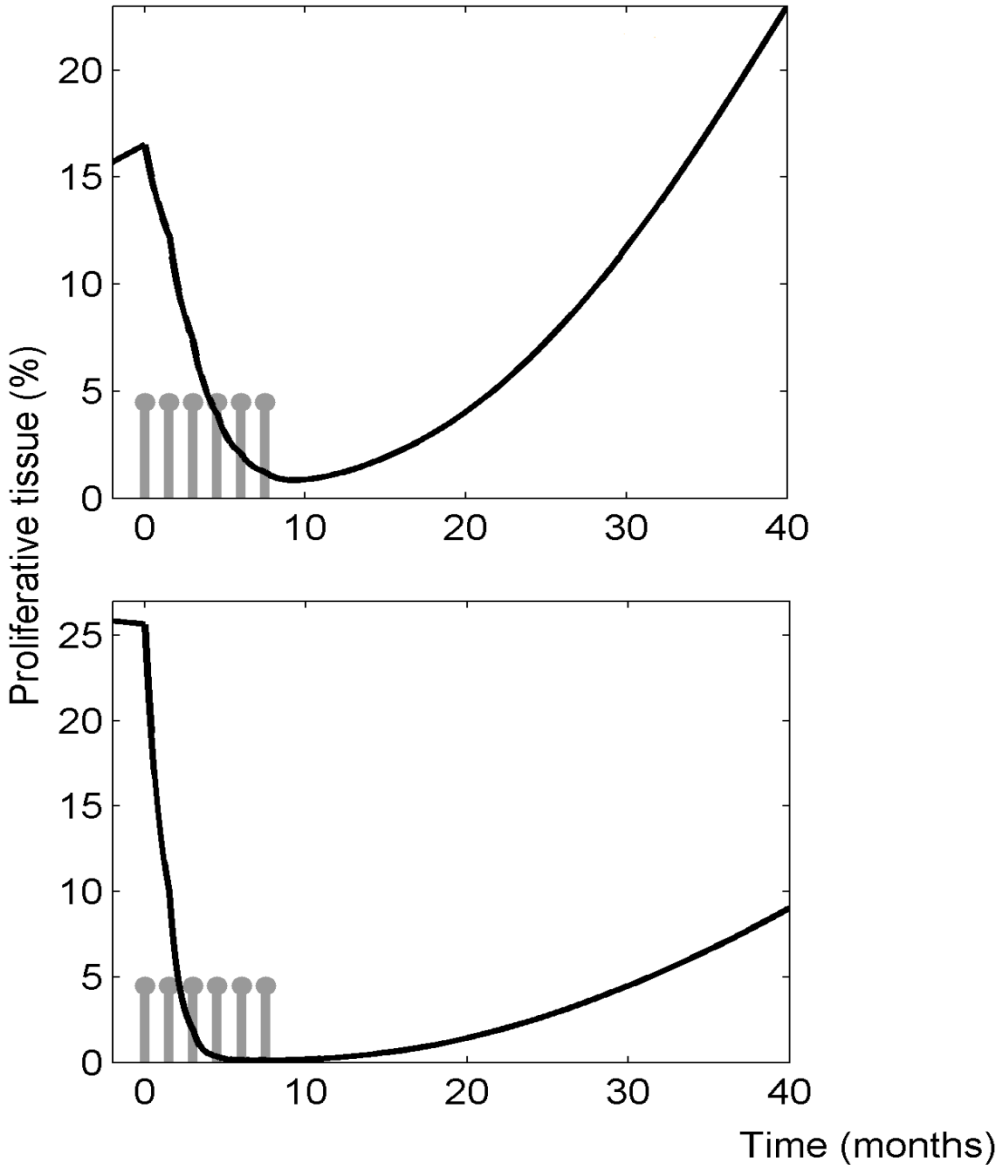
- Constraints for the modifications:
  - 6 PCV cycles
  - Same time interval between cycles

- Aims:
  - To prolong tumor response duration
  - To avoid tumor progression between PCV cycles

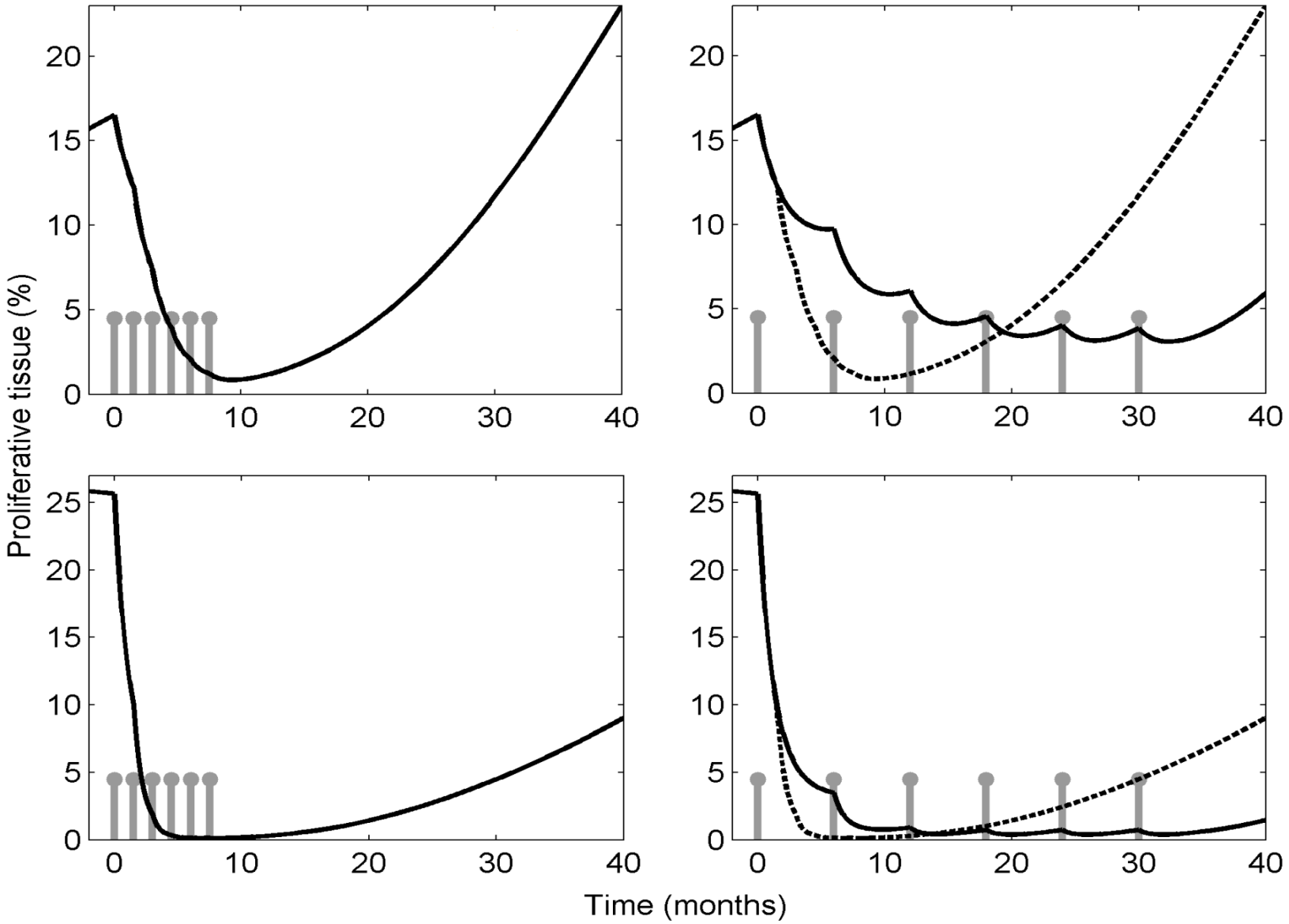
- Simulation of 1000 virtual LGG patients

[3] Mazzocco, P. et al., 2015. Increasing the time interval between PCV chemotherapy cycles as a strategy to improve duration of response in low-grade gliomas : results from a model-based clinical trial simulation, submitted to *Computational and Mathematical Methods in Medicine*.

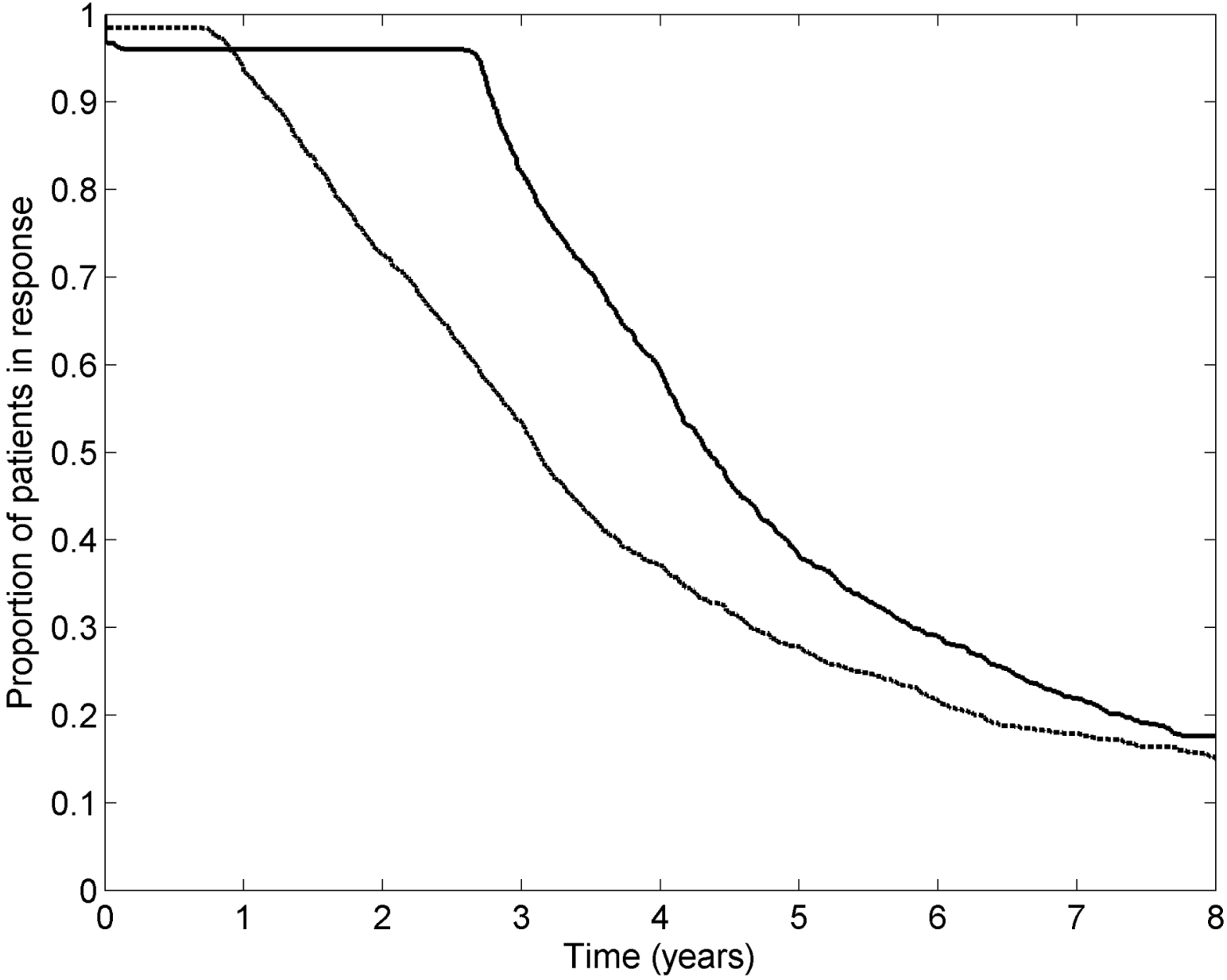
Individual fits with standard protocol



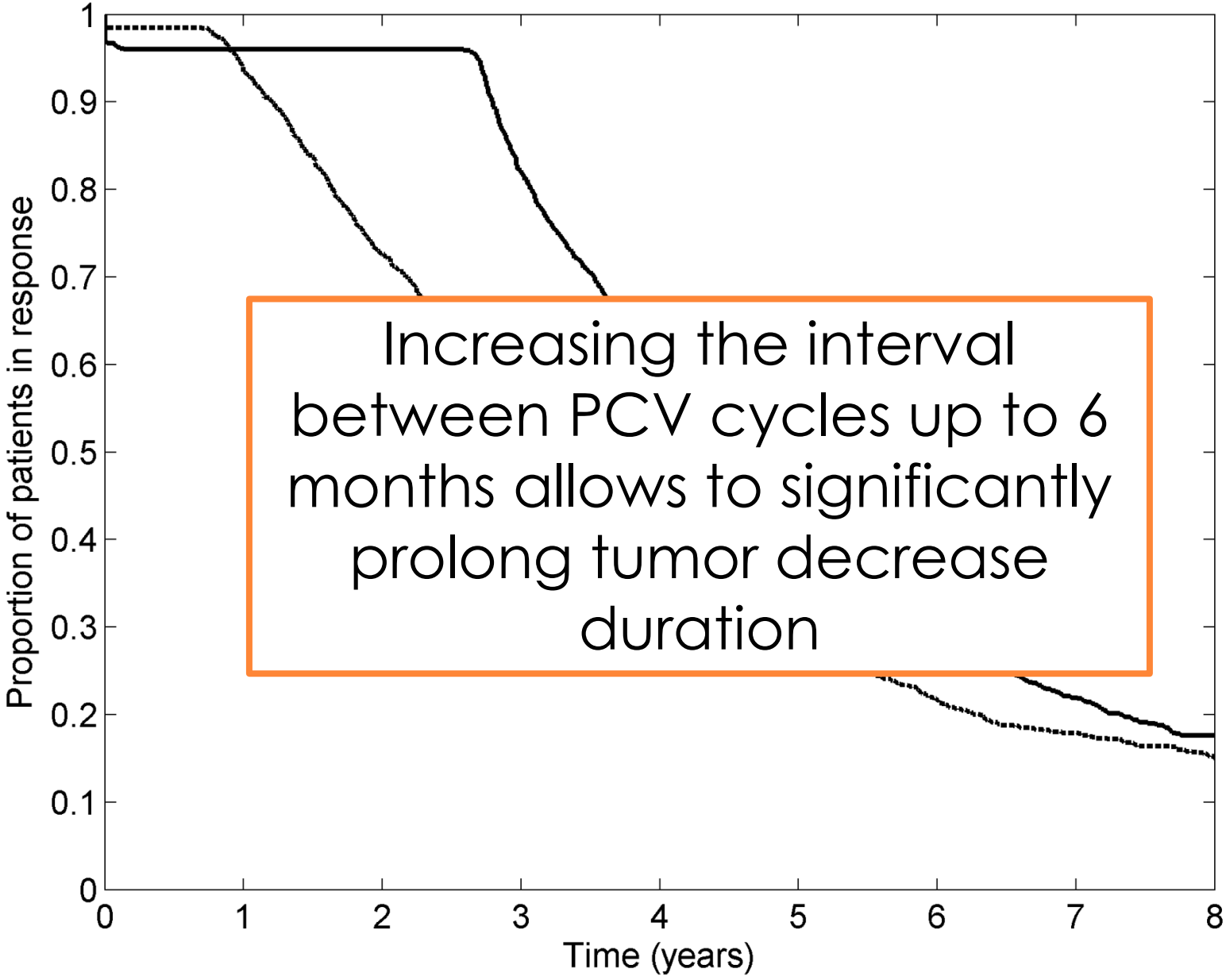
Individual fits with standard protocol Simulations with modified protocol



Population optimization



Population optimization



Increasing the interval between PCV cycles up to 6 months allows to significantly prolong tumor decrease duration

Modeling tumor resistance to TMZ, and optimization of treatment delivery

Resistance modeling

- Resistance to chemotherapy: one of the main reasons of treatment failure
- Due to random mutations and/or caused by the treatment itself[4]
- Usually described with $\gamma \times \exp(-res.t)$[5]
- Existence of models distinguishing between sensitive and resistant tumor cells[6]

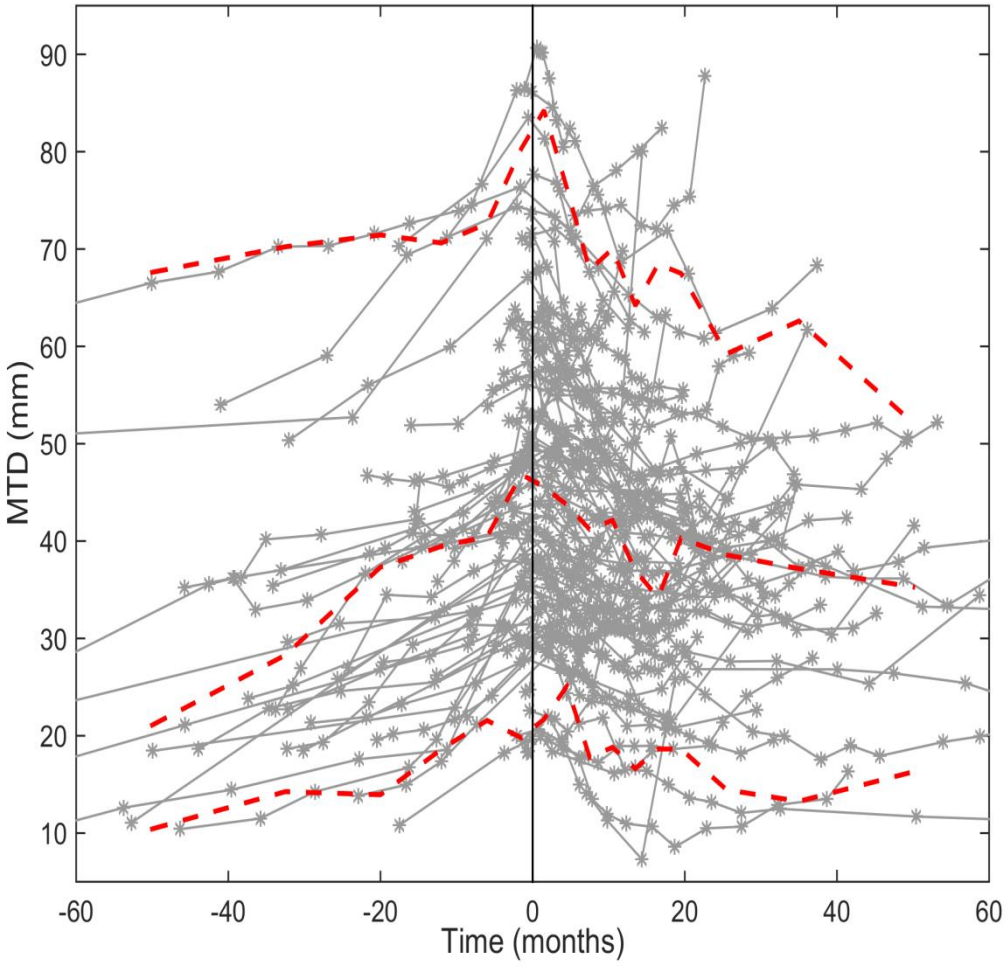
[4] Tomasetti, C. & Levy, D., 2010. An elementary approach to modeling drug resistance in cancer. *Mathematical biosciences and engineering : MBE*, 7(4), pp.905–918.
[5] Claret, L. et al., 2009. Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. *Journal of Clinical Oncology*, 27(25), pp.4103–8.
[6] Terranova, N., et al., 2015. Resistance Development: A Major Piece in the Jigsaw Puzzle of Tumor Size Modeling. *CPT:PSP,* 4, pp. 320-323

Resistance modeling

- Use of stochastic discrete models to describe the emergence of resistance[7]
- Issues with simulations and parameter estimations
- Possibility to use stochastic differential equations (SDE) (continuous time), but issues with parameter estimations
- ODE model: limit of SDE model with large initial population

[7] Coldman, A.J. & Goldie, J.H., 1986. A stochastic model for the origin and treatment of tumors containing drug-resistant cells. *Bulletin of mathematical biology*, 48(3-4), pp.279–292.

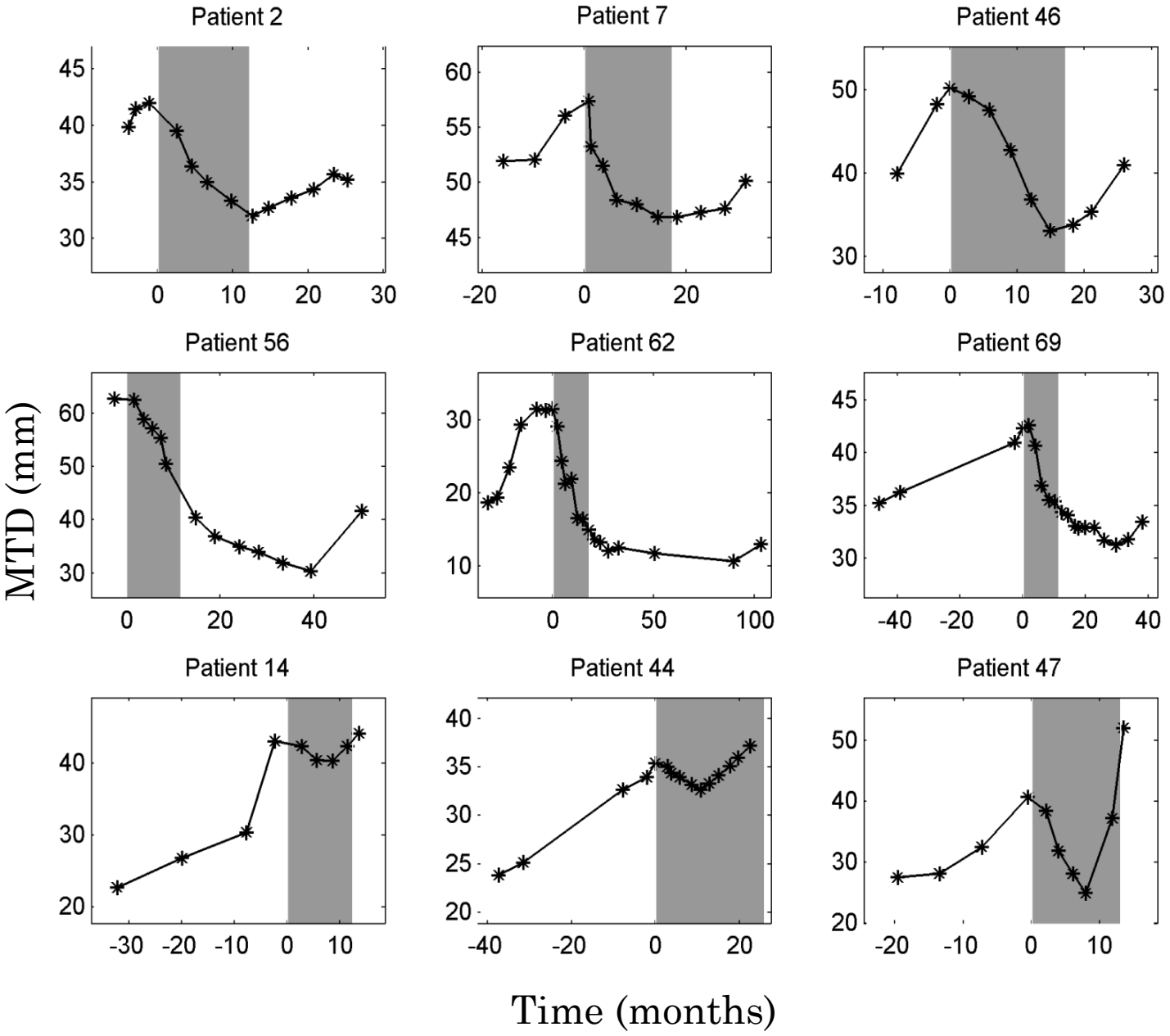
DATA[8]



- 77 patients treated with TMZ
- 952 tumor size observations in total
- Administration protocol: 200mg/m^2/d, from day 1 to day 5, every 28 days
- 18 cycles of TMZ in median (minimum 2, maximum 24)
- 34 patients experienced tumor progression during treatment
- 1p/19q co-deletion, p53 mutation and IDH mutation statuses available

[8] Ricard, D. et al., 2007. Dynamic history of low-grade gliomas before and after temozolomide treatment. *Annals of neurology*, 61(5), pp.484–90.

Individual profiles

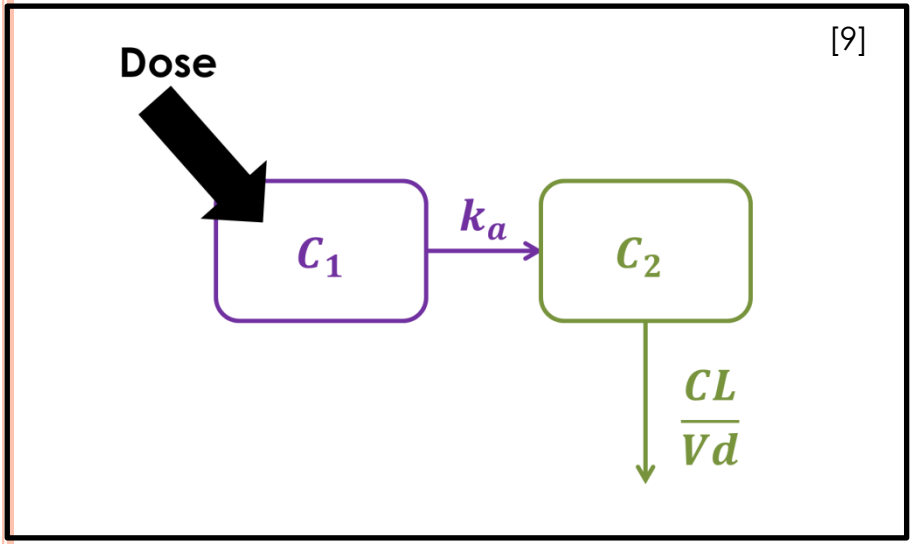


Tumor progression when treatment stops

Prolonged response

Failure of therapy: resistance to treatment

PK-PD Model



$$\frac{dC_1}{dt} = -k_a C_1 + Adm(t)$$

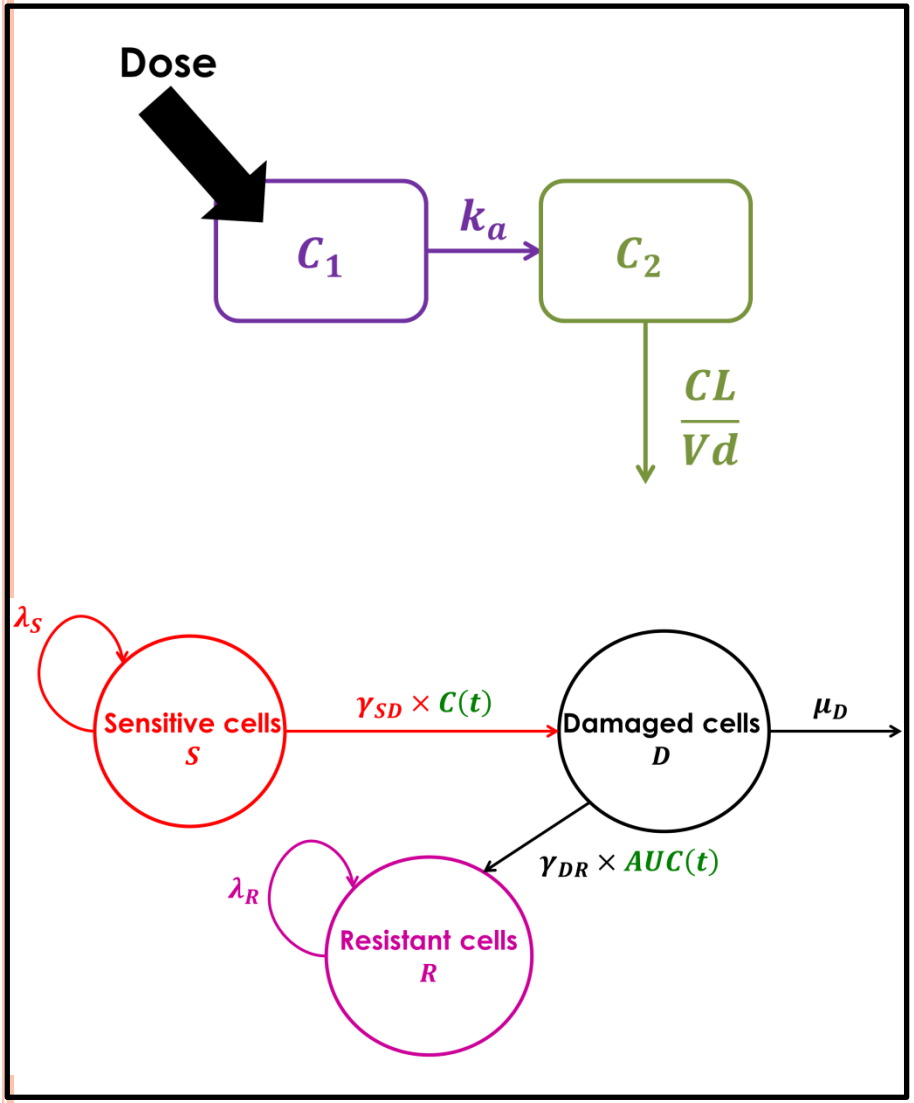
$$\frac{dC_2}{dt} = k_a C_1 - \frac{CL}{Vd} C_2$$

$$C(t) = \frac{C_2(t)}{Vd}$$

$$AUC(t) = \int_{t_0}^{t} C(x)dx$$

[9] Ostermann, S., et al., 2004. Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant glioma patients. *Clinical Cancer Research,* 10(11), pp.3728-3736.

PK-PD Model



$$\frac{dC_1}{dt} = -k_a C_1 + Adm(t)$$

$$\frac{dC_2}{dt} = k_a C_1 - \frac{CL}{Vd} C_2$$

$$C(t) = \frac{C_2(t)}{Vd}$$

$$AUC(t) = \int_{t_0}^{t} C(x)dx$$

$$\frac{dS}{dt} = \lambda_S S\left(1 - \frac{T}{100}\right) - \gamma_{SD} C(t) S$$

$$\frac{dR}{dt} = \lambda_R R\left(1 - \frac{T}{100}\right) + \gamma_{DR} AUC(t) D$$

$$\frac{dD}{dt} = \gamma_{SD} C(t) S - \mu_D D - \gamma_{DR} AUC(t) D$$

$$T = S + R + D$$

$$S_0 = Y_0 \times K, \qquad R_0 = Y_0(1 - K), \qquad D_0 = 0$$

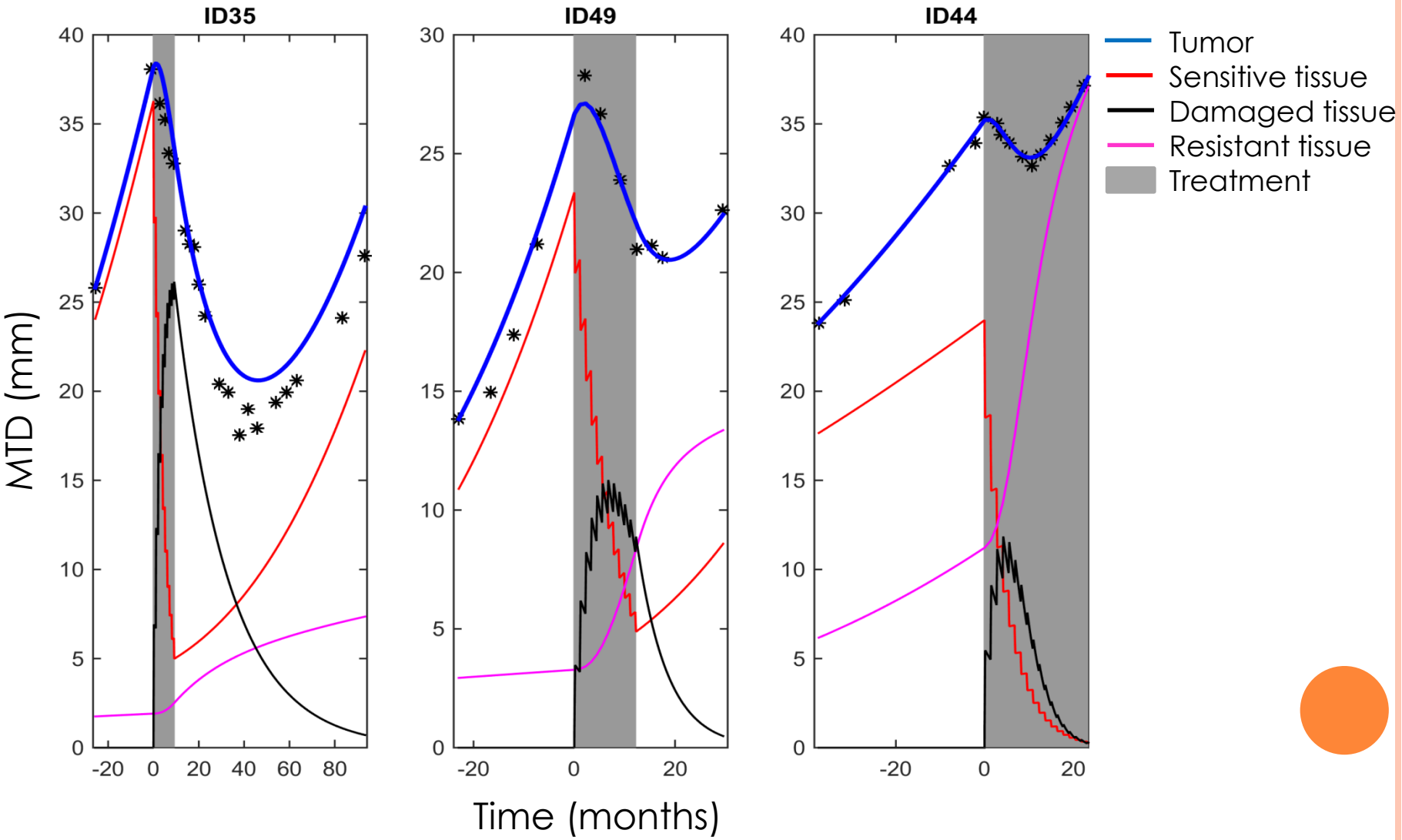
Article in preparation with E. Ollier, F. Ducray and A. Leclercq-Samson

Individual Fits

Low proliferation rate for cells S

Low proliferation rate for cells S but capacity to repair lesions

High proliferation rate for cells S and large capacity to repair lesions



Individual optimization - Method

- Optimization of TMZ administration protocol, on an individual level with CMA-ES algorithm

- Constraints:
  - 5 TMZ administrations per cycle
  - Same time interval between cycles (interval>5 days)
  - Dose≤200mg/m²/d

- Test of 3 different numbers of TMZ cycles per patient

- Aims:
  - To prolong tumor decrease duration (TTG)
  - To minimize tumor size (MTS)

- Optimization criteria: $\frac{TTG_{optim}}{TTG_{standard}} + \frac{MTS_{standard}}{MTS_{optim}}$

Evaluation of optimized protocols

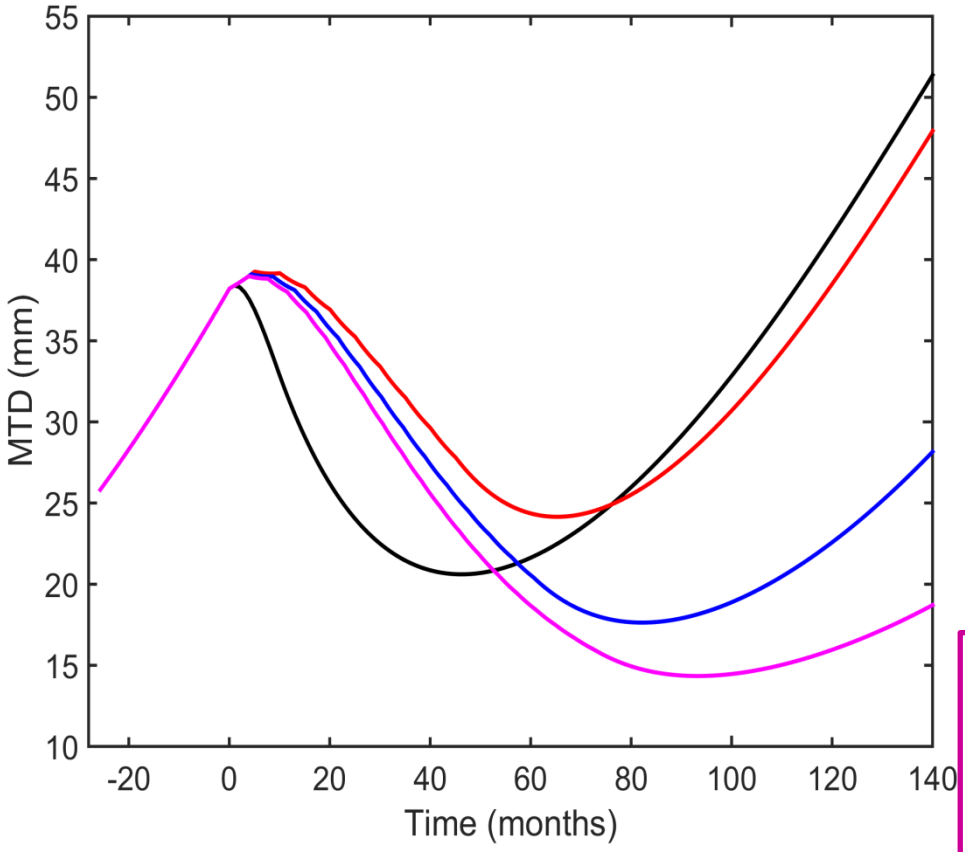
- Simulation of the optimized protocol with stochastic differential equations (SDE)
- Description of a random phenomenon (cell mutations) with a stochastic approach
- Robustness evaluation of model and method
- Stochastic equations, on resistant process, for resistant and damaged tissues:

$$\frac{dR}{dt} = \lambda_R R\left(1 - \frac{T}{100}\right) + (\gamma_{DR} + \sigma_{DR} \times \varepsilon)\, AUC(t) D$$

$$\frac{dD}{dt} = \gamma_{SD} C(t) S - \mu_D D - (\gamma_{DR} + \sigma_{DR} \times \varepsilon) AUC(t) D$$

where $\varepsilon \sim \mathcal{N}(0,1)$

Patient 35 – TMZ optimization



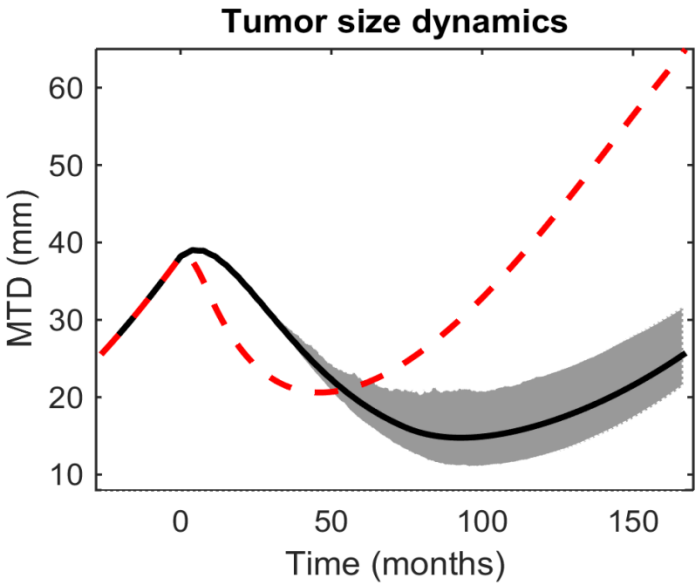
Standard protocol: 10 cycles, every 28 days, 200mg/m²/d

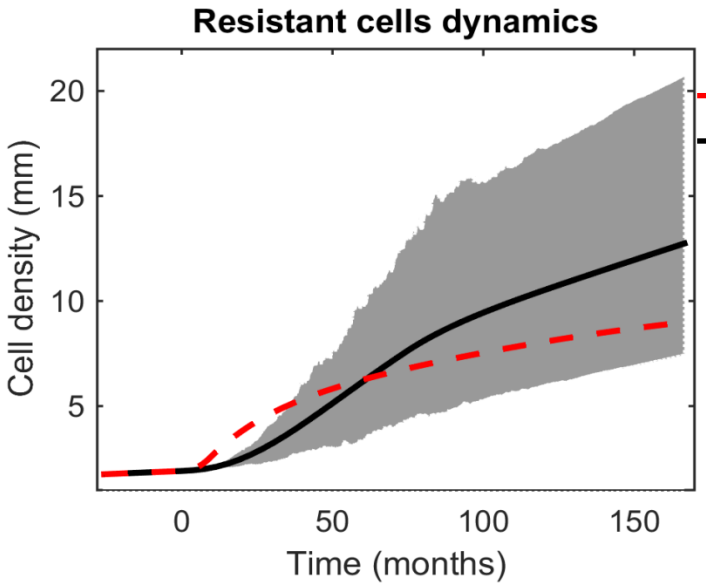
Optimized protocol 1: 10 cycles, every150 days (5 months), 200mg/m²/d

Optimized protocol 2: 15 cycles, every 130 days (4.3 months), 200mg/m²/d

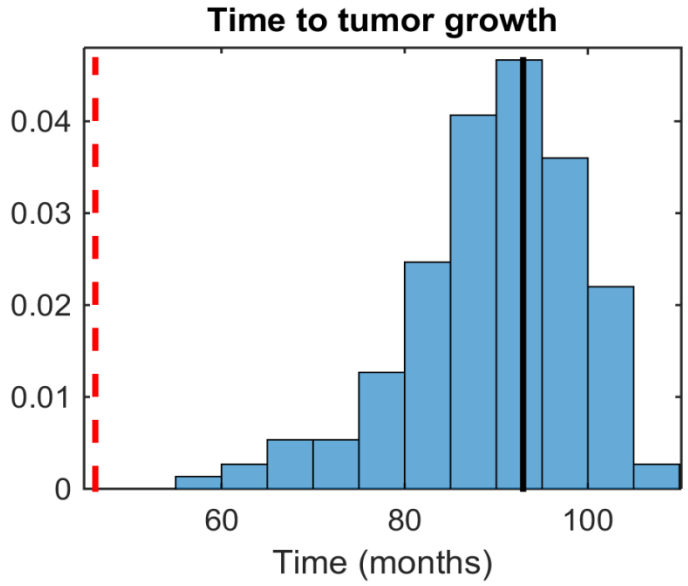
Optimized protocol 3: 20 cycles every 115 days (3.8 months), 200mg/m²/d

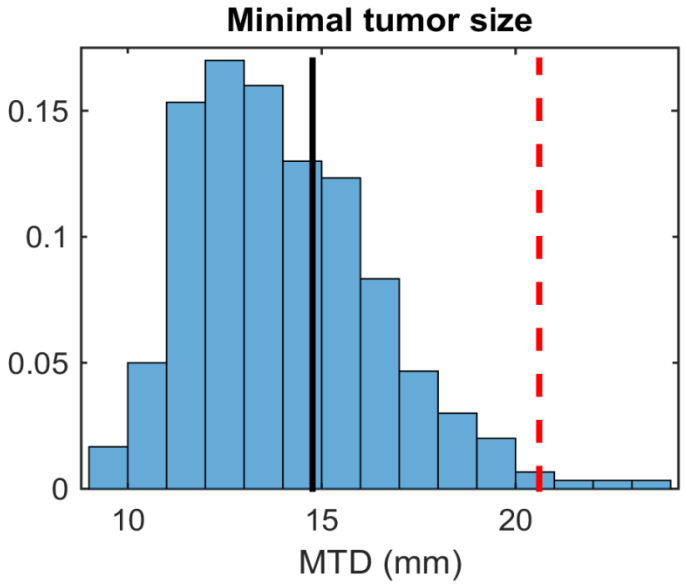
Patient 35 – Evaluation of optimized protocol



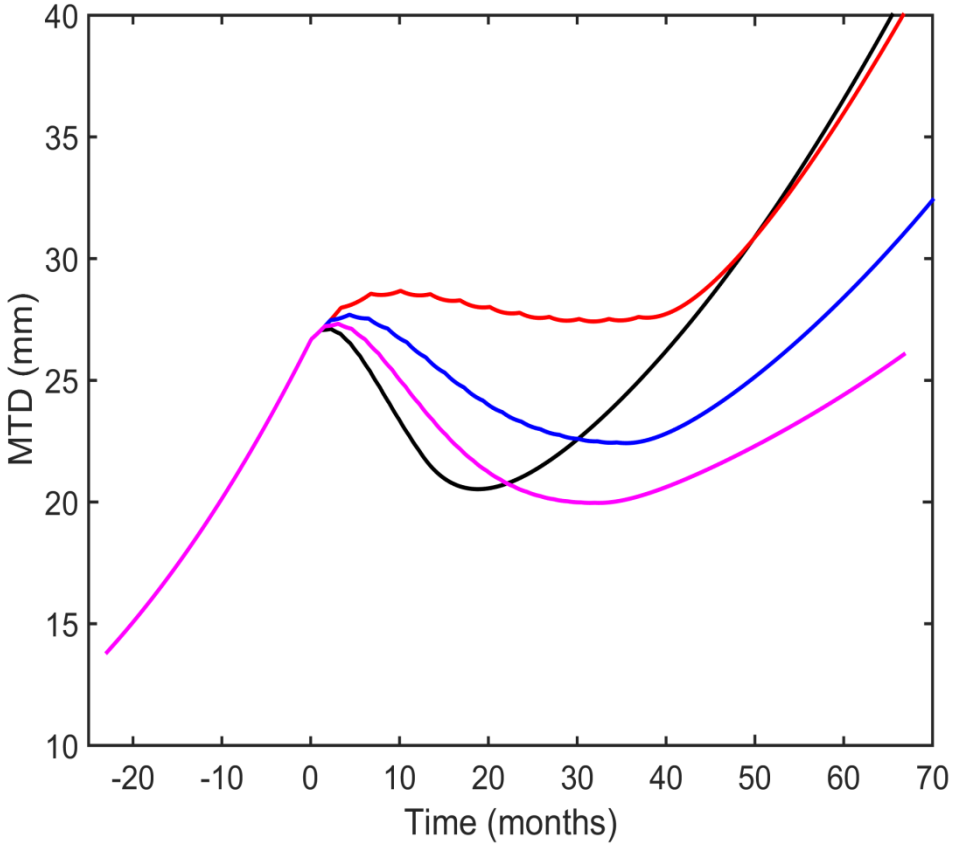


Standard protocol
Optimized protocol





Patient 49 – TMZ optimization



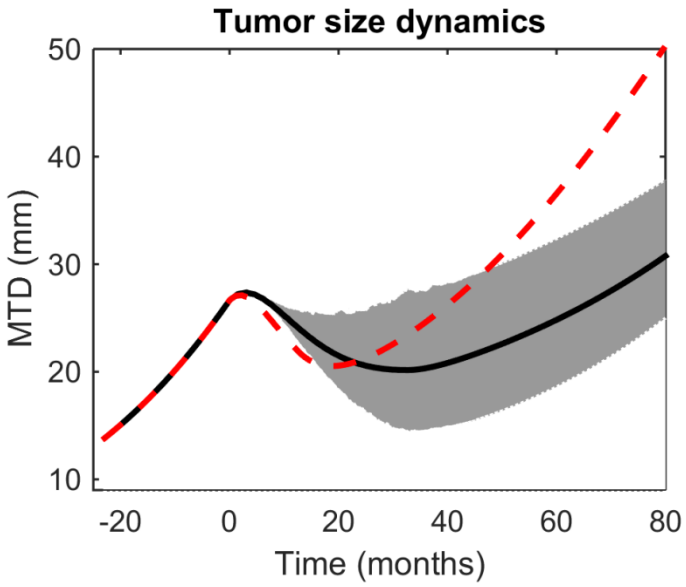
Standard protocol: 12 cycles, every 28 days, 200mg/m²/d

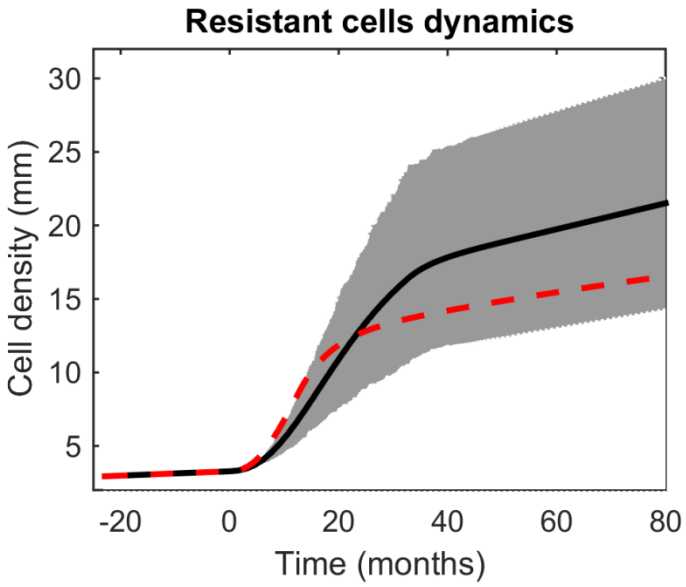
Optimized protocol 1: 12 cycles, every100 days (3.3 months), 200mg/m²/d

Optimized protocol 2: 17 cycles, every 65 days (2.2 months), 200mg/m²/d

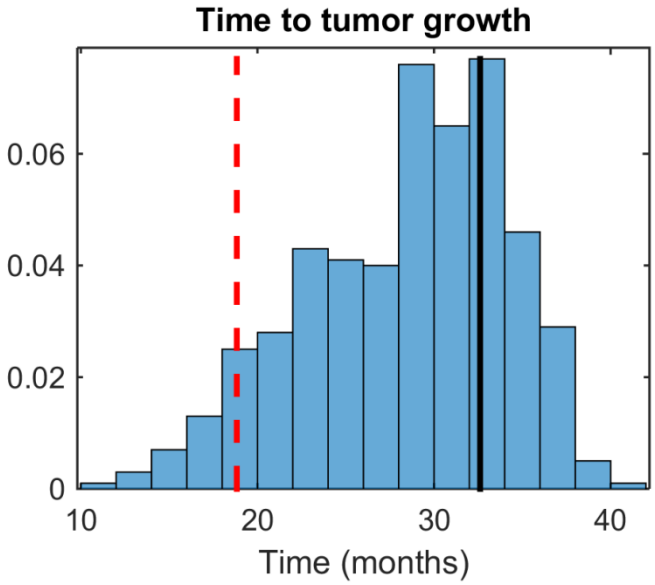
Optimized protocol 3: 22 cycles every 45 days (1.5 months), 200mg/m²/d

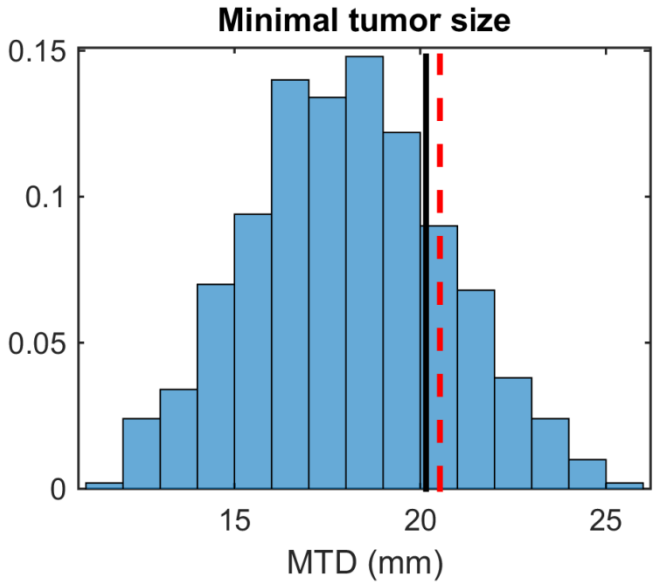
Patient 49 – Evaluation of optimized protocol



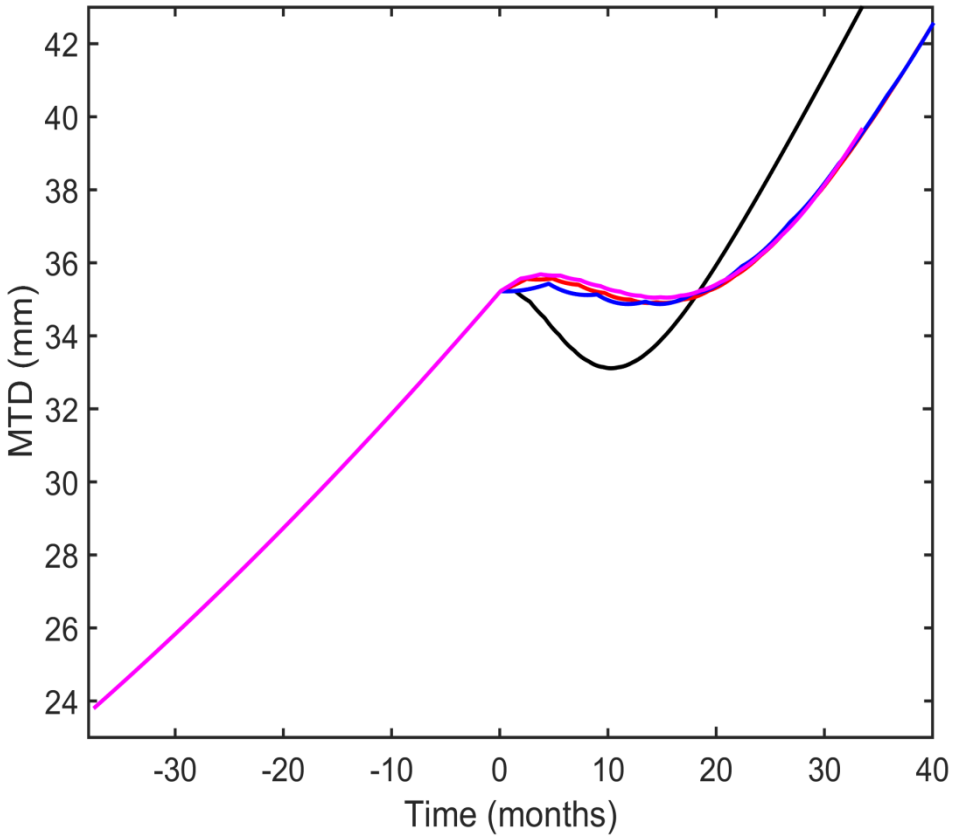


Standard protocol
Optimized protocol





Patient 44 – TMZ optimization



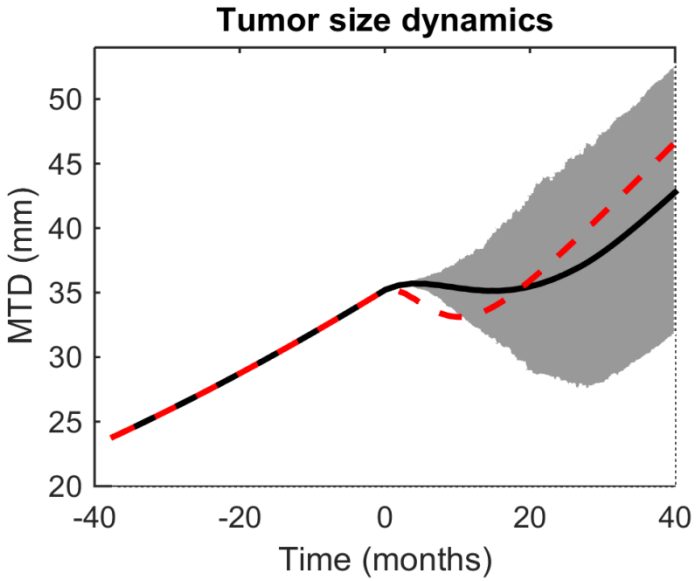
Standard protocol: 20 cycles, every 28 days, 200mg/m²/d

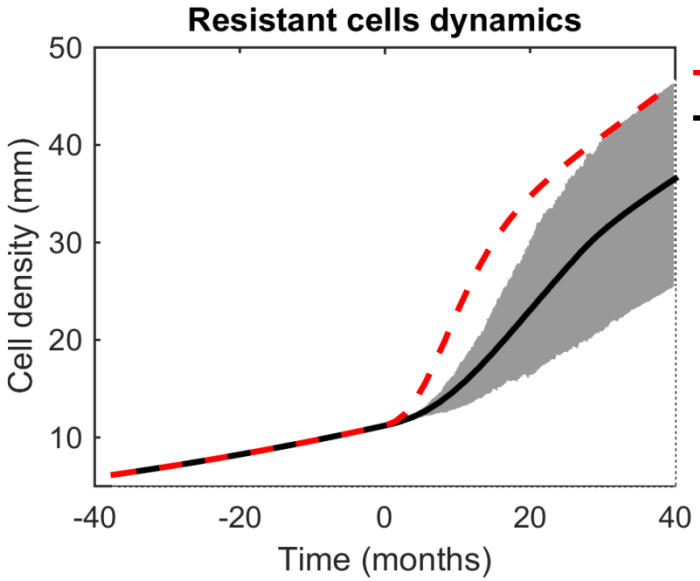
Optimized protocol 1: 20 cycles, every 72 days (2.4 months), 120mg/m²/d

Optimized protocol 2: 10 cycles, every 135 days (4.5 months), 200mg/m²/d

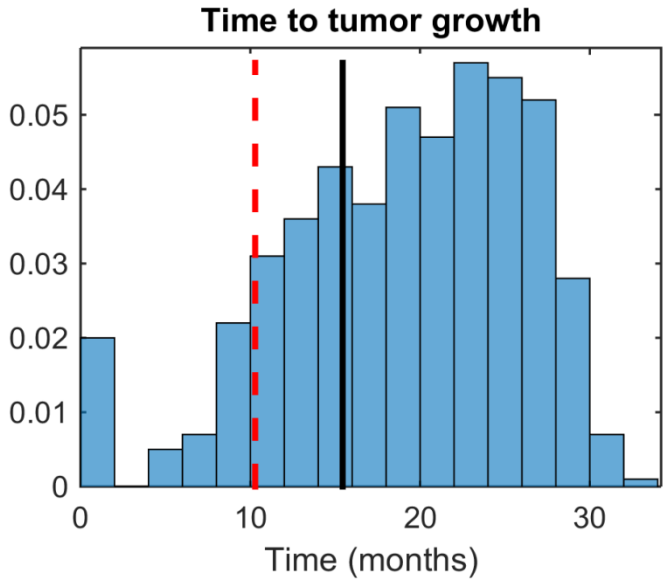
Optimized protocol 3: 15 cycles every 55 days (1.8 months), 90mg/m²/d

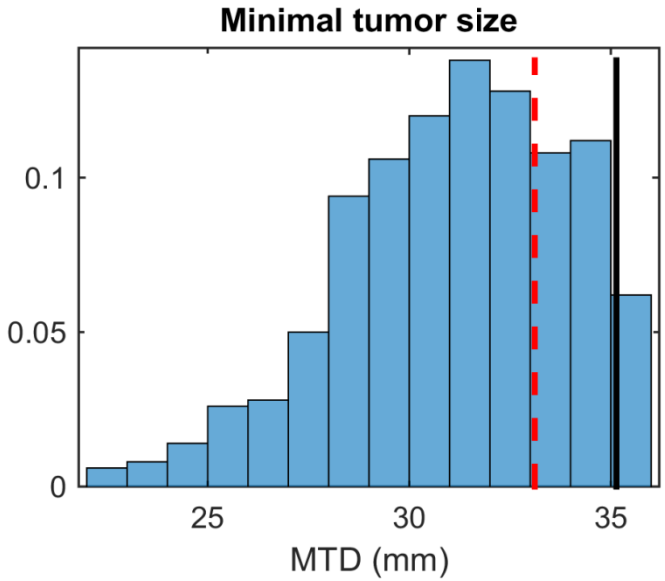
Patient 44 – Evaluation of optimized protocol





Standard protocol
Optimized protocol





Discussion

Conclusion

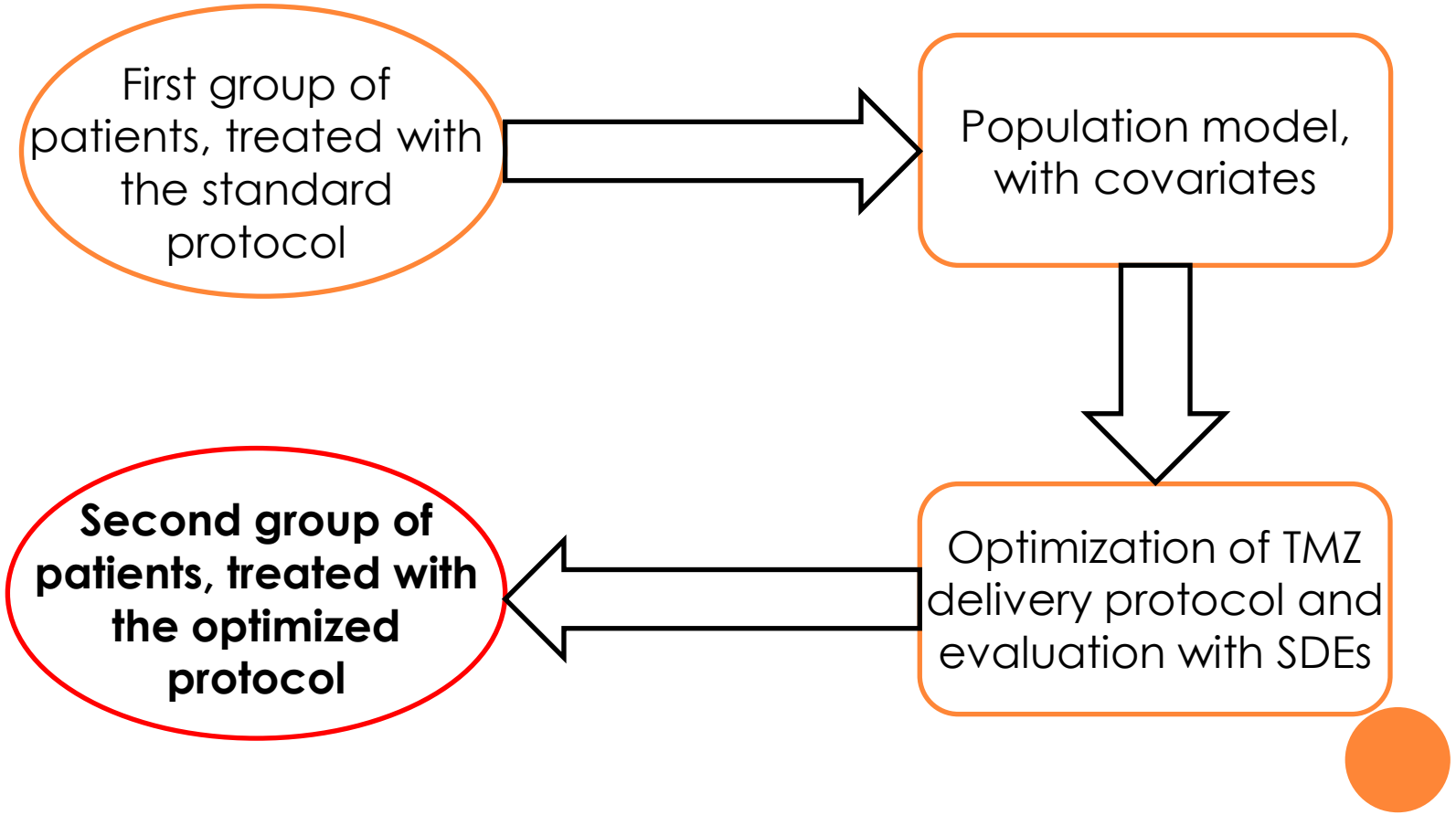
- Study of LGG patients treated with chemotherapy (PCV and TMZ)
- Population model to describe tumor dynamics
- Modification of PCV therapeutic protocol
- Optimization of TMZ delivery protocol on an individual level

Limits

- Few patients included in the analysis, in particular with covariates
- No available PK data

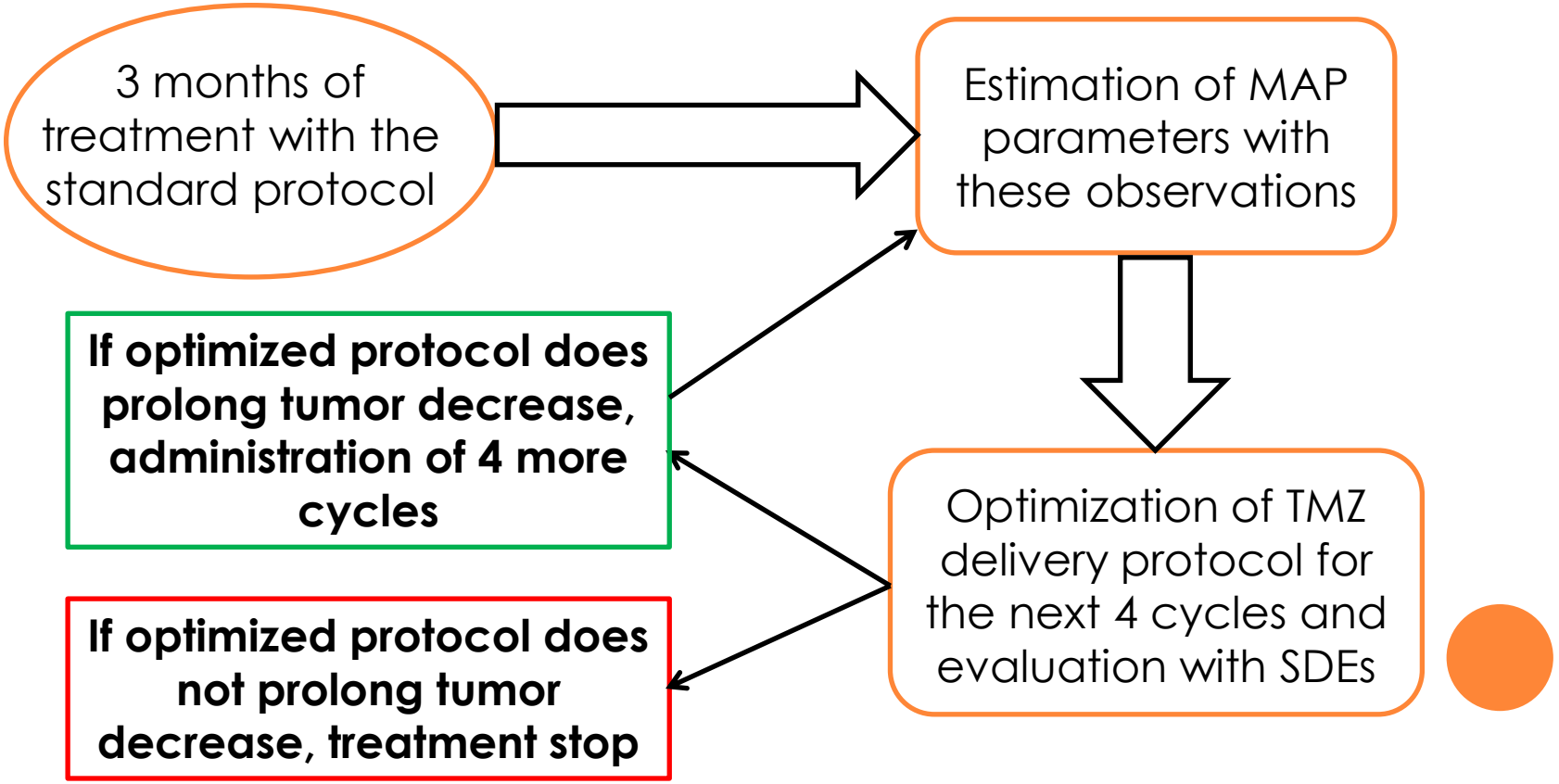
What can we do?

- Optimization of TMZ delivery protocol for a population



What can we do?

- Optimization of TMZ delivery protocol for a population
- Prediction and adjustment of TMZ delivery protocol for a patient



Thank you for your attention