Understanding potential benefits of adaptive therapy

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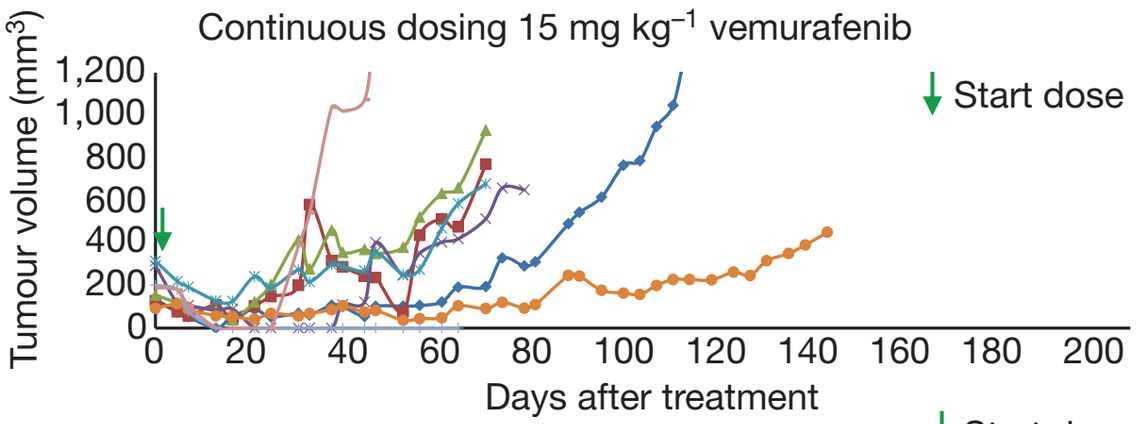
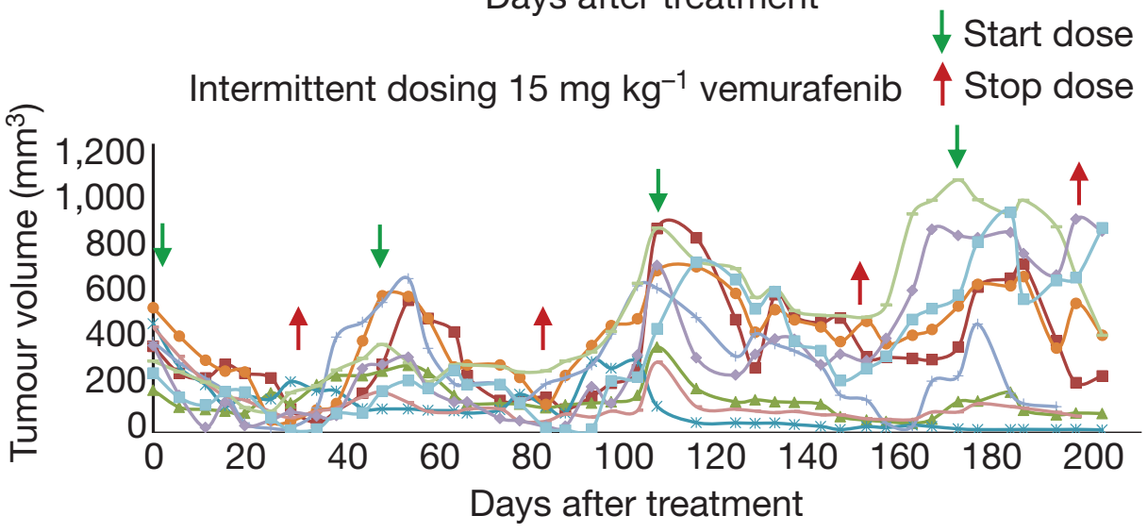
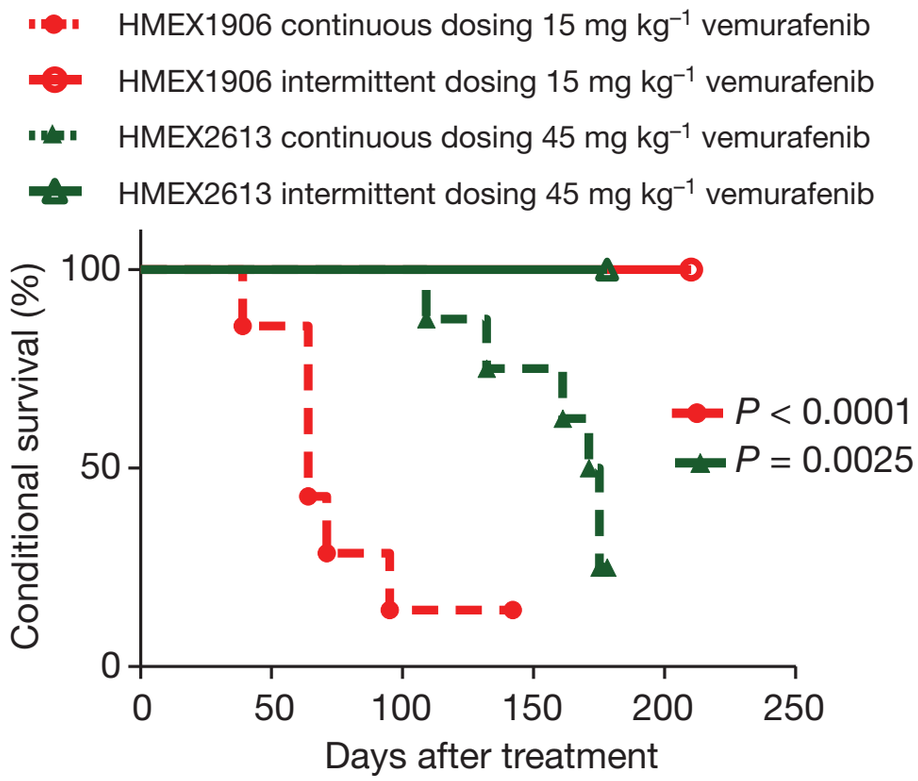
Melanoma intermittent therapy (in vivo)



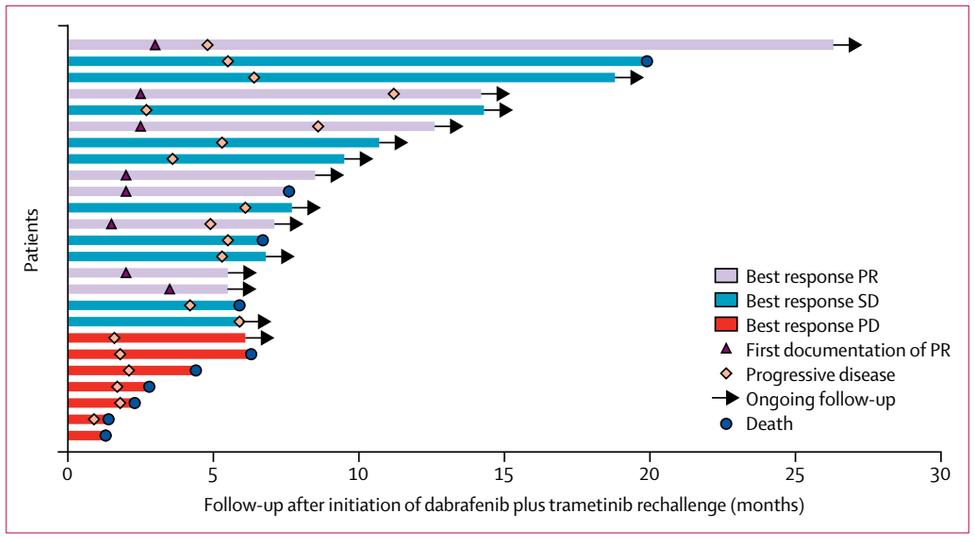


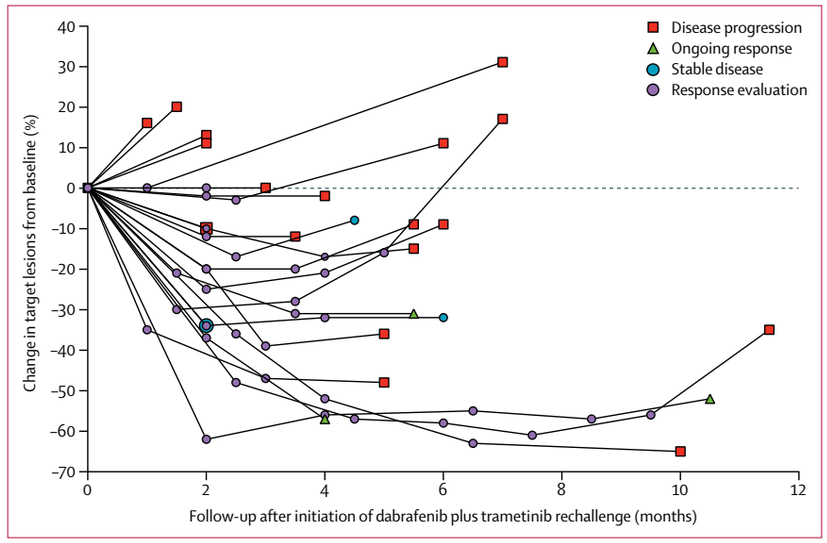


Das Thakur et al. Nature, 2013, 494:251-5

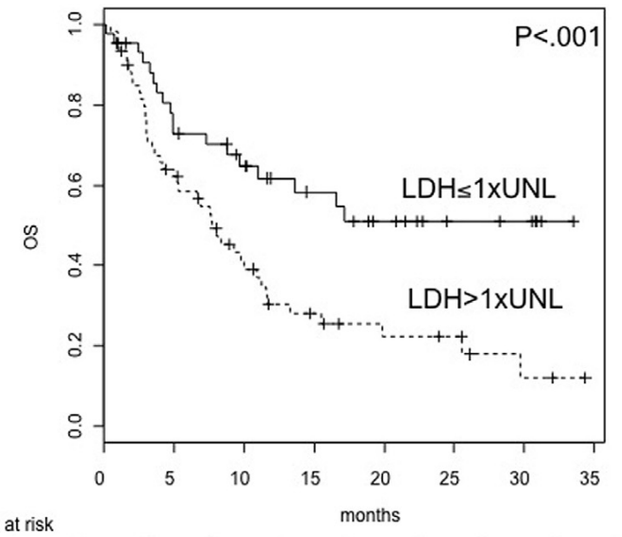
- Intermittent therapy (4 week on/2 week off) improves response in vivo
- Various responses: some regression vs. gradual increase
- Resistant cells become drug dependent for continued proliferation
- Cessation of drug leads to regression of drug-resistant cells

Intermittent therapy clinical trials





Schreur et al. Lancet Oncol, 2017



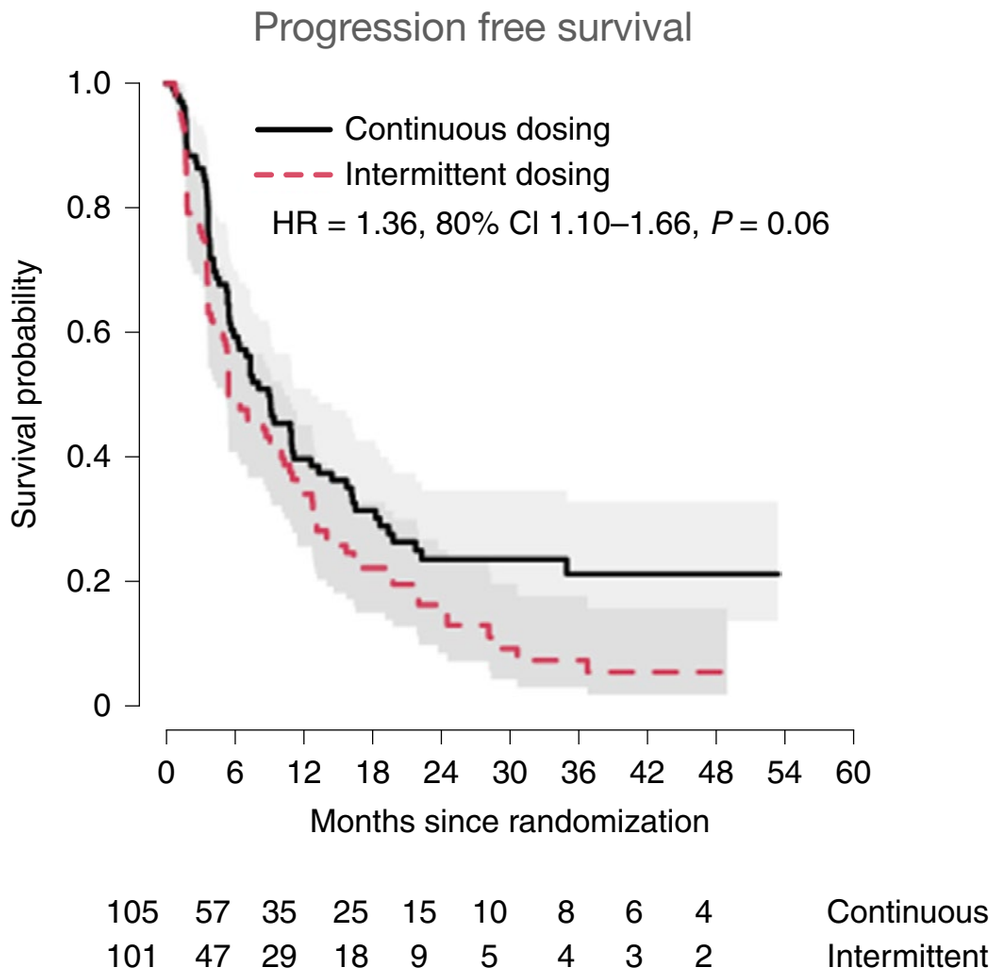
Number at risk

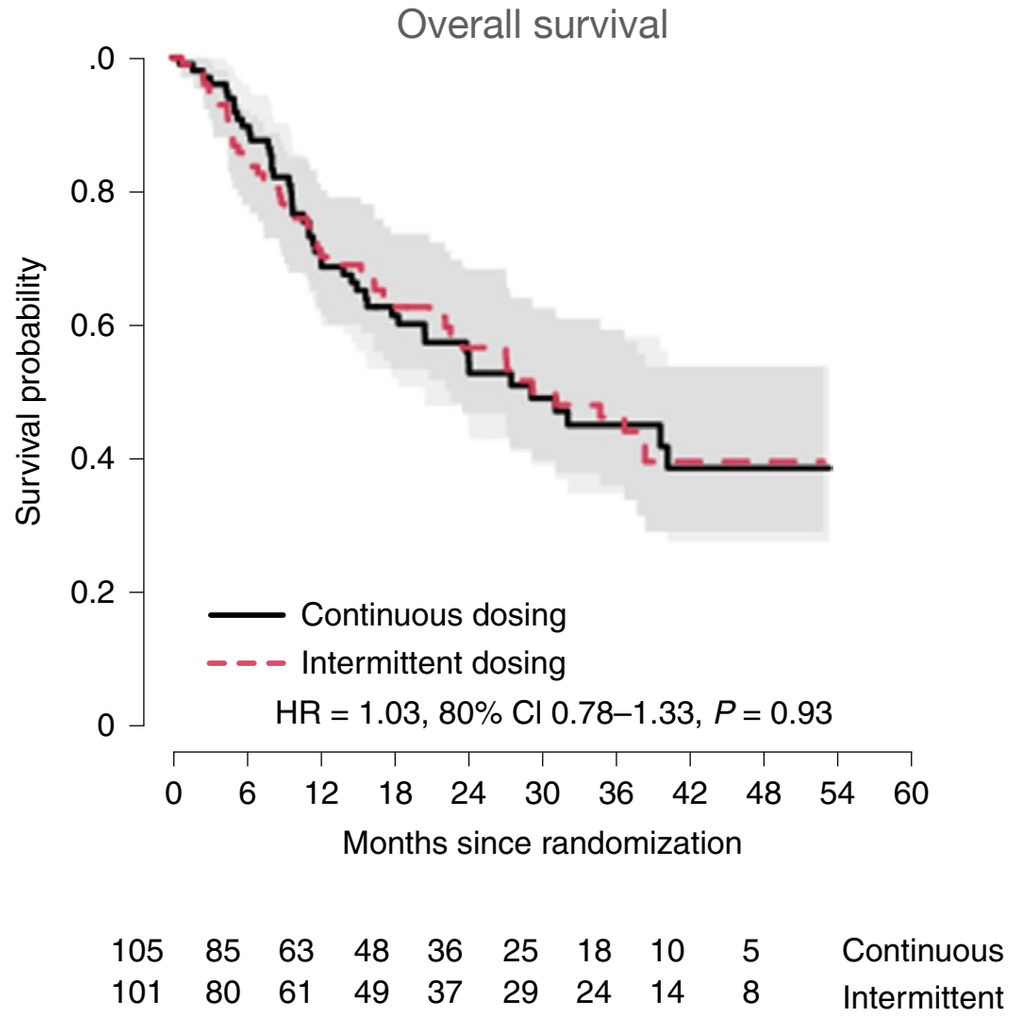
LDH≤1xUNL	31	21	18	15	12	7	6	1
LDH>1xUNL	73	47	29	17	10	10	3	3

Valpione et al. Eur J Cancer, 2018

- Re-challenge after treatment break or other therapy due to progression or other causes
- Drug holidays: 4-12 weeks
- Re-challenge clinically meaningful
- Diverse response and duration

Intermittent therapy clinical trials

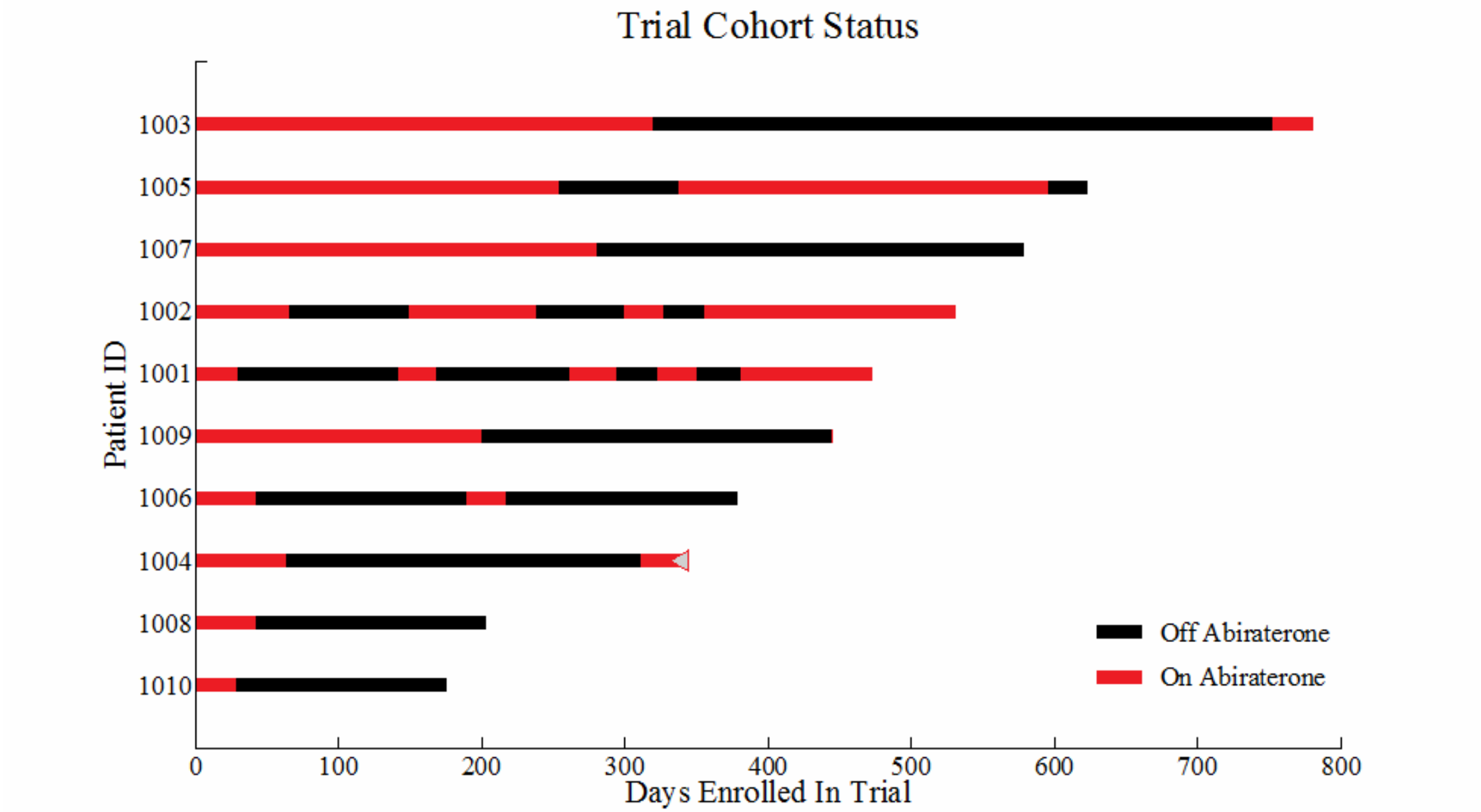




- Algazi et al. Nature Medicine, 2020, 26:1564-1568

- Phase 2 trial of intermittent therapy
- 8 week continuous therapy lead in, 3 week off and 5 week on or continuous therapy
- Intermittent dosing did not improve progression free survival
- No difference in the overall survival and the overall toxicity
- This one-size-fits-all approach unlikely to be optimal clinically

Inter-patient variability



Zhang et al. Nature Comm, 2017

Melanoma adaptive therapy in vivo

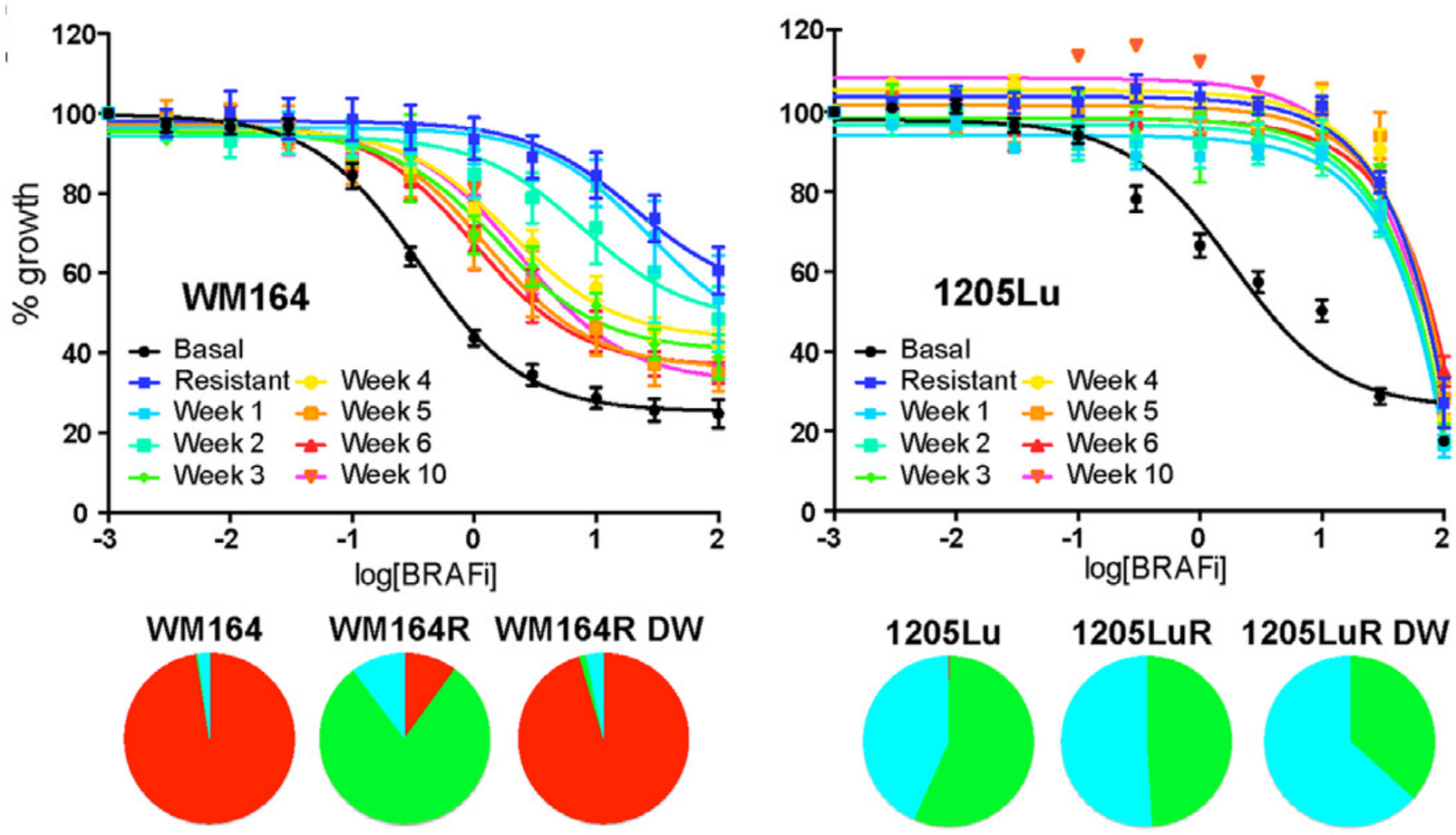
Continuous

2 weeks ON, 1 week OFF

→ Measure tumors every 2-3 days → Continue Tx

Adaptive (personalized) → Measure tumors every 2-3 days → Re-evaluate Tx

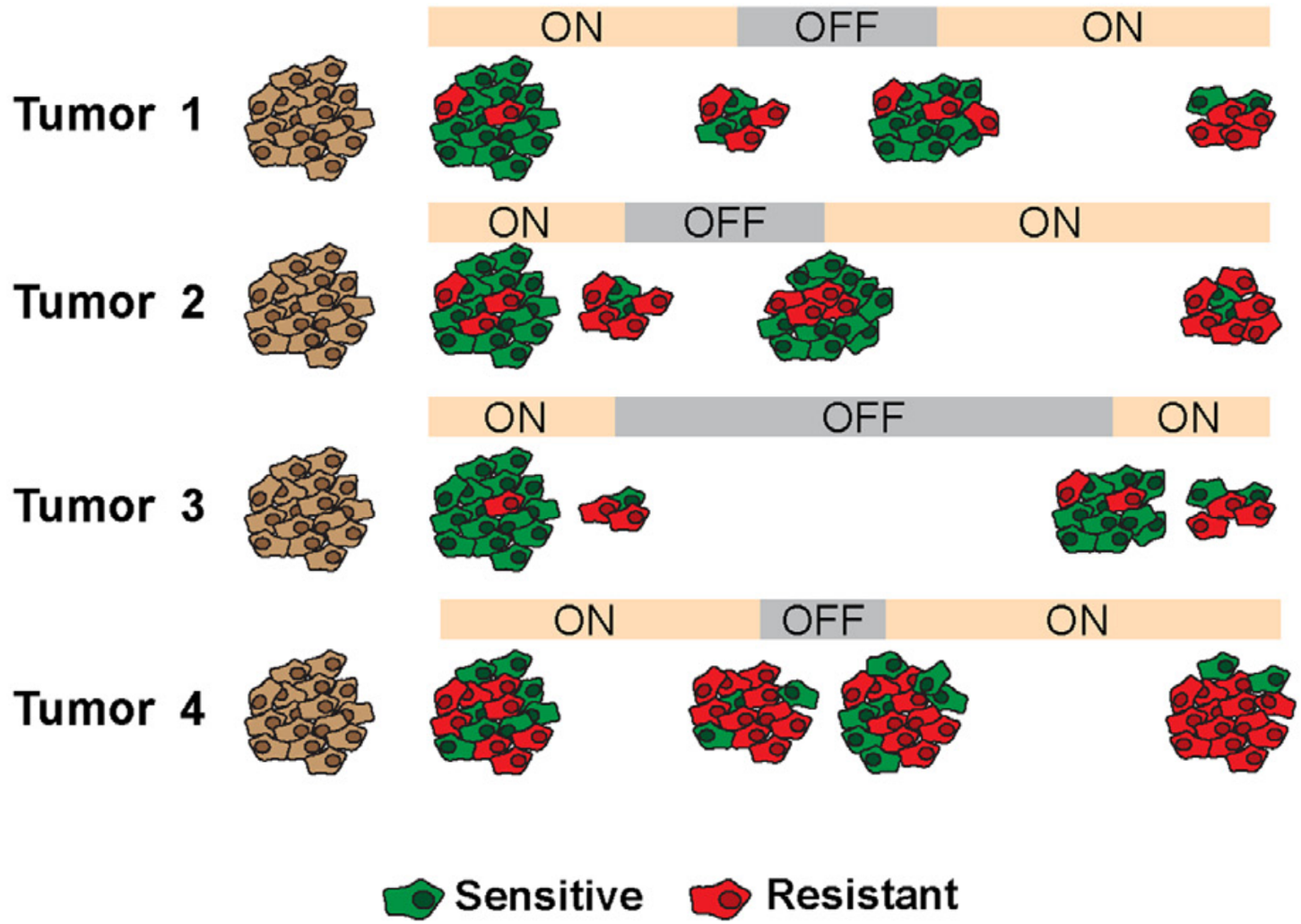
Melanoma adaptive therapy in vivo



Smalley et al. Ebiomedicine, 2019

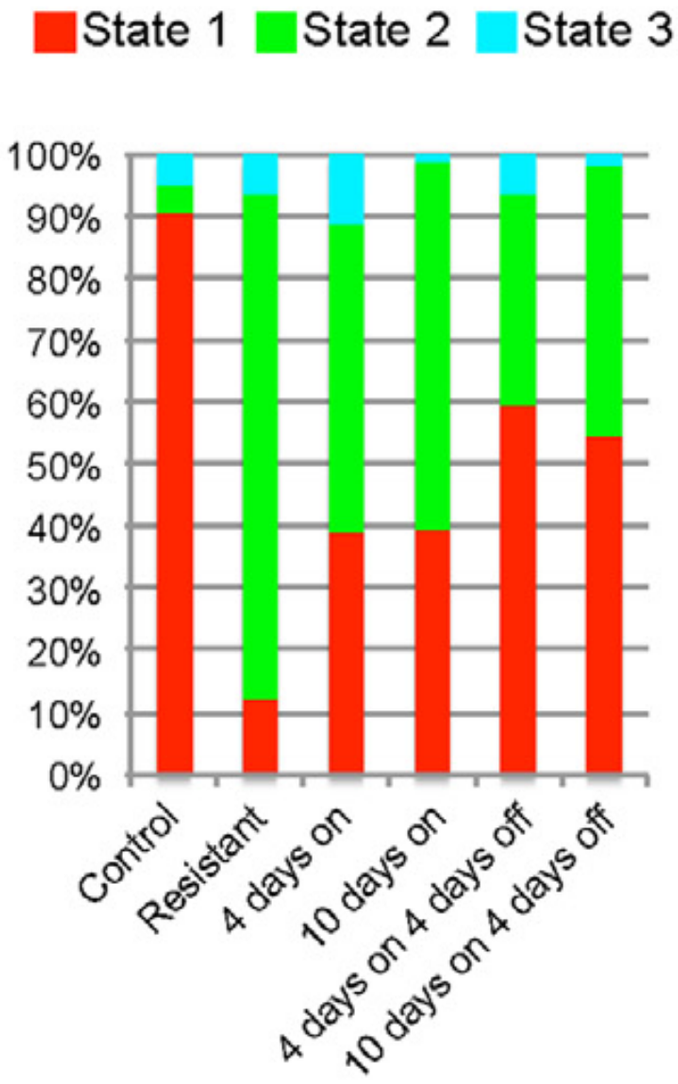
- Transcriptional heterogeneity in melanoma cell lines
- Drug induced distribution changes
- WM164 cell lines seems to be recovering drug sensitivity
- Inhibition of growth in 4-10 week off WM164 vs. drug sensitivity of basal cell line
- Decided to use WM164 cell line xenograft model

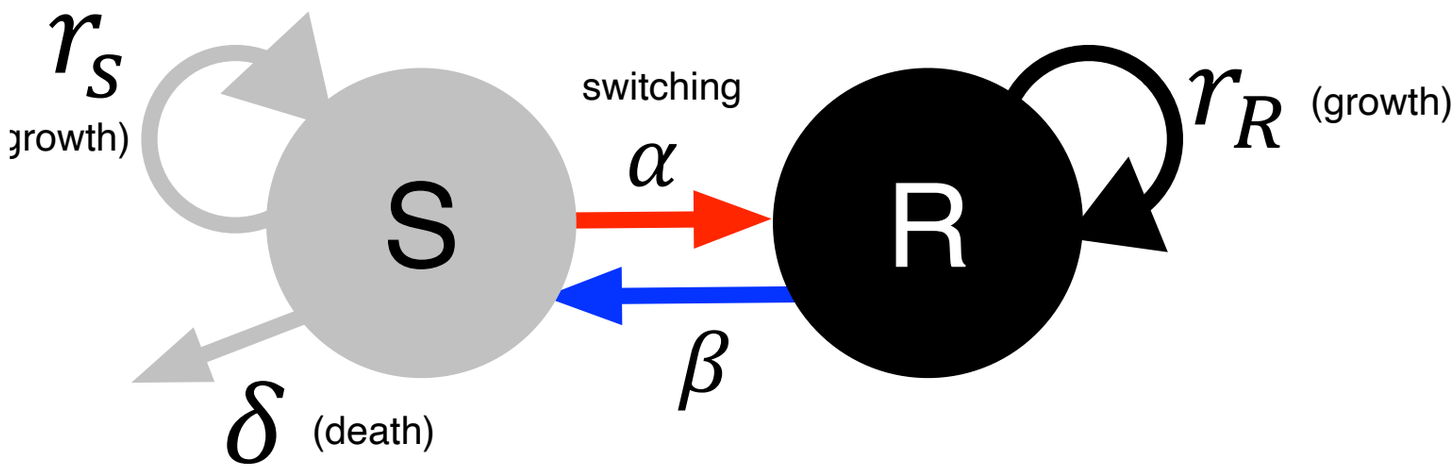
Melanoma adaptive therapy in vivo



- Goal: maintain drug-sensitive transcriptional states through adaptive dosing
- Mathematical model guided scheduling
- Drug holiday associated with drug sensitivity

Mathematical model



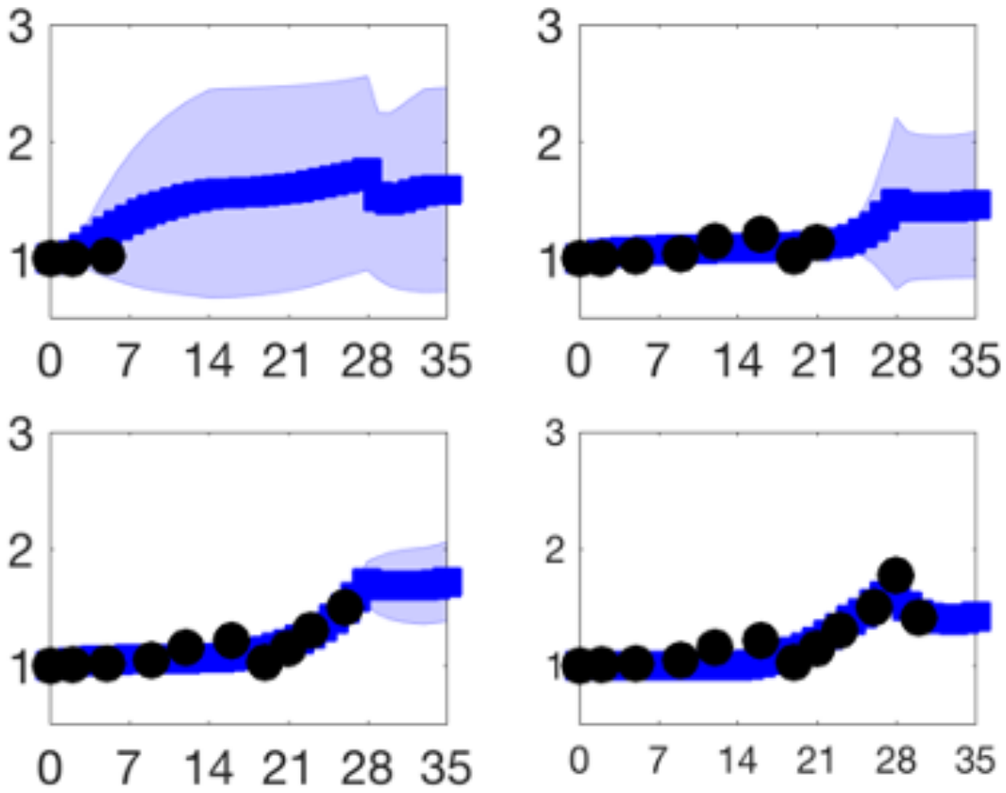


Smalley et al. Ebiomedicine, 2019

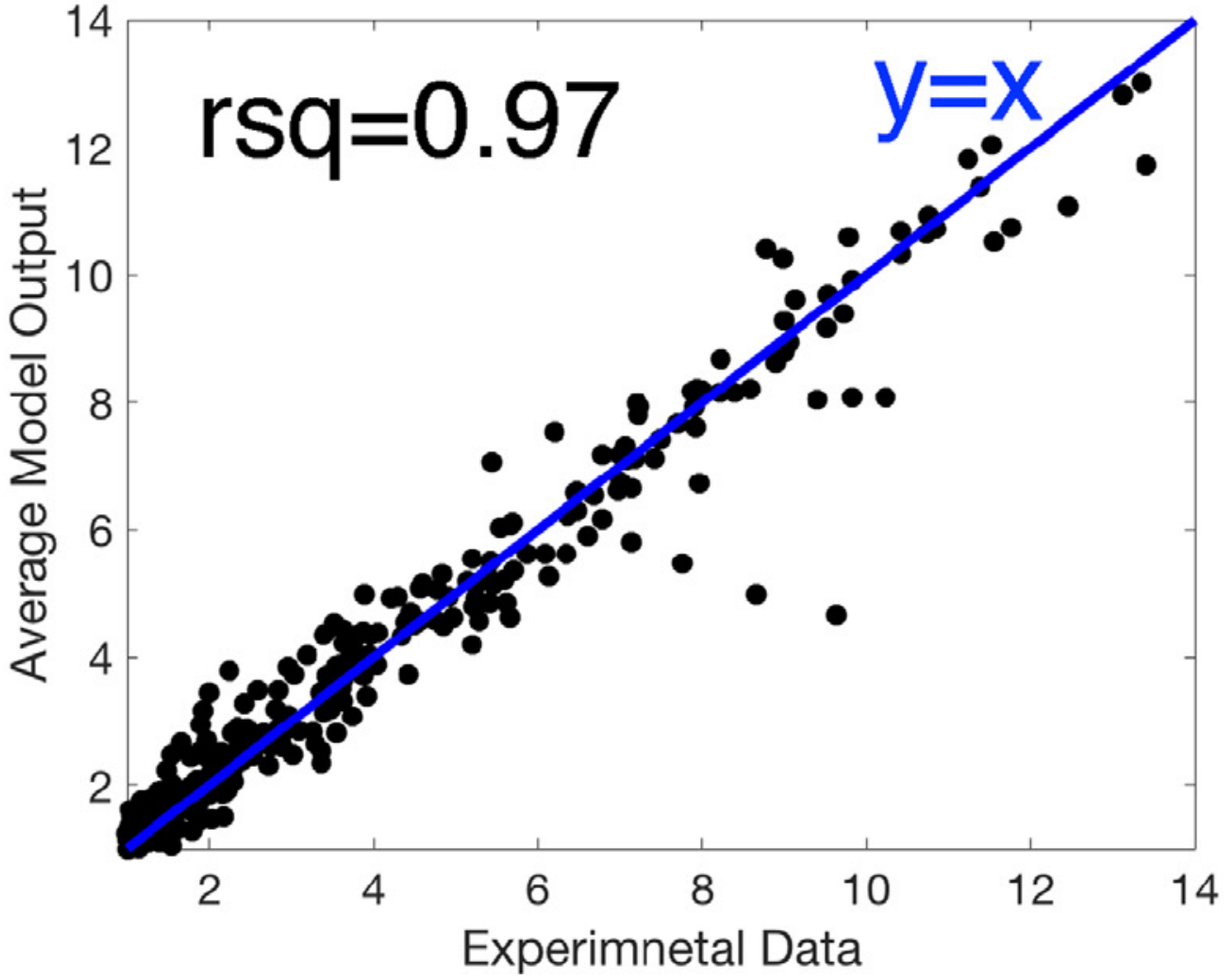
$$\frac{dS}{dt} = r_S\left(1 - \frac{S+R}{K}\right)S - \delta S - \alpha S + \beta R,$$

$$\frac{dR}{dt} = r_R\left(1 - \frac{S+R}{K}\right)R + \alpha S - \beta R.$$

Model calibration & prediction



$$\min f(H) = \min \sqrt{\sum_i (V(t;H) - D(t)/D(0))^2}$$



- 11 one-side xenograft models
- Measure individual mouse tumor volume changes every 2~3 days
- Estimate model parameters (H) that minimize the difference between model predicted tumor volume and mouse tumor volume every 2~3 days

Model calibration & prediction

Mouse #	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	Tumor Growth
1																																							297.88%
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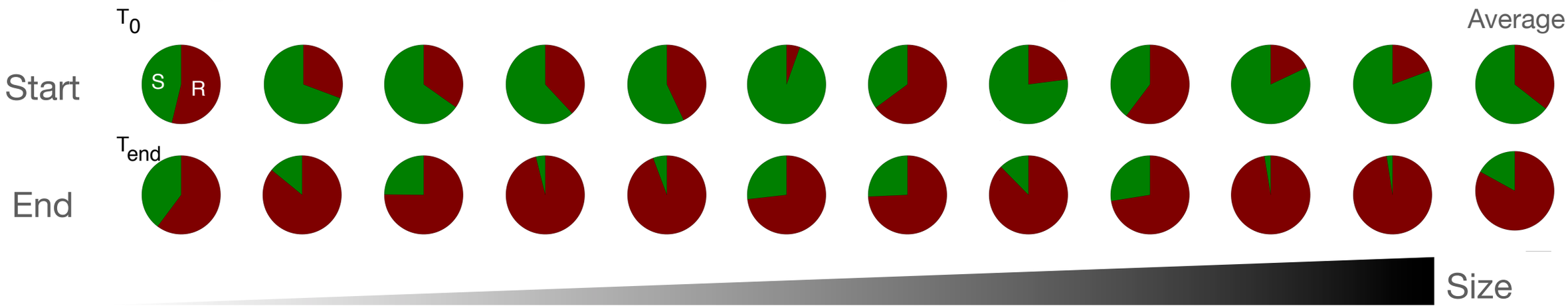
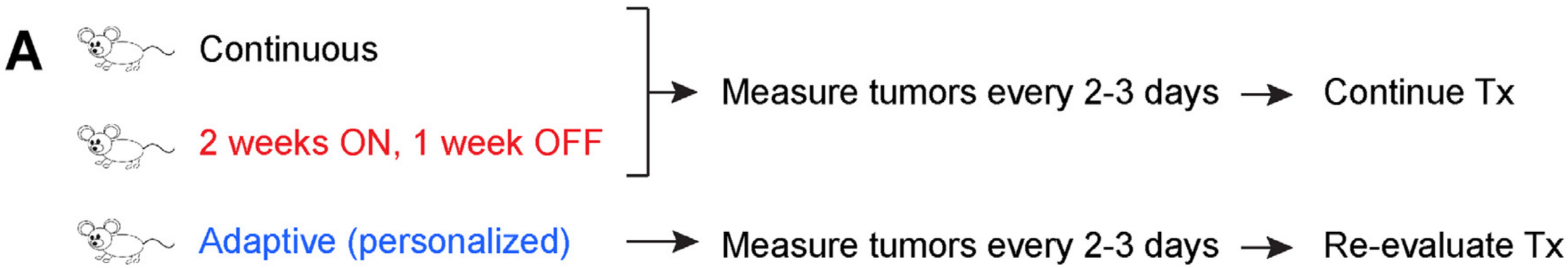
Smalley et al. Ebiomedicine, 2019

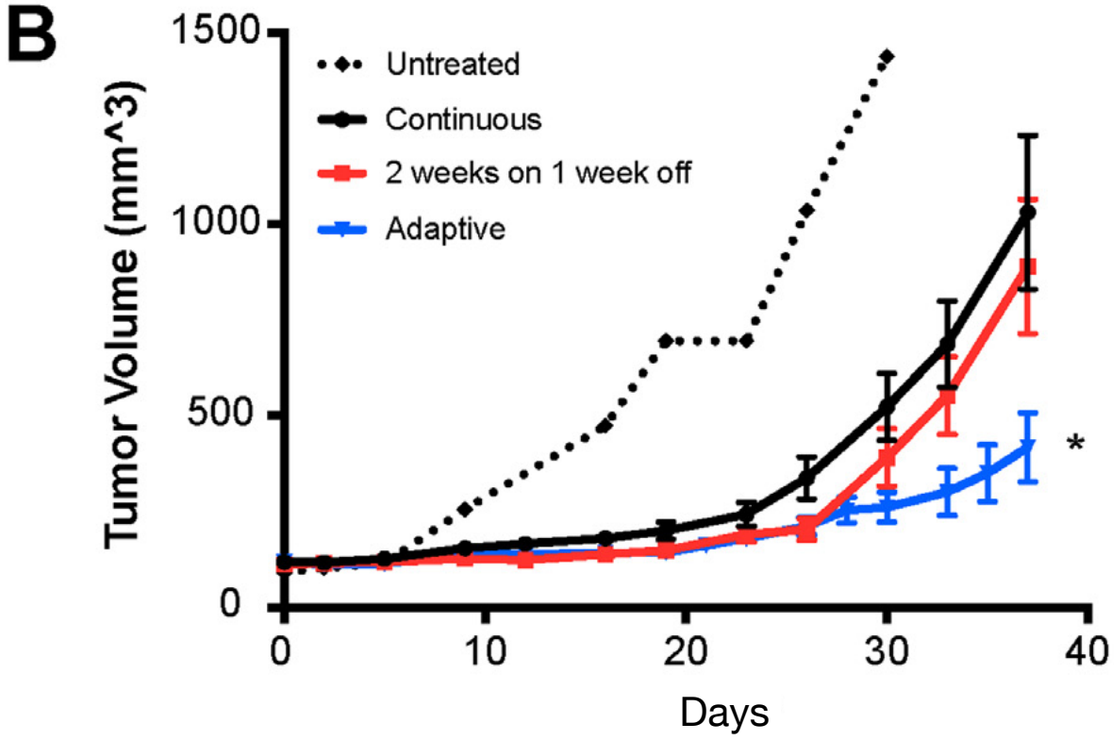
Predicted drug sensitive (S) and resistant (R) proportion change

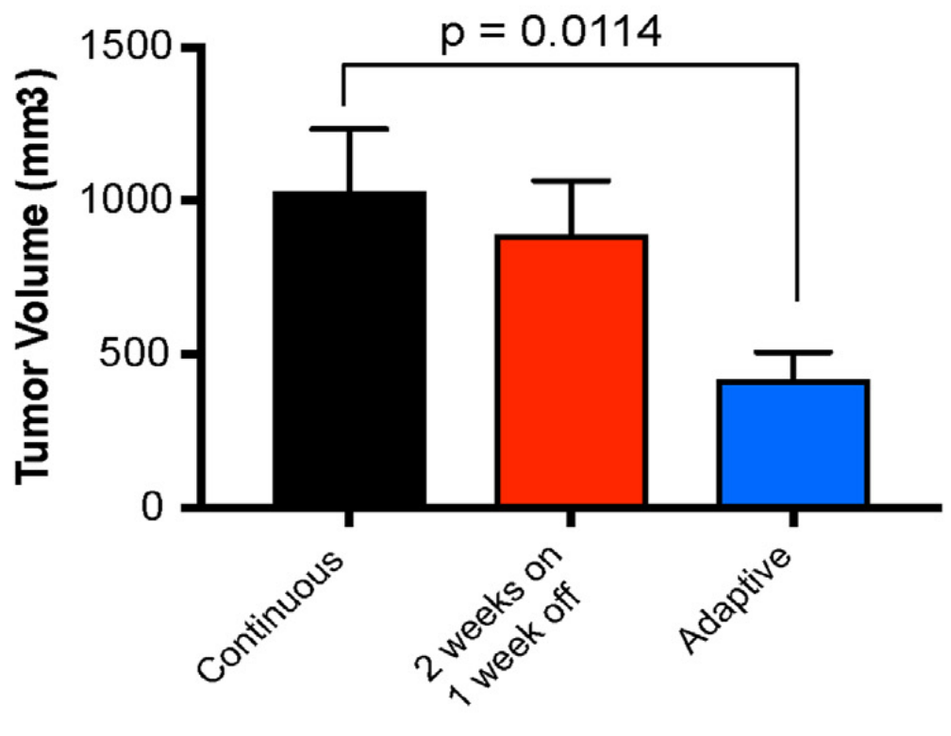


- Make predictions of tumor volume changes in 2 treatment scenarios: on and off
- Follow model predicted treatment decision (on or off) for subsequent 2~3 days
- Diverse treatment on and off schedule
- ~ 50% less tumor volume & ~64% dose rate compared to continuous MTD
- Not all xenograft model benefits from adaptive therapy

In vivo study summary

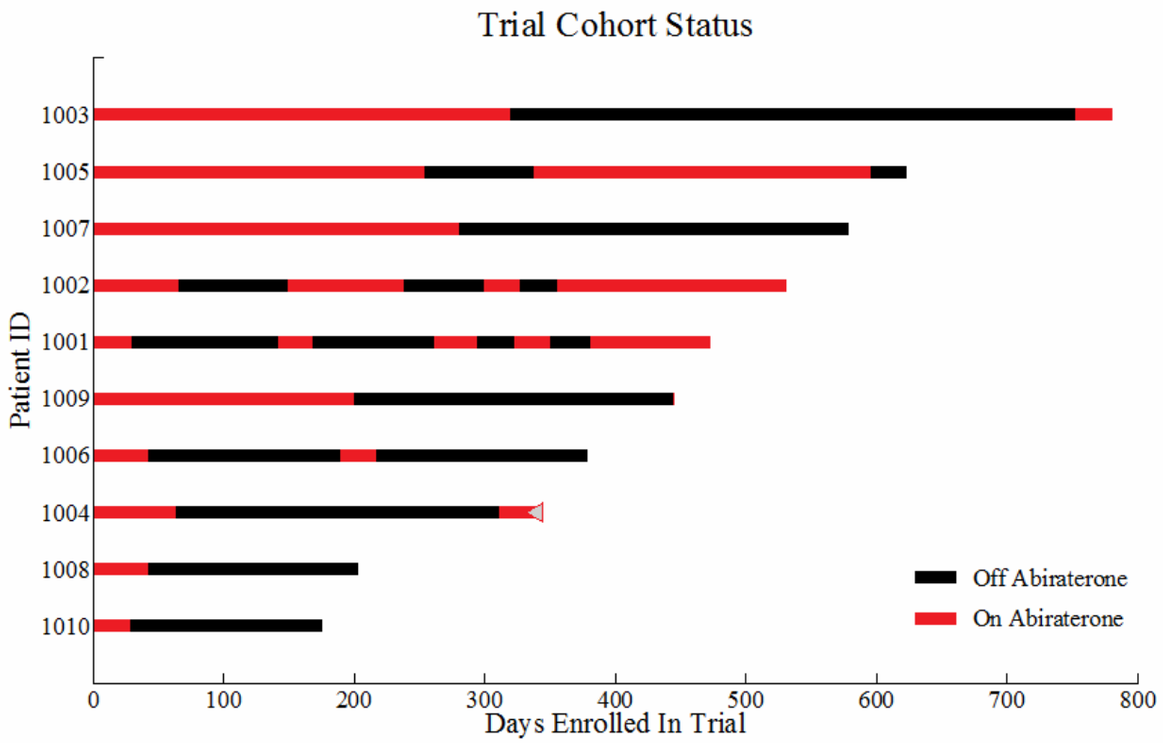




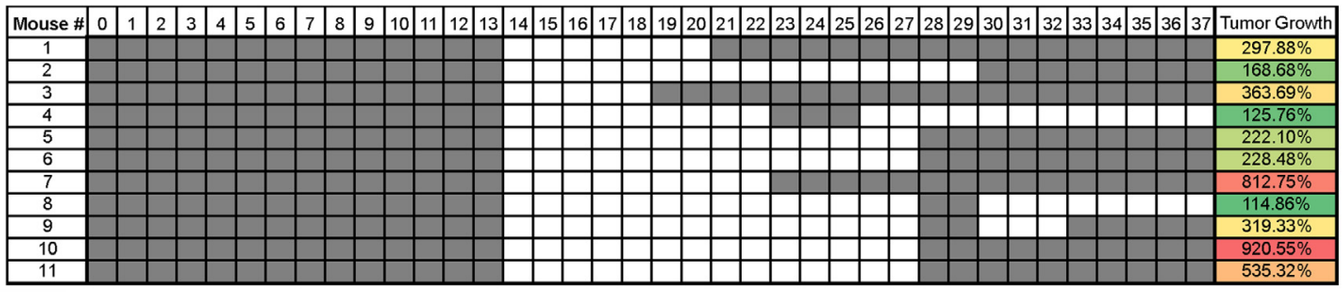


Smalley et al. Ebiomedicine, 2019

Benefits of adaptive therapy diverse



Zhang et al. Nature Comm, 2017



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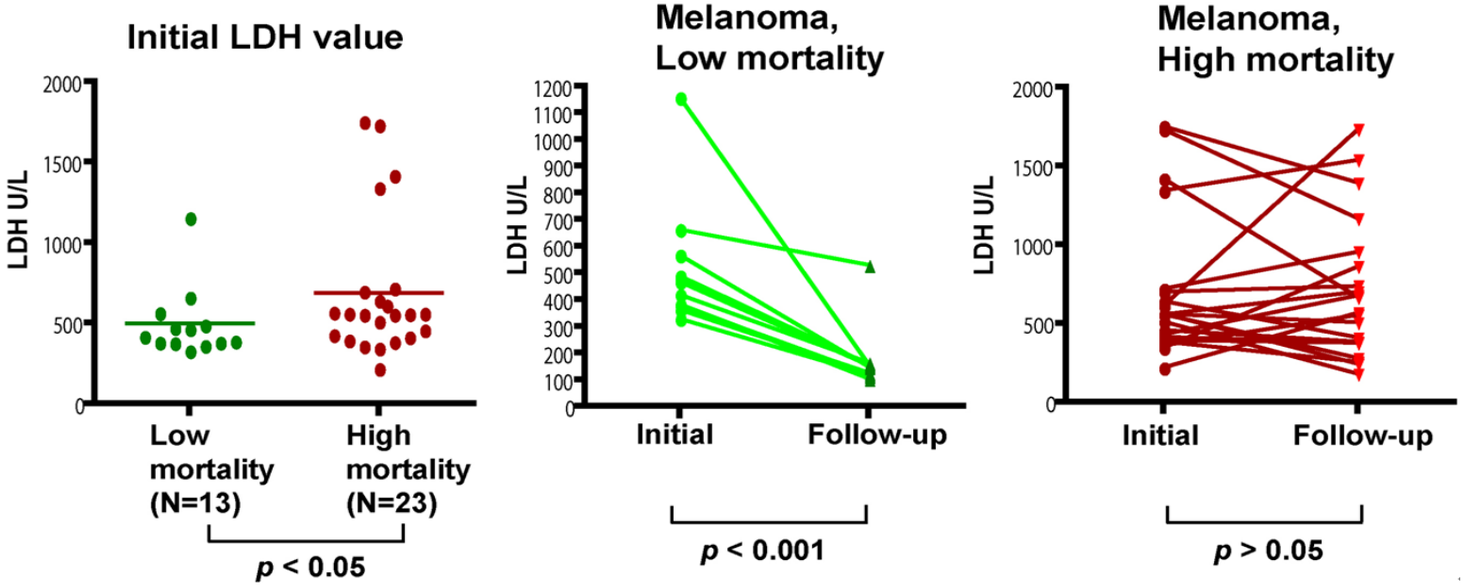
Smalley et al. Ebiomedicine, 2019

- Effectiveness of adaptive therapy will vary among patients
- Who will likely benefit most from adaptive therapy?
- Predictive factors

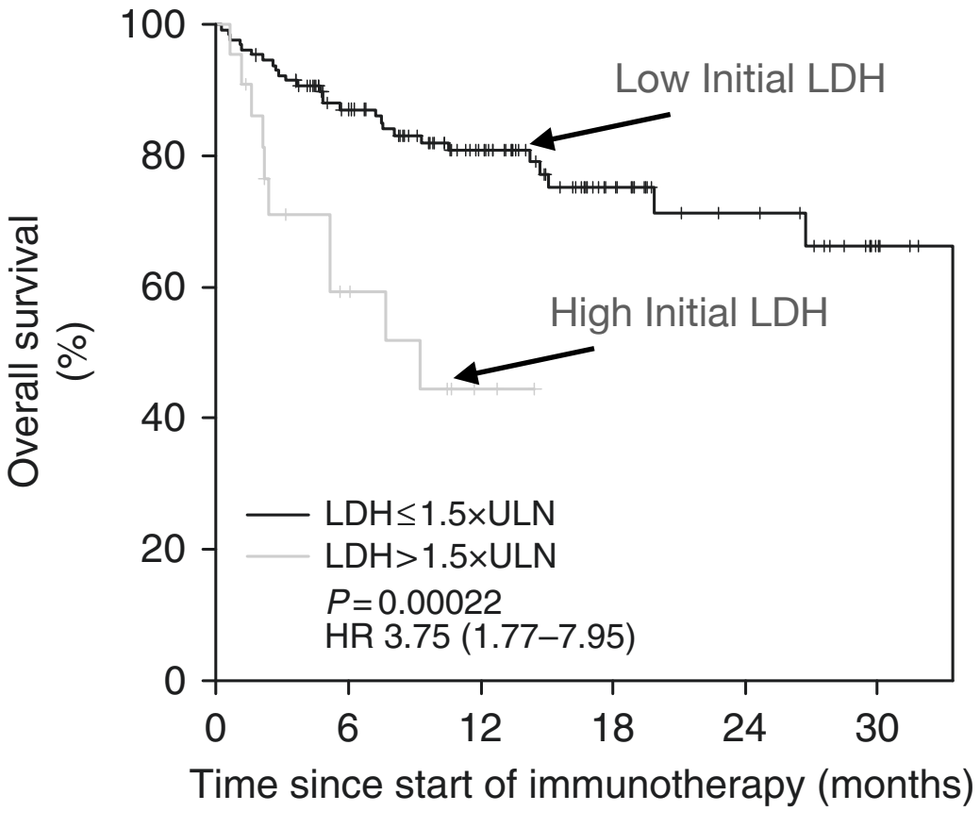
- Who will likely benefit most from adaptive therapy?

- What are predictive factors?

Melanoma tumor burden marker



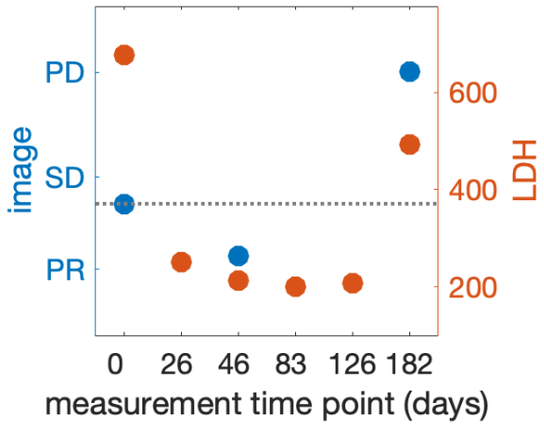
Zhang et al. Int. J. Mol. Sci, 2011

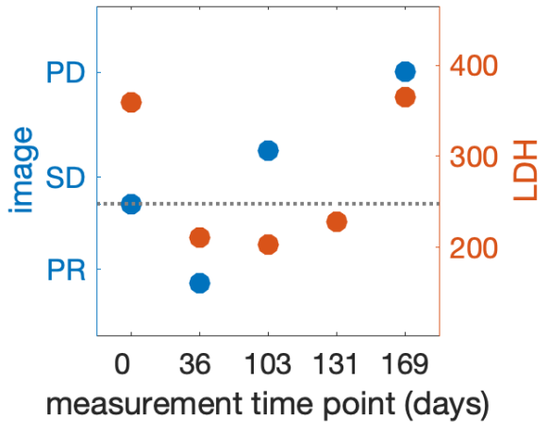


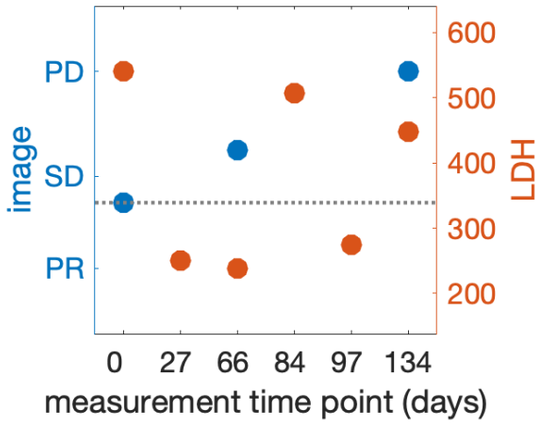
Wagner et al. Br. J. Cancer, 2018

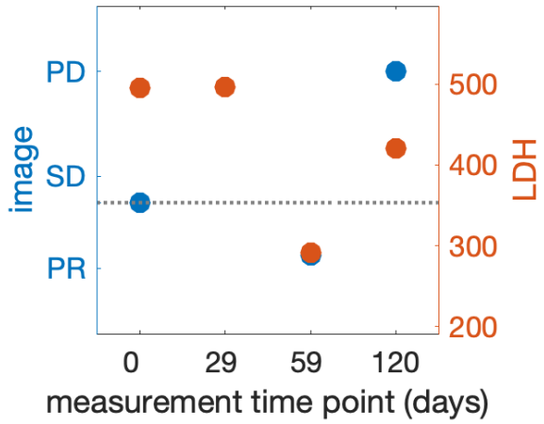
- Critical to obtain tumor burden as frequent as possible
- Serological marker that can be measured frequently
- Melanoma tumor burden marker: LDH, lactate dehydrogenase
- LDH is only serologic marker used for monitoring advanced melanoma in US
- Elevated serum LDH is associated with worse outcomes in patients treated with BRAF/MEK inhibitors

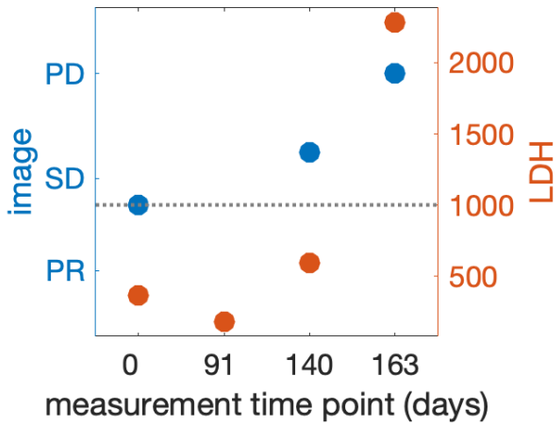
Applying the model to patient data

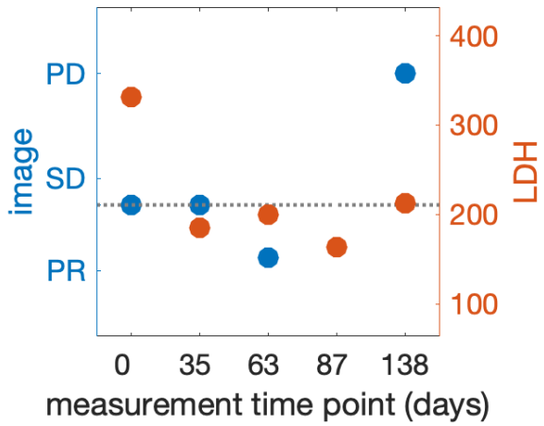


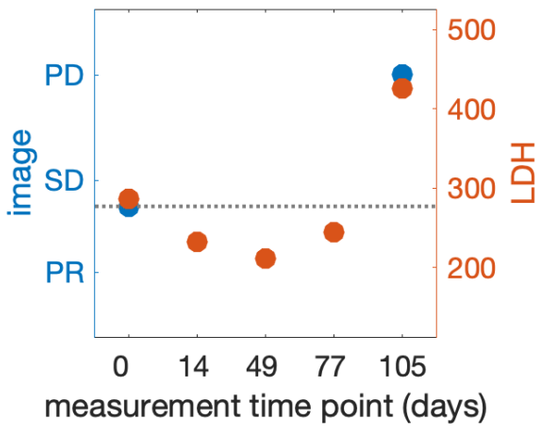


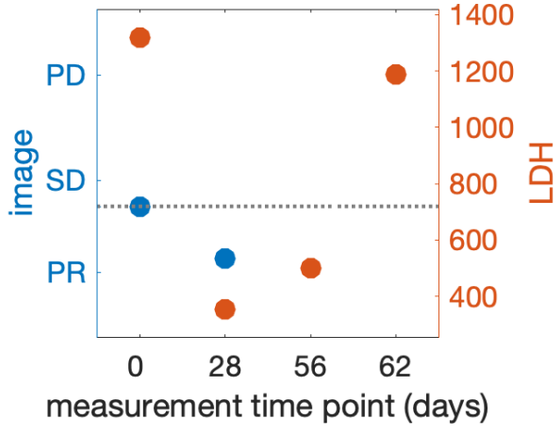






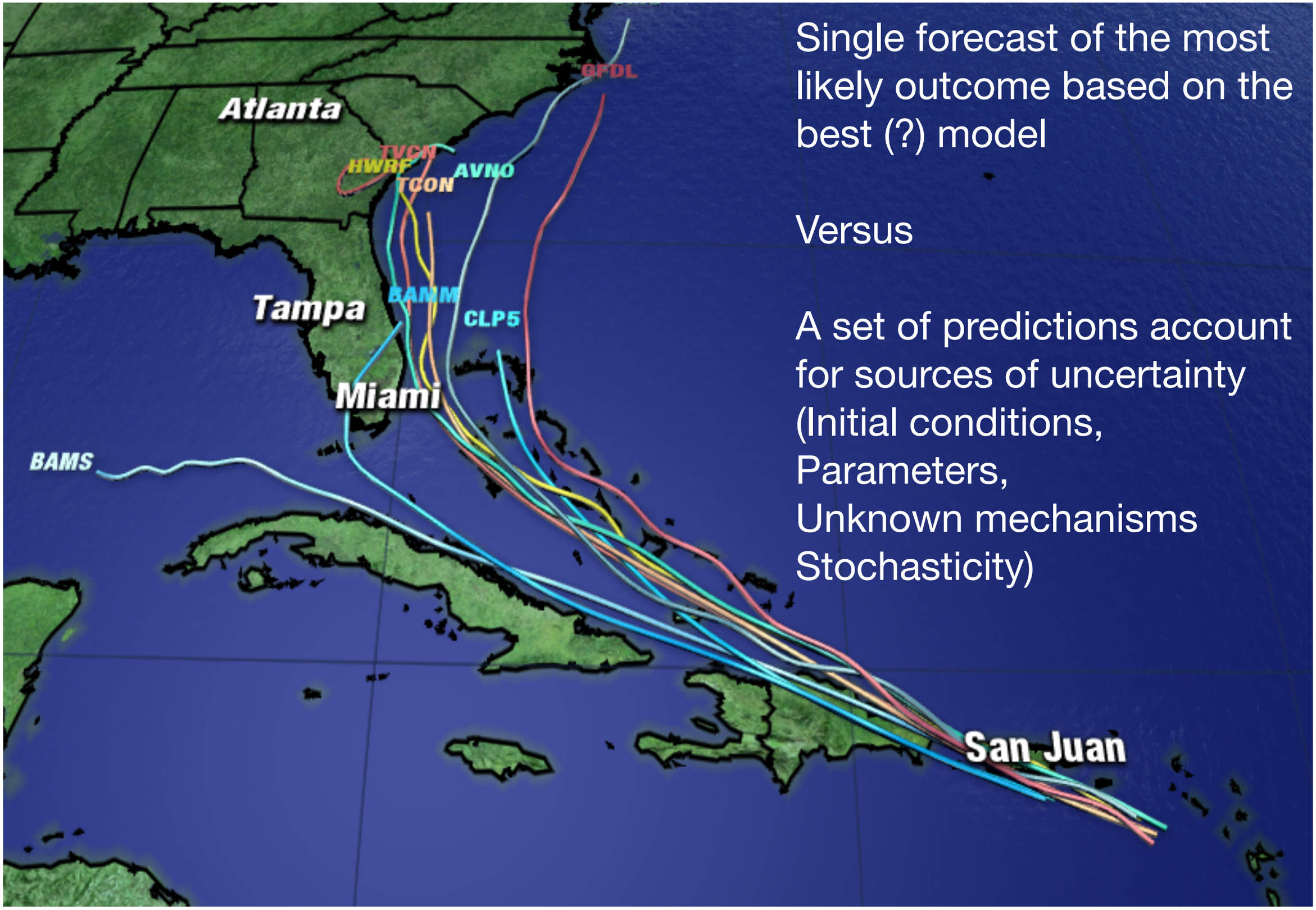






- 8 patients with metastatic melanoma, treated with continuous MTD BRAF/MEK
- LDH: every 2~4 weeks
- PD: progression disease (> +20%), SD: stable disease (<= +20%), PR: partial response (< -25%)

Ensemble prediction

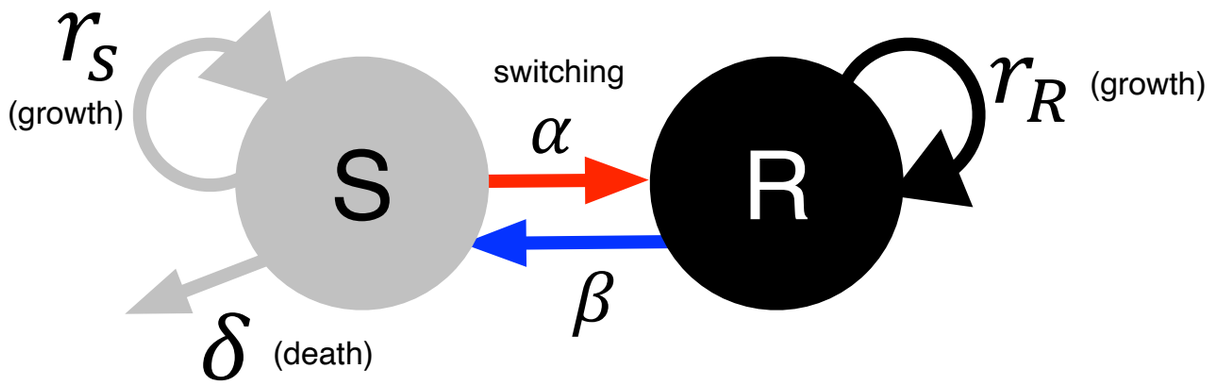


Single forecast of the most likely outcome based on the best (?) model

Versus

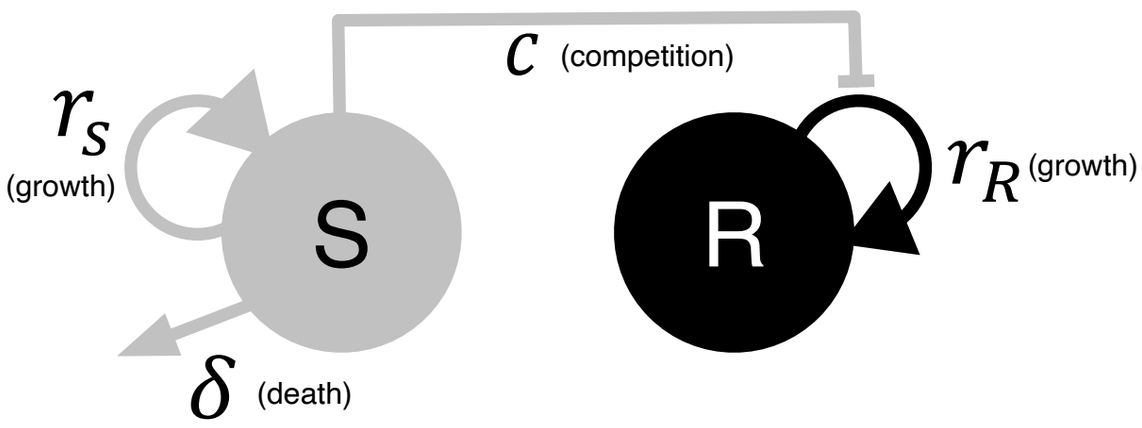
A set of predictions account for sources of uncertainty (Initial conditions, Parameters, Unknown mechanisms Stochasticity)

Two different mathematical models



$$\frac{dS}{dt} = r_S\left(1 - \frac{S+R}{K}\right)S - \delta S - \alpha S + \beta R,$$

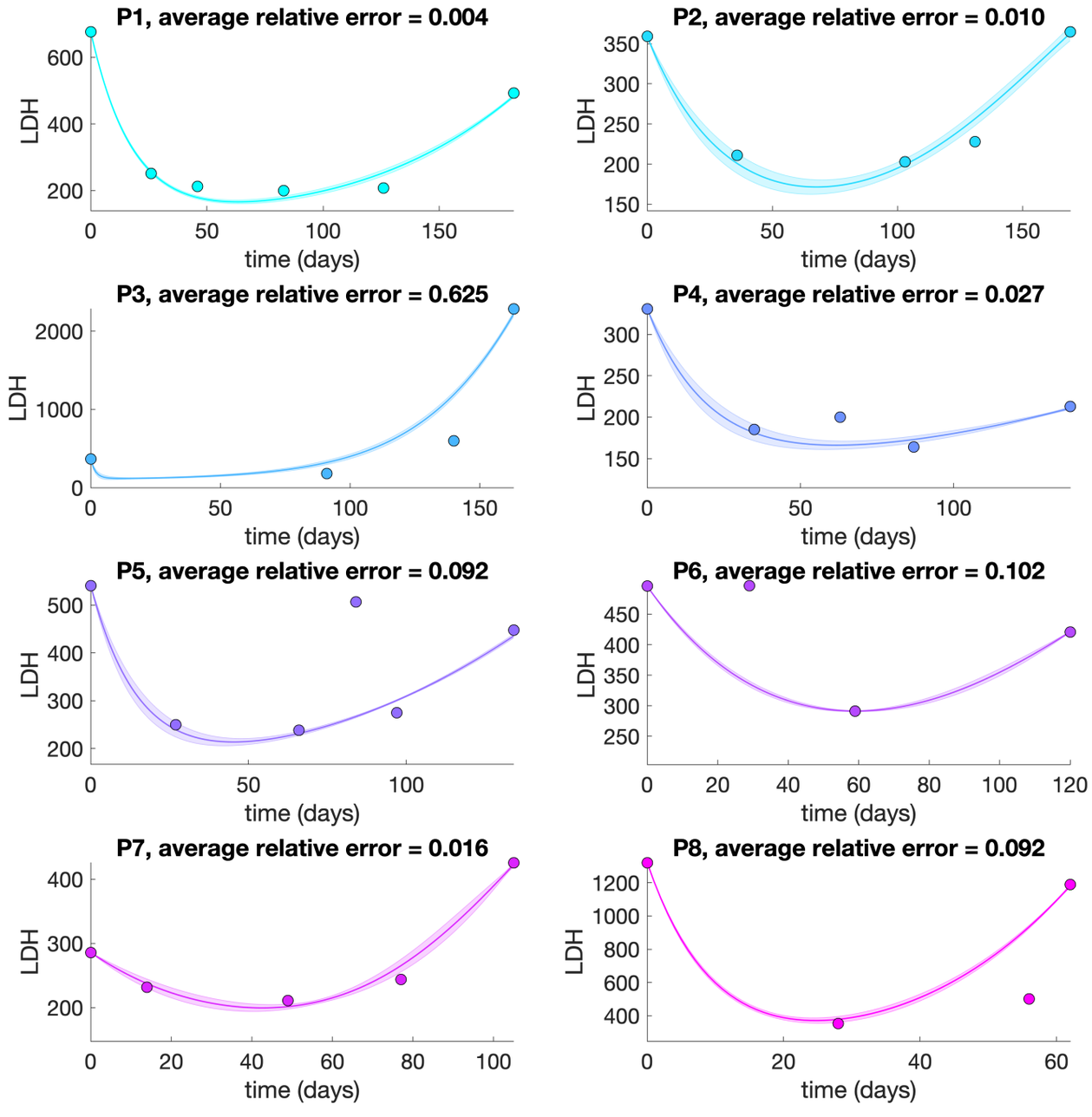
$$\frac{dR}{dt} = r_R\left(1 - \frac{S+R}{K}\right)R + \alpha S - \beta R.$$



$$\frac{dS}{dt} = r_S\left(1 - \frac{S+R}{K}\right)S - \delta S,$$

$$\frac{dR}{dt} = r_R\left(1 - \frac{C*S+R}{K}\right)R.$$

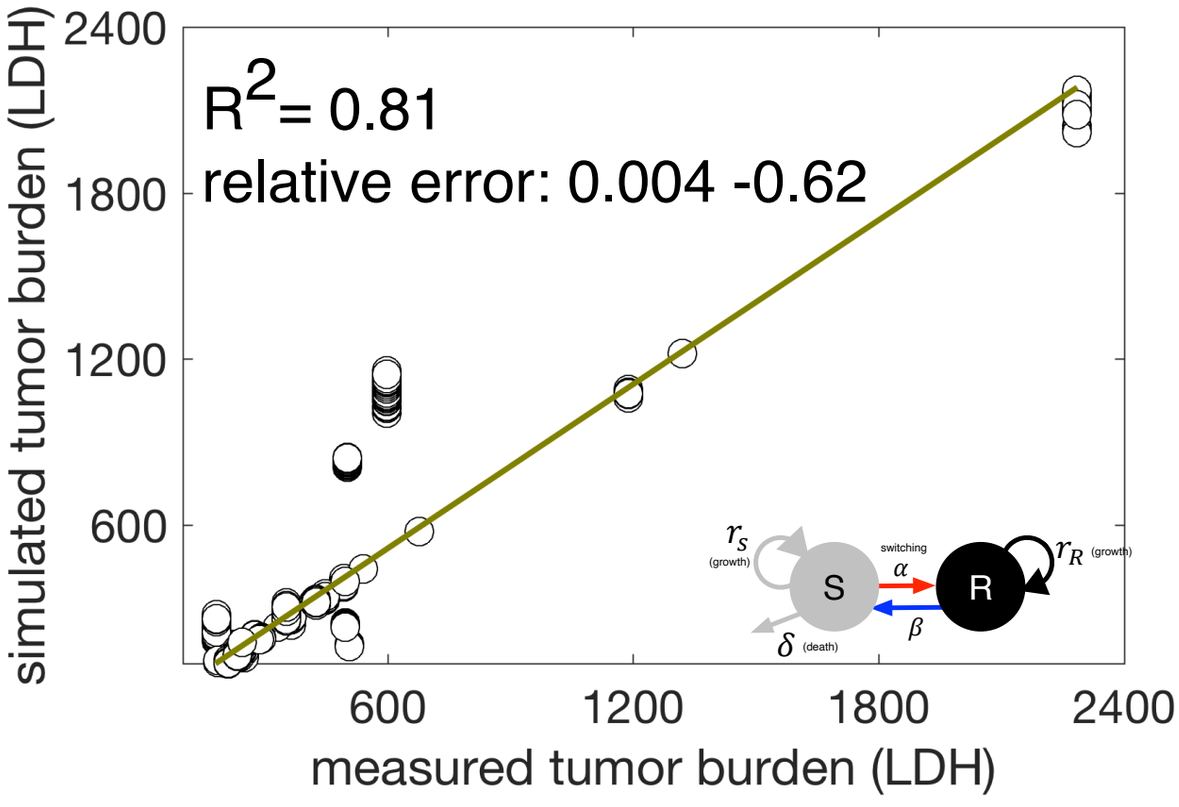
Model calibration



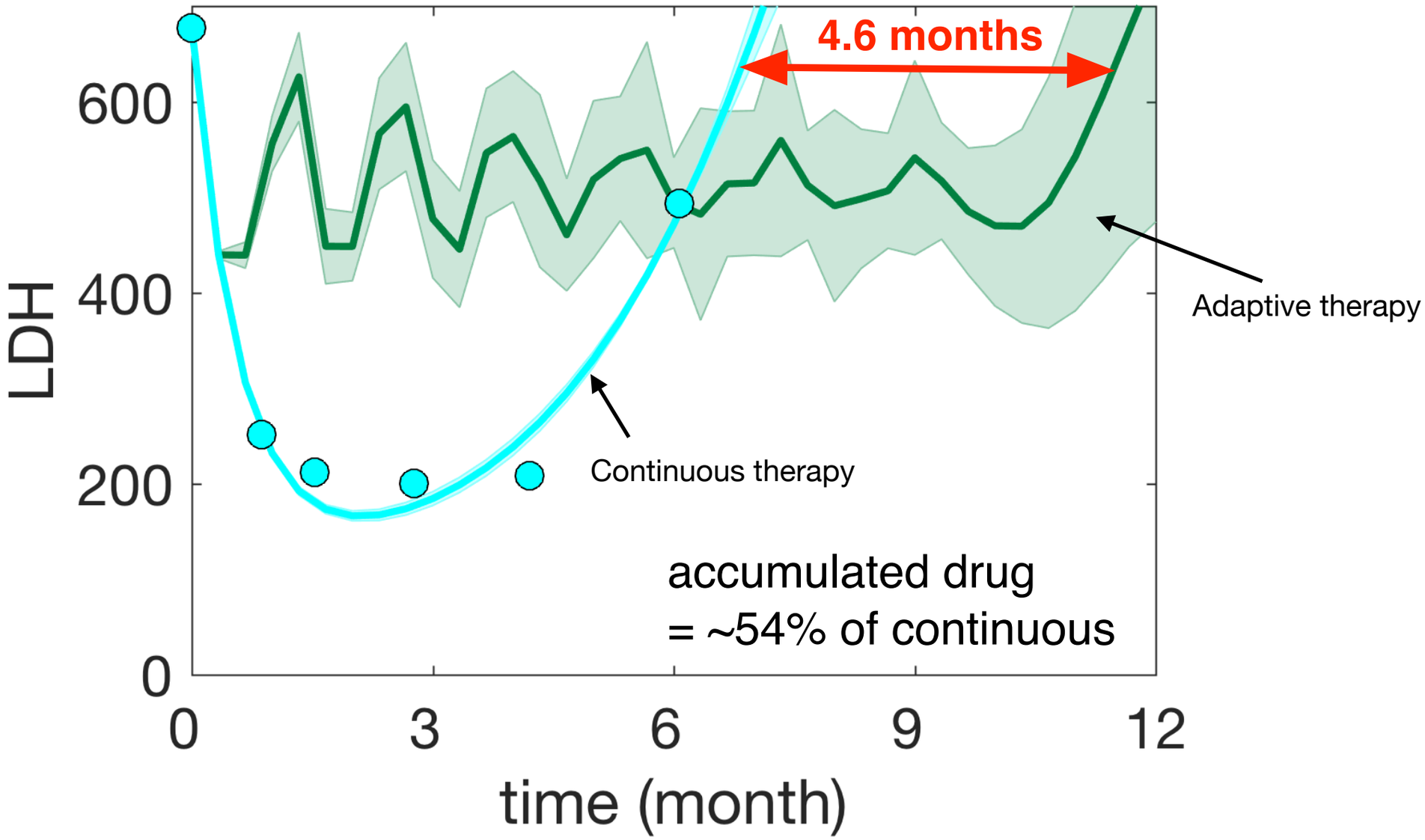
$$\min_{\vec{\theta}} \left\| V\left(t;\vec{\theta}\right) - L(t) \right\|_2^2,$$

$$\theta = \{S_0, K, \delta, r_R, \alpha\}$$

$r_S = 0$, when therapy is on

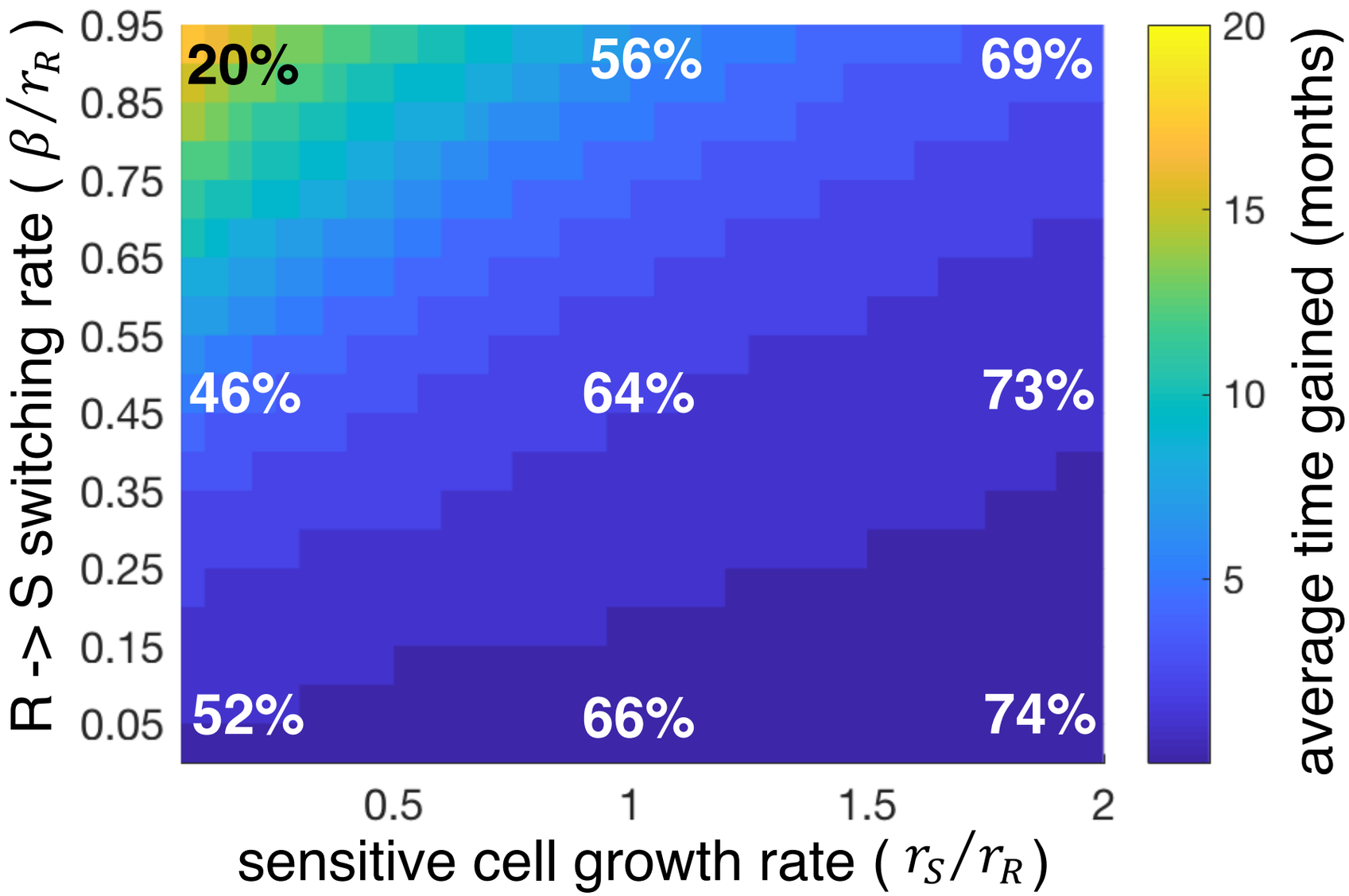


Model predicted adaptive therapy



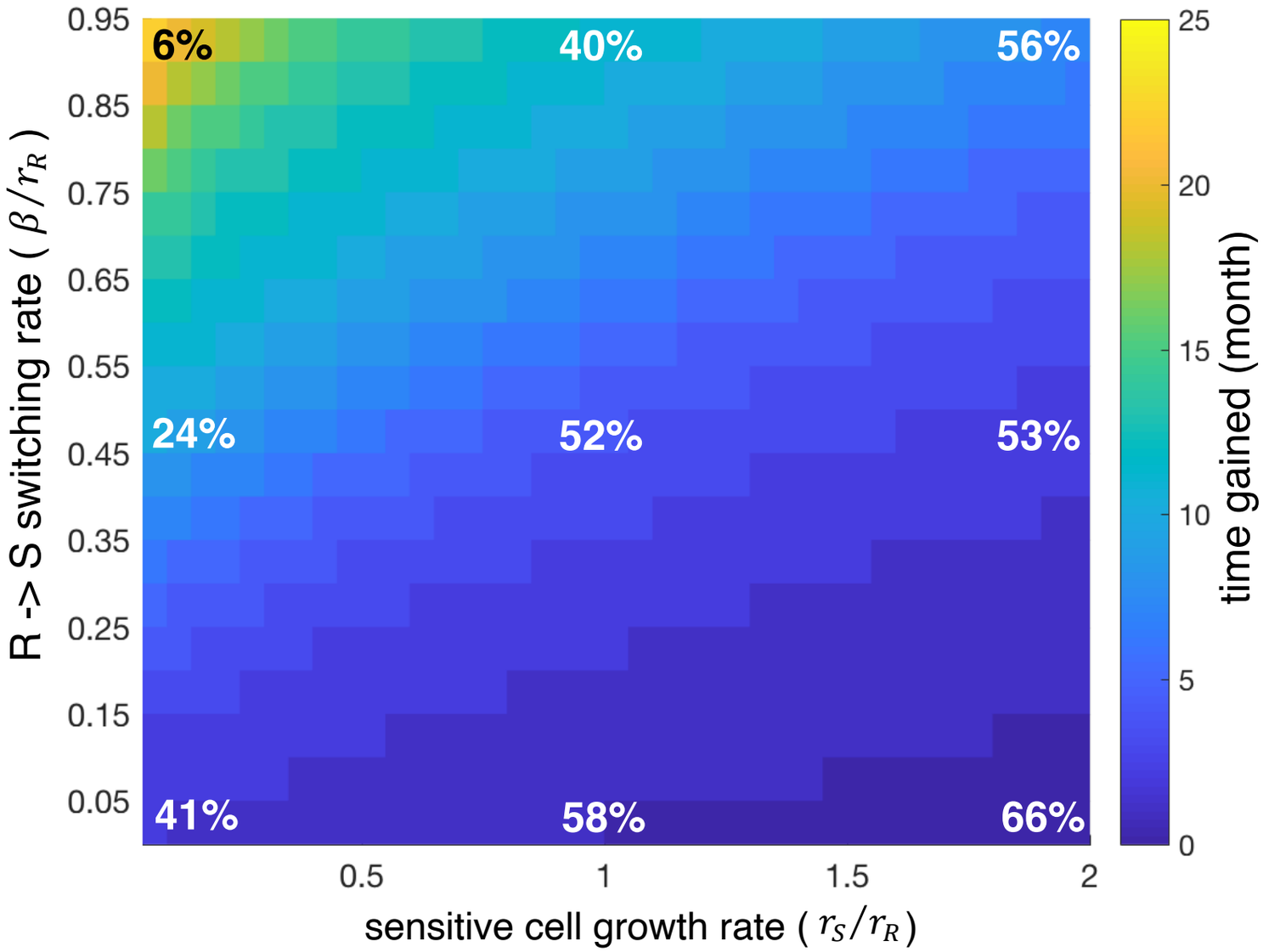
- Treatment stop when LDH <= -50% of initial, re-start: LDH = initial
- Adaptive therapy delayed time to progression: ~4.6 months with ~54% dose rate compared to continuous MTD

Predicted benefit



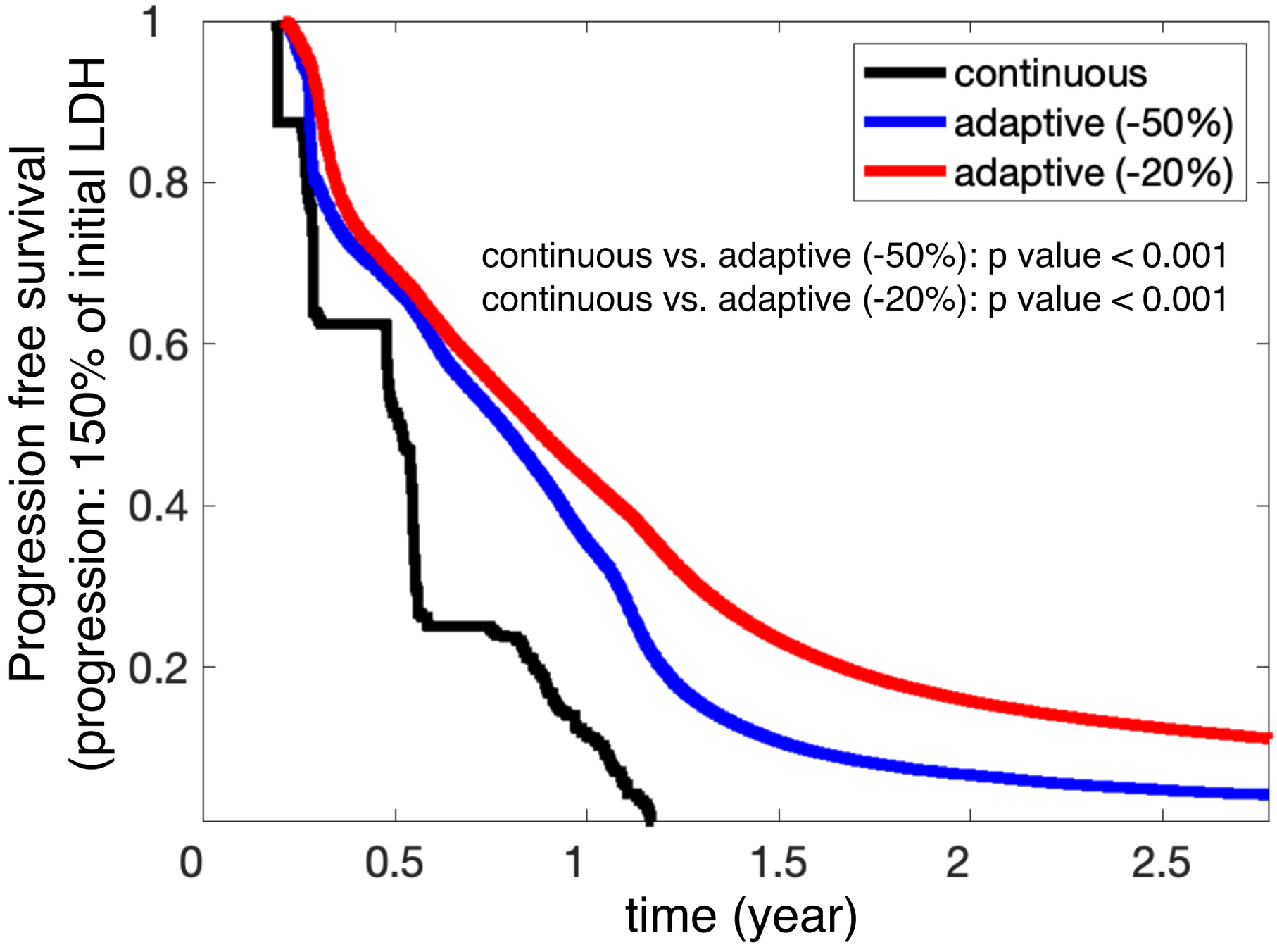
- Various parameters (not estimated) considered
- Time gained from continuous therapy: ~ 20 months
- Dose rate: 20~74% of continuous MTD
- Most beneficial: R—>S switching rate is high & sensitive cell growth rate is low

Different threshold:-20%



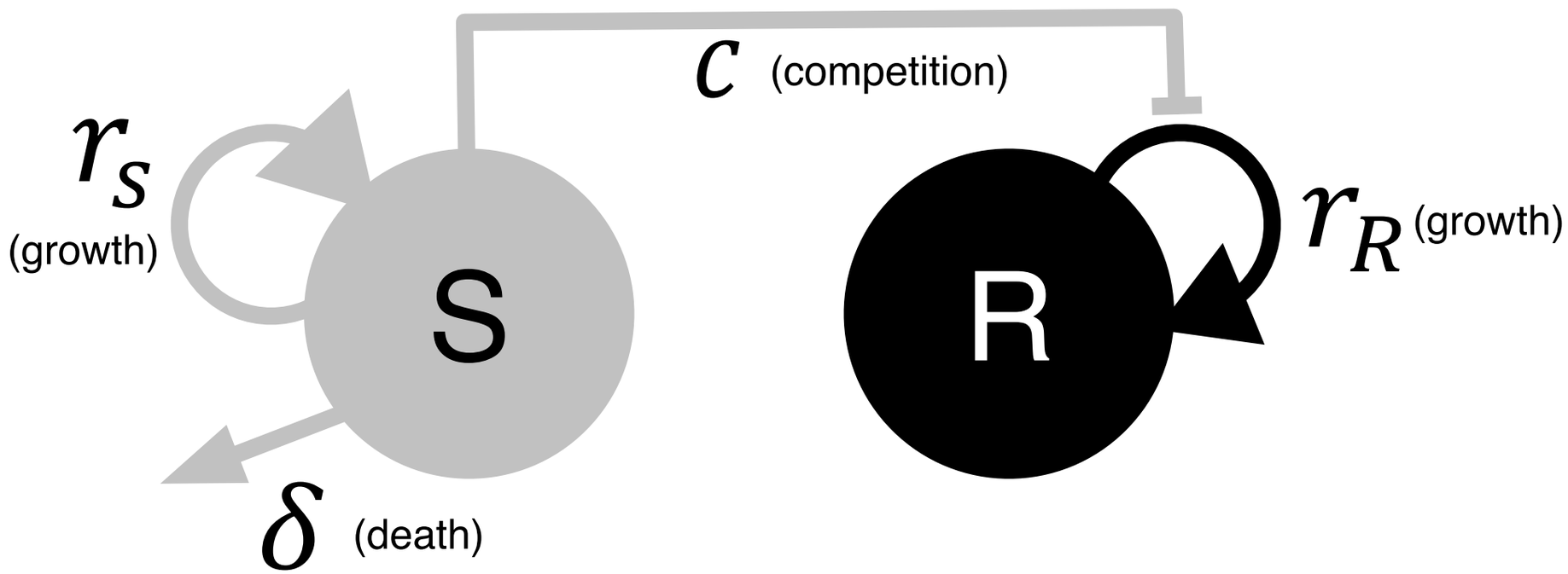
- Treatment stop when LDH <= -20% of initial, re-start: LDH = initial
- Time gained from continuous therapy: up to 25 months
- Dose rate: 6~66% of continuous MTD

Progression free survival



- PFS of adaptive therapy is significantly higher than MTD
- -20% is better than -50% stopping criteria

Mathematical model: competition



$$\frac{dS}{dt} = r_S\left(1 - \frac{S+R}{K}\right)S - \delta S,$$

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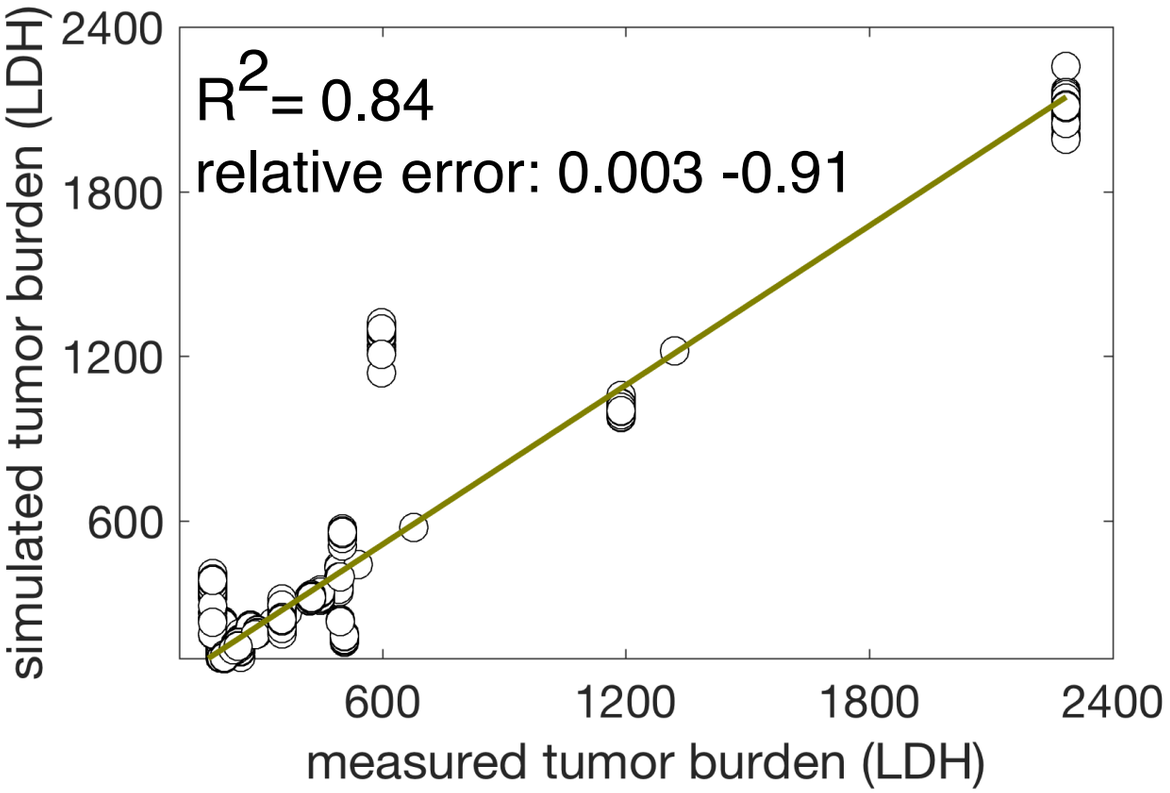
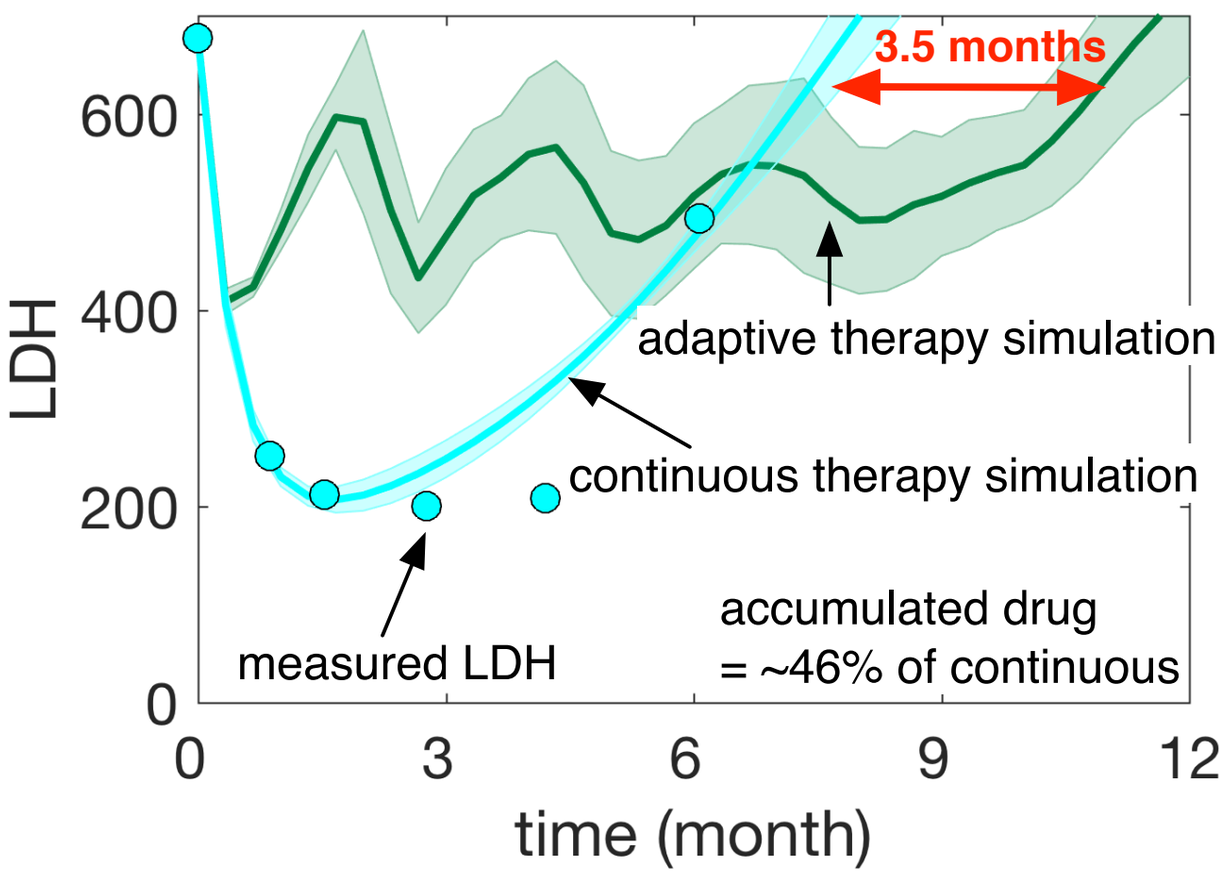
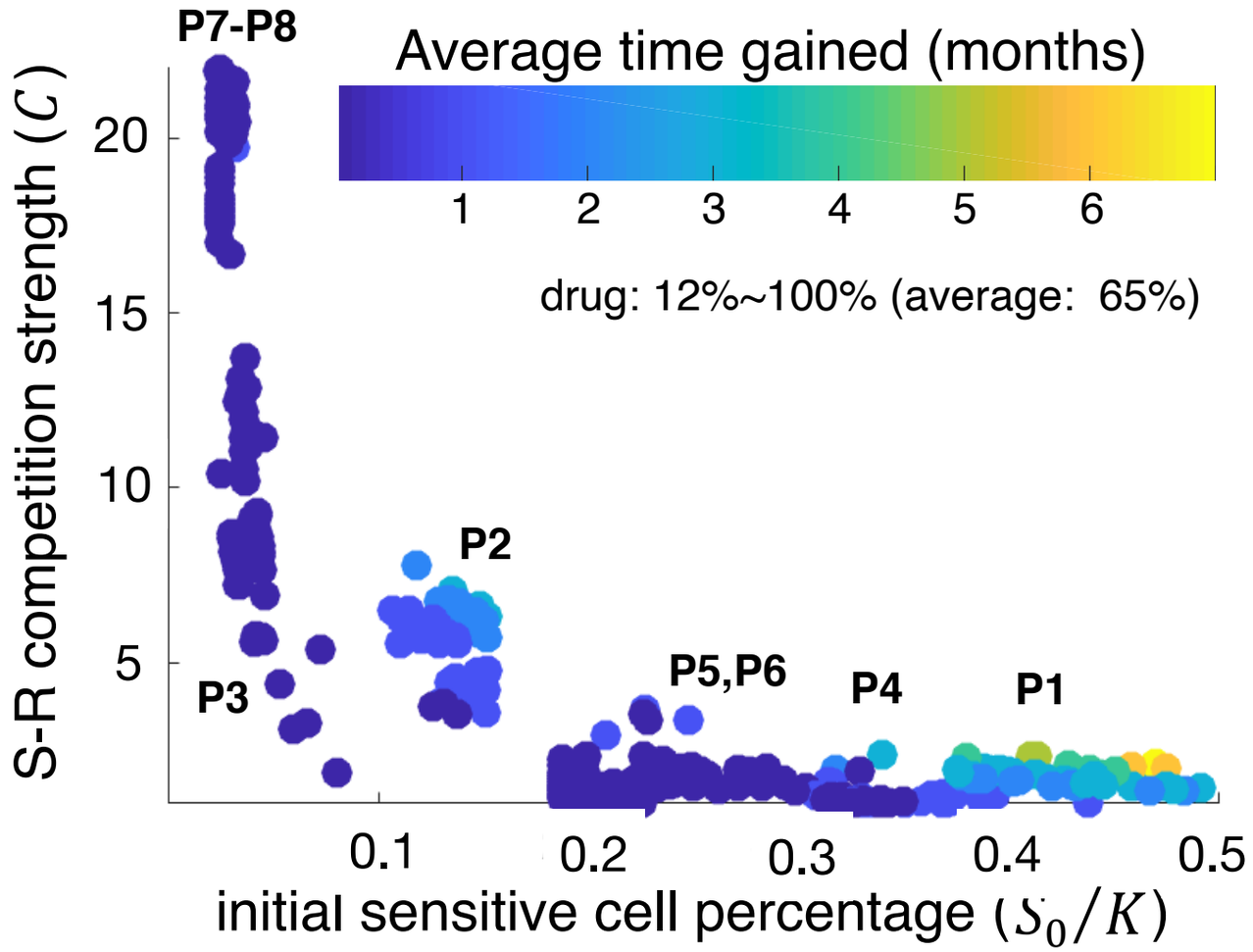
Model calibration & prediction





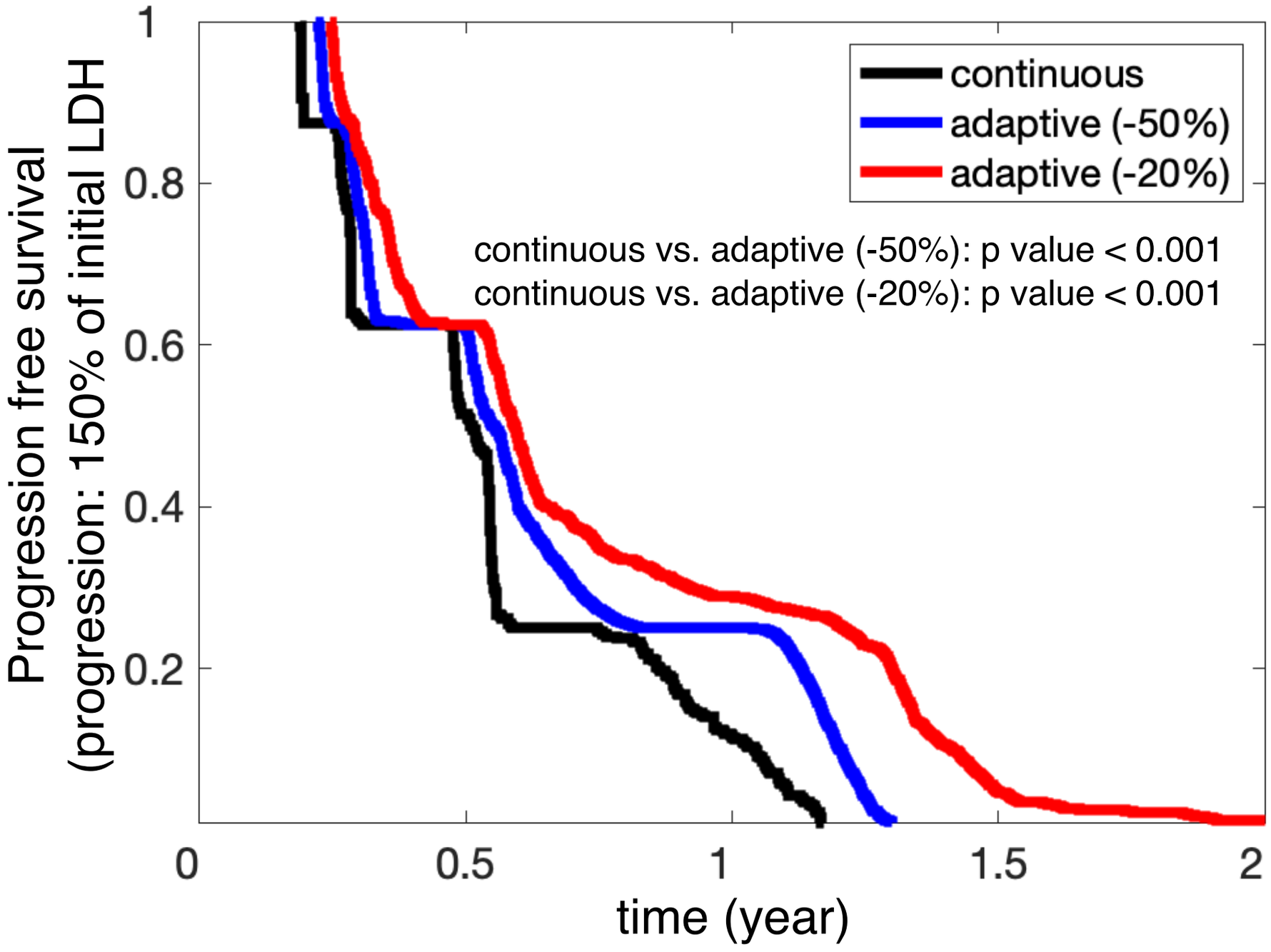
- Predicted time gained: ~3.5 months (vs. 4.3 months from the previous model)
- Dose rate: ~46% of continuous MTD

Predicted benefit



- Various growth rates of sensitive cell population considered: r_S: 0~95% of r_R
- Dot: average time gained for each patient
- Time gained: ~6 months (vs. 20 months from the drug induced resistance model)
- Dose rate: 12~100% of continuous MTD
- Most beneficial: large number of initial sensitive cells

Progression free survival



- PFS of adaptive therapy is significantly higher than MTD
- -20% is better than -50% stopping criteria

Conclusion

- Effectiveness of adaptive therapy varies among patients
- Understanding the underlying mechanism for the variability for patient selection
- Multiple mathematical and computational models may be required
- Two different mathematical models: competition and plasticity

- Adaptive therapy improves progression free survival compared to MTD continuous therapy
- Key predictive factors: initial number of sensitive cell population, switching rate from R to S, and growth rate of drug sensitive cell population

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