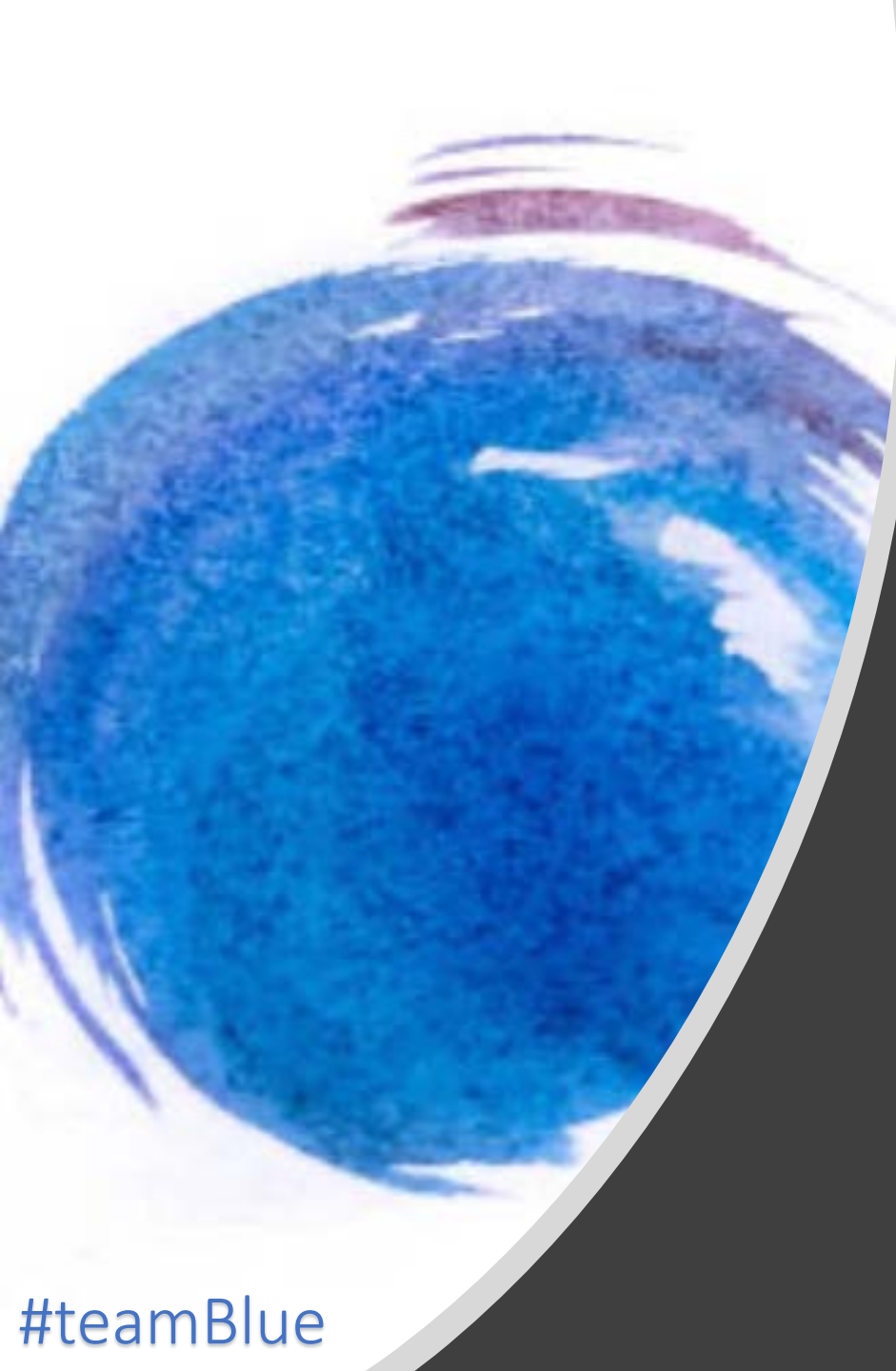




Fatal Attraction

Using cancer traps
against glioblastoma



Sarah, Stefano, Lito, Jeff, Renee, Dung-Tsa,
Zach, Katejan, Daniel, Nam, Ray, Mohammad,
Junyan, Chris, Solmaz, Heiko

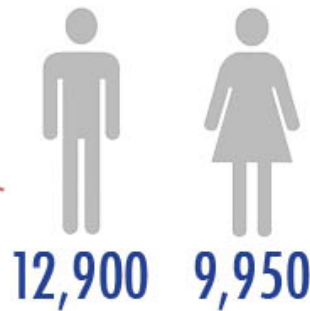
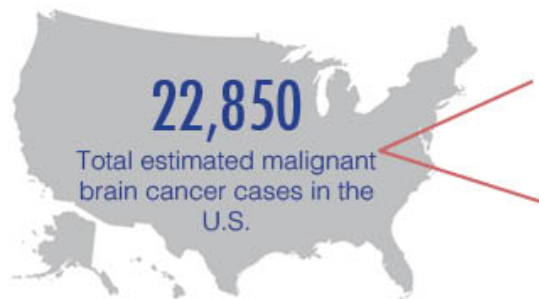
#teamBlue



Glioblastoma background



2015 Brain Cancer Facts & Figures



Only one in **140** men and one in **180** women will develop a malignant tumor of the brain or spinal cord in his or her lifetime all cancer diagnoses.

Source: American Cancer Society



Cure Brain Cancer
FOUNDATION

Brain cancer is deadly

Five-year survival rates...

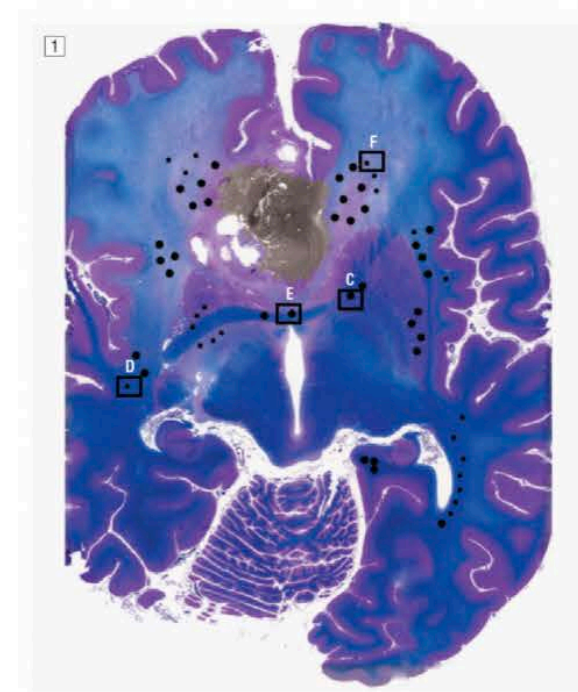
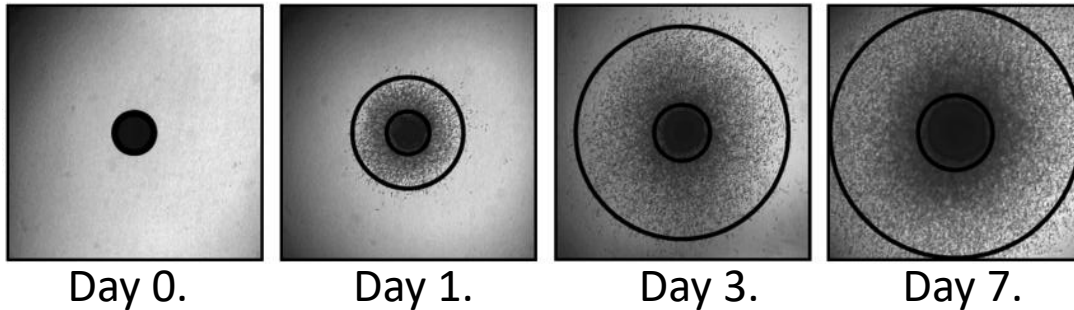


Source: AIHW National Cancer Statistic



GBM biology that drives failure

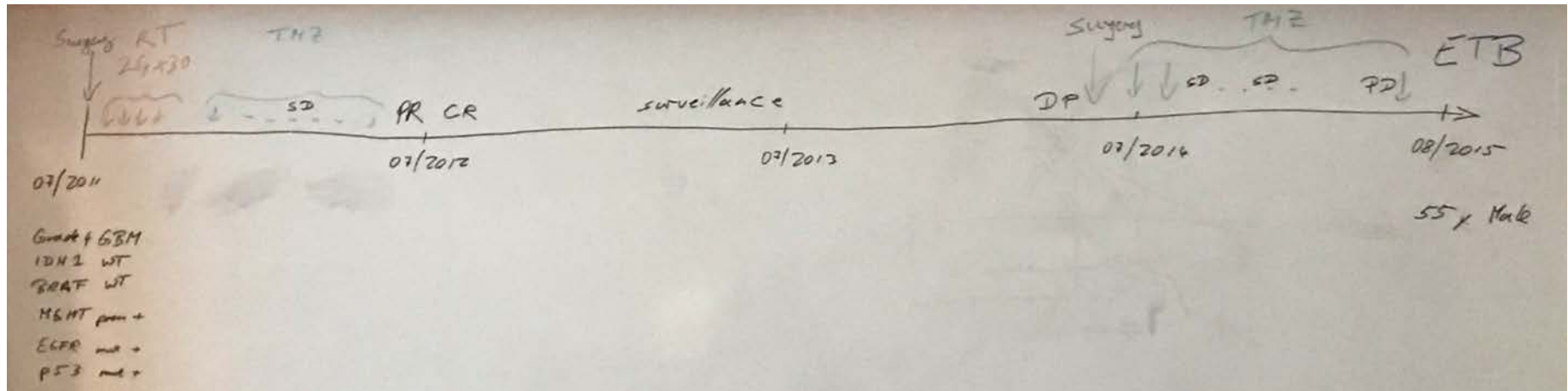
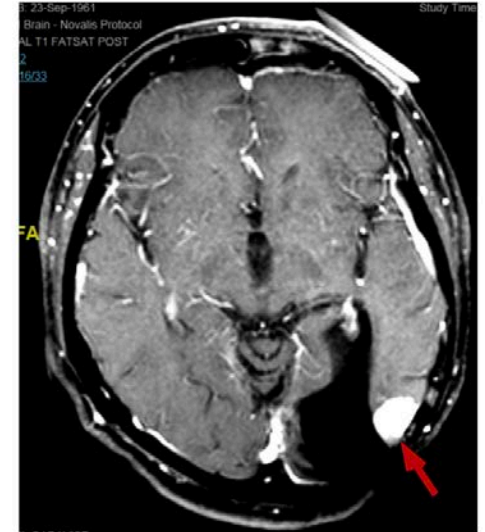
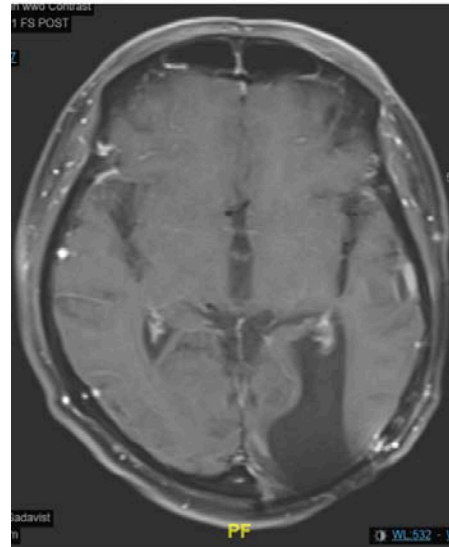
- Multifocal and diffusive disease – cells invade beyond surgery and radiation margin



- Residual cells develop resistance to continuous maximum tolerable dose treatment

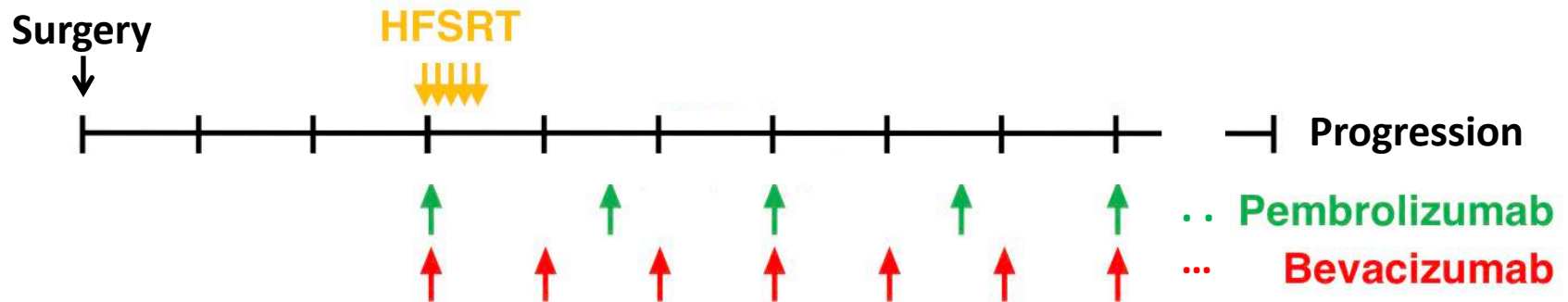


Patient presentation





Clinician-choice treatment





Response rates

Bev	Anti PD1 (e.g. Pembro)	Pembro+ Bev	HFSRT+ Bev	HFSRT+ Bev + Pembro
23.1%	7.8%	26.0%	52%	83.3%
95% CI: 16.7%-30.5%	95% CI: 4.1 %-13.3%	95% CI: 16.3-41.5	95% CI: 28 %-89%	95% CI: 62 % - 95%

Bev: Bevacizumab, Anti-angiogenic agent

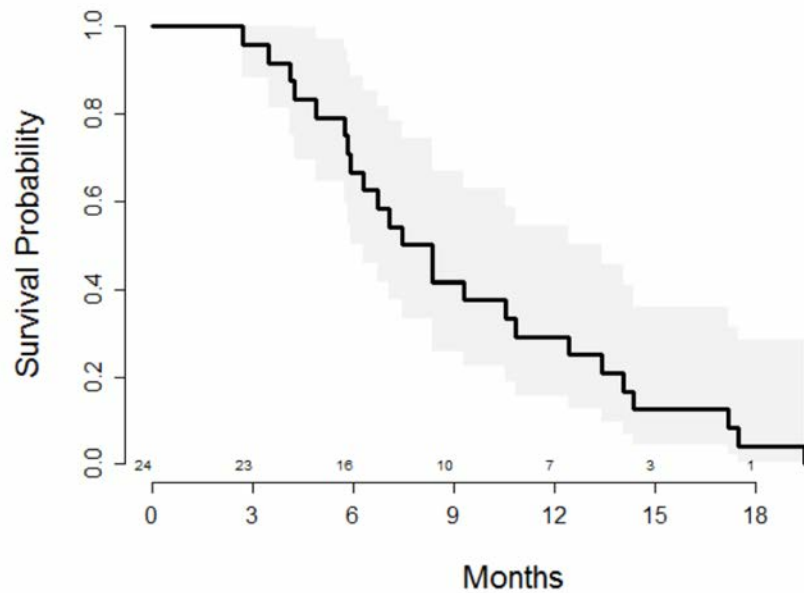
Pembro: Pembrolizumab, Anti-PD1 (immunotherapy)

HFSRT: Hypofractionated Stereotactic Radiotherapy

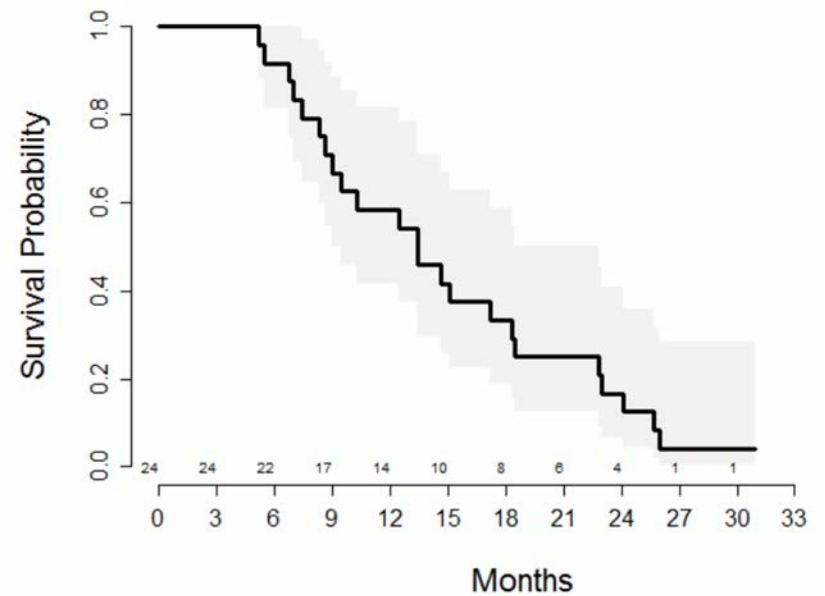


Survival analysis

Progression Free Survival



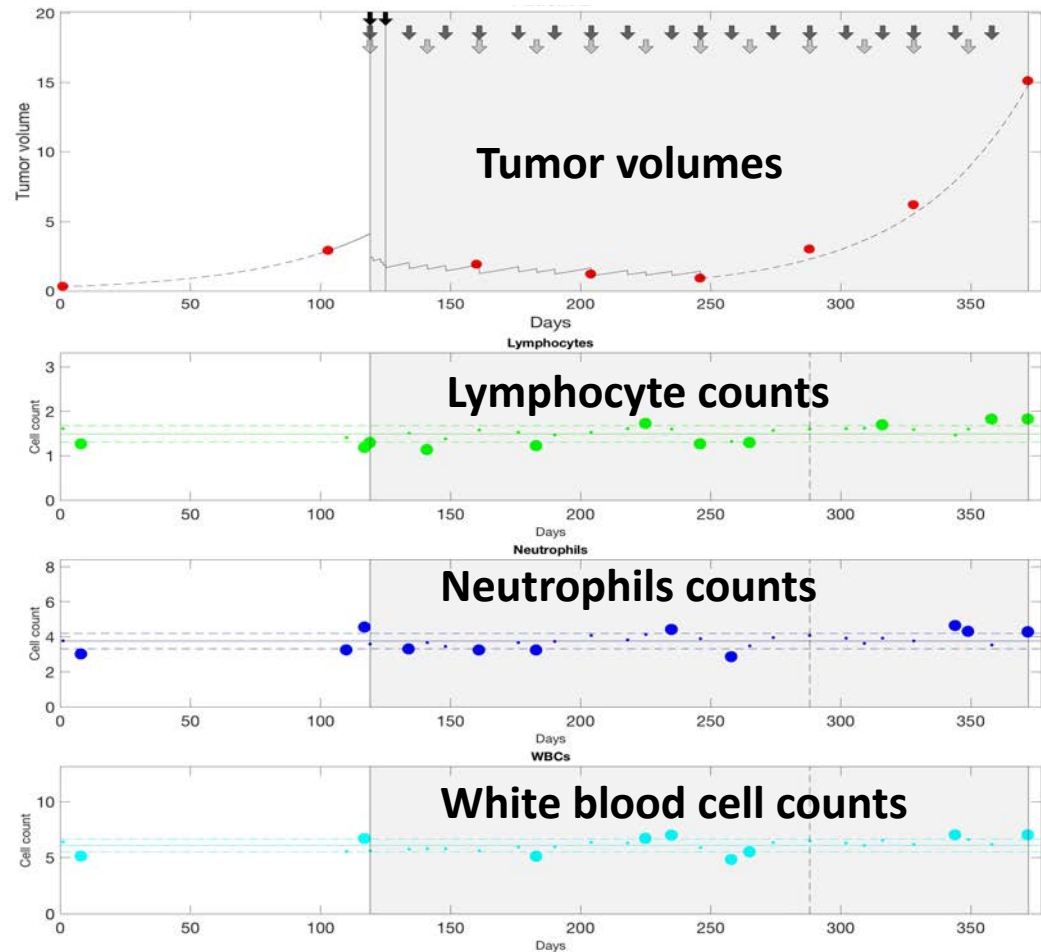
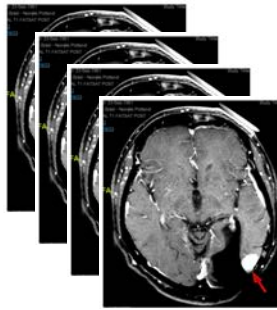
Overall Survival





Data to inform ETB, N=31

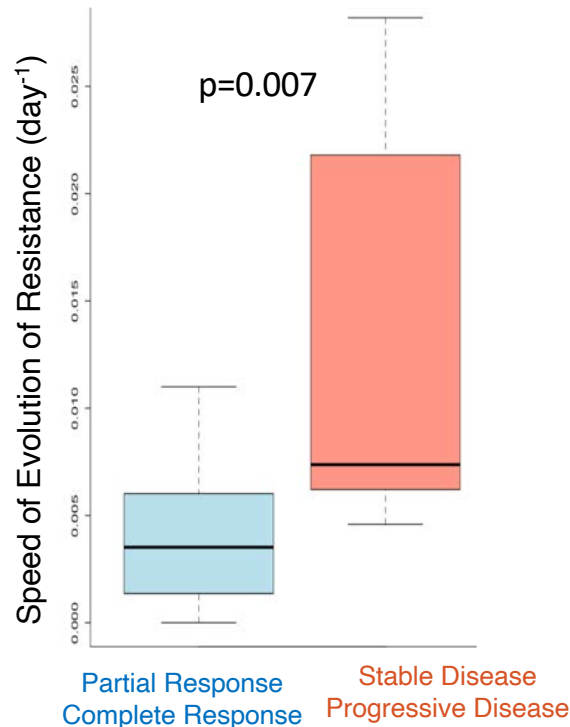
Histopathology	
Glioblastoma	13
Anaplastic astrocytoma	1
Sex	
Male	9
Female	5
Age	
< 50 years	6
≥ 50 years	8
Number of recurrence	
1 st	9
2 nd	5
RANO progression criterion	
T1post	2
T2/FLAIR	8
T1post & T2/FLAIR	2
Clinical deterioration	2
MGMT promoter methylation	
Methylated	7
Unmethylated	6
Unknown	1
IDH mutation	
Positive	3
Negative	10
EGFR vIII mutation	
Positive	5
Negative	5
Equivocal	1
Unknown	3



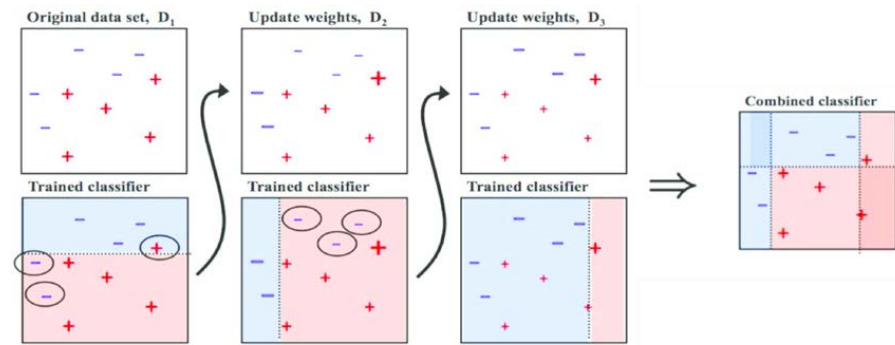


Statistics-based prediction for clinician-choice therapy based on clinical trial data

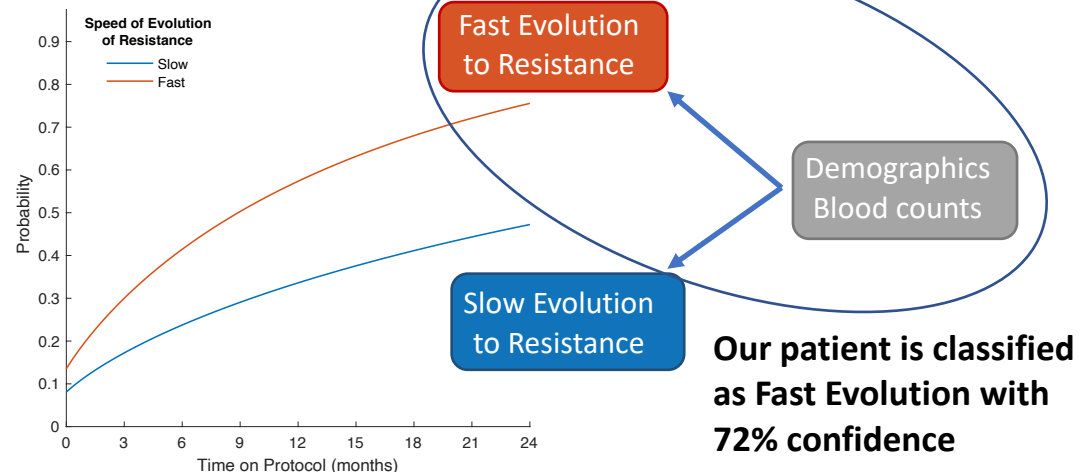
Speed of evolution of resistance correlates with patient response to clinical trial protocol



Machine learning classifiers

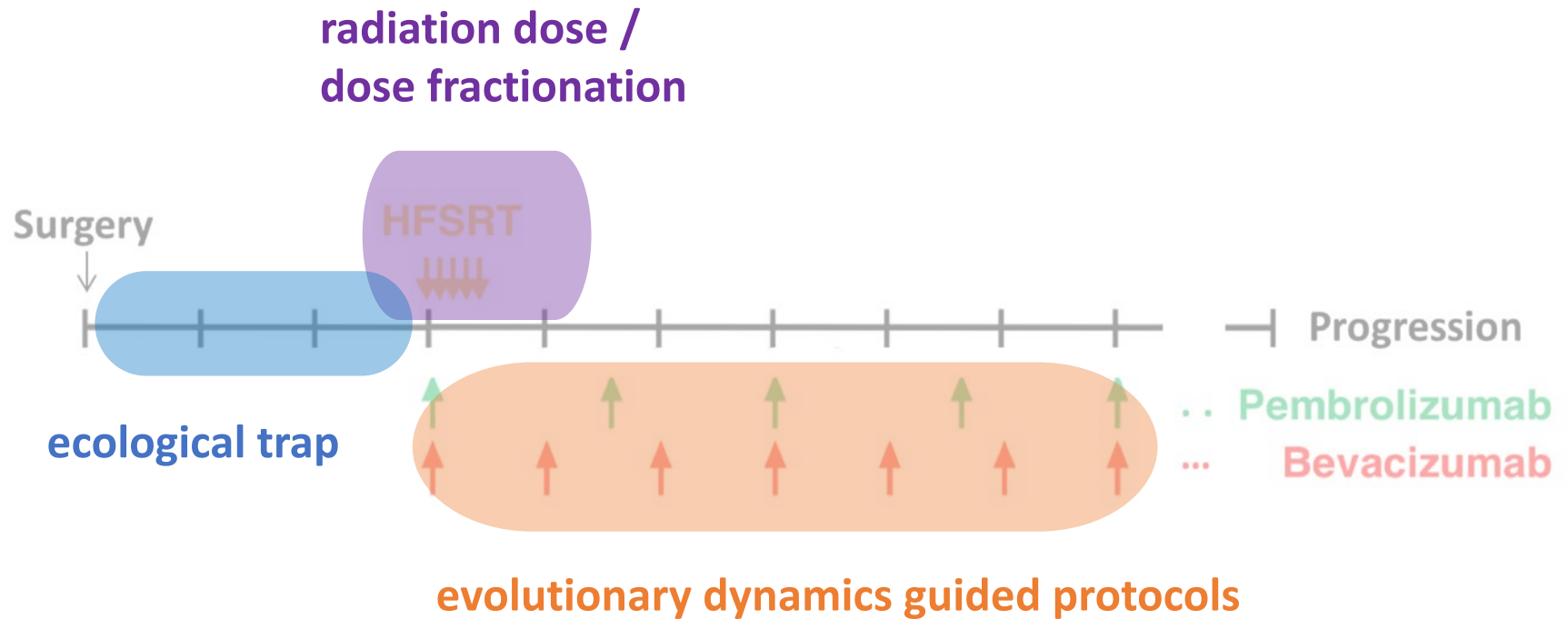


Predicting time-dependent probability of disease progression



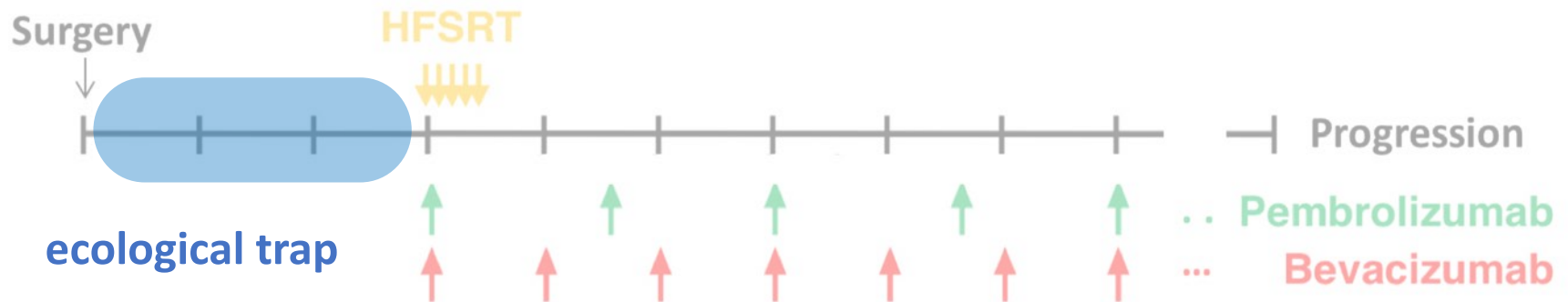


Evolutionary Tumor Board





Evolutionary Tumor Board



Ecological Trap to direct cells to the surgical cavity to be irradiated



Ecological trap

Habitat or other feature in an environment that appears to be fitness-enhancing, but actually reduces fitness



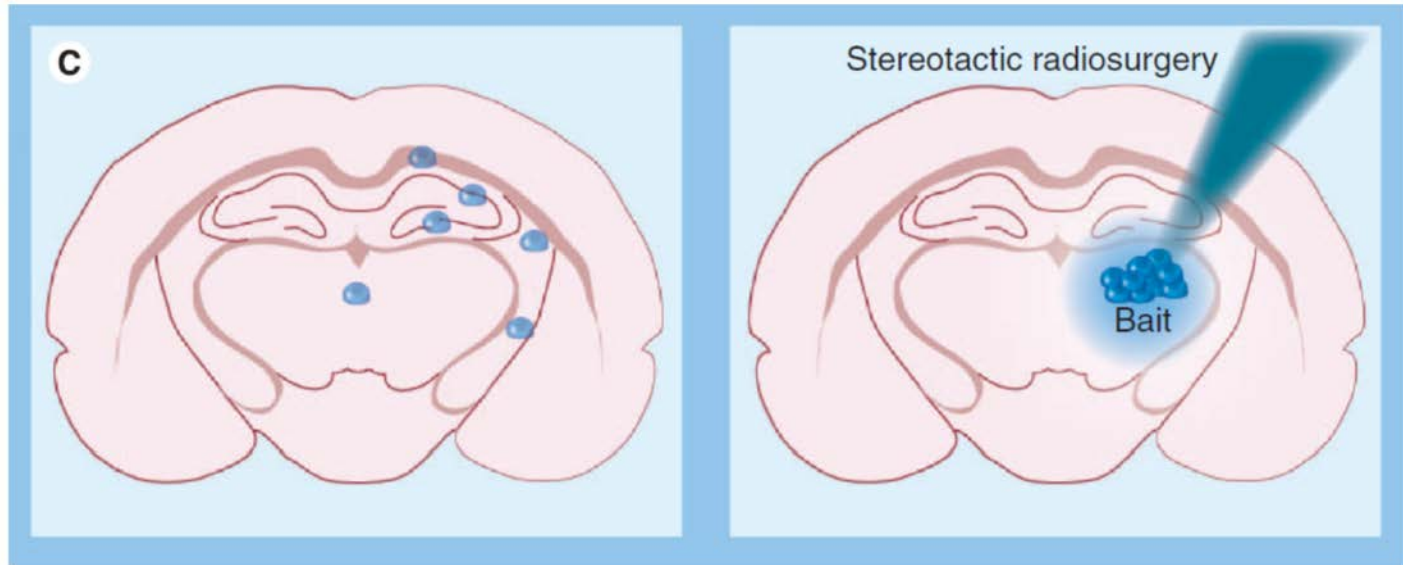
Wood thrush



New Zealand fantail



Ecological trap in GBM



- Therapeutic ecological trap: invasion of glioma cells throughout brain parenchyma.
- The cancer cell trap diverts the cancer cell migratory potential for therapy.
- A high radiation dose is delivered to cancer cells attracted to the trap.



Ecological trap in GBM

Perspective

Future Oncology

Translation of the ecological trap concept to glioma therapy: the cancer cell trap concept

Boudewijn van der Sanden^{1,2}, Florence Appaix¹, François Bergeri^{1,2}, Laurent Selek¹, Jean-Paul Issartel¹ & Didier Wion^{*1}

¹INSERM U836, Grenoble Institut des Neurosciences, Université Joseph Fourier, CHU Michallon, Grenoble, France

²CLIMATEC, Centre de Recherche Edmond J. Safra, MINATEC Campus, CEA, Grenoble, France

*Author for correspondence: didier.wion@ujf-grenoble.fr

Acta Biomaterialia 84 (2019) 268–279



Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat



Full length article

A new glioblastoma cell trap for implantation after surgical resection

Lila Autier^{a,b,c}, Anne Clavreul^{a,b,e}, Maximiliano L. Cacicedo^d, Florence Franconi^{e,f}, Laurence Sindji^b, Audrey Rousseau^{b,g}, Rodolphe Perrot^h, Claudia N. Montero-Menei^b, Guillermo R. Castro^d, Philippe Menei^{a,b}



frontiers
in Pharmacology

REVIEW
published: 12 August 2019
doi: 10.3389/fphar.2019.00887



Reversing the Tumor Target: Establishment of a Tumor Trap

Mathie Najberg^{1,2}, Muhammad Haji Mansor^{1,2}, Frank Boury¹, Carmen Alvarez-Lorenzo^{2†} and Emmanuel Garcion^{1†}

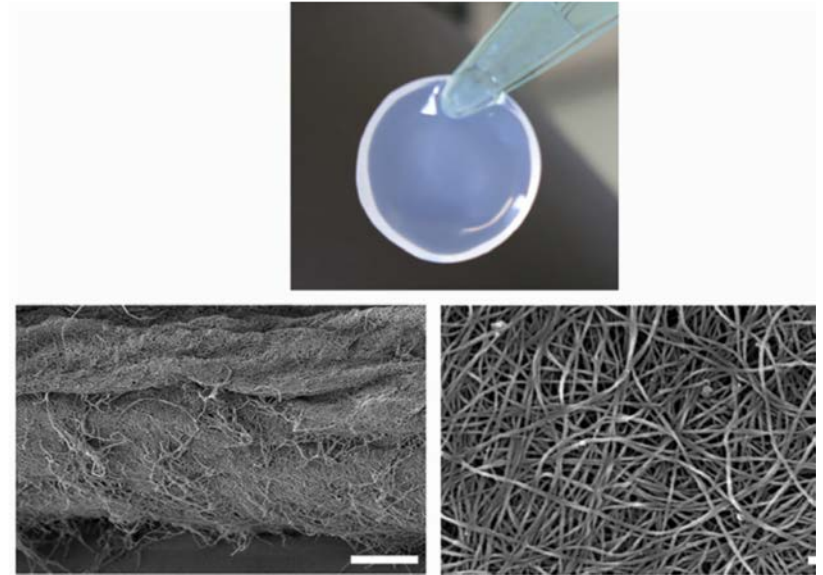
¹ CRCINA, INSERM, Université de Nantes, Université d'Angers, Angers, France, ² Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, R + D Pharma Group (GI-1645), Facultad de Farmacia, Universidad de Santiago de Compostela, Santiago de Compostela, Spain, [†] Center for Education and Research on Macromolecules (CERM), Université de Liège, Liège, Belgium



Ecological trap in GBM

The cancer trap: *Autier et al. (2019)*

- bacterial cellulose membrane
- close to FDA approval
- visible on MRI



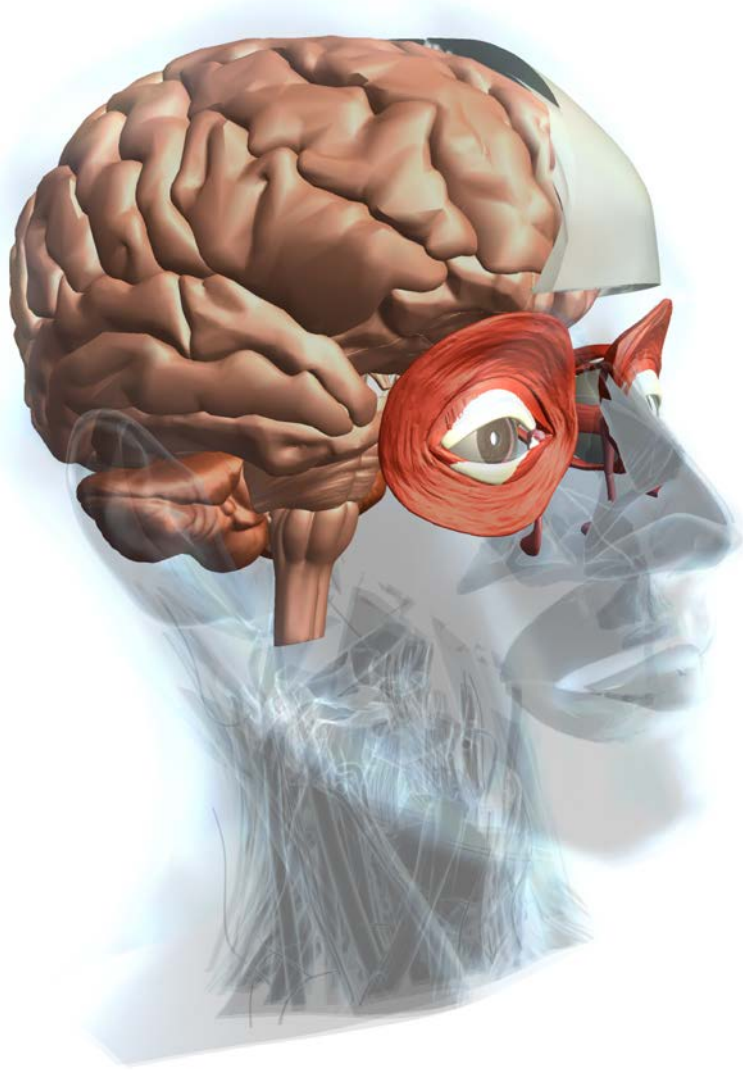
The bait: *Hira et al. (2017)*

- Stromal Cell-derived Factor-1 (SDF-1 or CXCL12)
- SDF-1 localized in GBM niches
- SDF-1 regulates migration of many cancer cell types (including in GBM)
- SDF-1 facilitates homing of glioma stem-like cells to tumor niches

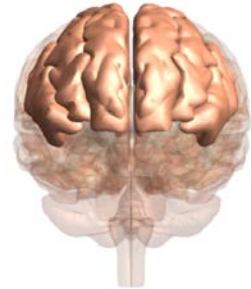


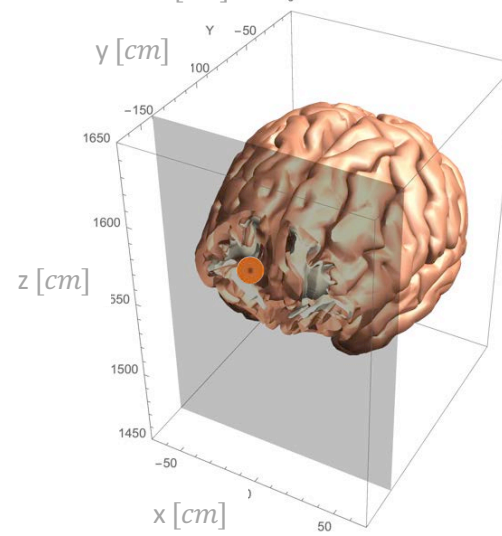
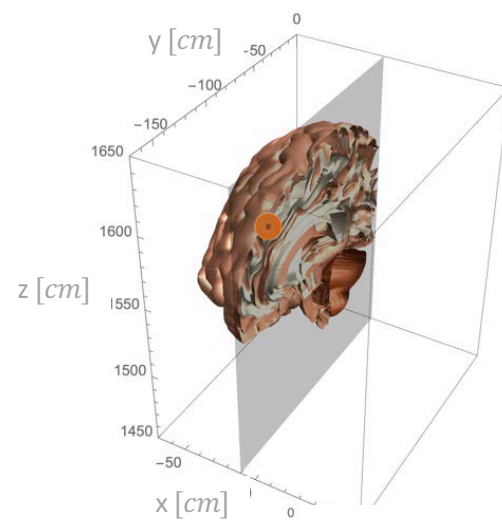
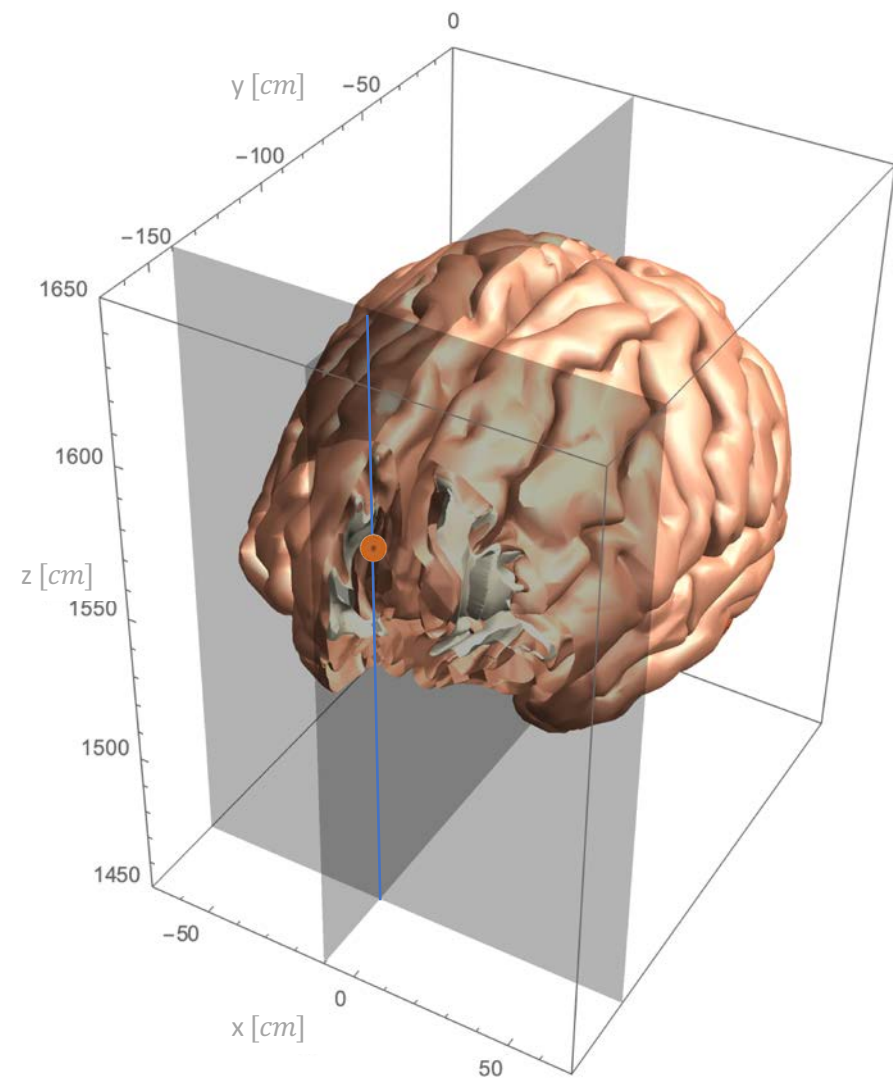
Ecological trap in GBM

- Implant the cellulose membrane with attractant during surgery
- Glioma cells trapped for 4-6 weeks while patient recovers from surgery
- Trapped cells eradicated with high-dose radiotherapy

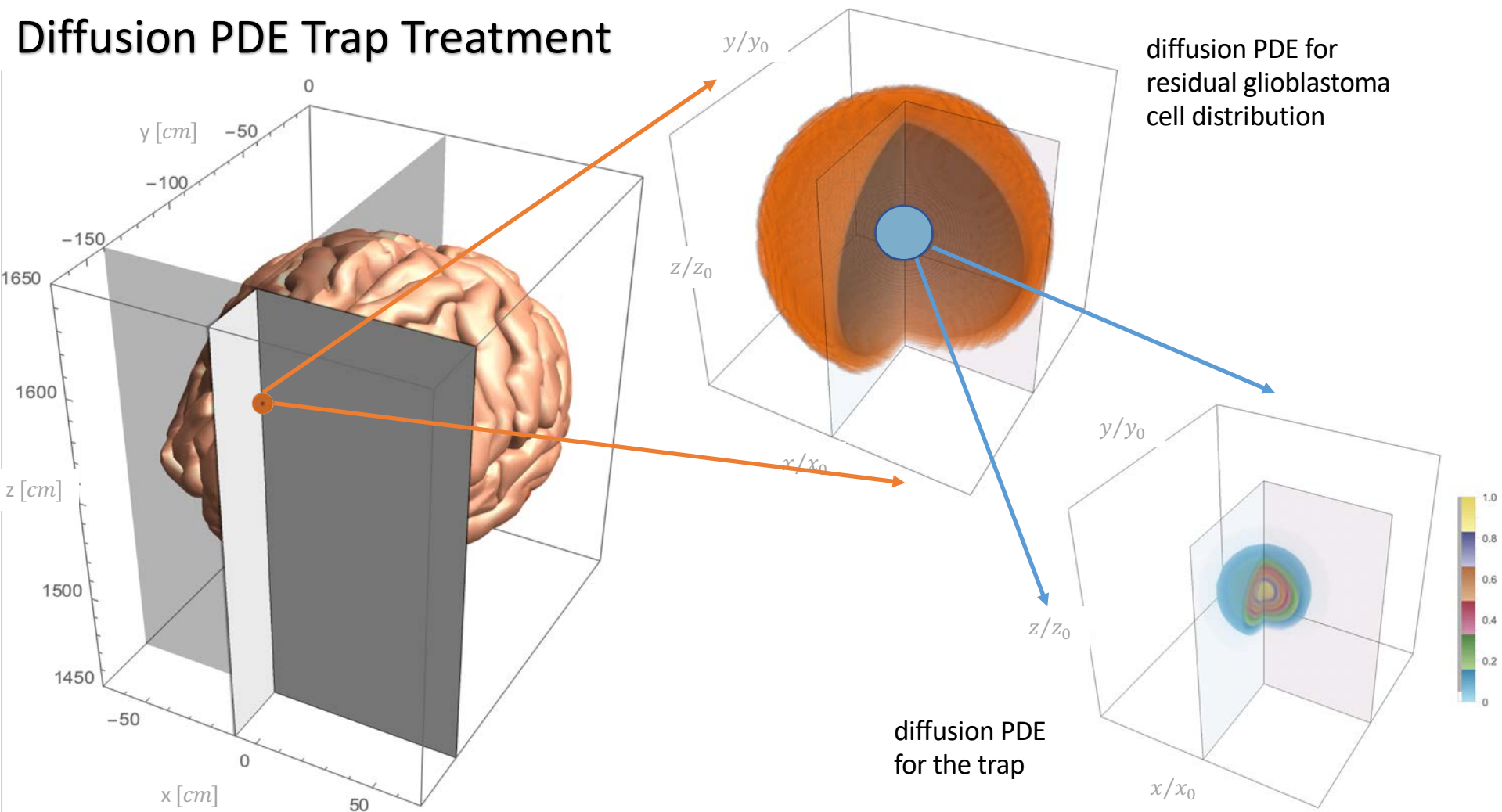


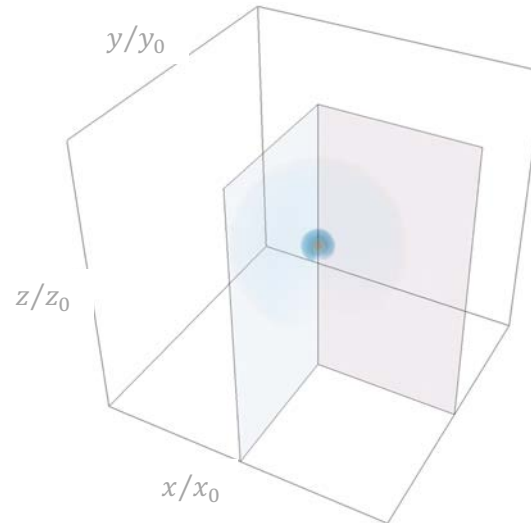
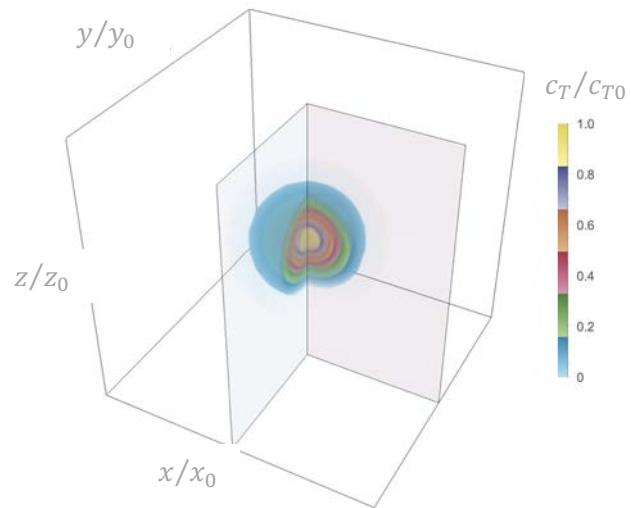
Prefrontal Cortex



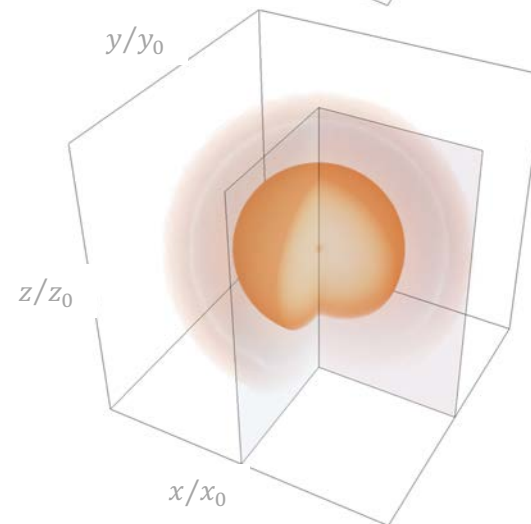
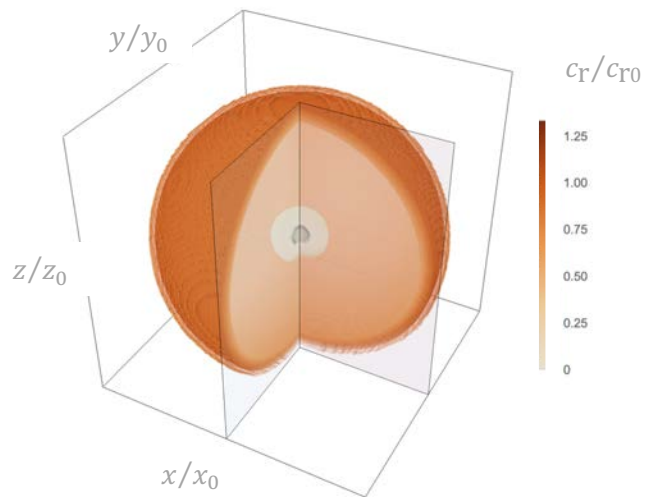


Diffusion PDE Trap Treatment



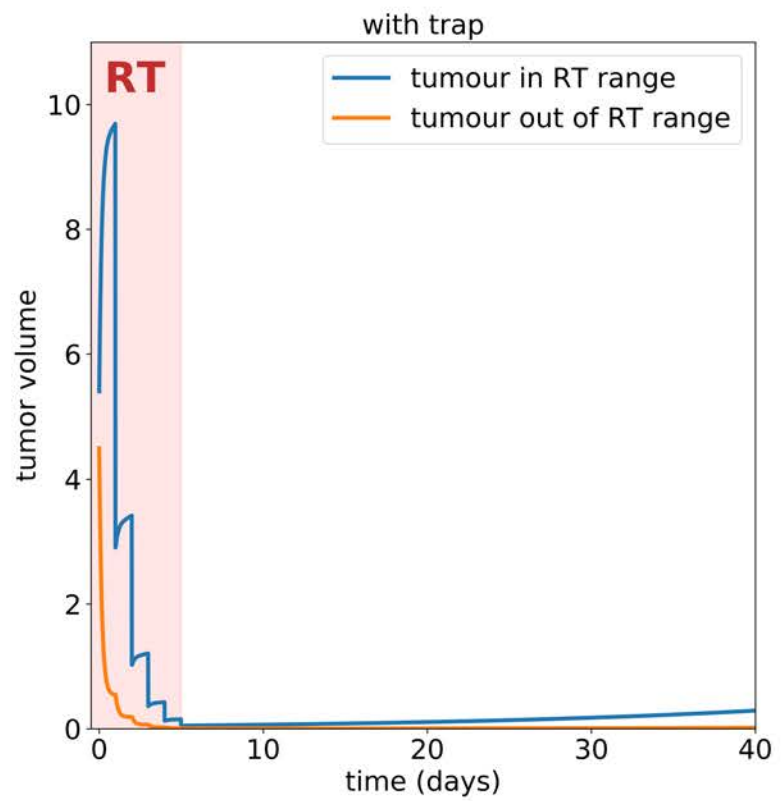
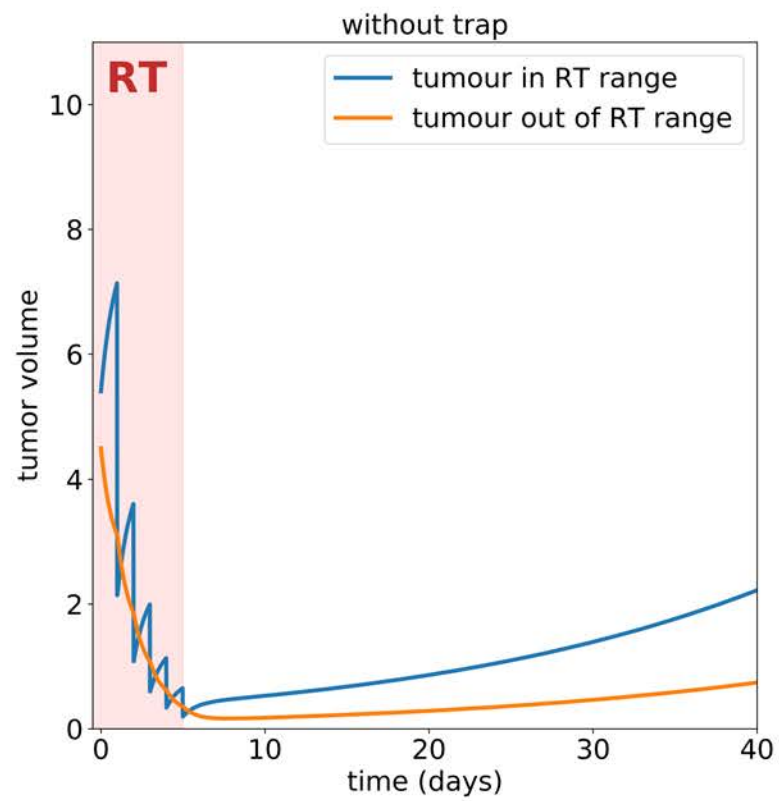


trap
spatial-temporal
evolution



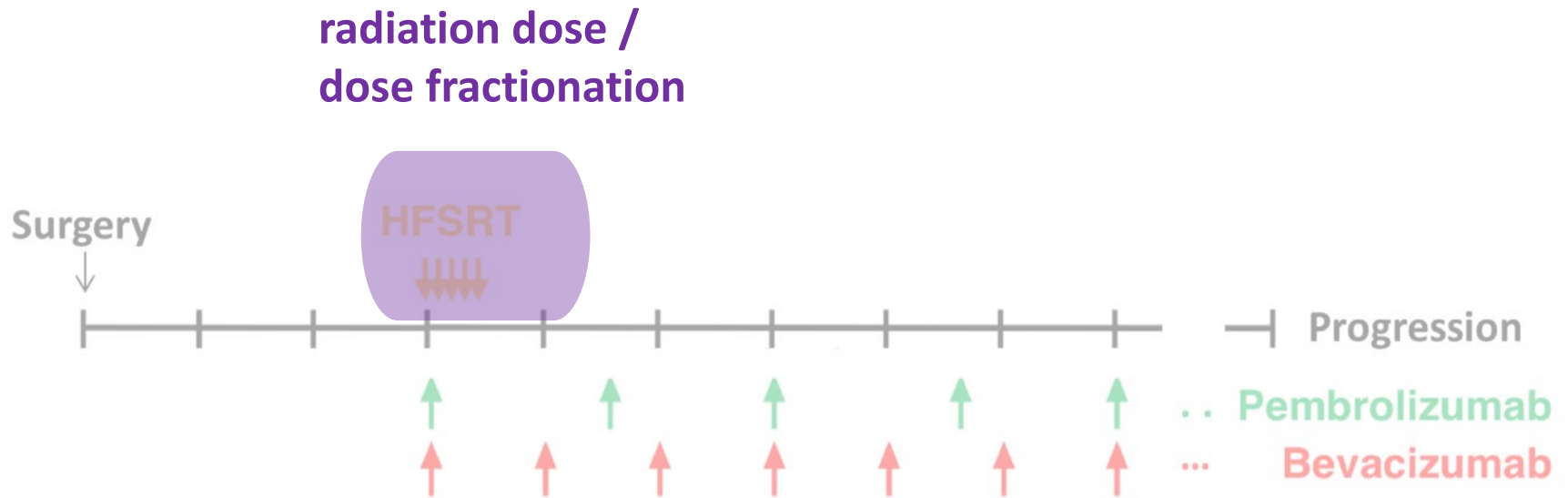
residual cell
distribution
shrinks

time

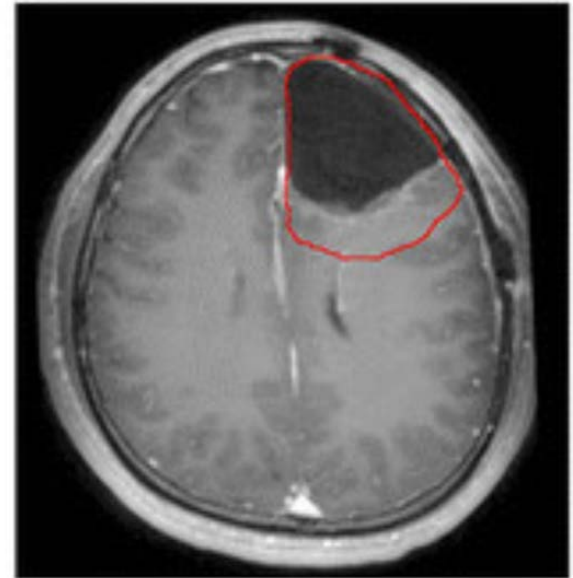
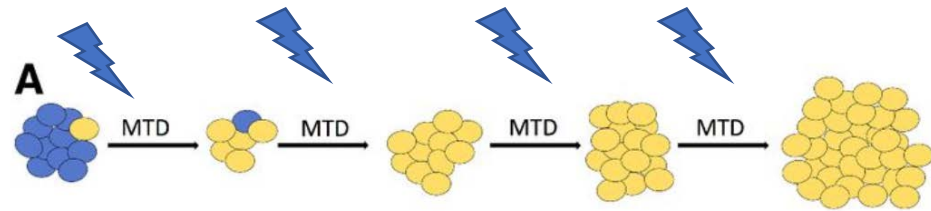




Evolutionary Tumor Board



RT Today

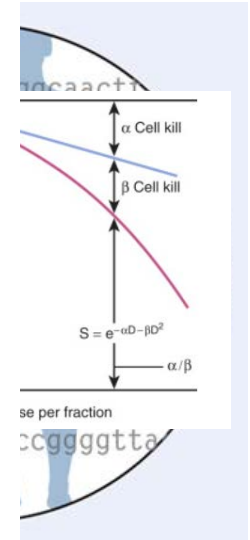
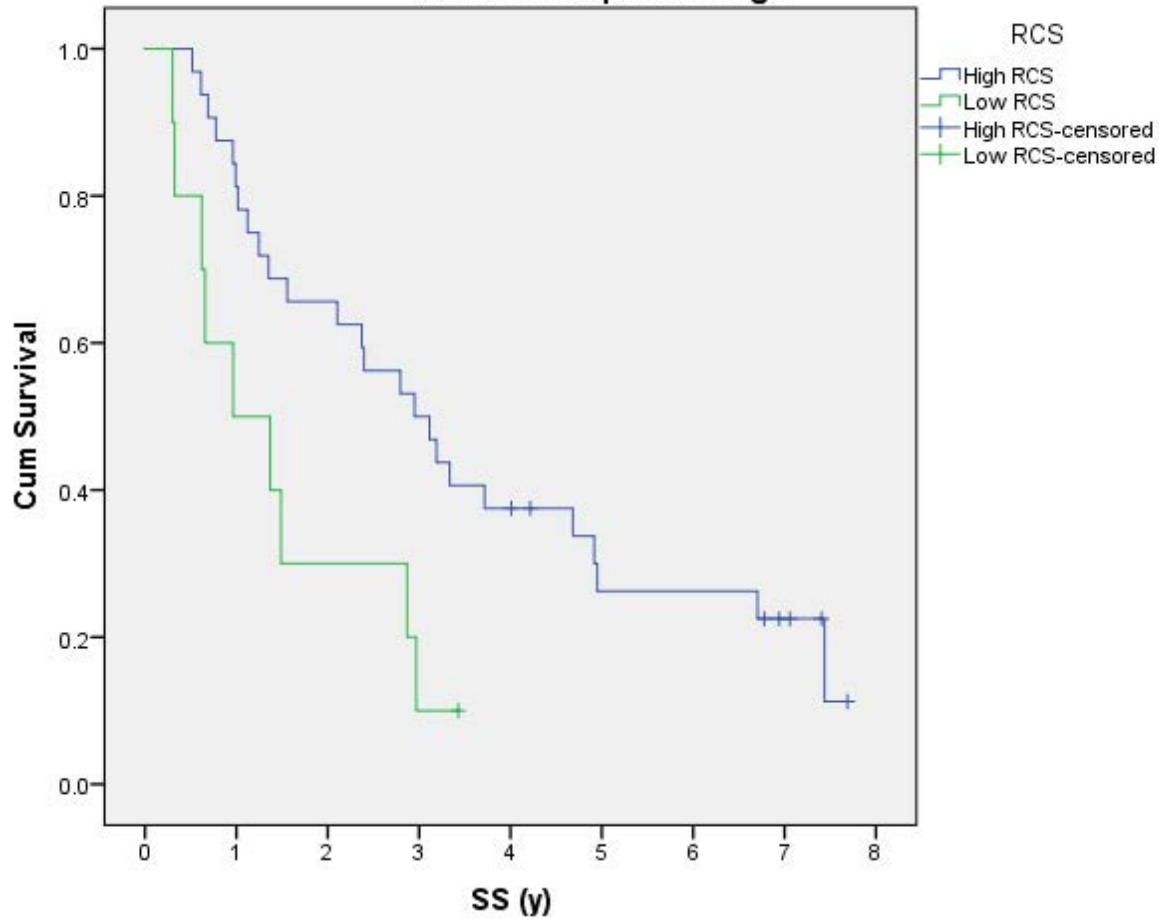


RT + \$50k in funding tomorrow

EORTC Anaplastic Oligo



Patients

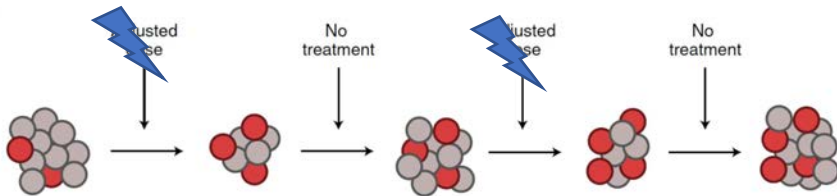




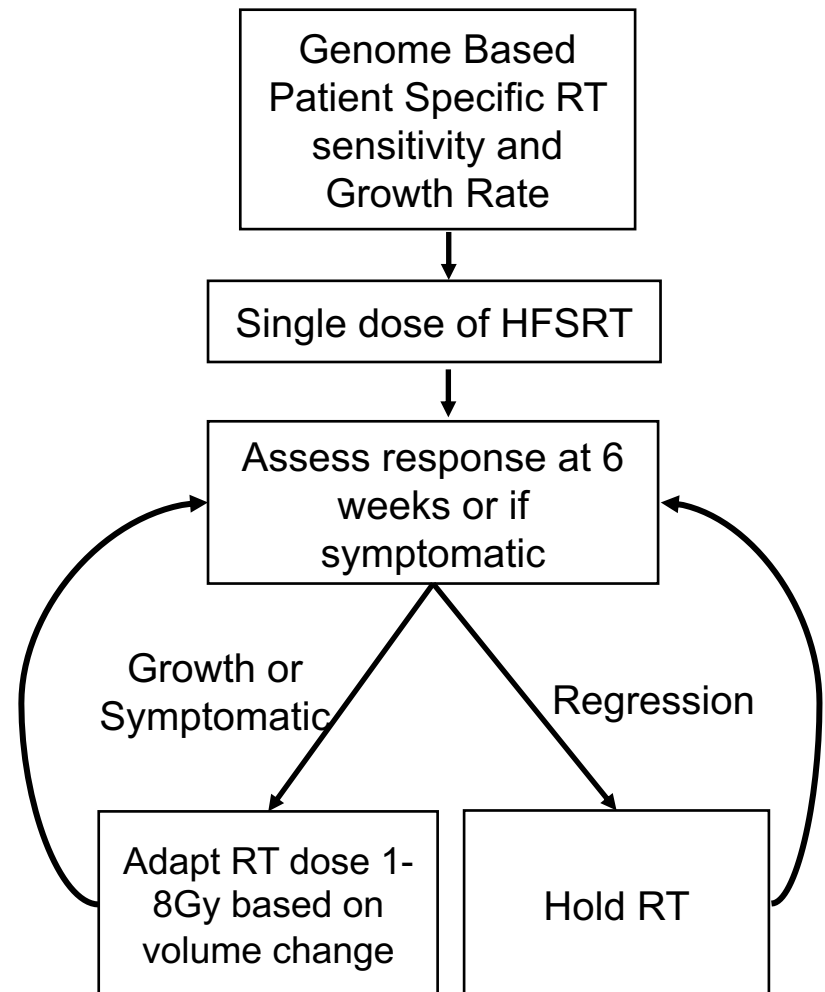
Modelling Radiation response

Challenges:

- Considers evolution of resistance to adapt RT dose
- Resampling antigens to immune system
- Target new sites of disease of progression

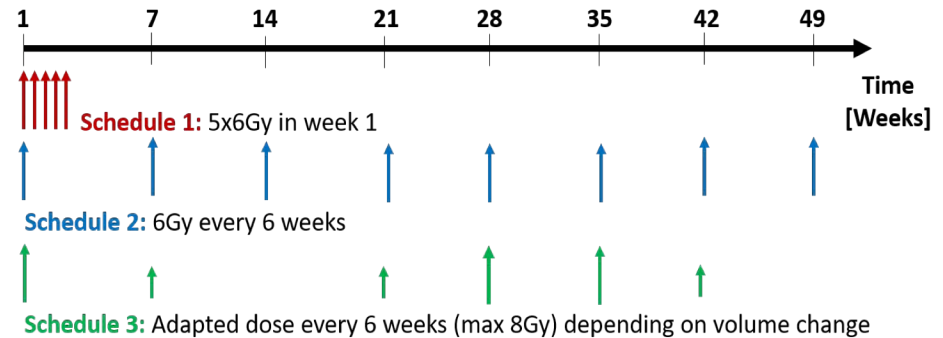
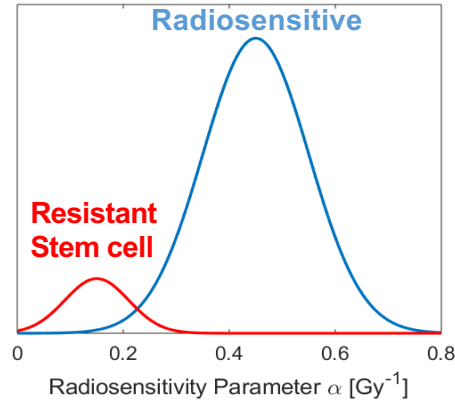
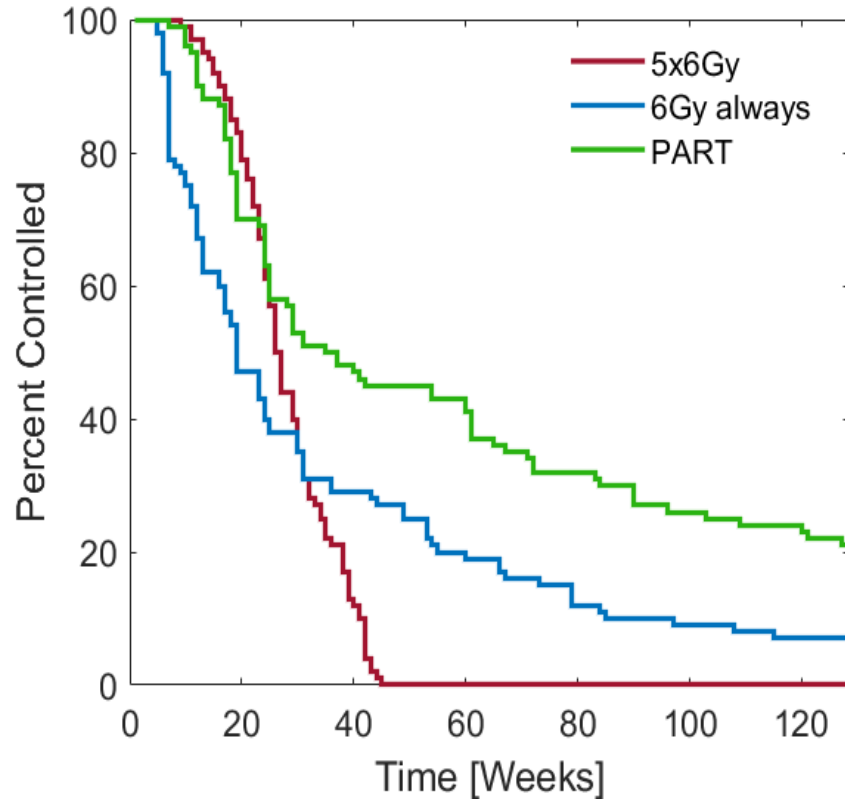


Personalized Adapted radiotherapy:





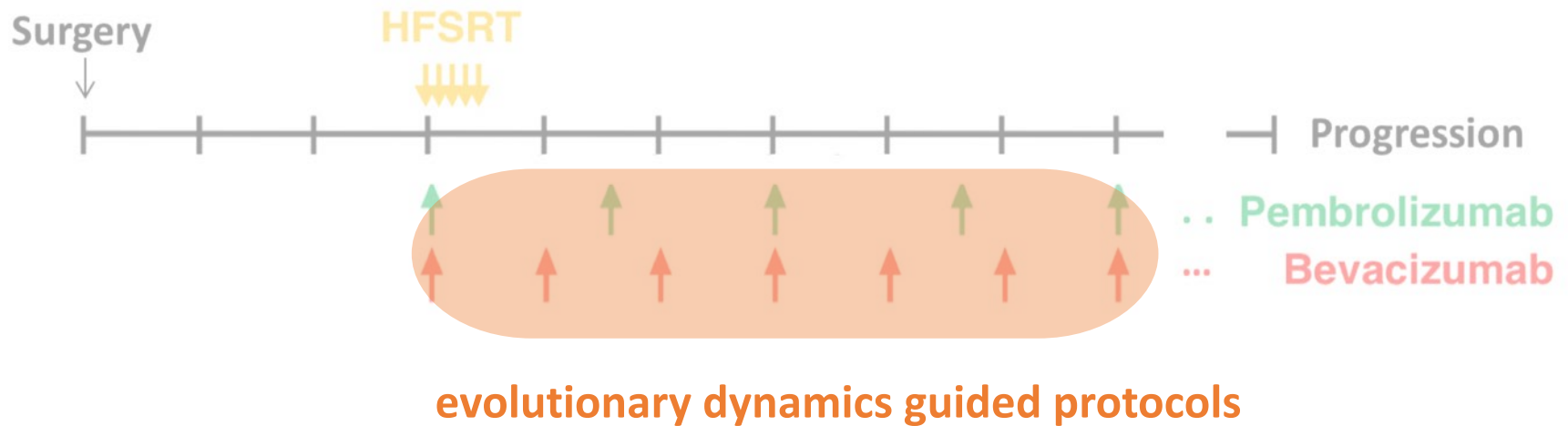
In silico trial



- 5x6Gy – kills fast growing populations but non repeatable
- 6Gy every 6 weeks – No control of fast growth + Resistance builds up
- **PART** optimizes at a patient level and at every time step



Evolutionary Tumor Board





Evolutionary dynamics during Avastin / Pembrolizumab Tx

A Non-mechanistic Model of Tumor Volume over Time

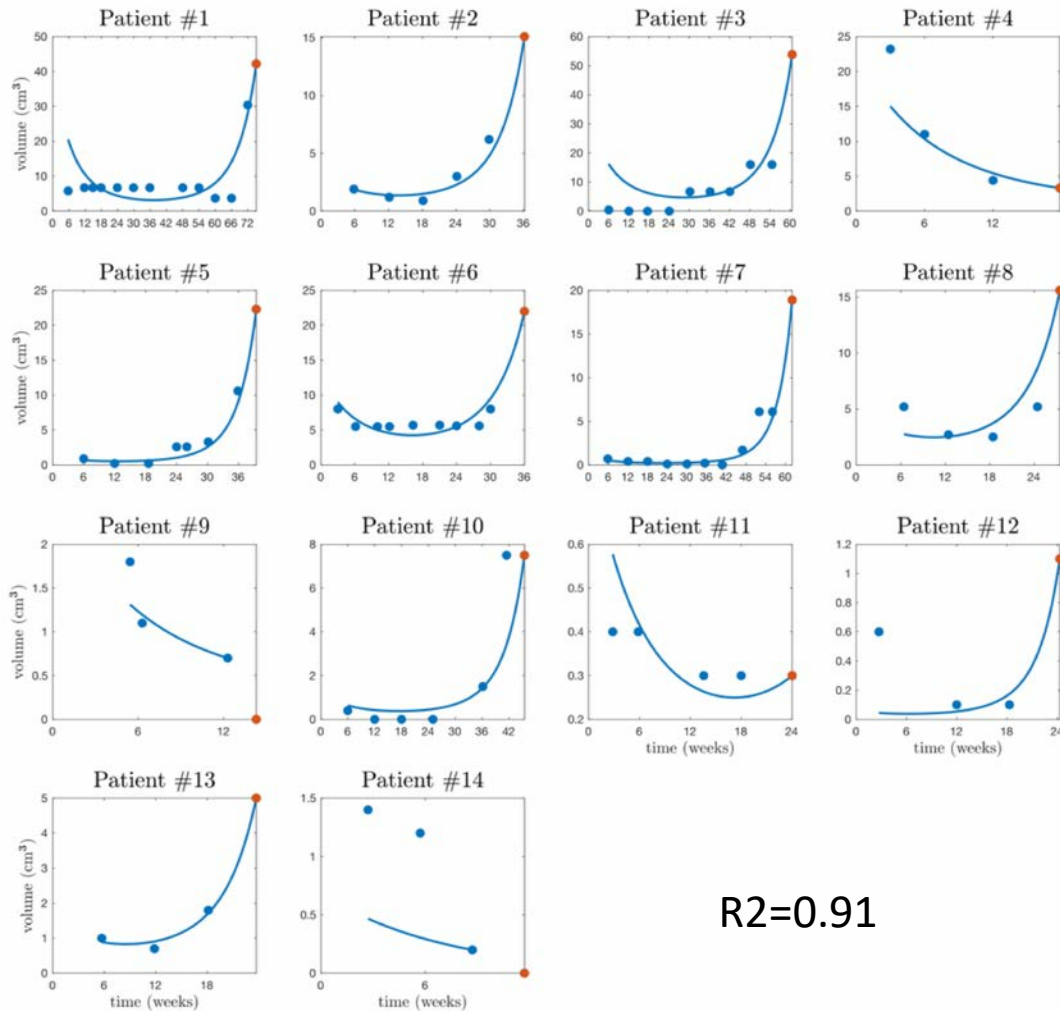
$$\frac{dV(t)}{dt} = (\lambda - \gamma(t))V(t)$$
$$\frac{d\gamma(t)}{dt} = -\epsilon\gamma(t)$$

- With no treatment: Tumor grows exponentially
- With treatment: Tumor shrinks with rate $\gamma(t)$ and the drug sensitivity decreases exponentially with rate ϵ

- Continuous therapy: Keep using treatment
- Adaptive therapy: Treat if tumor volume exceeds initial volume, and stop treatment if volume decreases



Evolutionary dynamics during Avastin / Pembrolizumab Tx

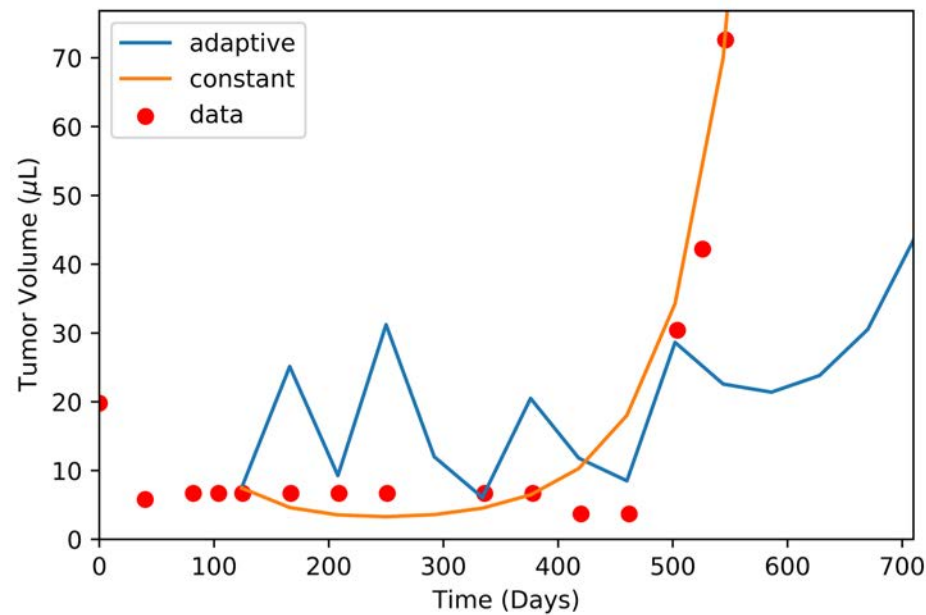


$R^2=0.91$

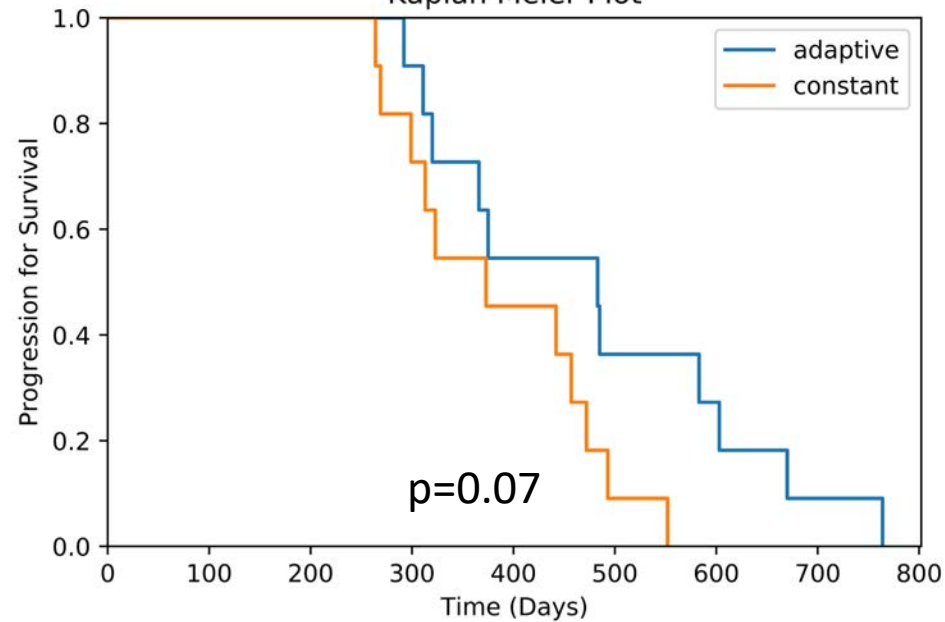


Evolutionary dynamics during Avastin / Pembrolizumab Tx

Tumor Volume as a Function of Time

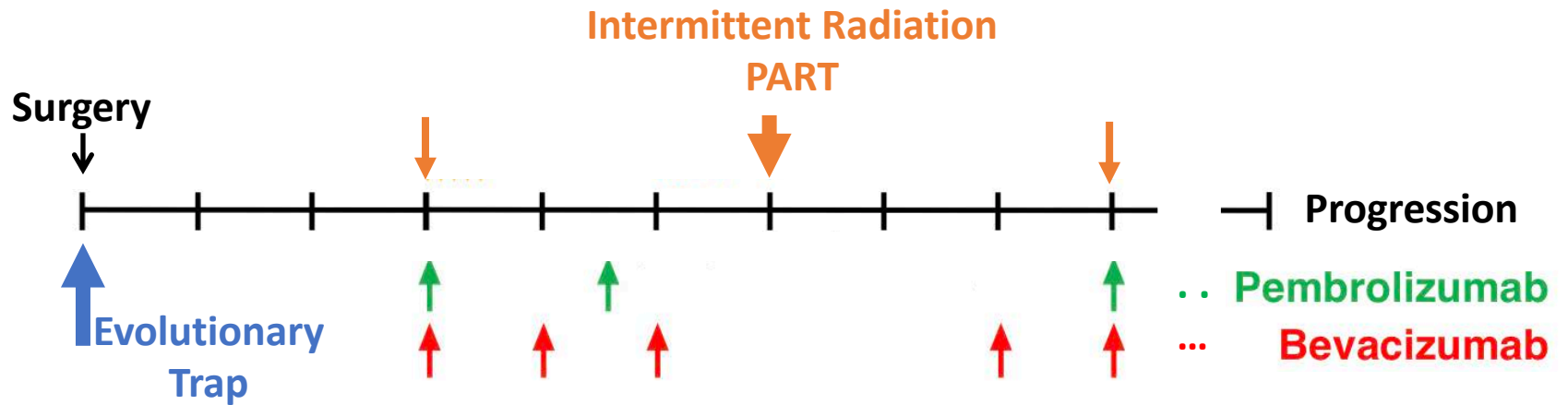


Kaplan Meier Plot



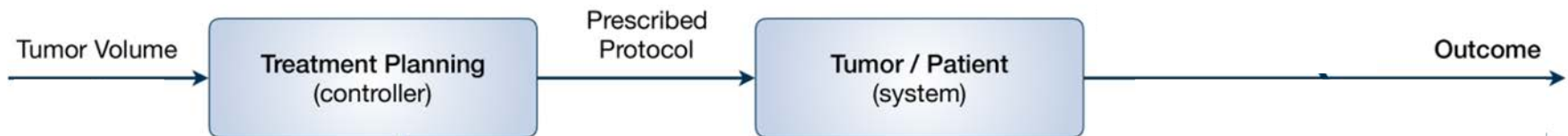


Treatment Recommendation



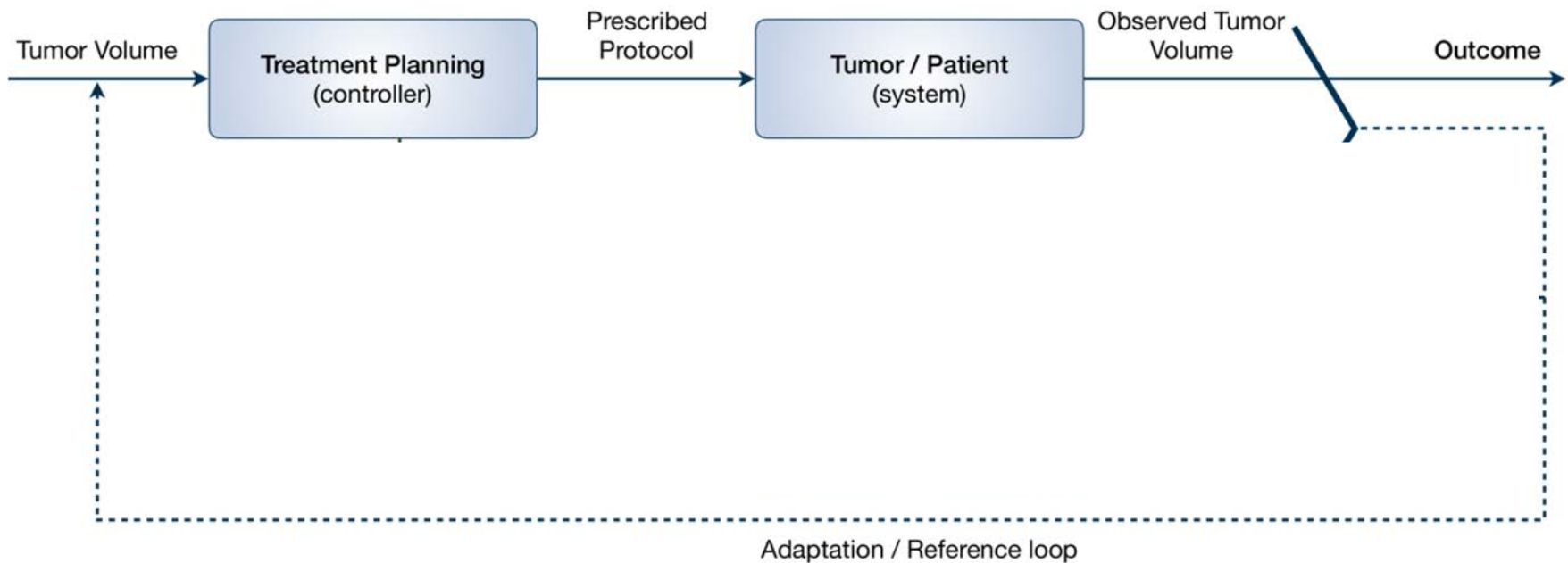


Adaptive control



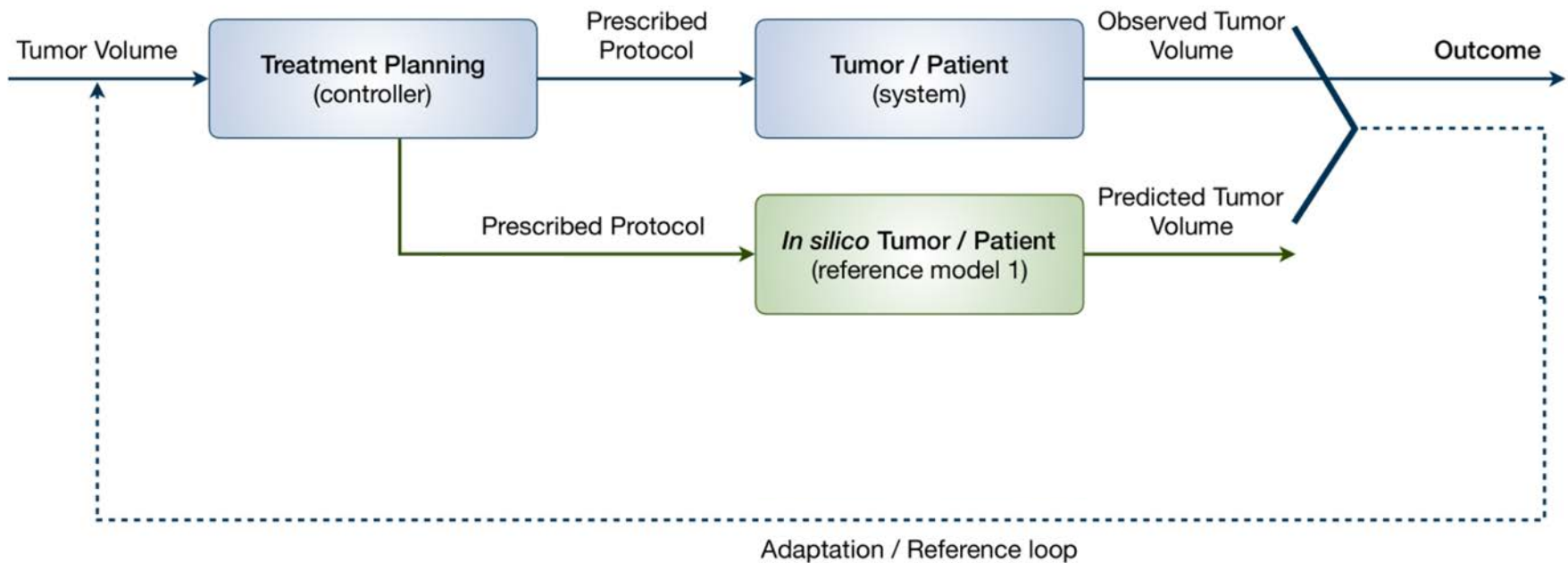


Adaptive control



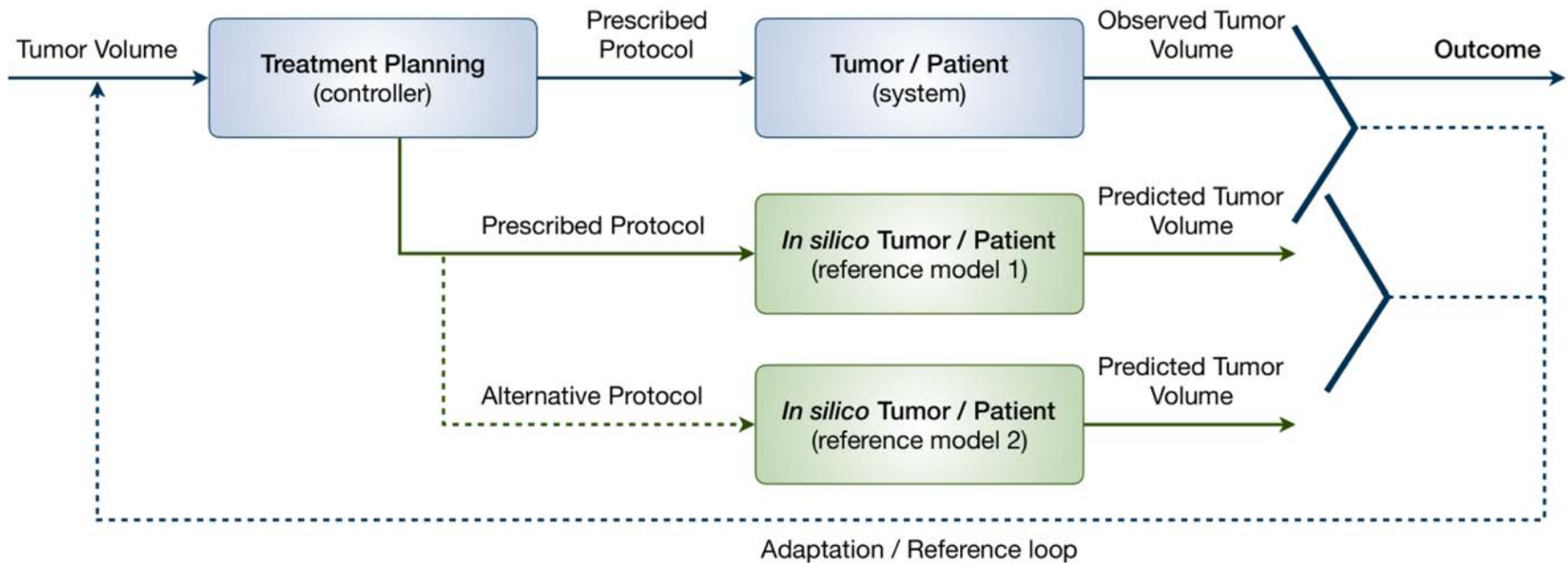


Adaptive control



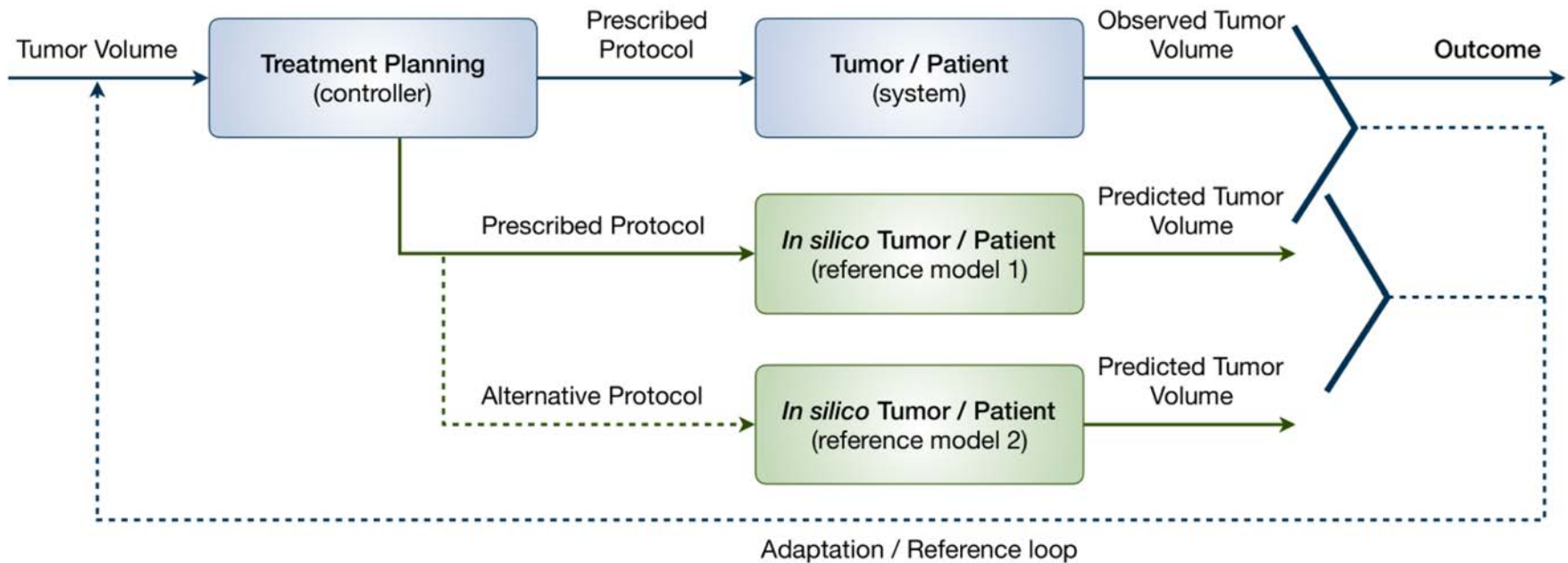


Adaptive control





Adaptive control



Evolutionary Evolutionary Tumor Board



Specific Aims

Specific Aim 1.

To analyze the response dynamics (tumor volume every 4-6 weeks, neutrophil & lymphocyte count every 2-4 weeks)

of **N=104** recurrent high-grade GBM patients treated with either

avastin alone (N=20),

pembrolizumab alone (N=20),

HFSR+avastin (N=20),

RT+avastin+pembro (N=32; MCC 17978) and

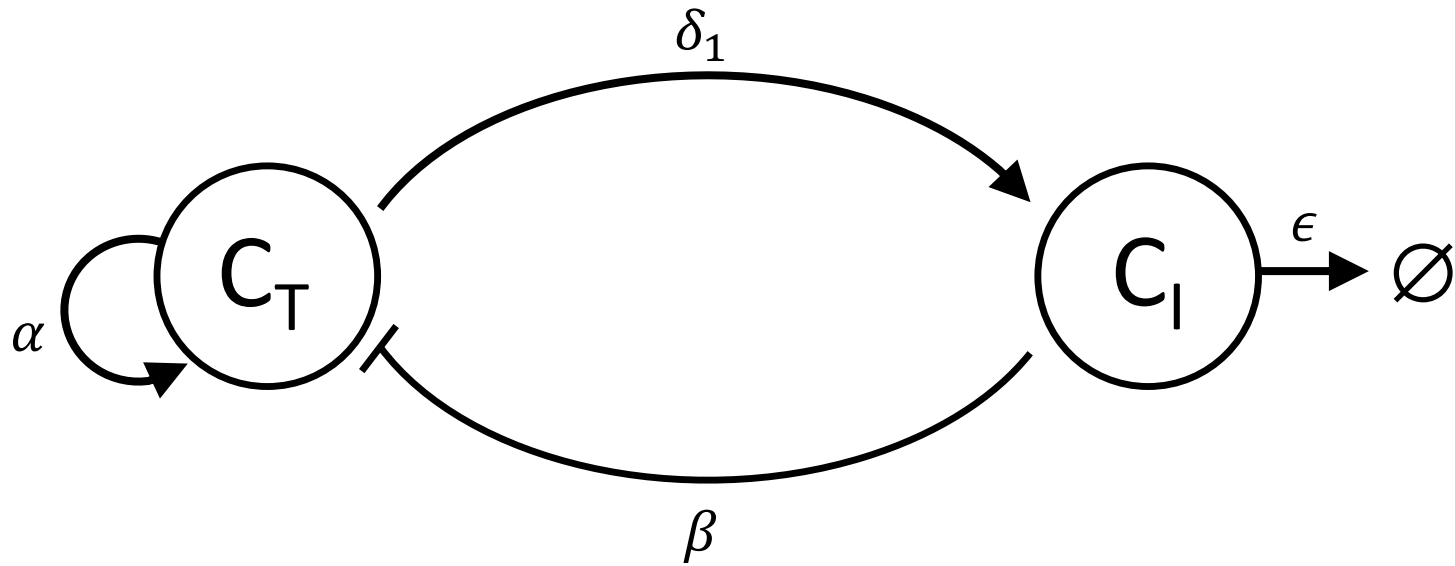
RT+avastin+pembro+nivolumab (N=32; MCC 18661).

Specific Aim 2.

To simulate evolutionary therapies and evaluate model predictions vs. actual patient responses and outcomes.



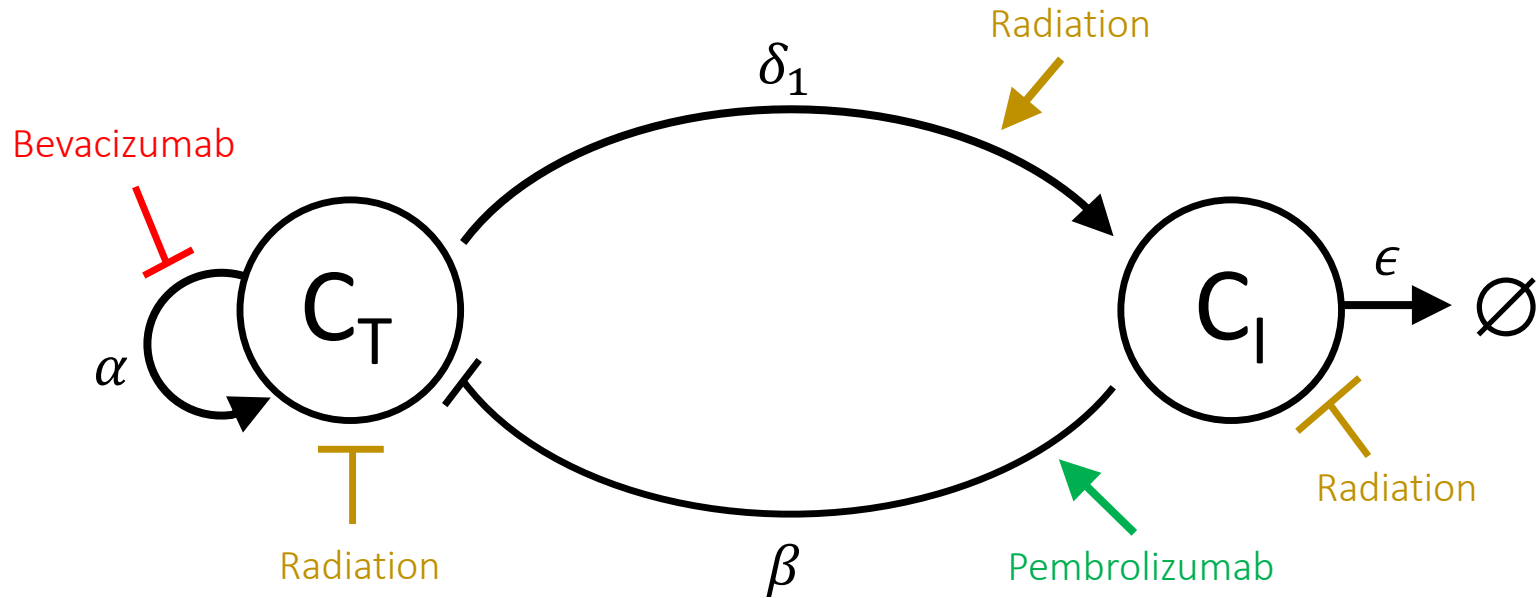
Mechanistic Model of Avastin/Pembrolizumab Tx



$$\frac{dC_T}{dt} = \alpha C_T - \beta C_T C_I$$

$$\frac{dC_I}{dt} = \delta_1 C_T C_I - \epsilon C_I$$

Mechanistic Model of Avastin/Pembrolizumab Tx



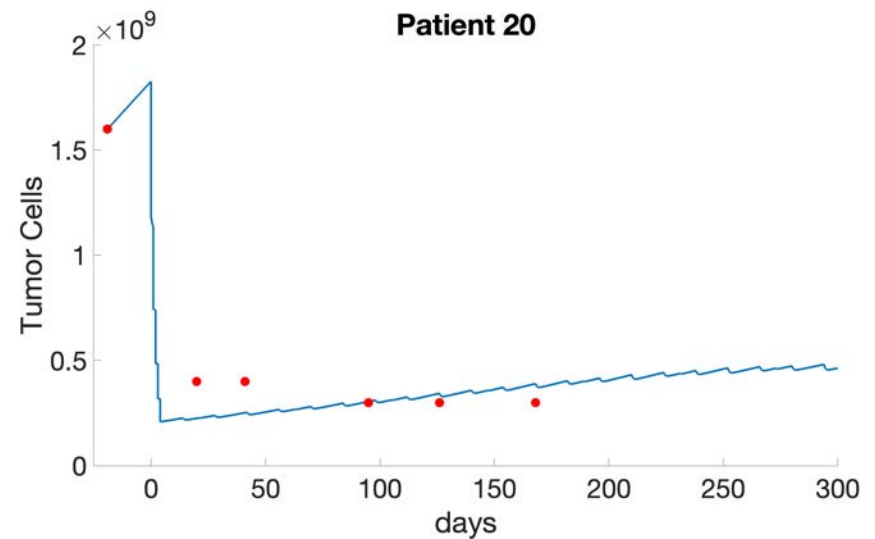
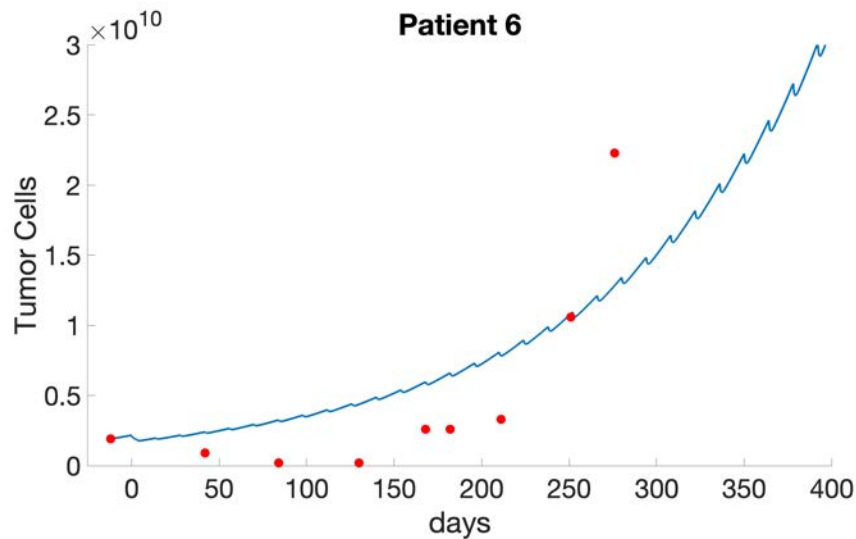
$$\frac{dC_T}{dt} = \alpha C_T f(\text{Bev}) - \beta C_T C_I f(P)$$

$$\frac{dC_I}{dt} = \delta_1 C_T C_I - \epsilon C_I + \delta_2 f(R) C_T C_I$$

Low Evolution of
Resistance Case

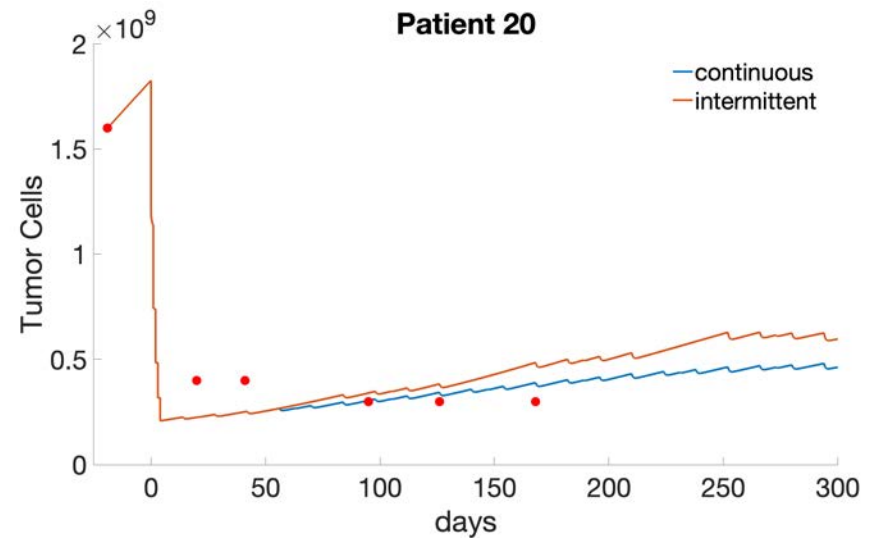
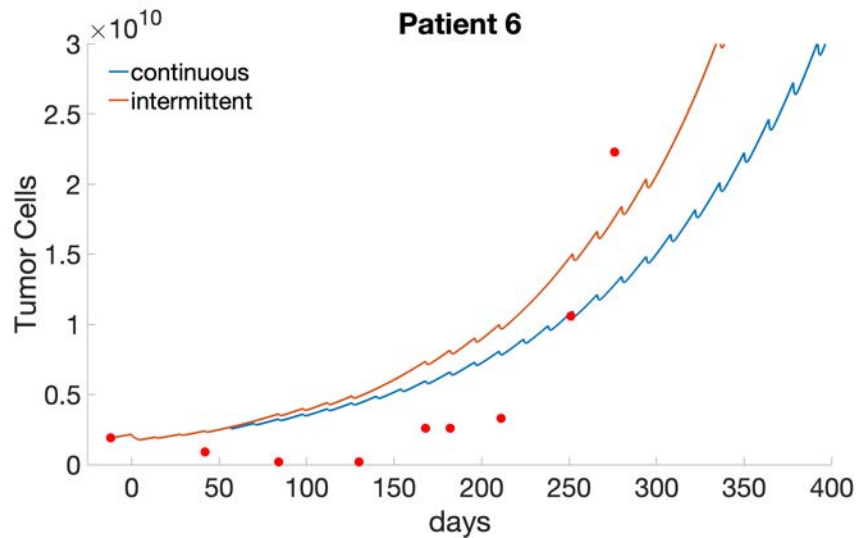


Mechanistic Model of Avastin/Pembrolizumab Tx





Mechanistic Model of Avastin/Pembrolizumab Tx

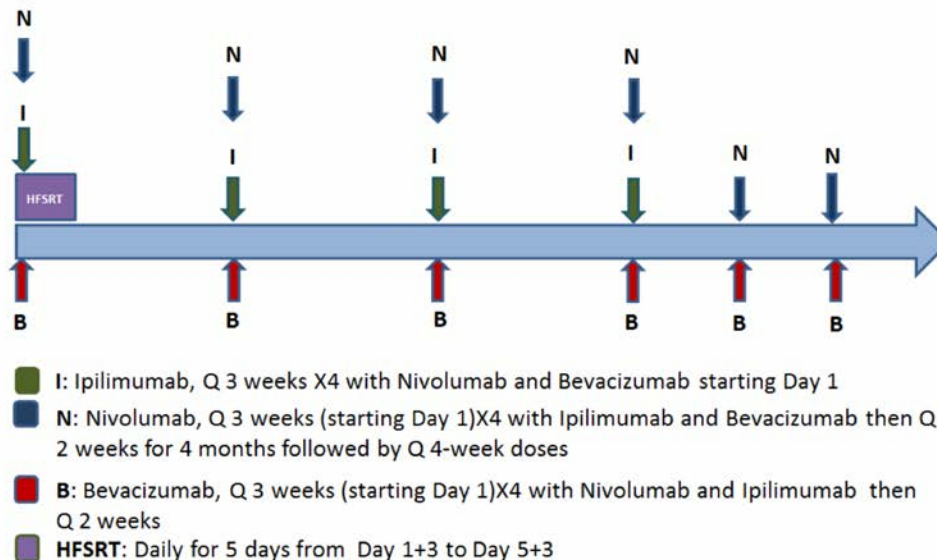


Low evolution of resistance case $\rightarrow$
intermittent therapy is not beneficial



Outcomes & Deliverables

Phase I Trial of Hypofractionated Stereotactic Irradiation (HFSRT) Combined with Nivolumab, Ipilimumab and Bevacizumab in Patients with Recurrent High Grade Gliomas (NCT02829931)





Budget

- \$10K data abstraction
- \$20K graduate student
- \$10K postdoc mentor
- \$7K statistical analysis
- \$3K publication fee



Acknowledgement

- Patient J.D., evaluated by ETB
- Sandy Anderson
- Danae Paris
- Chef Anderson
- Ms. Francoeur & Mr. Butler
- Moffitt PSOC

