An adaptive patient-specific treatment approach for EGFR-driven stage IV lung cancer

Team Lung:
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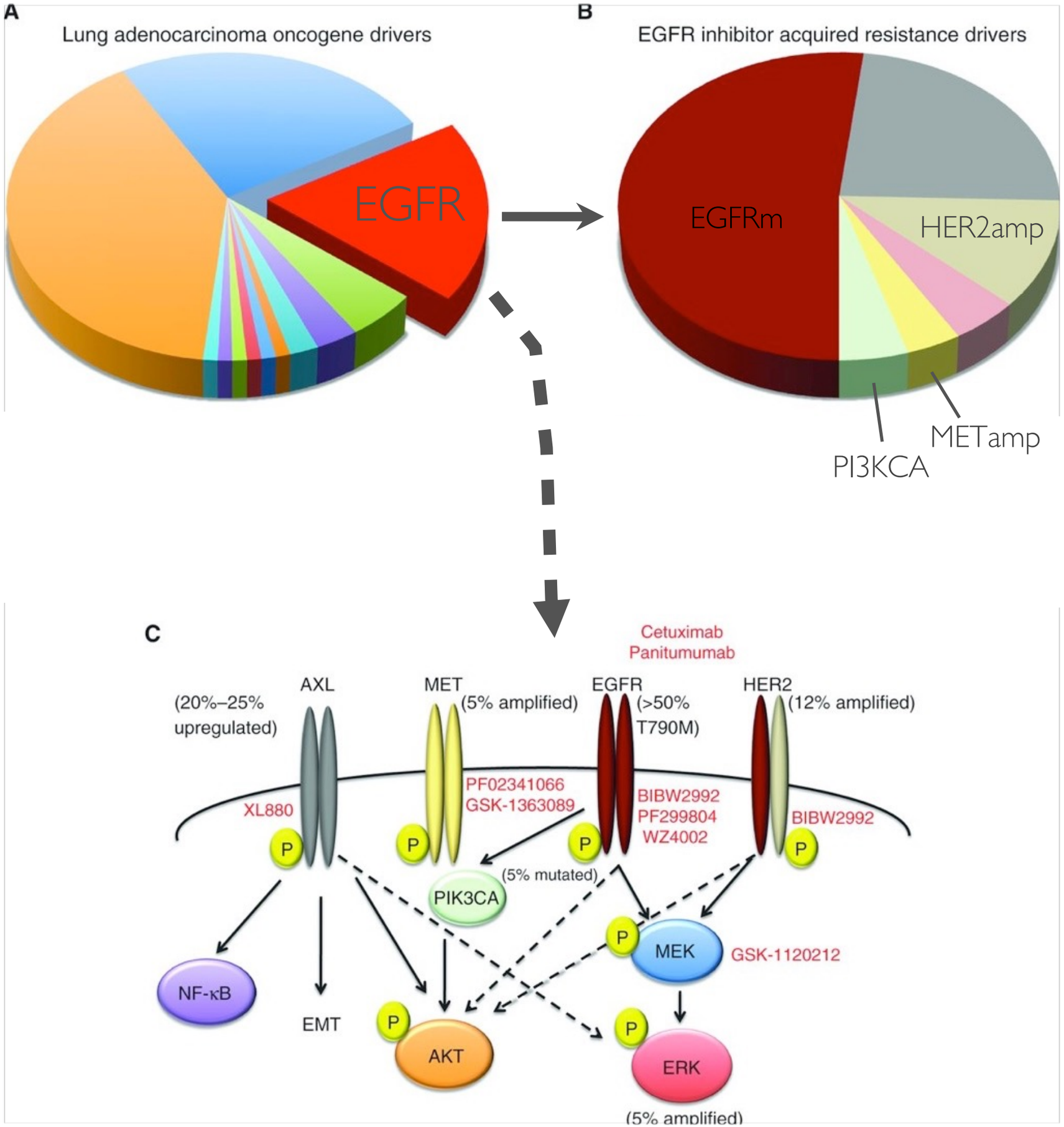
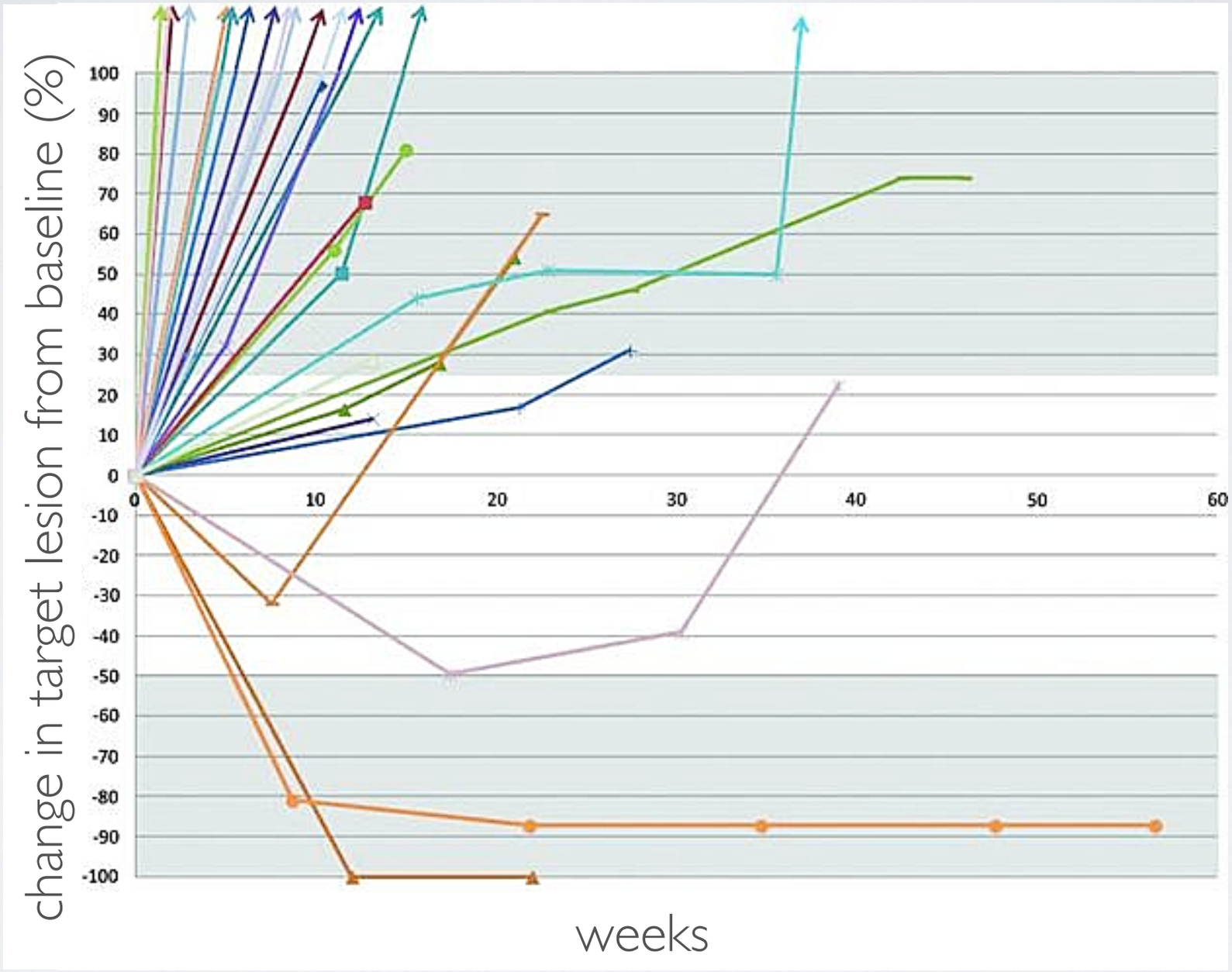
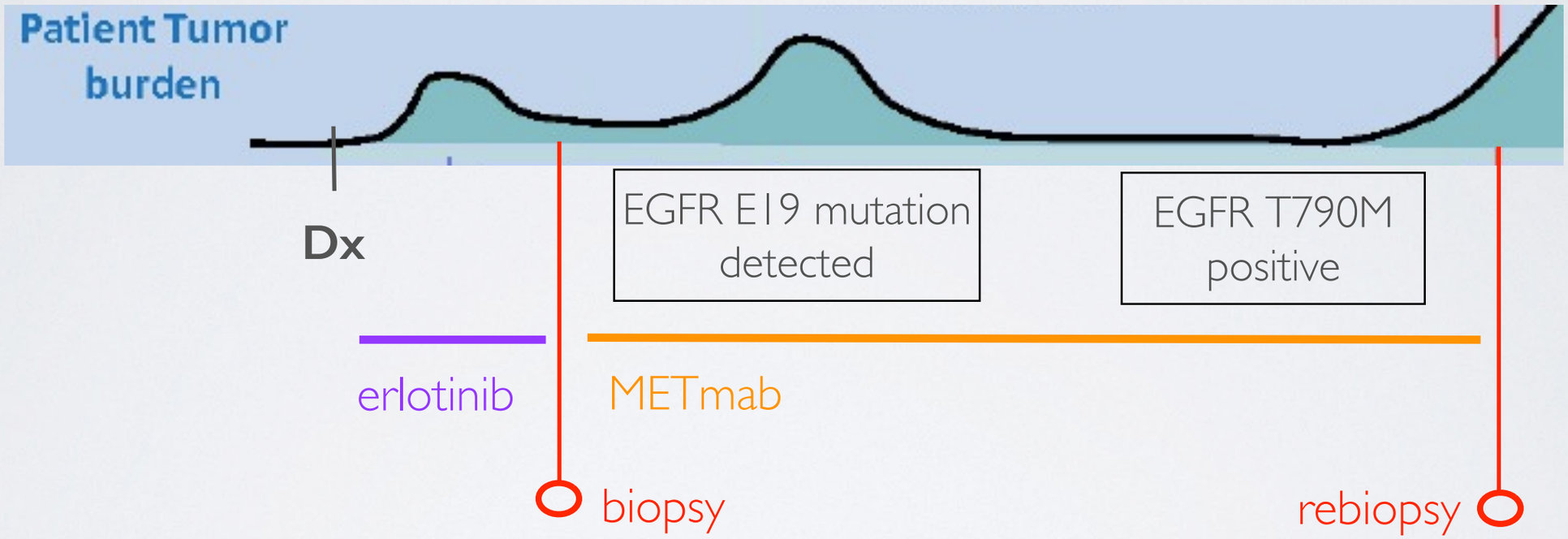

A
Lung adenocarcinoma oncogene drivers
EGFR
B
EGFR inhibitor acquired resistance drivers
EGFRm
HER2amp
METamp
PI3KCA
C
Cetuximab
Panitumumab
AXL
(20%–25%
upregulated)
MET
(5% amplified)
EGFR
(>50%
T790M)
HER2
(12% amplified)
XL880
PF02341066
GSK-1363089
BIBW2992
PF299804
WZ4002
BIBW2992
P
(5% mutated)
PIK3CA
MEK
GSK-1120212
NF-κB
EMT
AKT
ERK
(5% amplified)

Patient-specific treatment response



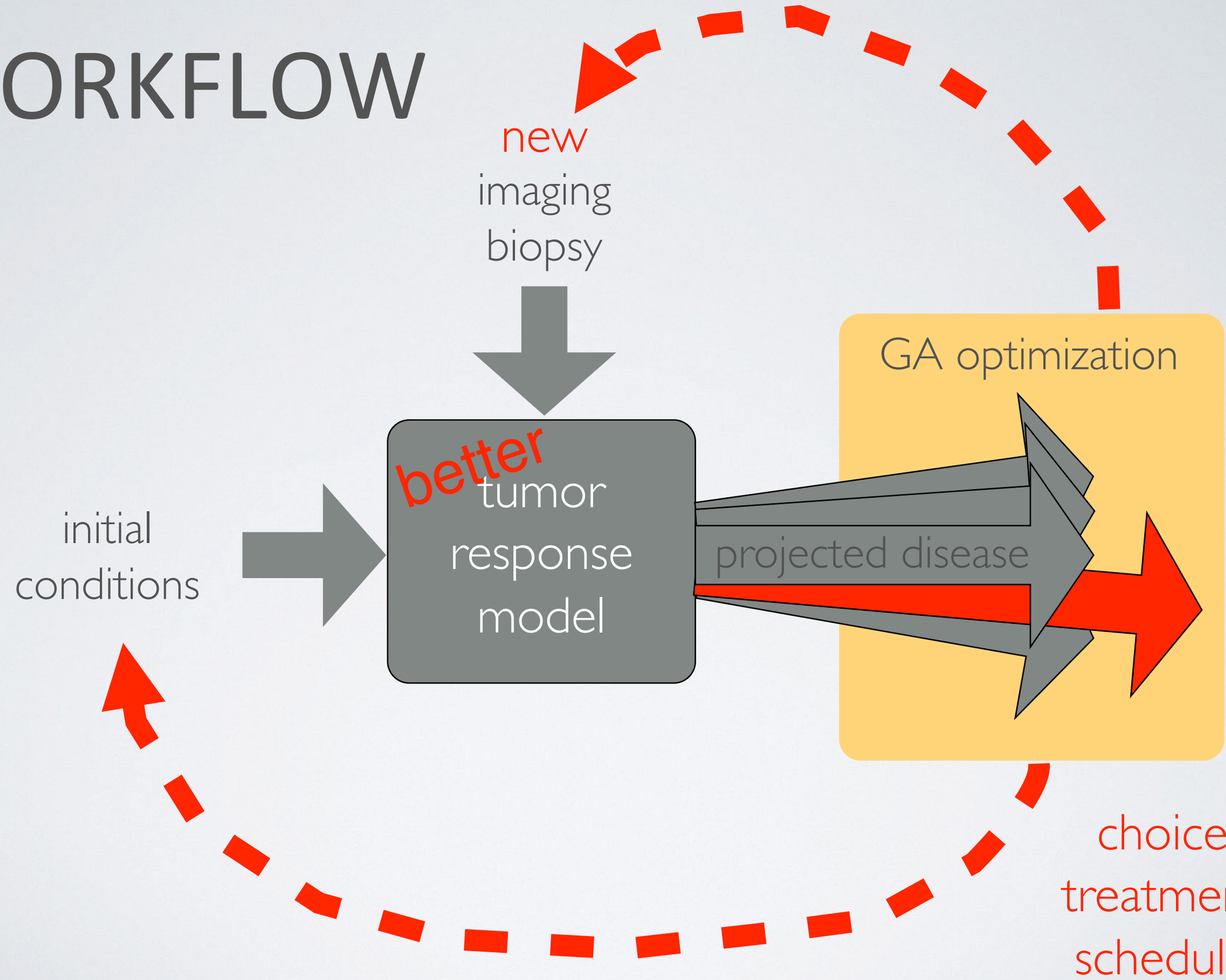
Using math modeling with patient-specific data, maximize days gained while avoiding toxicity



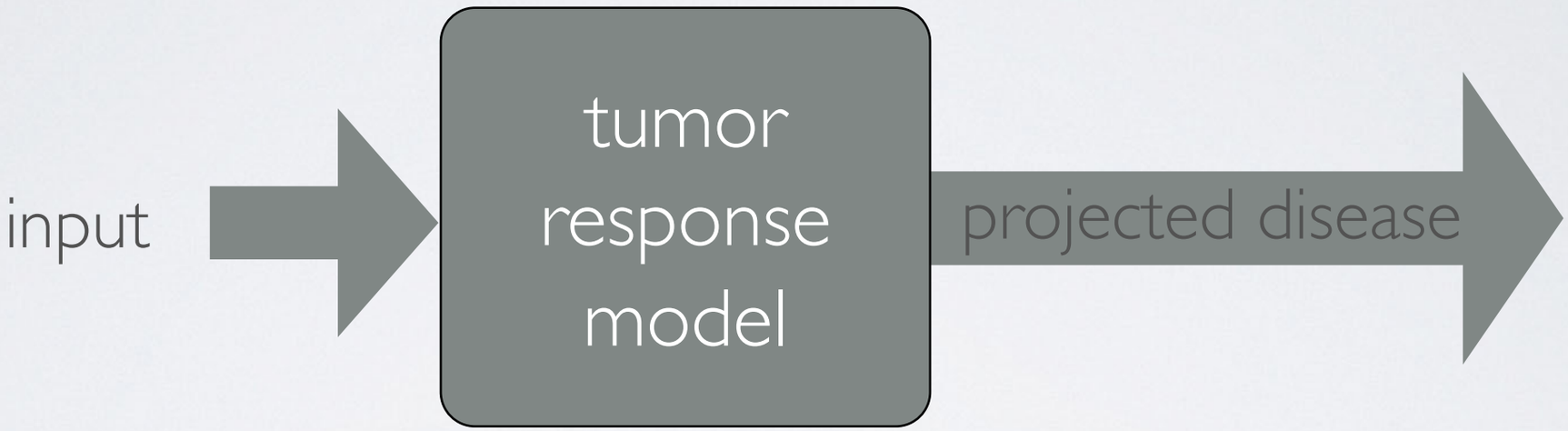
Outline

- Strategy
- Signaling network model
- Optimization technique
- Feedback/Refinement

WORKFLOW

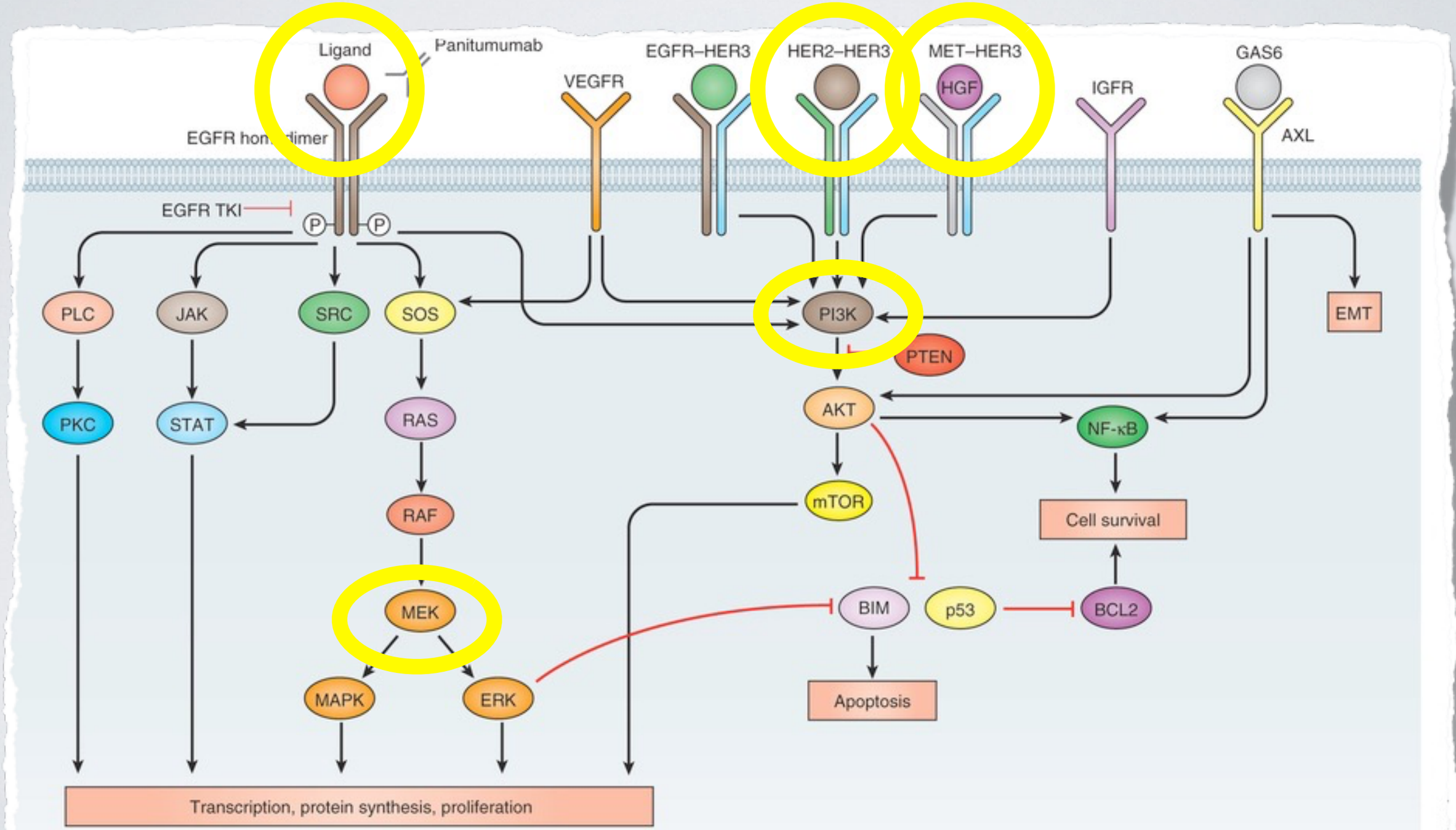

new
imaging
biopsy
better
tumor
response
model
initial
conditions
GA optimization
projected disease
choice
treatment
schedule

Less is more.

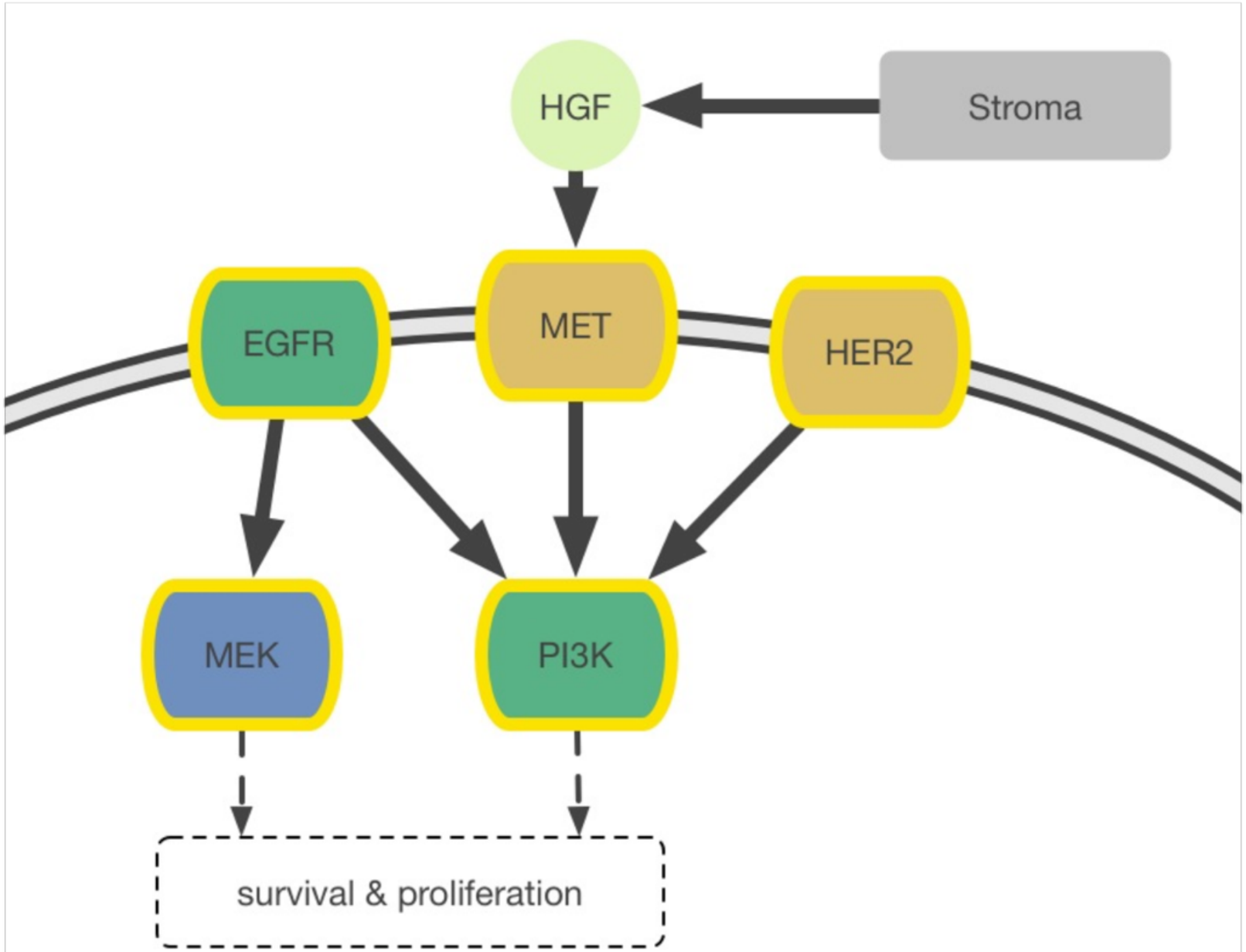


signaling network model

EGFR PATHWAY



Chong & Janne, 2013

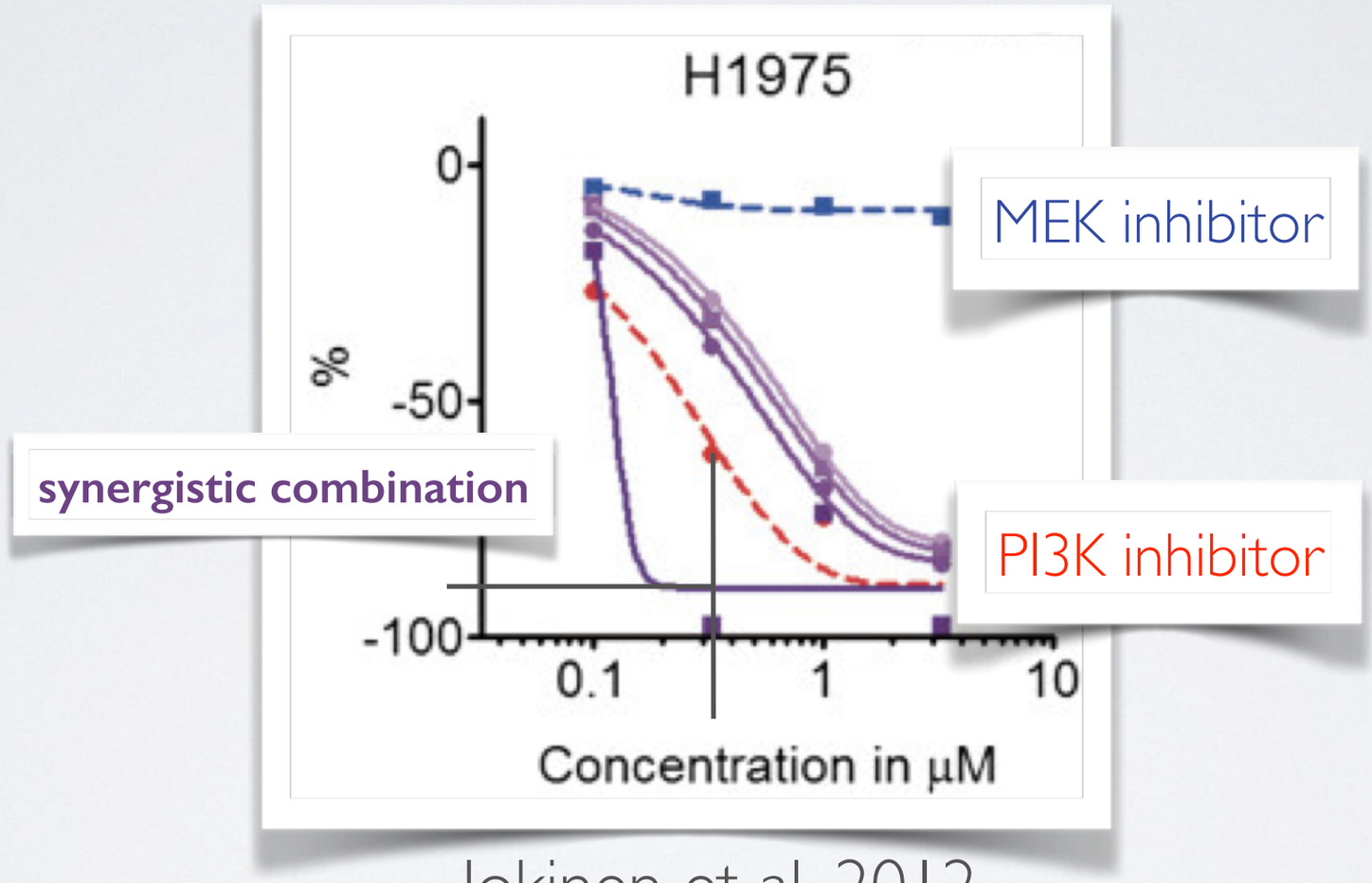


druggable targets

escape routes

possible resistant nodes

synergism with MEK & PI3K inhibition



Jokinen et al, 2012

$$\begin{aligned}\mathrm{EGFR} &= 1\\ \mathrm{MET} &= 2\\ \mathrm{HER2} &= 3\\ \mathrm{MEK} &= 4\\ \mathrm{PI3K} &= 5\end{aligned}$$

EQUATIONS

clone dynamics

$$\frac{\mathrm{d}N_i(t,d)}{\mathrm{d}t} = \overbrace{\left(\alpha_0 + \alpha_i^d - \beta_i^d\right) N_i}^{\text{total birth and death}} + \overbrace{\sum_{i'} W_{i'i} N_{i'}}^{\text{mutations}} + \overbrace{S_i^d M^\tau}^{\text{stromal stimulation}}$$

$$i = n_1 n_2 n_3 n_4 n_5$$

$$d = d_1 d_2 d_3 d_4 d_5, \text{ where } d_i \in \{0,1\}$$

size

$$M = \sum_{i'} N_{i'},$$

amplification

$$\alpha_i^d = \delta_{n_2 1}\delta_{d_2 0}\alpha_M + \delta_{n_3 1}\delta_{d_3 0}\alpha_H$$

death response

$$\begin{aligned}\beta_i^d = {} & \delta_{n_1 0}\delta_{d_1 1}\beta_E + \delta_{n_2 1}\delta_{d_2 1}\beta_{\mathrm{MET}} + \delta_{n_3 1}\delta_{d_3 1}\beta_H + \delta_{d_4 1}\beta_{\mathrm{MEK}} + \delta_{n_5 0}\delta_{d_5 1}\beta_P^{(1)} \\ & + s_{4,5}\delta_{d_4 1}\delta_{n_5 0}\delta_{d_5 1}\left(\beta_{\mathrm{MEK}} + \beta_P^{(1)}\right) + \delta_{n_5 0}\delta_{n_1 0}\delta_{d_1 0}\delta_{n_2 1}\delta_{d_2 0}\delta_{n_3 1}\delta_{d_3 0}\beta_P^{(2)}\end{aligned}$$

synergism

$$S_i^d = \left(1 + \eta_M \delta_{n_2 1}\right)\delta_{d_2 0}$$

toxicity

$$\frac{\mathrm{d}\Phi}{\mathrm{d}t} = \varphi_m - \kappa\Phi$$

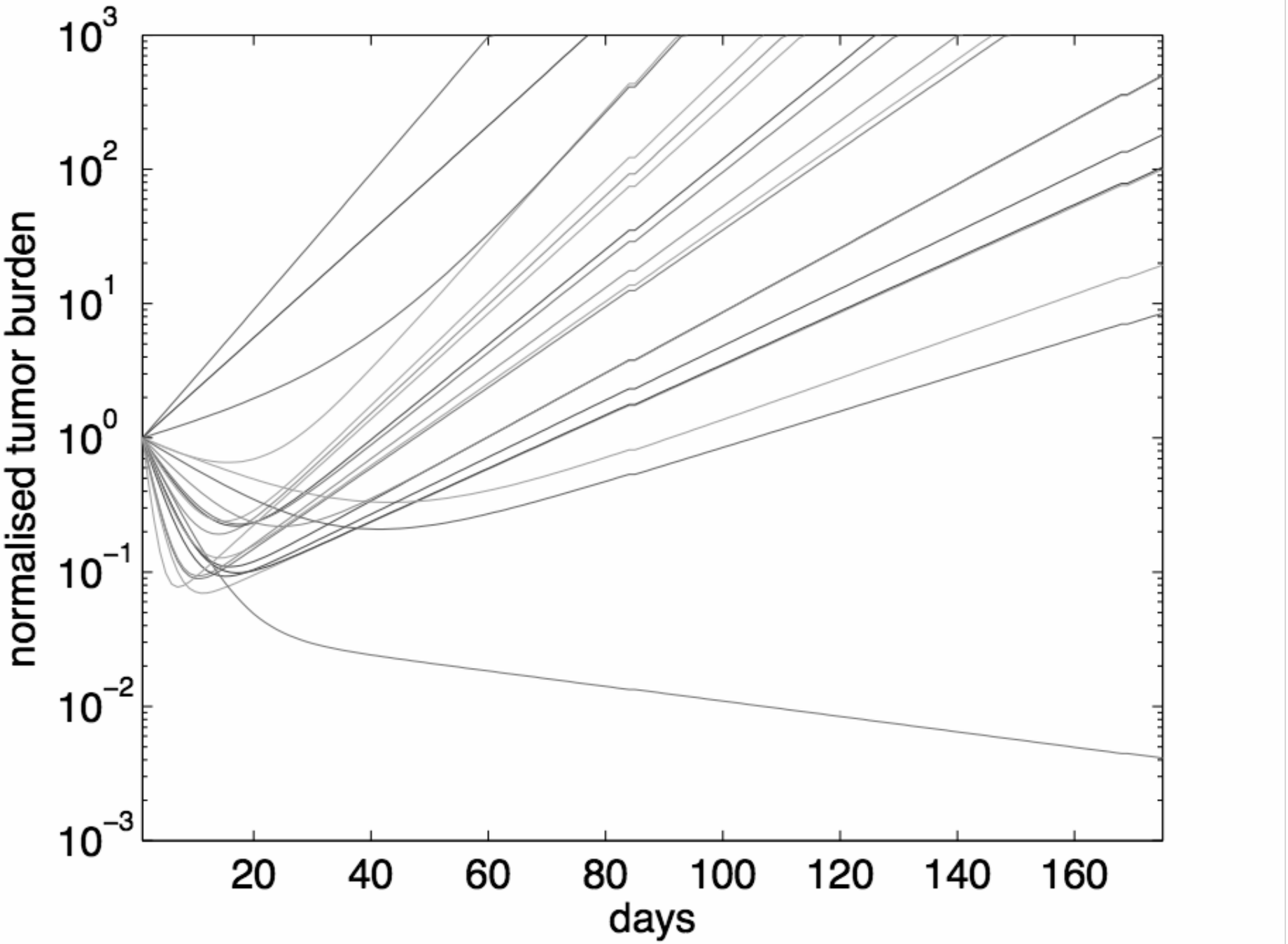
estimated parameters

Parameter	Meaning	Value	Ref.
α_M	growth from MET-overexpression	$\alpha_0/2$ day^{-1}	Navab *et al.* Neoplasia 2009
α_H	growth from HER2-overexpression	$\alpha_0/2$ day^{-1}	Based on α_M
μ	mutation rate	10^{-7} day^{-1}	Tomlinson *et. al*, PNAS, 1998
η_M	degree of MET-overexpression	10	Navab *et al.* Neoplasia 2009
γ_M	sensitivity to HGF	10^{-2} cell$^{1/3}$day^{-1}	-
$s_{4,5}$	synergism between MEK & PI3K	0.5	Jokinen *et al.*, 2012
σ_β	std. of drug sensitivity	$\alpha_0/2$	model specific
κ	decay of toxicity	2.0	model specific
α_0	baseline growth rate	$0.2 \log 2$ day^{-1}	-
τ	surface/volume ratio	2/3	-
β_E	sensitivity to EGFR-inhibitor	0.53 day^{-1}	Rosell *et al.*, 2012
β_{MET}	sensitivity to MET-inhibitor	0.18 day^{-1}	Landi *et al.*, 2013
β_H	sensitivity to HER2-inhibitor	0.21 day^{-1}	Greve, J.D., 2012
β_P	sensitivity to PI3K-inhibitor	0.1 day^{-1}	Besse *et al.*, 2011
β_{MEK}	sensitivity to MEK-inhibitor	0.038 day^{-1}	Jokinen *et al.*, 2012

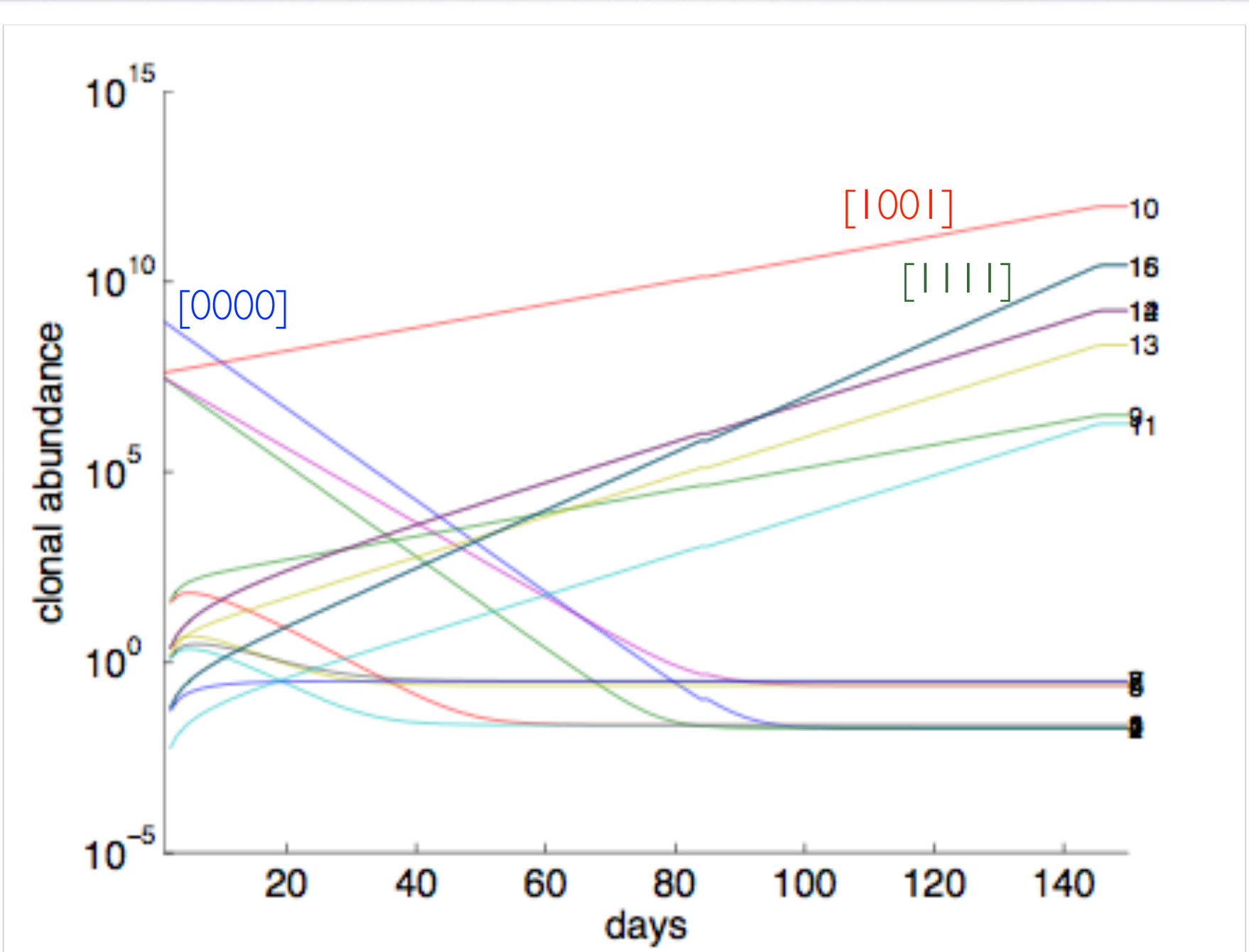
response rates

Targeted gene	Drug	Clinical Benefit	β-value	Ref.
EGFR	Erlotinib	85–90%	0.53	Rosell *et al.*, 2012
EGFR-T790M	Erlotinib	0%	0	Yang *et al.*, 2012
MET-amp	MetMAb (+ erlotinib)	55%	0.18	Landi *et al.*, 2013
HER2-amp	Afatinib	60–70%	0.21	Greve *et al.*, 2012
PI3Kwt	GDC-0941	44%	0.1	Besse *et al.*, 2011

VIRTUAL PATIENT COHORT: RESPONSE TO ERLOTINIB (SOC)



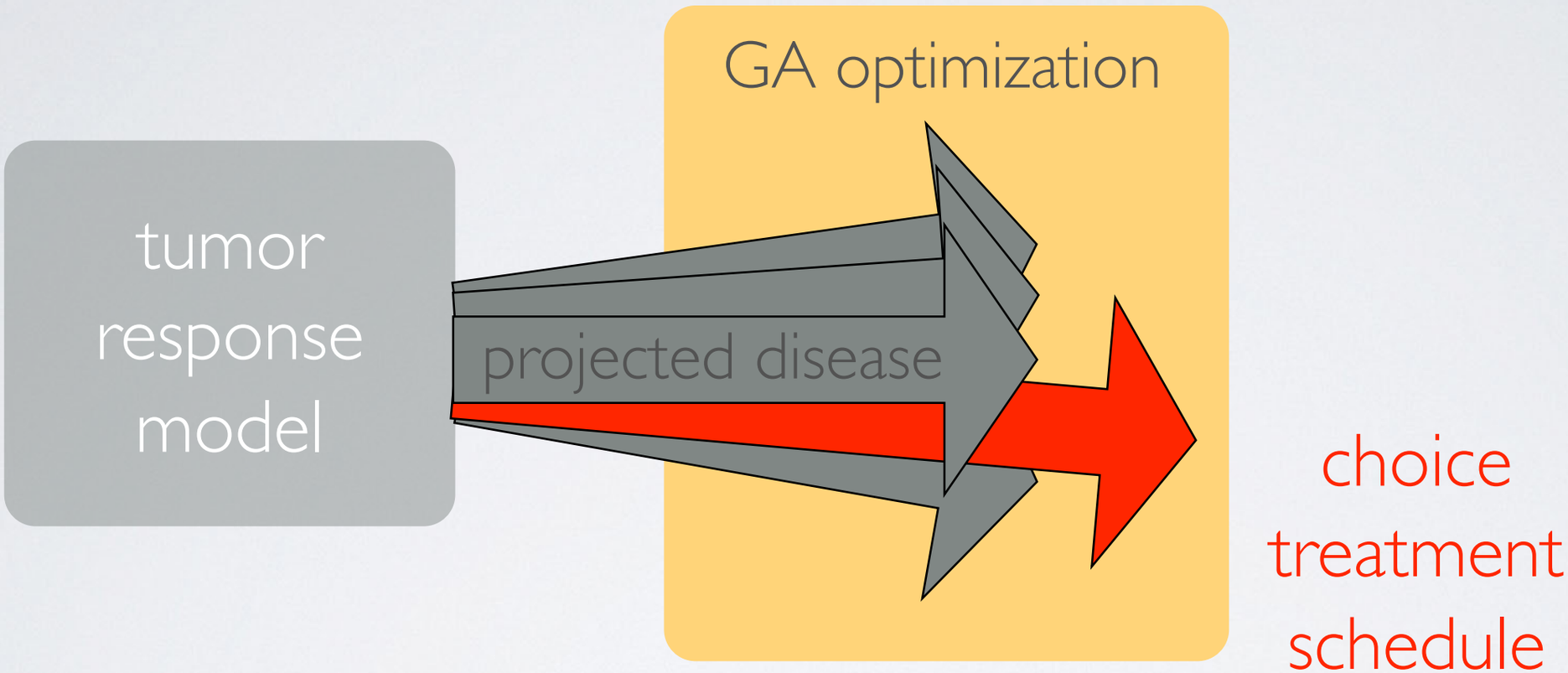
ERLOTINIB (SOC) CLONAL EVOLUTION



HER2
EGFR
[####]
MET
PI3K

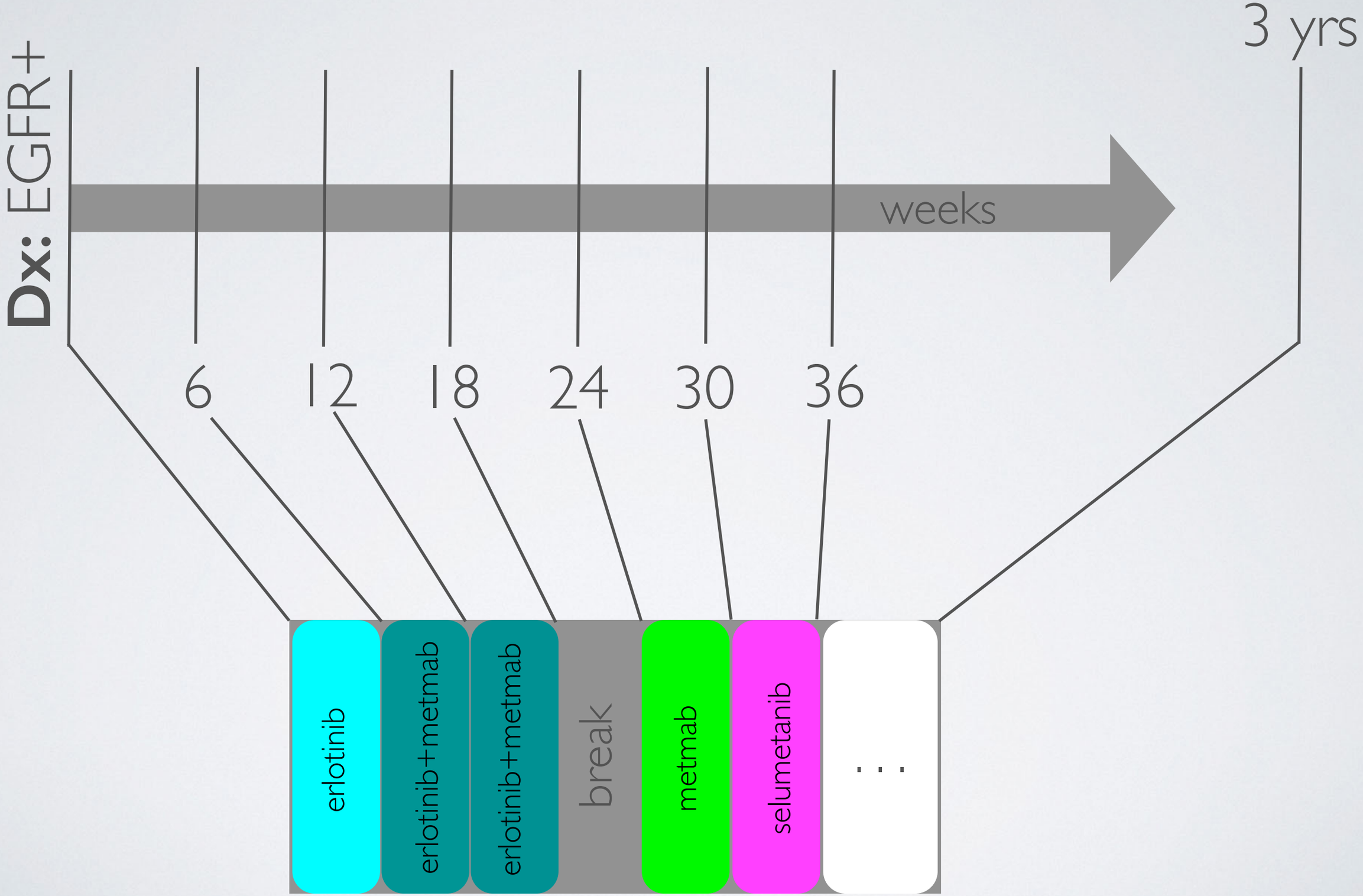
where
0=wt
1=mut

More is more.



Optimization technique

possible patient timeline



break

break

break

break

break

recombination

break

break

break

optimal

Tx

50 days gained

Φ>1

22 days gained

Φ<1

break

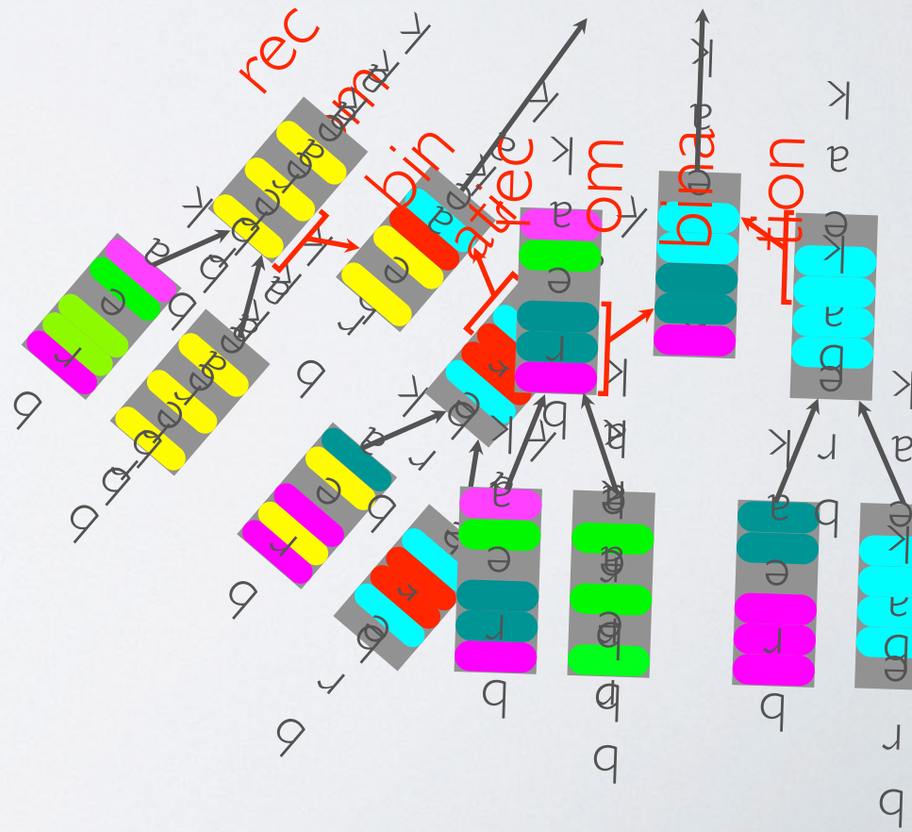
break

break

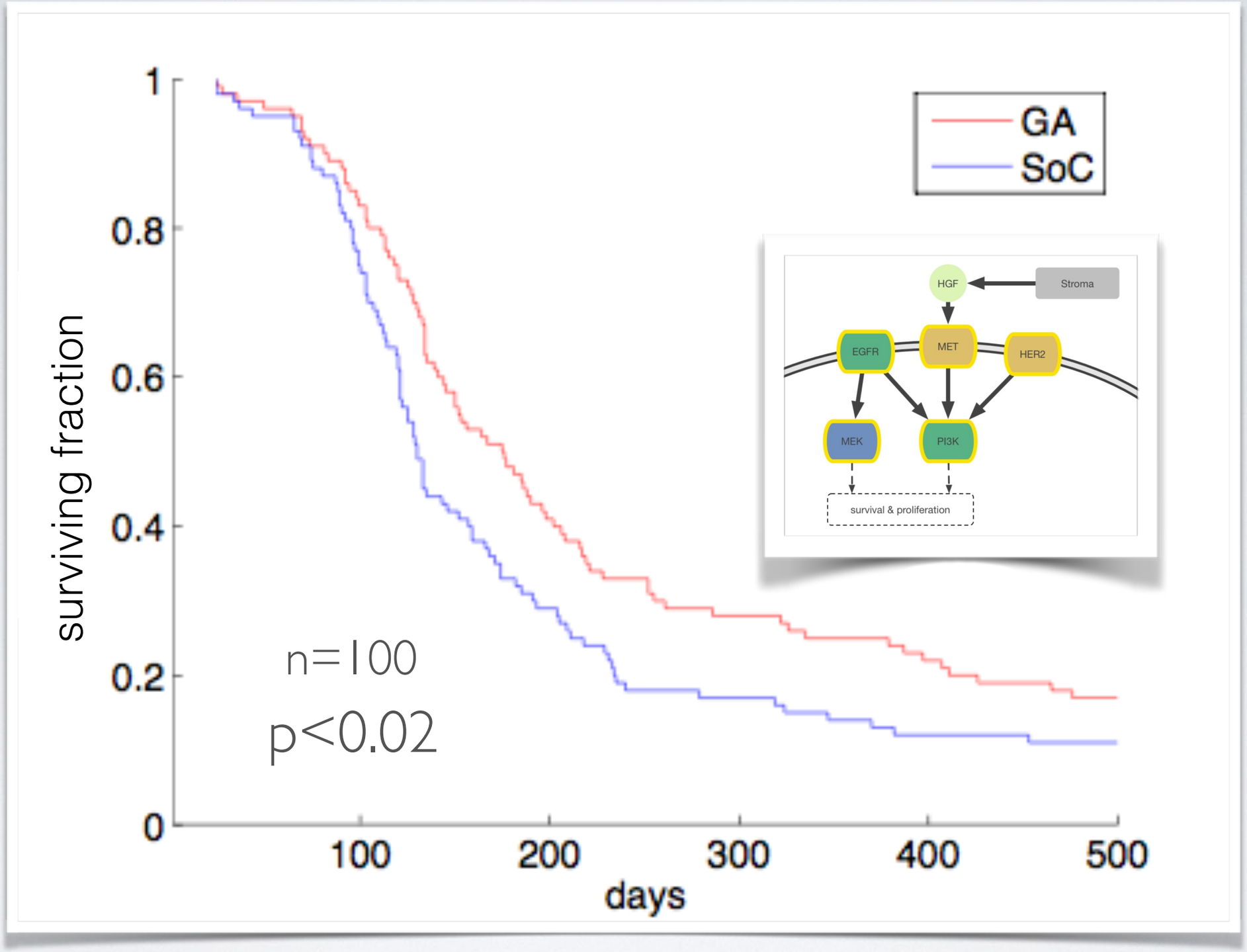
break

break

break



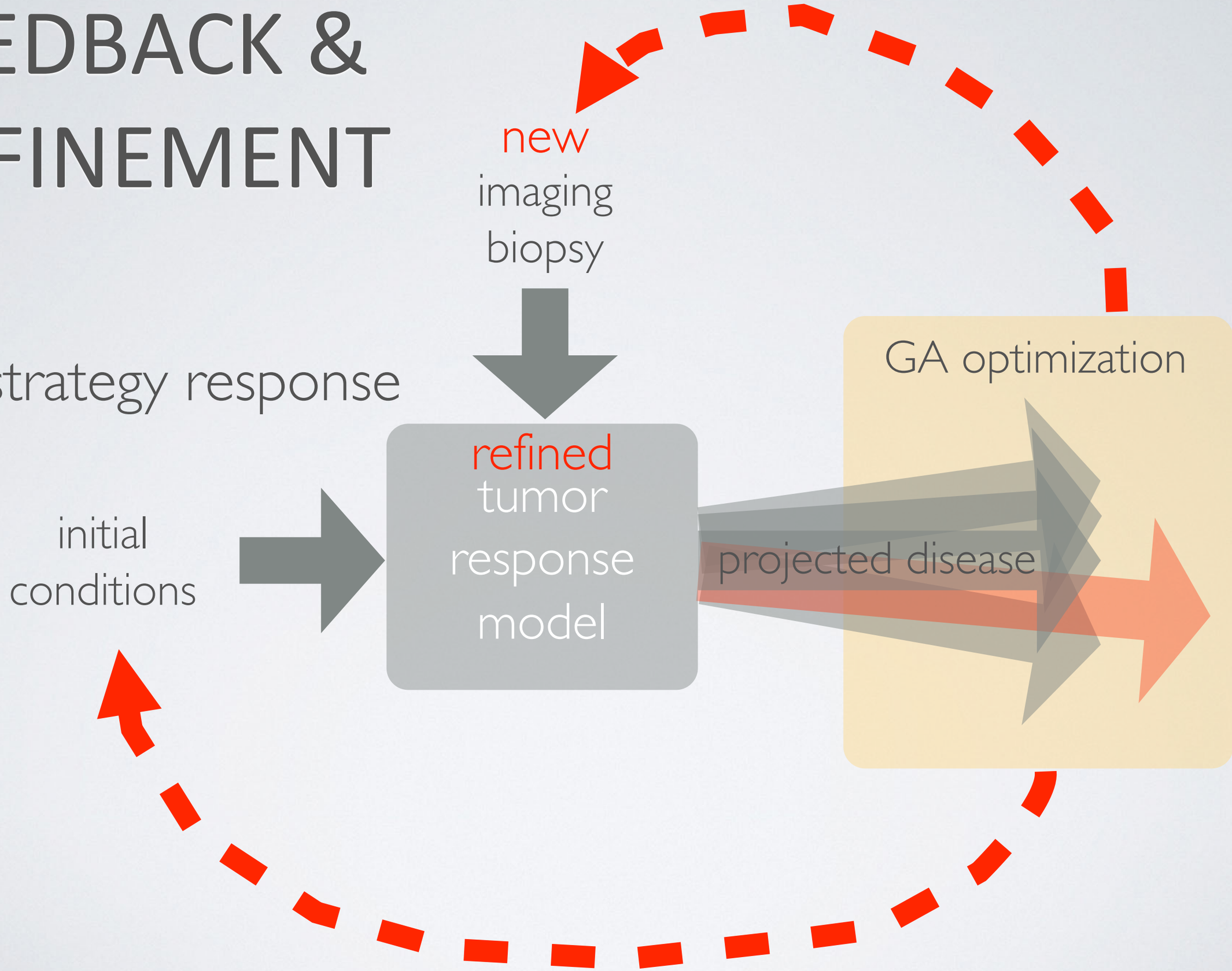
SOC VS. GA-DERIVED TX SCHEDULE



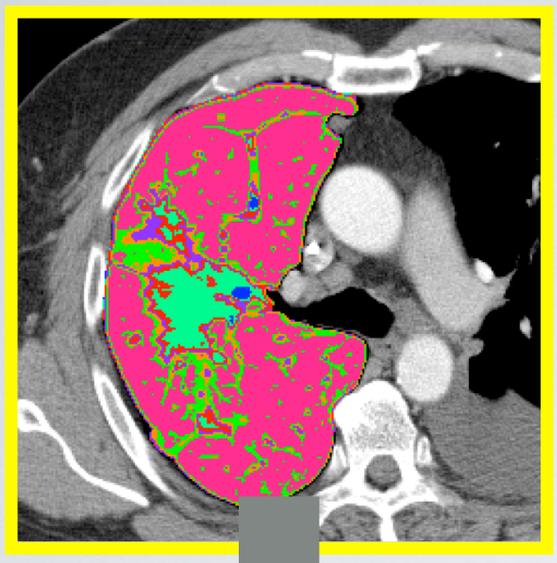
SOC: erlotinib

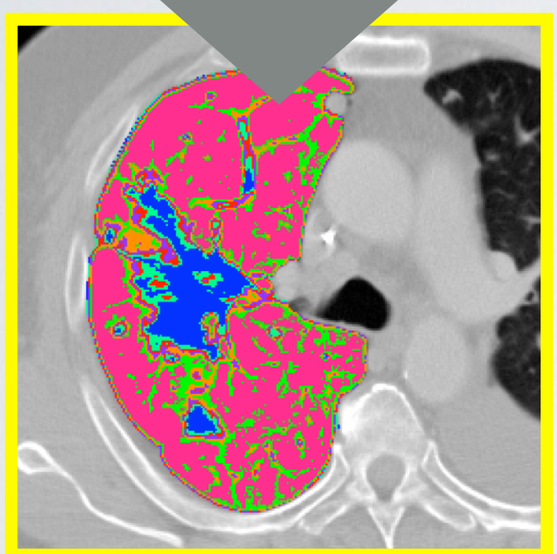
GA: erlotinib+everolimus → metmab+everolimus → erlotinib+metmab → erlotinib+everolimus

FEEDBACK & REFINEMENT

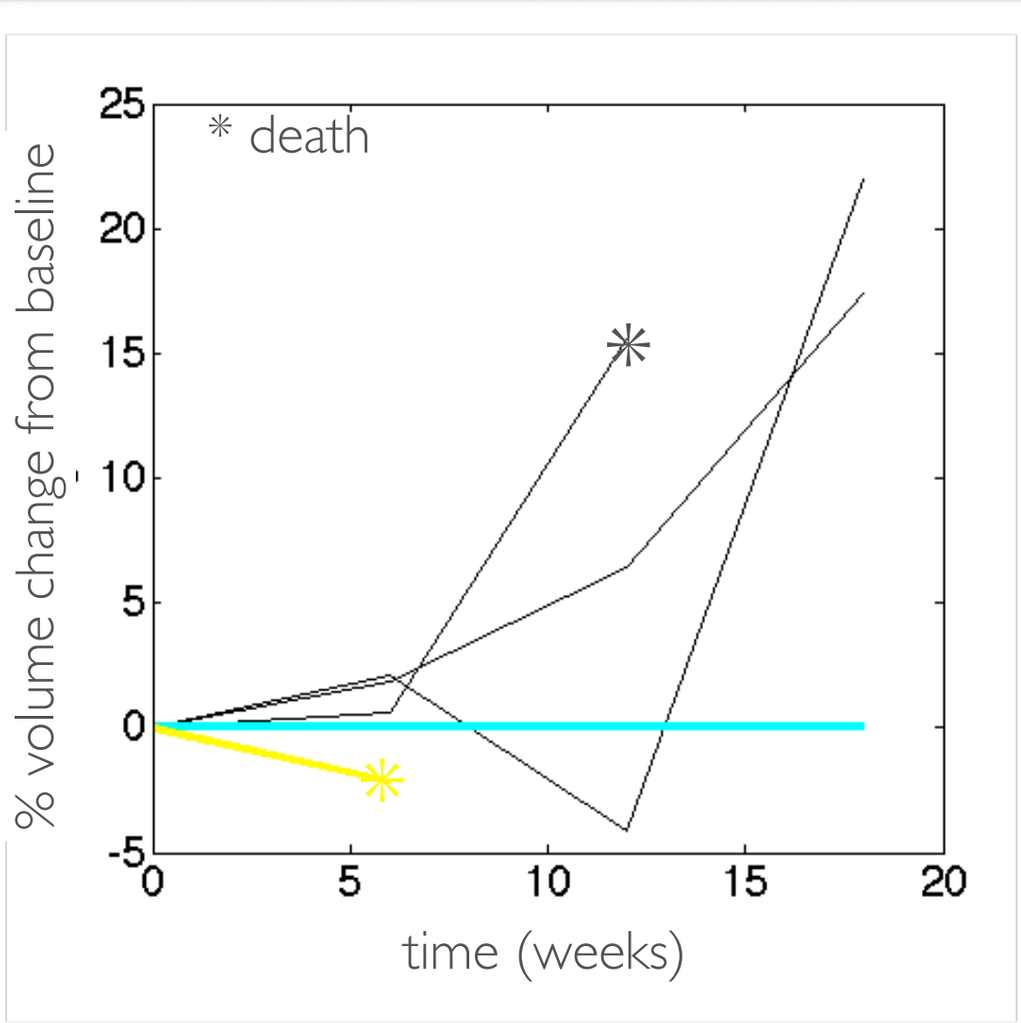


worst case

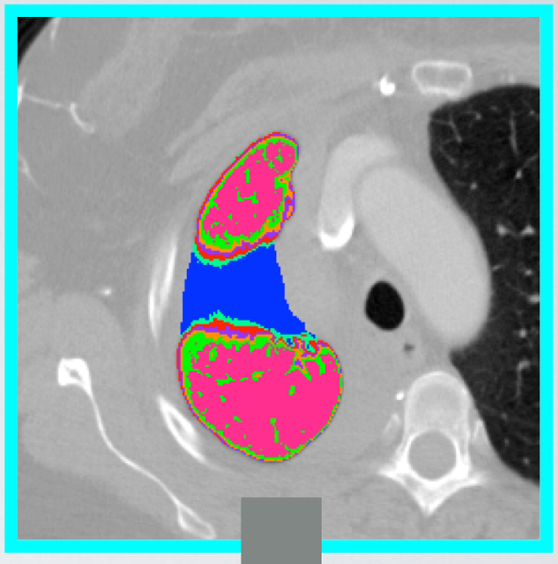


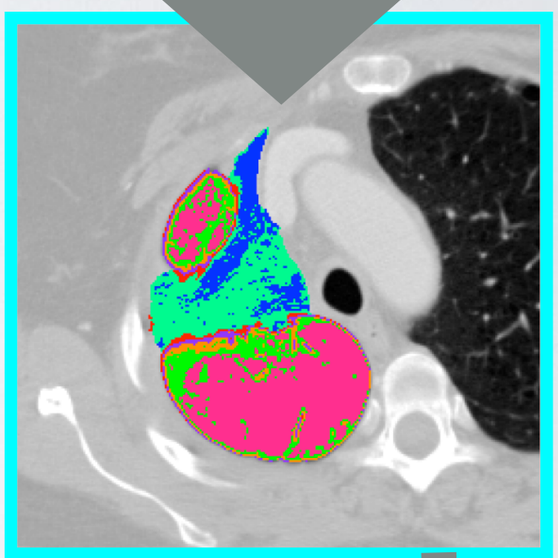


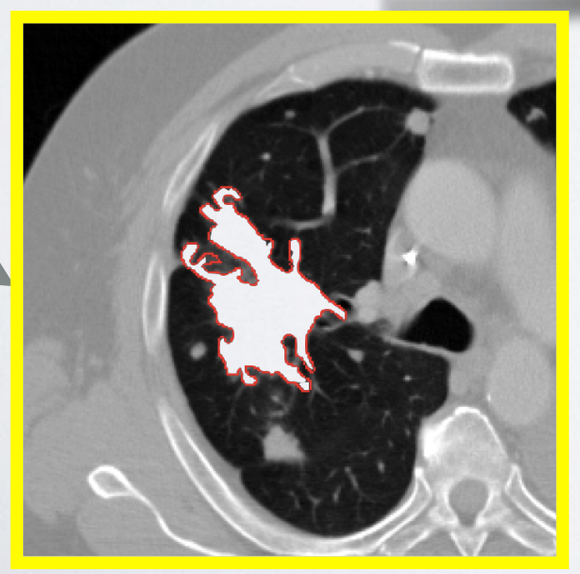
new patient data



Best case



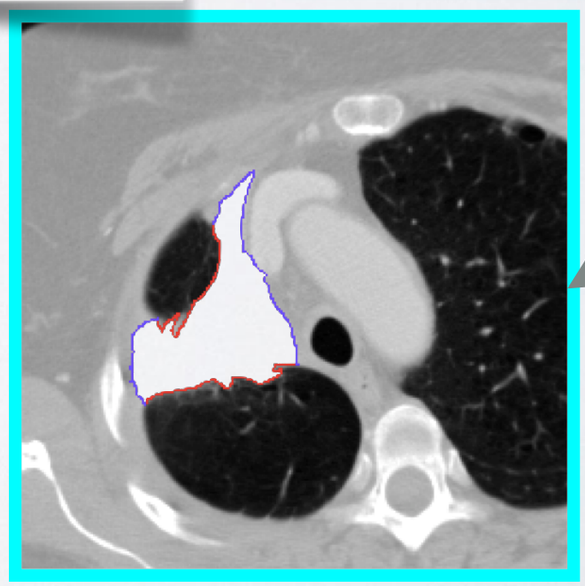




change in stromal component

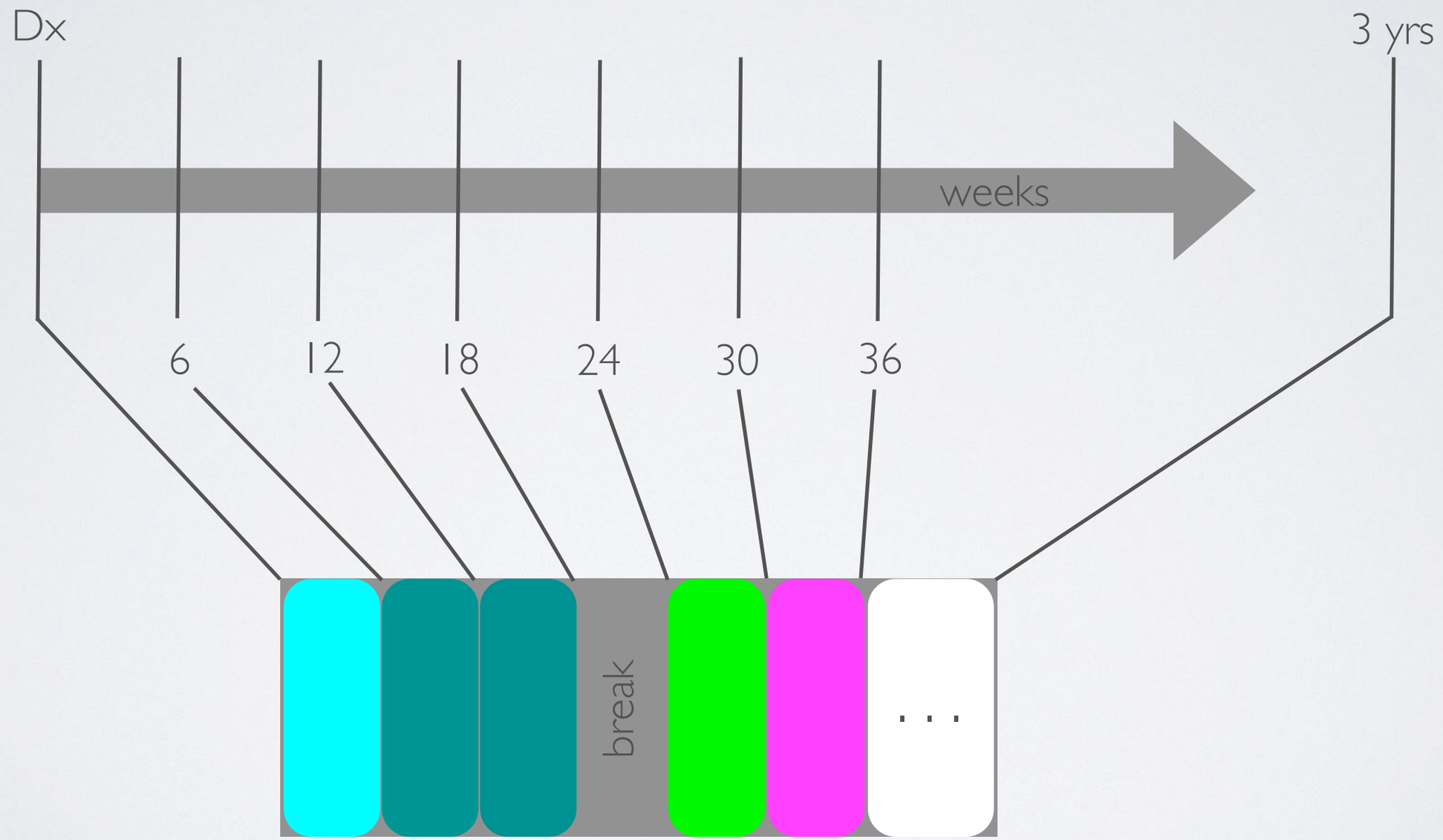
160 px

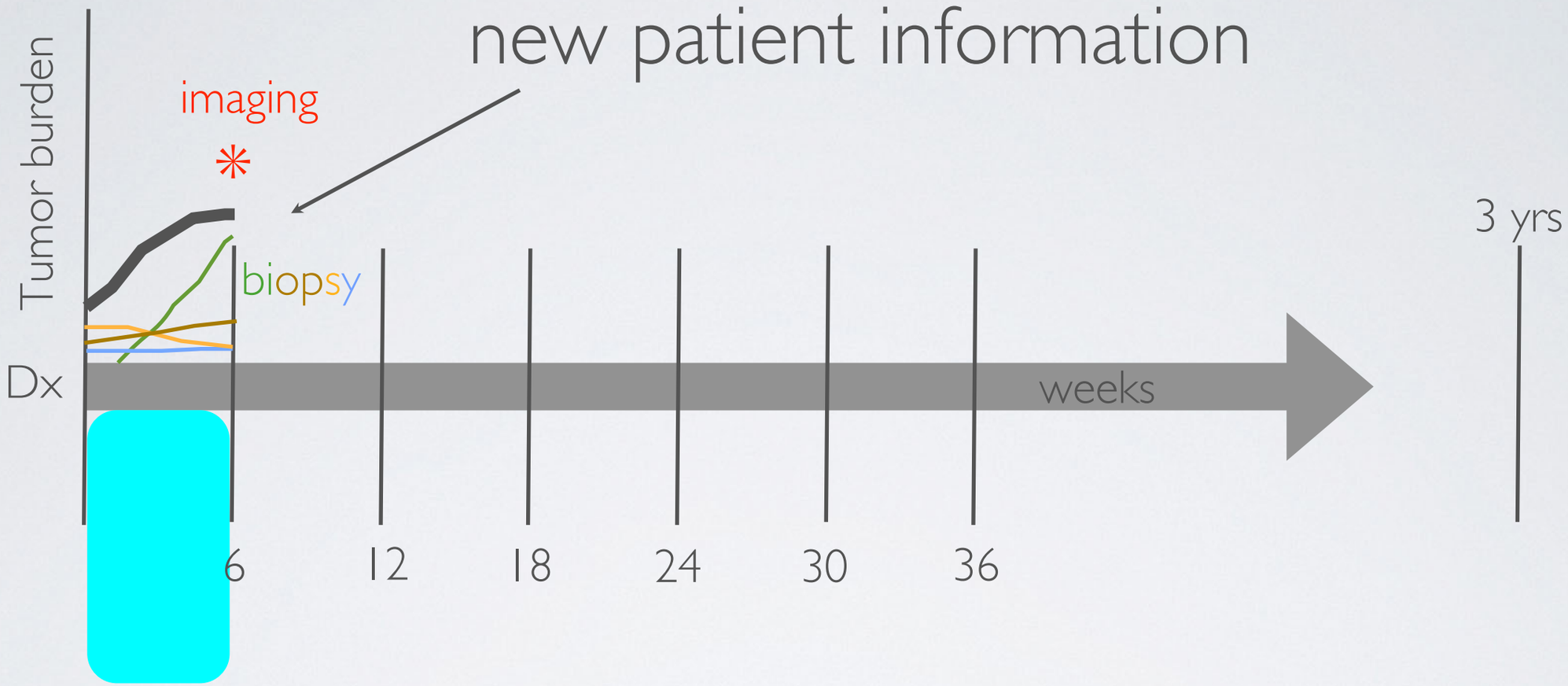
18 px



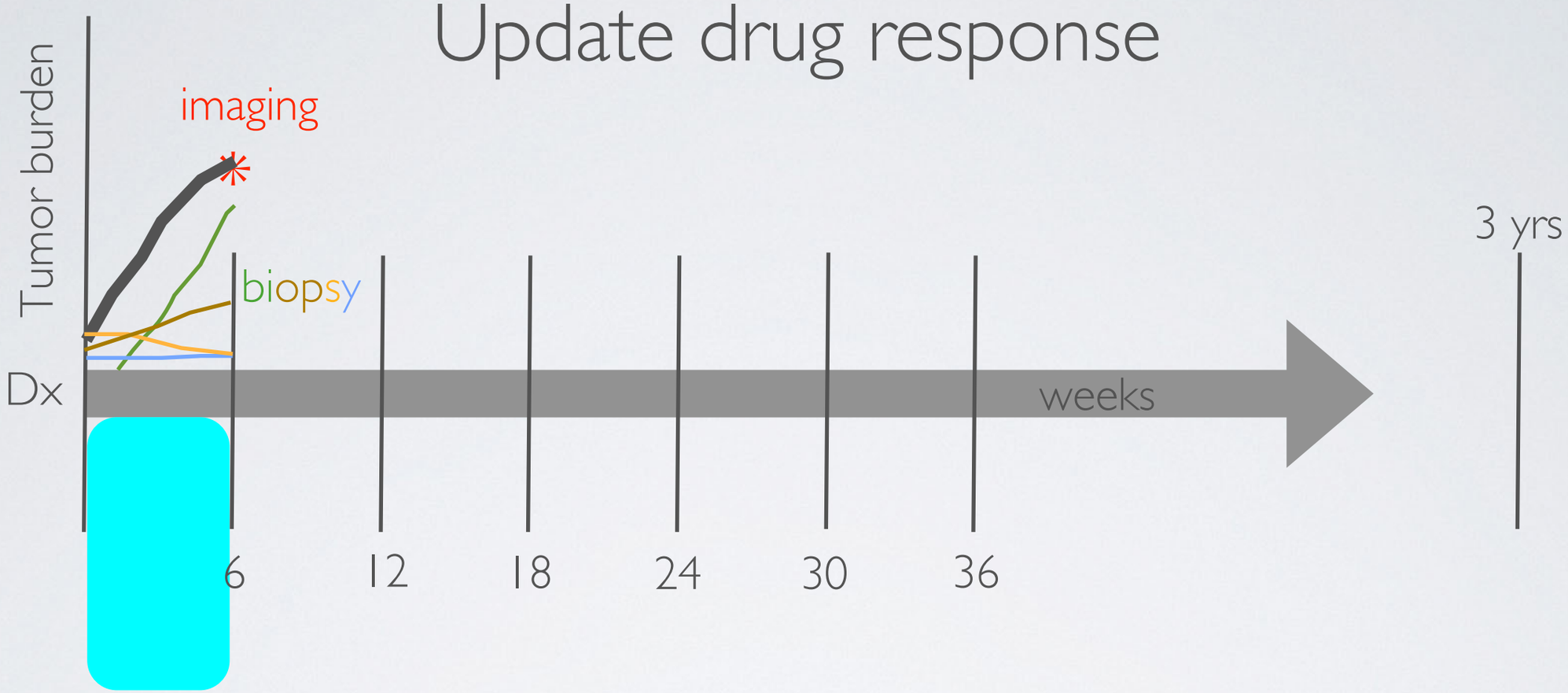
serum HGF & biopsy

GA finds optimal treatment schedule at Dx

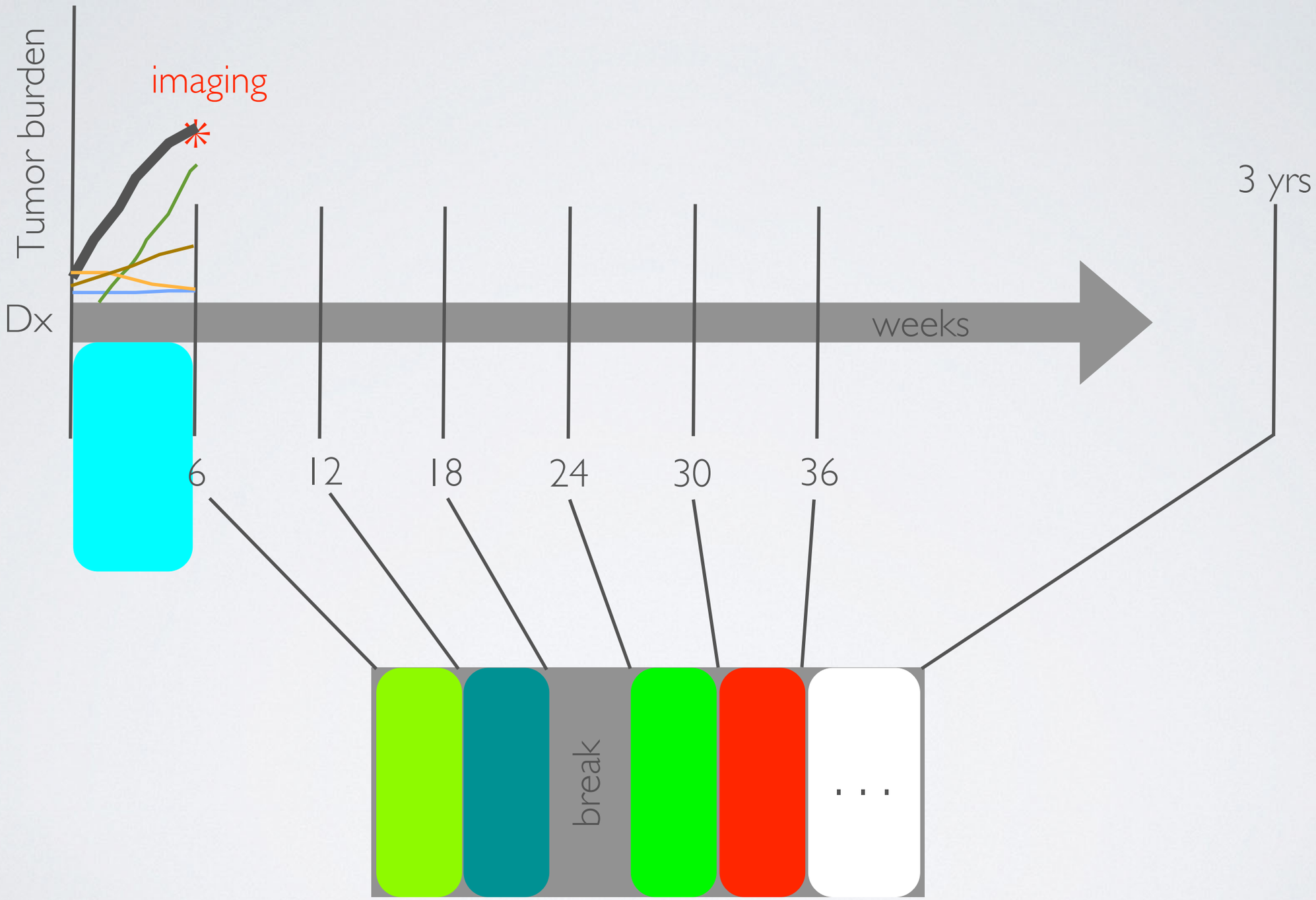


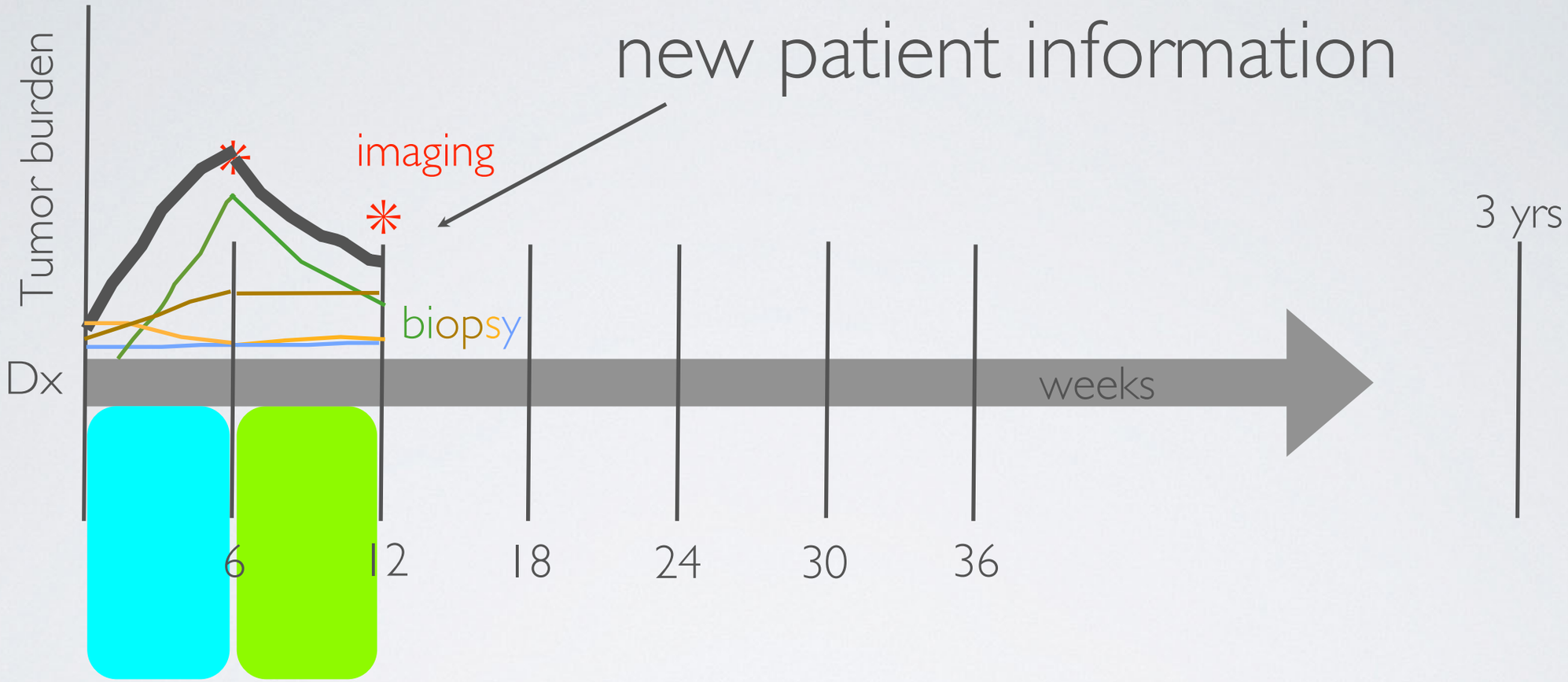

new patient information
imaging
Tumor burden
biopsy
Dx
weeks
3 yrs
6
12
18
24
30
36

Update drug response



New optimal Tx schedule




new patient information
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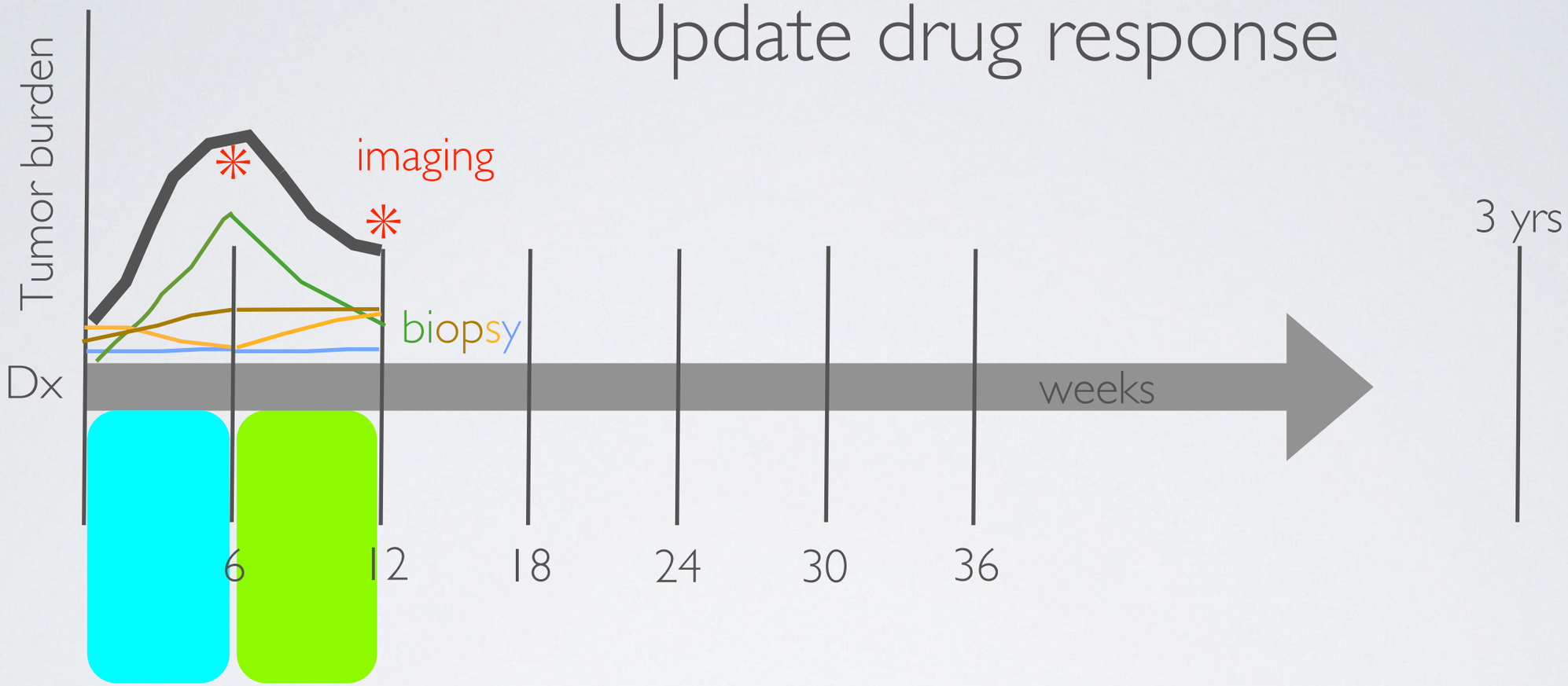
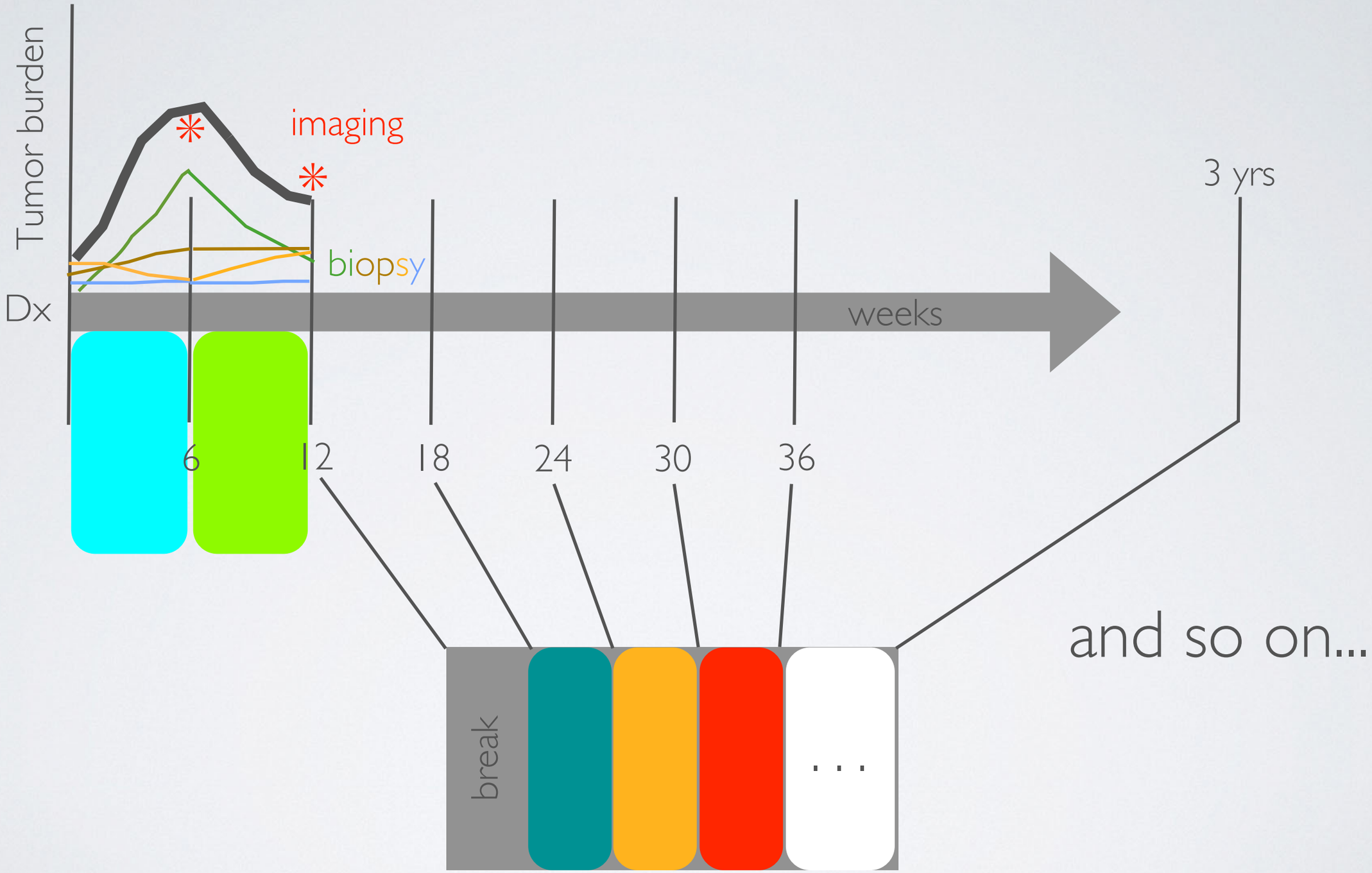
Update drug response



New optimal Tx schedule



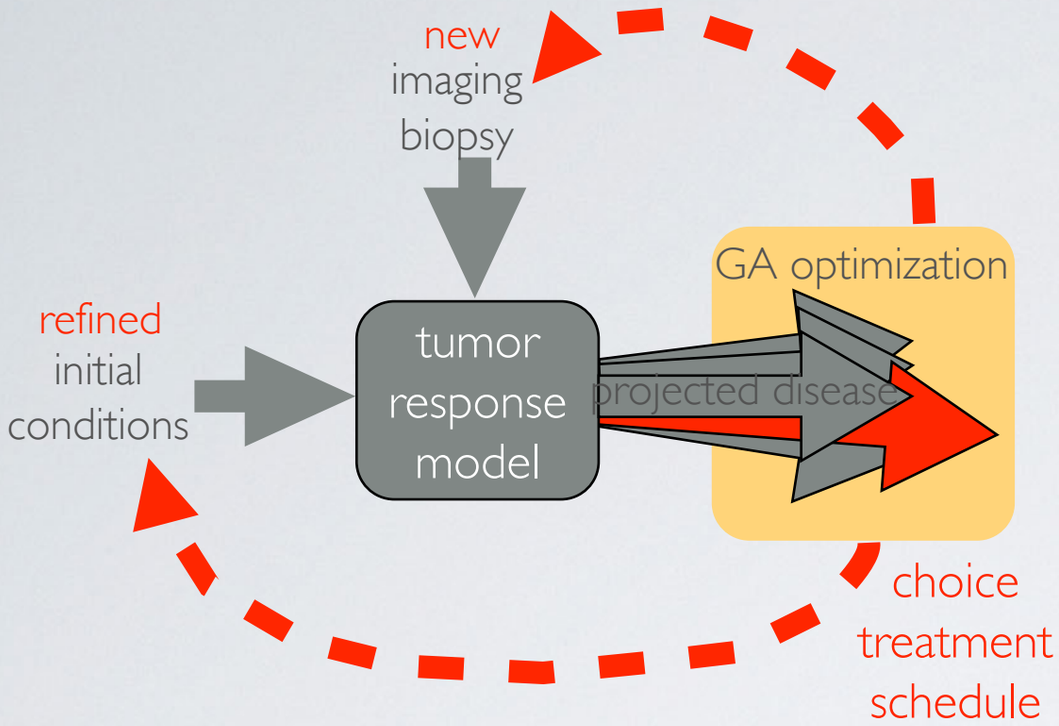
and so on...

Conclusions

1) We have built a model that captures clonal dynamics of EGFR driven lung cancers.

2) Using a GA to optimize treatment scheduling of combinations of known drugs, the model predicts a treatment schedule that prolongs survival (45 days past that of standard of care).

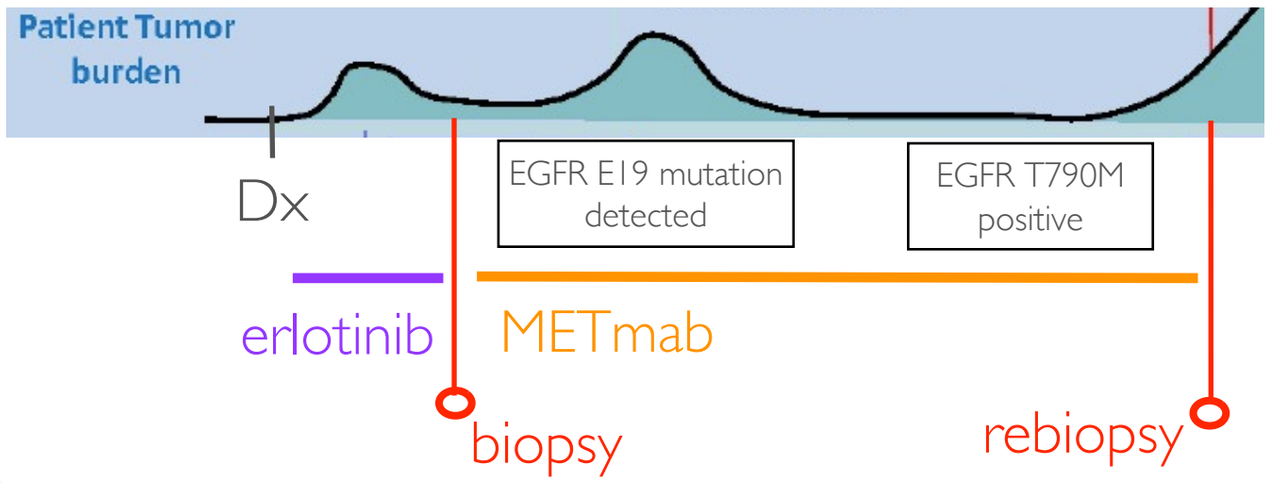
3) Periodic updating and refinement of the model from patient-specific data should improve the model and the prediction of the treatment by the GA.

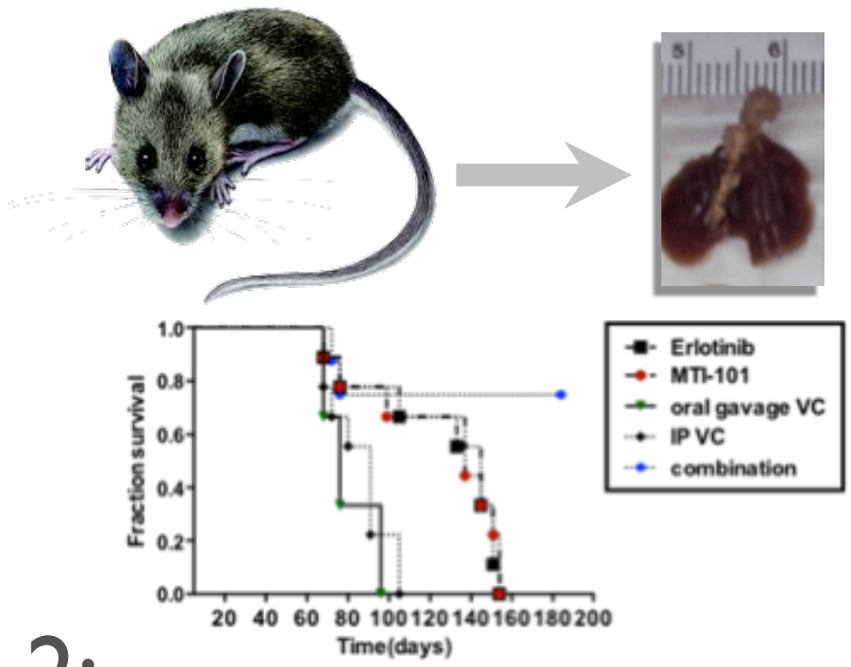


HYPOTHESIS: Pretreatment molecular phenotypes with real-time clinical variables obtained from plasma and imaging can be used to predict optimal drug sequence and thereby extend progression free survival.

AIM 1:

Refine the mathematical model using clinical data from a retrospective institutional cohort of advanced EGFR+ lung cancer patients.

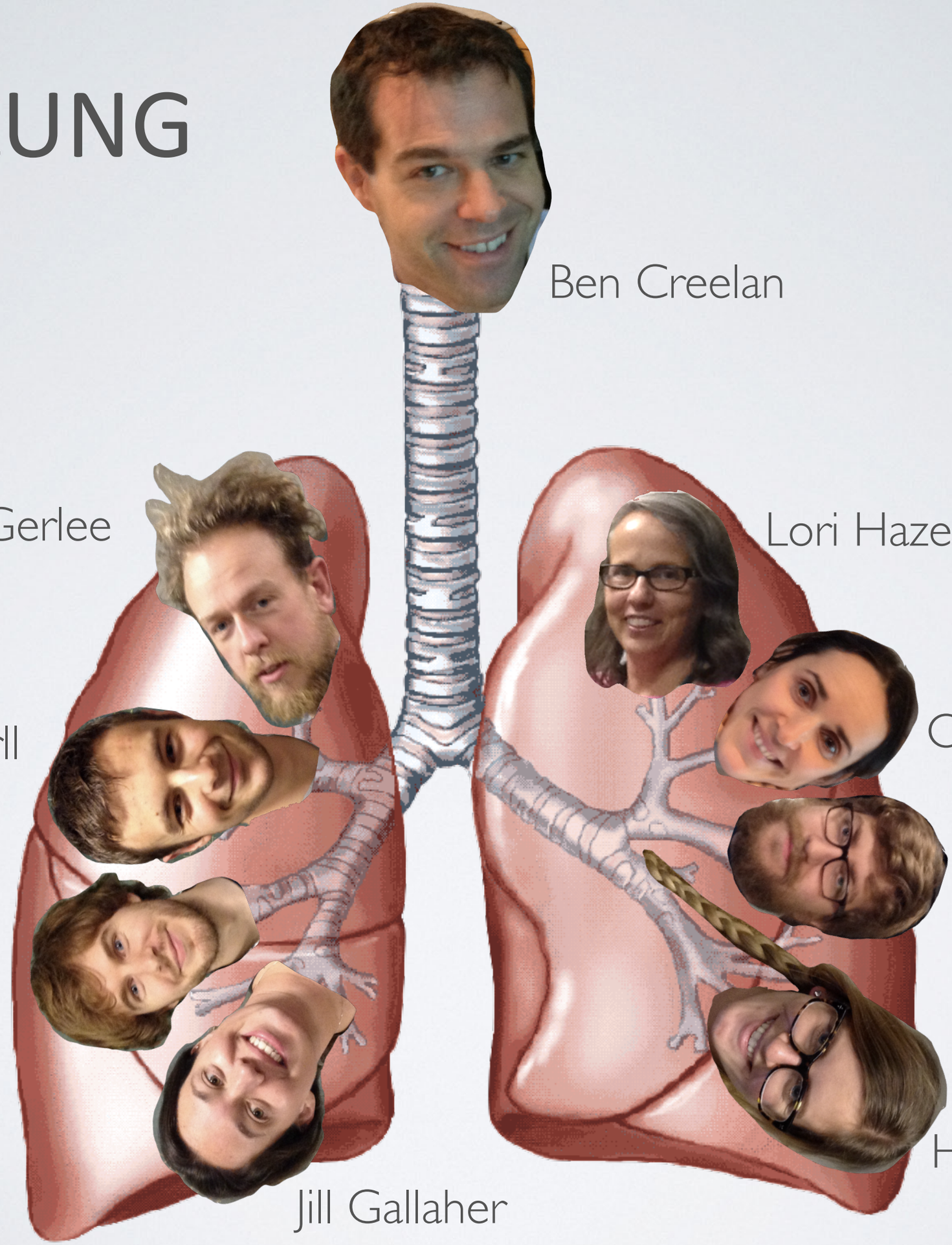




AIM 2:

Utilize model-derived novel drug combination schedules and compare with standard of care using a metastatic EGFR driven *in vivo* model.

TEAM LUNG



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