FDA-ISoP Public Workshop: Model Informed Drug Development (MIDD) for Oncology Products
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Optimizing Novel-Novel Dose Combinations via Simultaneous Exposure-Toxicity & Exposure-Efficacy Modeling

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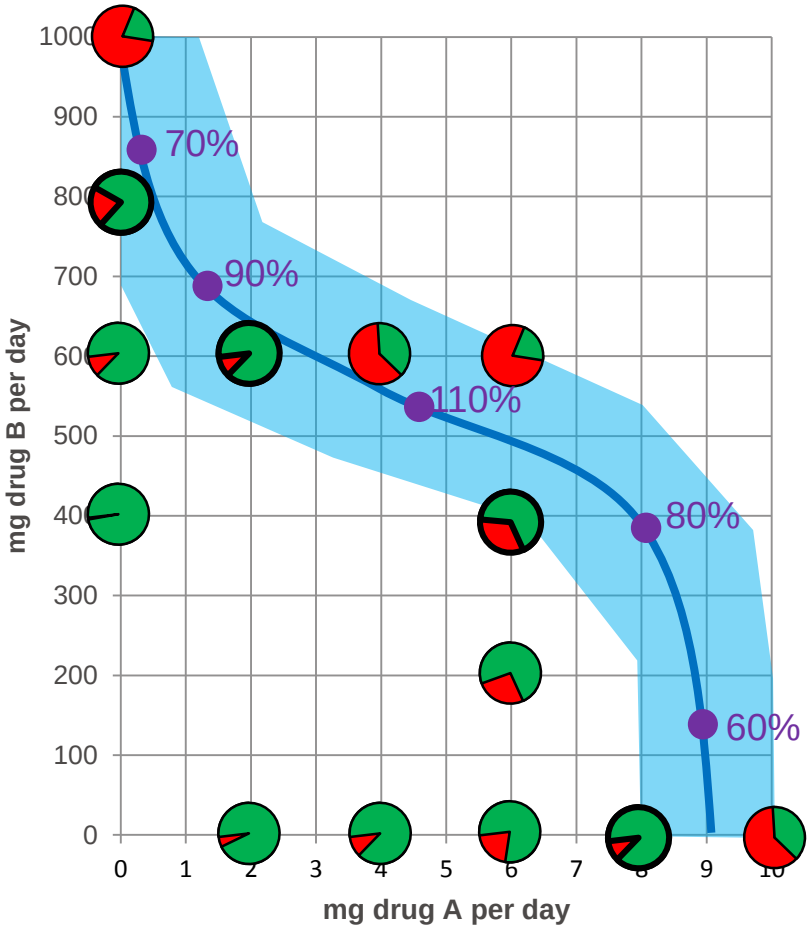
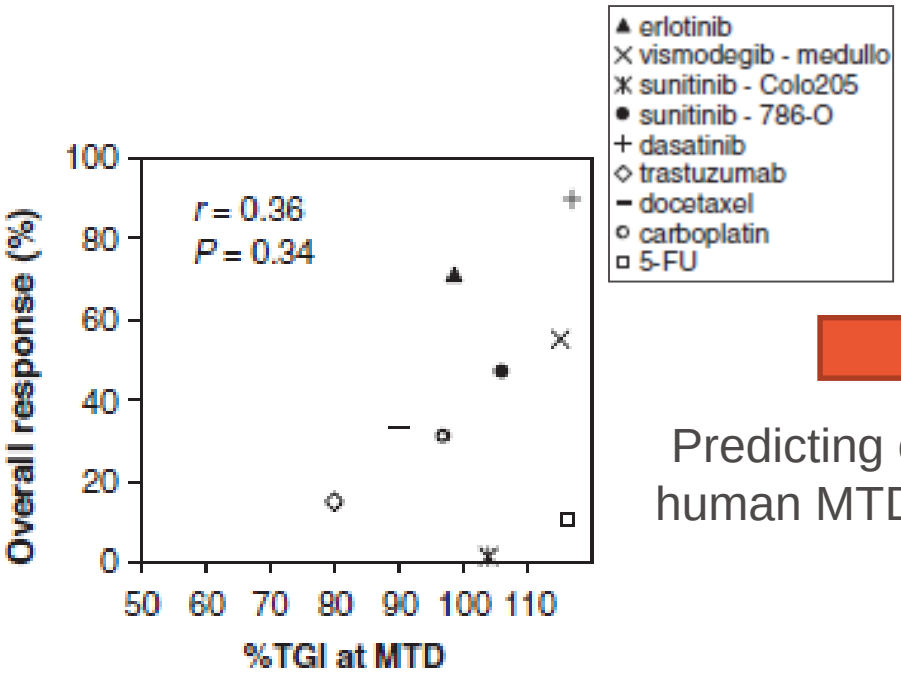
Combo Dose Escalation and Optimization Platform …beyond the “backbone” paradigm

- X,Y axes = drug A,B doses
- Given observed fraction of patients at dose levels (A,B) with DLT or no DLT…
- Unlike monotherapy, MTD is not a single number but a curve in dose (A,B) space.
- RP2D is point on MTD curve giving maximum tumor Growth Rate Inhibition (GRI) as predicted from
  - Clinical effect observations
  - Preclinical modeling…

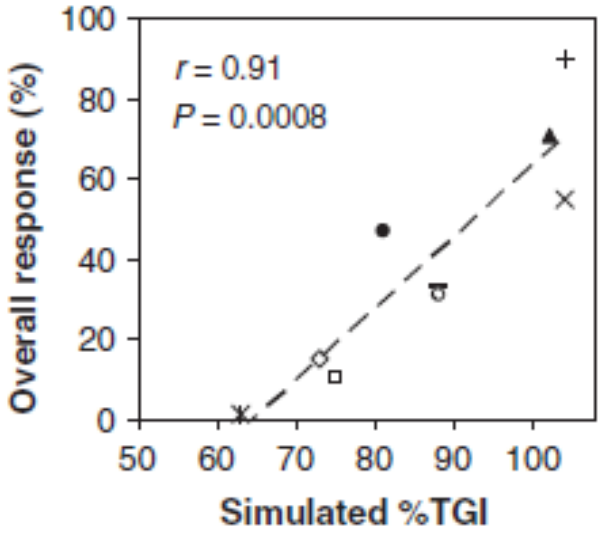


DLT = Dose-Limiting Toxicity
MTD = Maximum Tolerated Dose
RP2D = Recommended Phase 2 Dose

Mouse models predict human tumor response rates at matching free-fraction clinically attainable exposures



Predicting efficacy at human MTD exposure



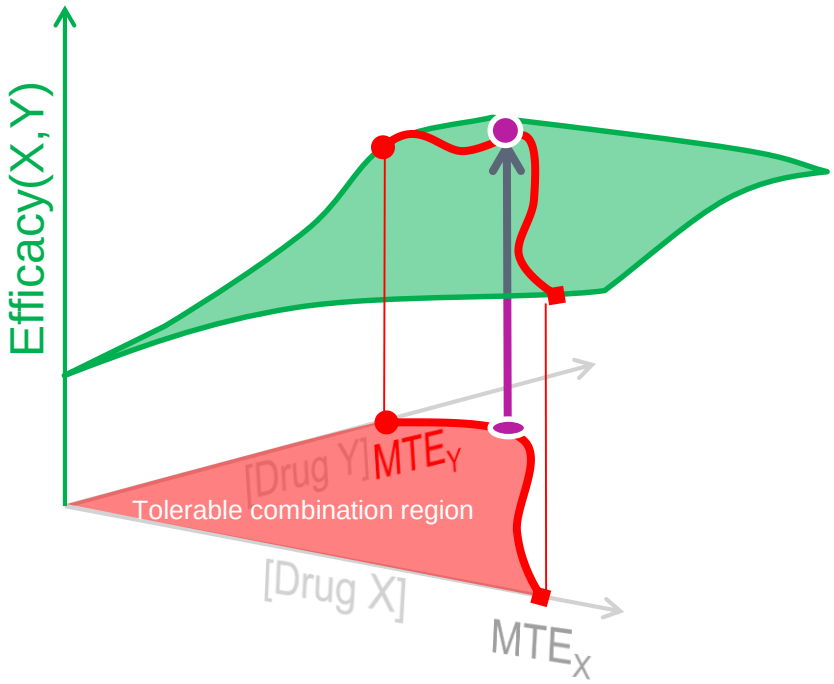
→ Use exposure as driver of efficacy and toxicity

→ Convert " $RP2E^2$ " back to combo dose and schedule

TGI = Tumor Growth Inhibition (see Wong)
MTD = Maximum Tolerated Dose
$RP2E^2$ = Recommended Phase 2 (combo) Exposure-Exposure

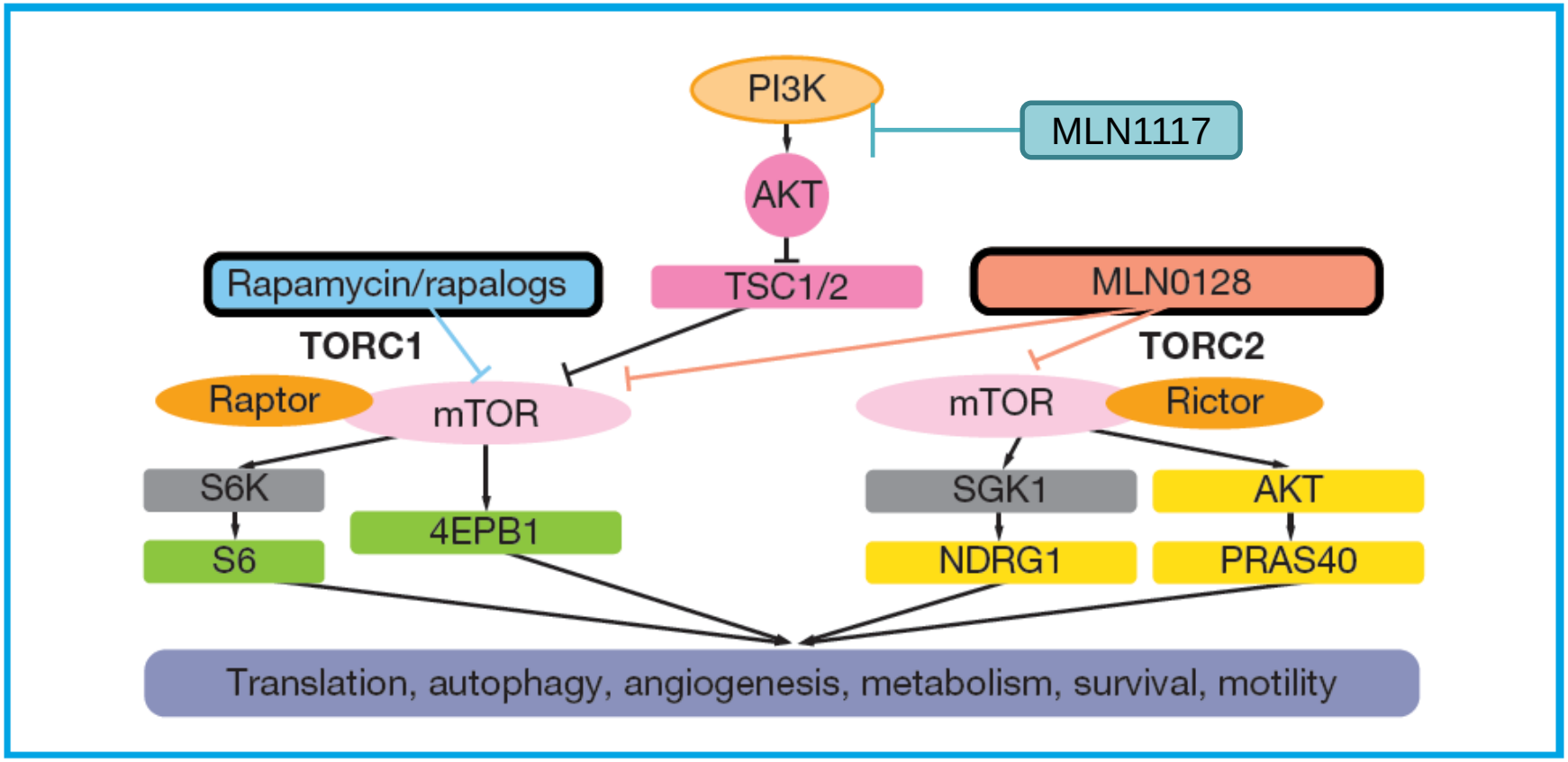
Wong et al, CCR 2012 Jul 15;18(14):3846-55.

This is just a 2-D constrained optimization problem!



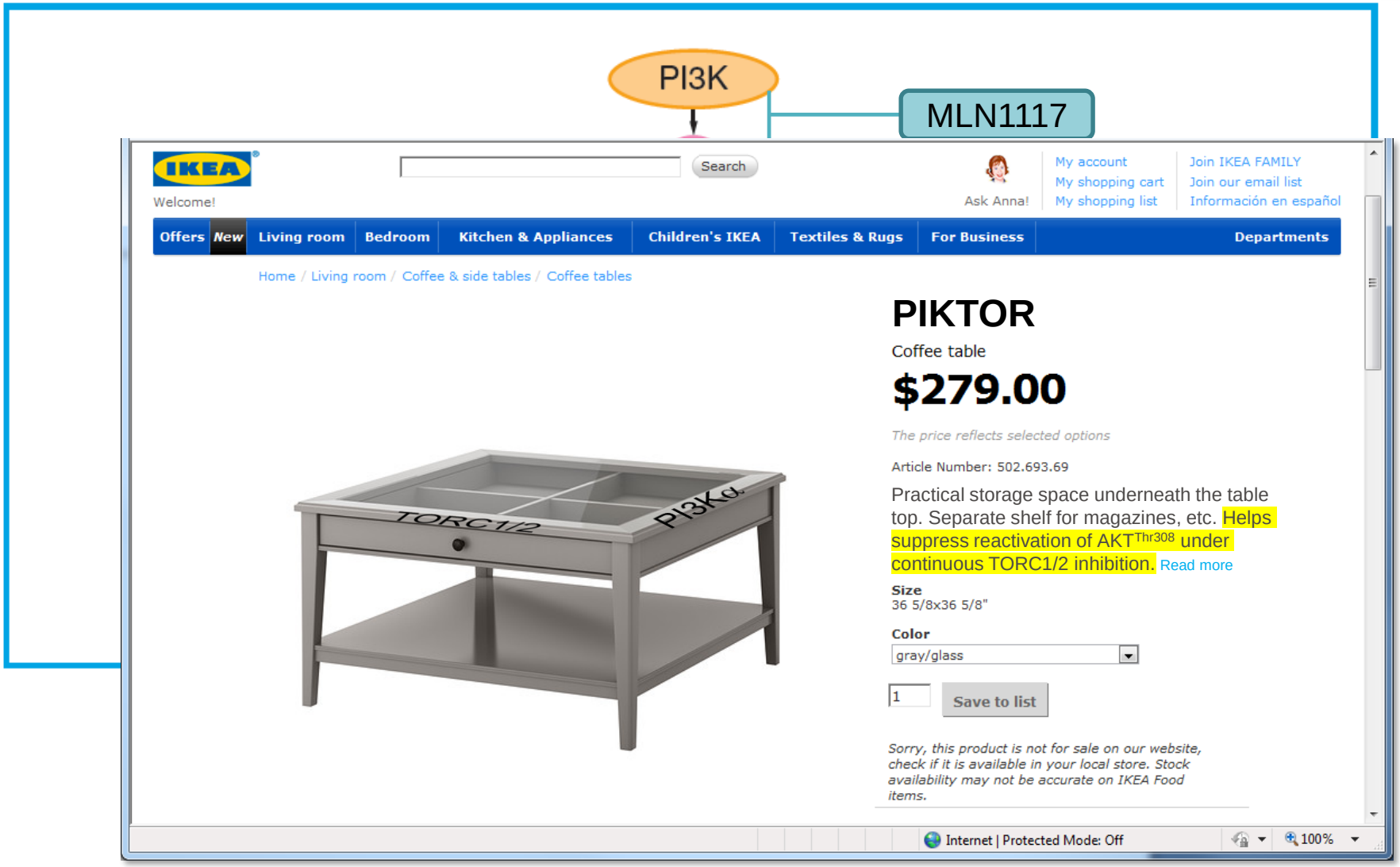
- Given:
  - an efficacy surface E(X,Y) defined for all *exposure* combinations of X & Y
  - A toxicity constraint curve in X,Y space
- Find:
  - Point (X,Y) in tolerable combination region that maximizes E(X,Y)
- Hint:
  - for sufficiently boring efficacy surfaces and toxicity curves, the max is somewhere on the tox constraint curve.

Case study: TAK-117/TAK-228 “PIKTOR” Combination

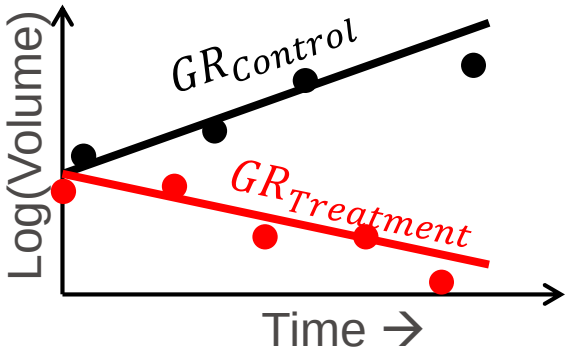


TAK-117=MLN1117=PI3Ka inhibitor (PIK3CA gene codes for PI3Ka)
TAK-228=MLN0128=TORC1/2 inhibitor

Case study: TAK-117/TAK-228 “PIKTOR” Combination

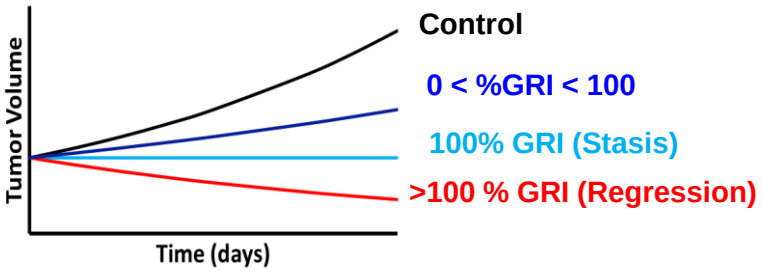


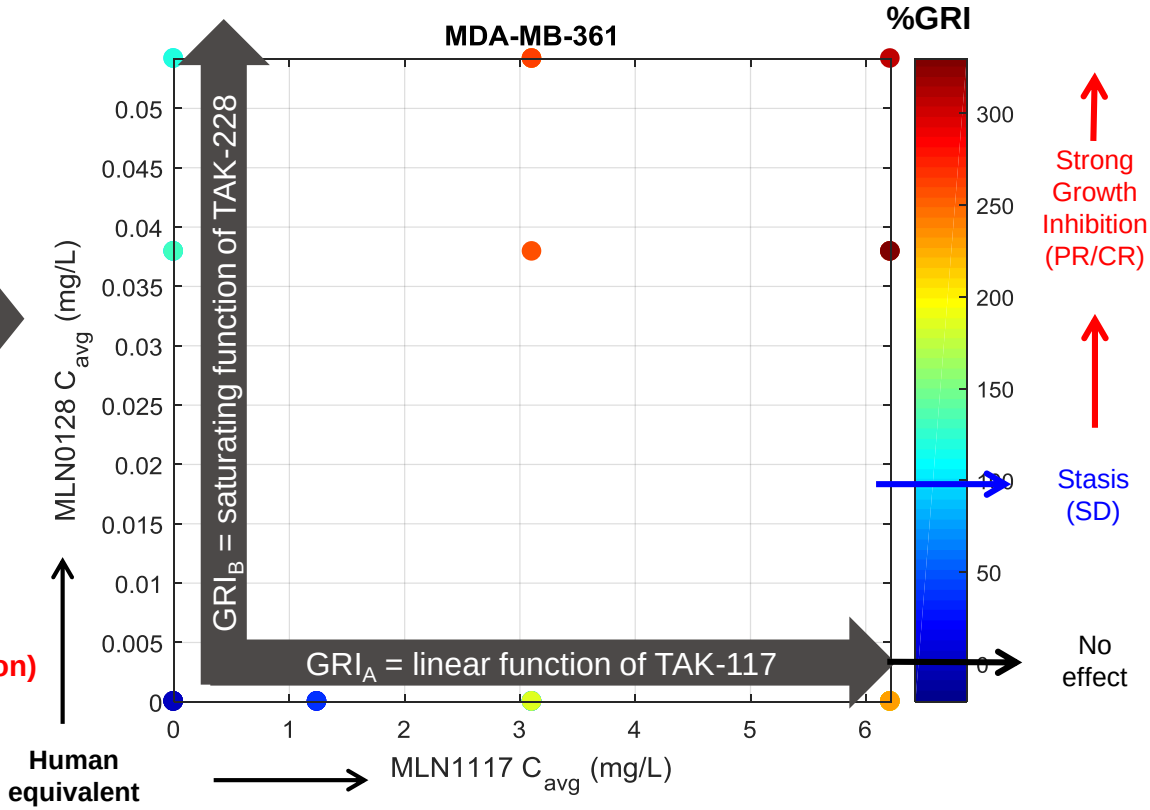
Step 1: Model mouse tumor growth inhibition data, converting mouse exposures to free-fraction equivalent human exposures



$$GRI_* = 100\left(\frac{GR_{Control} - GR_{Treatment}}{GR_{Control}}\right)$$

GRI = Growth Rate Inhibition (~TGI)
PR = Partial Response
CR = Complete Response
SD = Stable Disease





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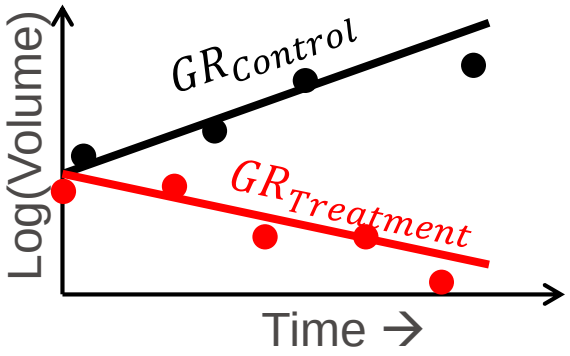
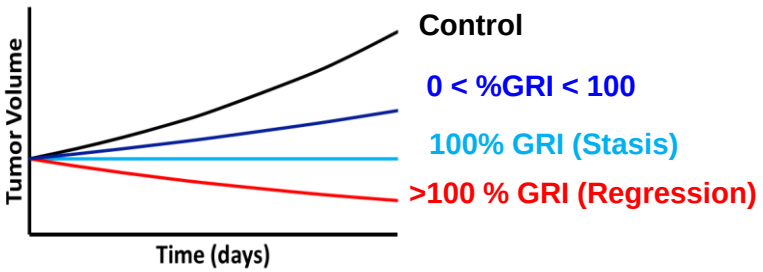
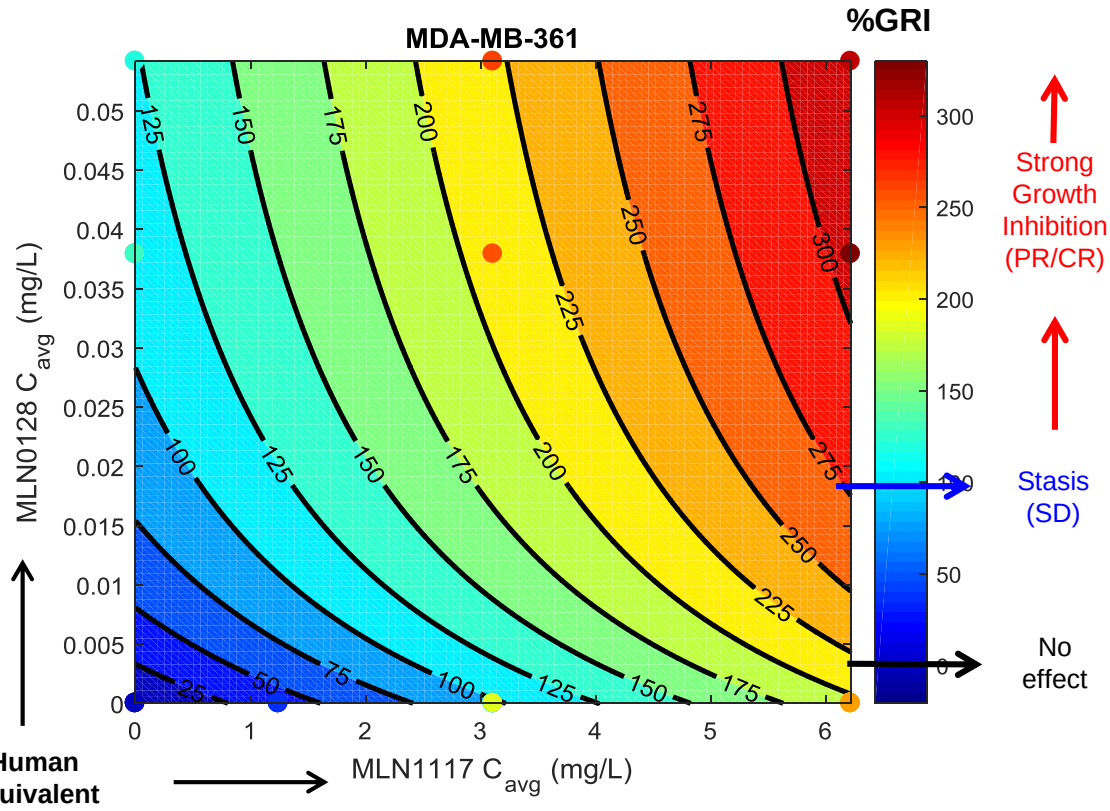


$$GRI_{*} = 100\left(\frac{GR_{Control} - GR_{Treatment}}{GR_{Control}}\right)$$

$$\%GRI_{X,Y} = GRI_X + GRI_Y + \beta \times GRI_X \times GRI_Y$$

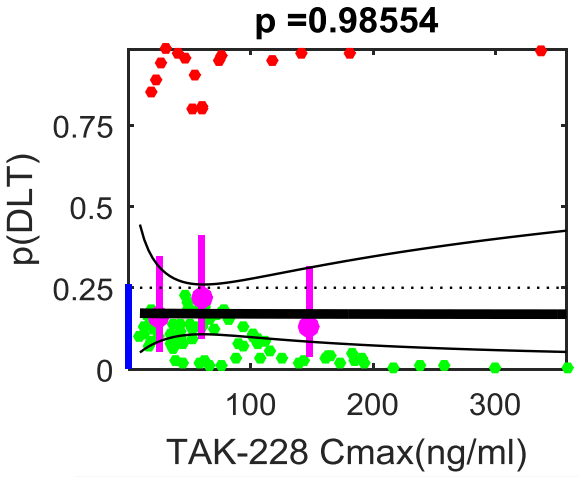


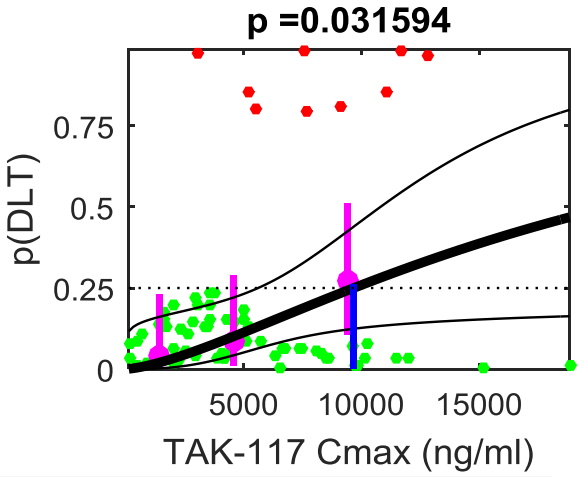


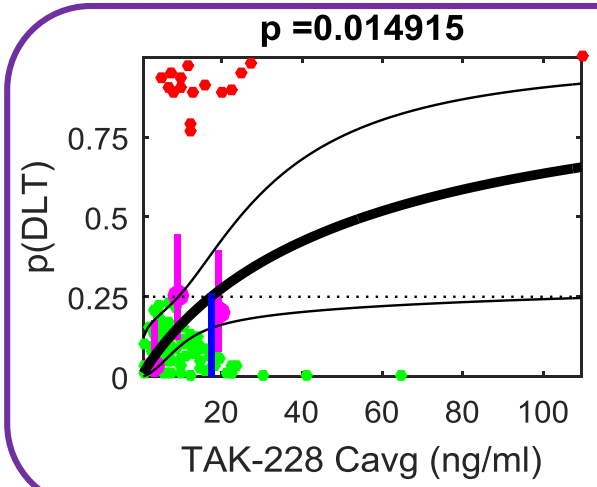
MLN1117 & MLN0128 are synergistic in mouse tumor growth inhibition

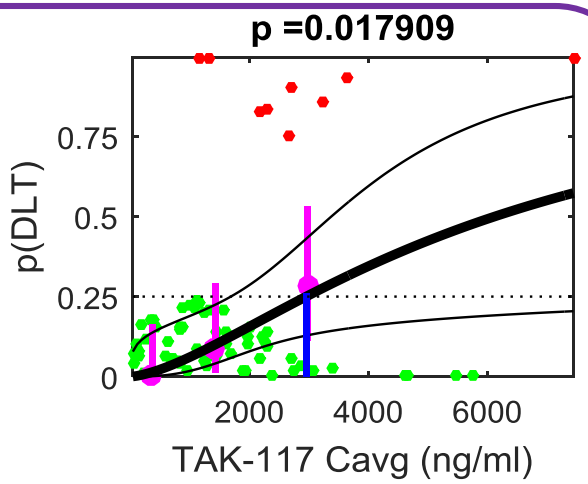
Step 2: Determine Maximum Tolerated Exposure (MTE) curve

A. Identify PK drivers of tox for single agents









$$\ln\left(\frac{p}{1-p}\right) = mx + b$$

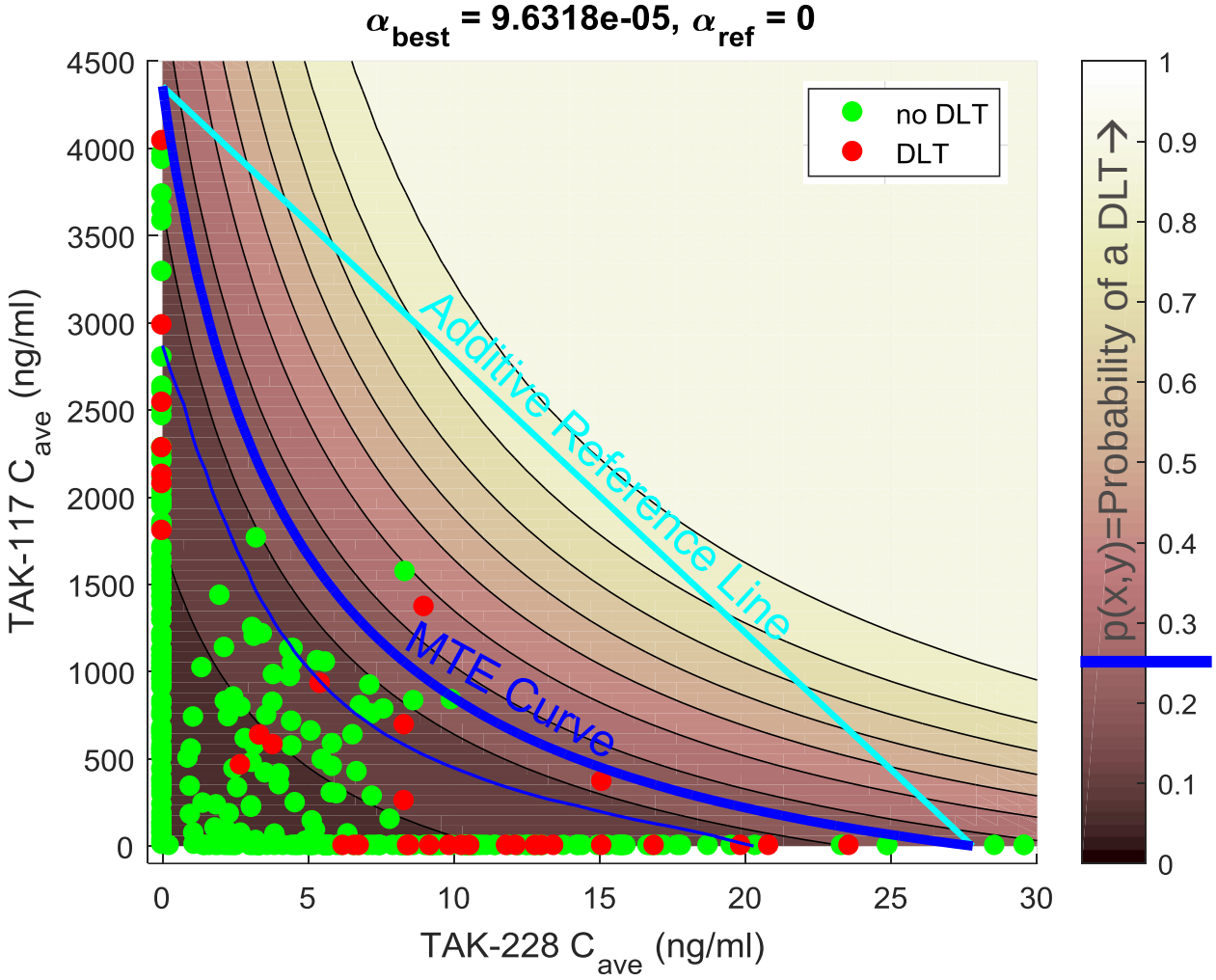
Average concentration was the best driver of toxicity for both TAK-228 and TAK-117 as single agents

DLT events
nonDLT events

Step 2: Determine Maximum Tolerated Exposure (MTE) curve

B. Fit exposure-Pr(DLT) surface; MTE curve = (X,Y): Pr(DLT|X,Y)=25%

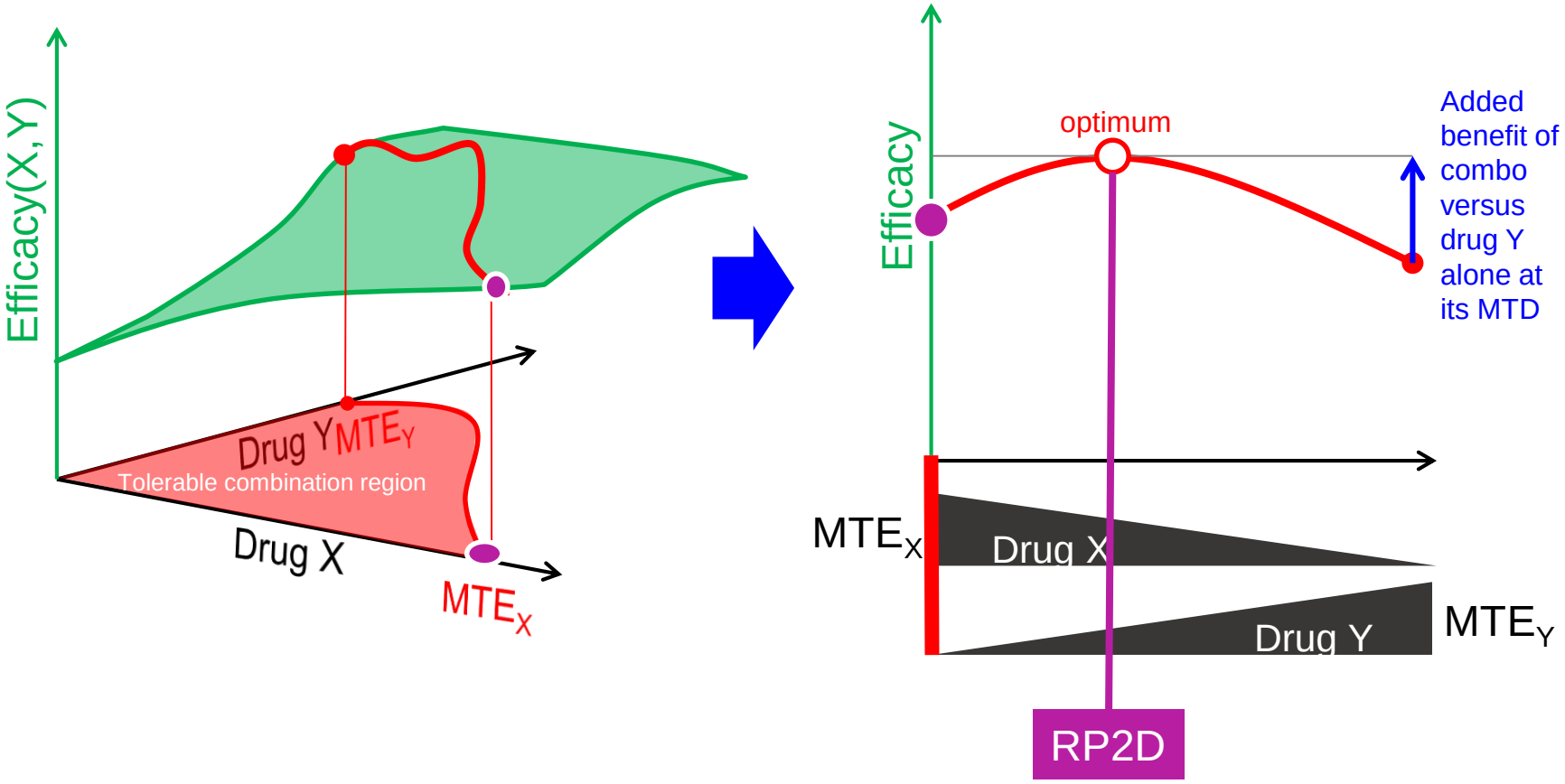
$$\ln\left(p/(1-p)\right) = b + m_x x + m_y y + \alpha xy$$



MTE curve is all (X,Y) exposures resulting in 25% probability of toxicity

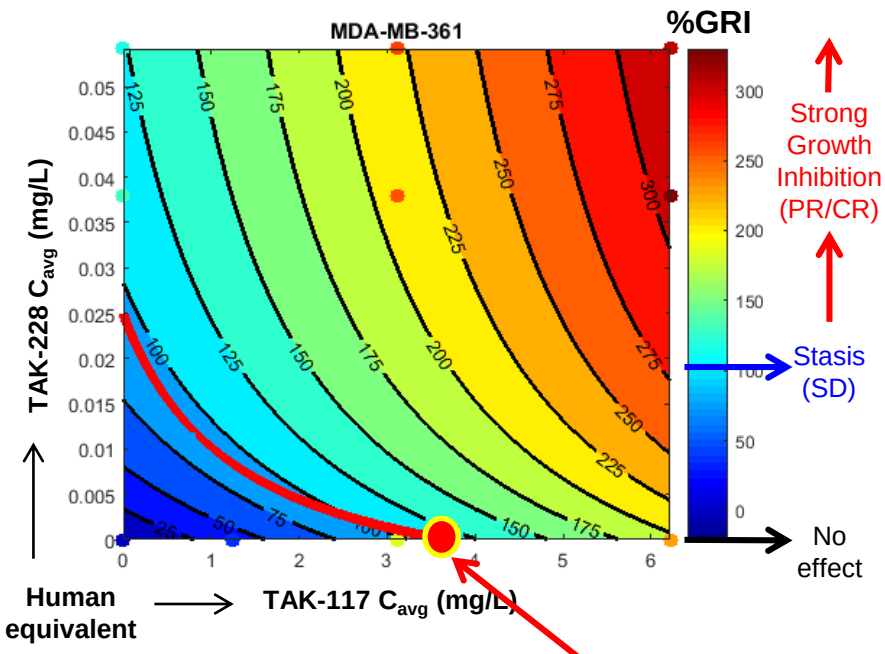
Step 3: What is the predicted efficacy as we walk along the max tolerated exposure (MTE) 'fence' ?

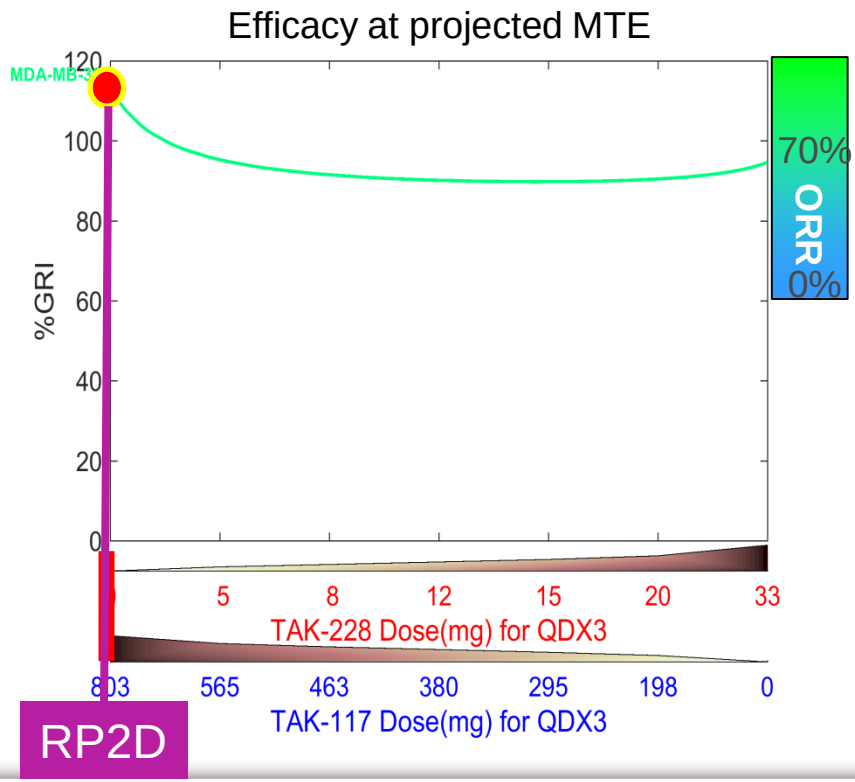
To aid visualization we can cut vertically along the fence and look at the "height" from the cut side…



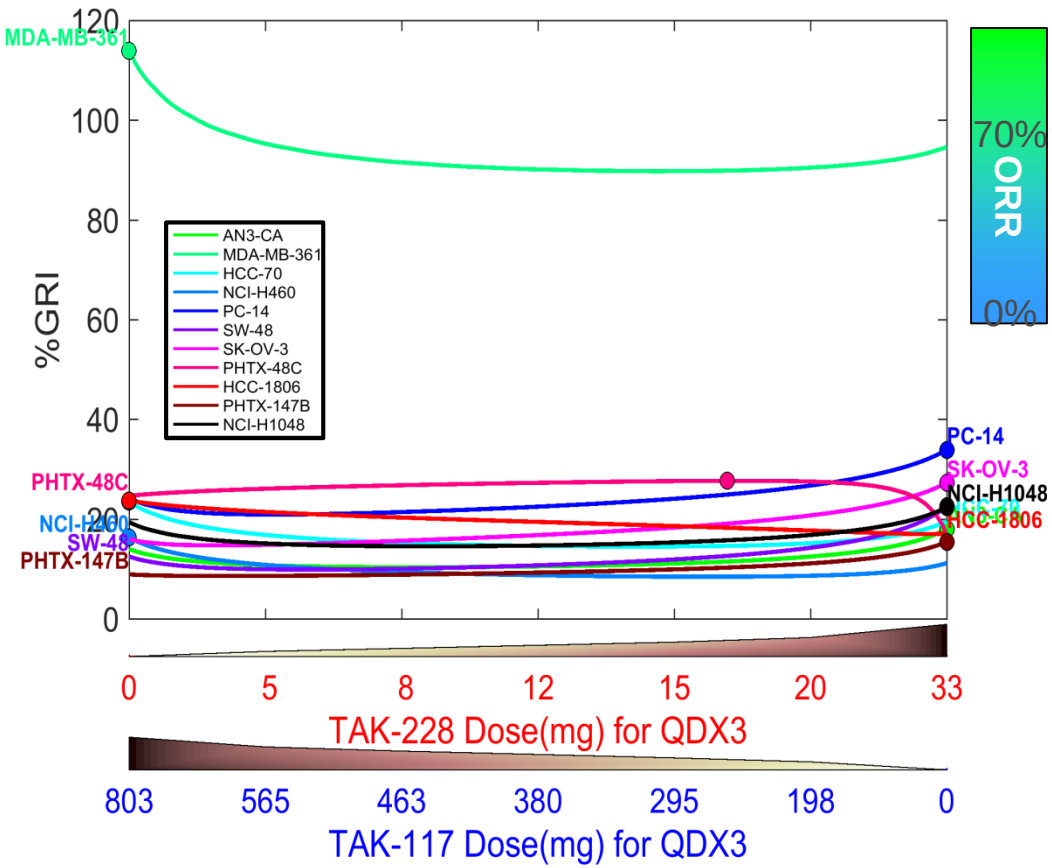
Step 3: Plot predicted efficacy as we walk along the Maximum Tolerated Exposure (MTE) 'fence'

$$\%GRI = GRI_X + GRI_Y + \beta \times GRI_X \times GRI_Y$$





Across different xenograft models, the optimum point is always associated with either of the single agent MTD



Solid filled circles represents the optimal combination (maximum efficacy + minimum toxicity) observed in given tumor xenograft model

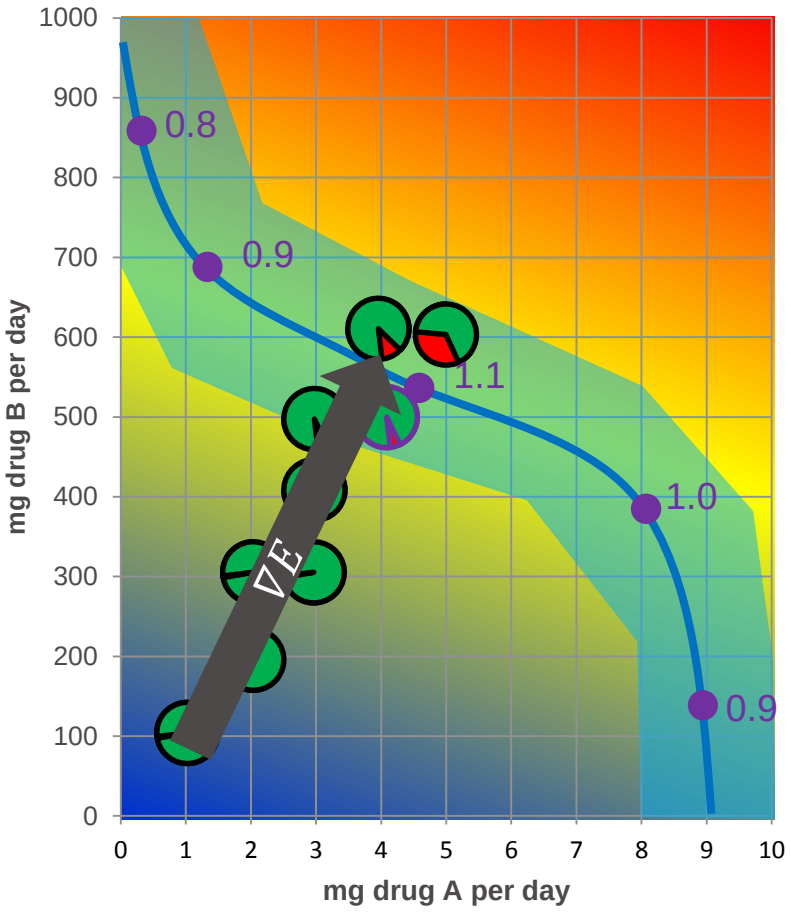
Indication	Cell line
Breast	MDA-MB-361 HCC70 PHTX-147B HCC1806
Endometrial	AN3-CA
Colon	PHTX-48C SW-48
SCLC	NCI-H1048 NCI-H460 PC-14
Ovarian	SKOV3

These predictions can be revisited once we have n=30 patients in PIKTOR arms in C31005 (RCC) or C31004 (Endometrial) studies.

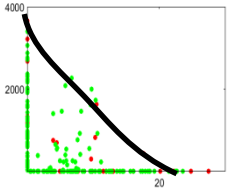
RCC = Renal Cell Carcinoma

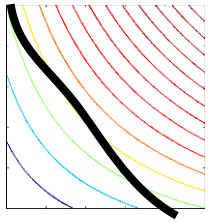
Potential impacts of general methodology

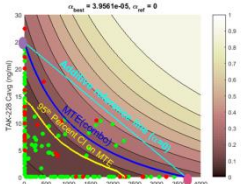
- Protocol development:
  - Characterize efficacy surface, understand tox “targets”
  - Optimize escalation design to identify MTD curve (“shortest path” to optimal efficacy…)
- During escalation:
  - After each cohort/PK batch, update MTE curve estimate
  - Potentially adjust next dose combo based on MTE and efficacy projections
- After escalation:
  - Predict optimal RP2D for expansion

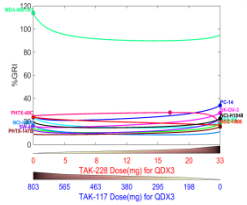


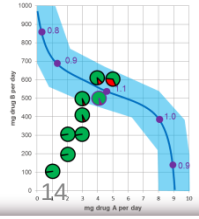
Take-home messages







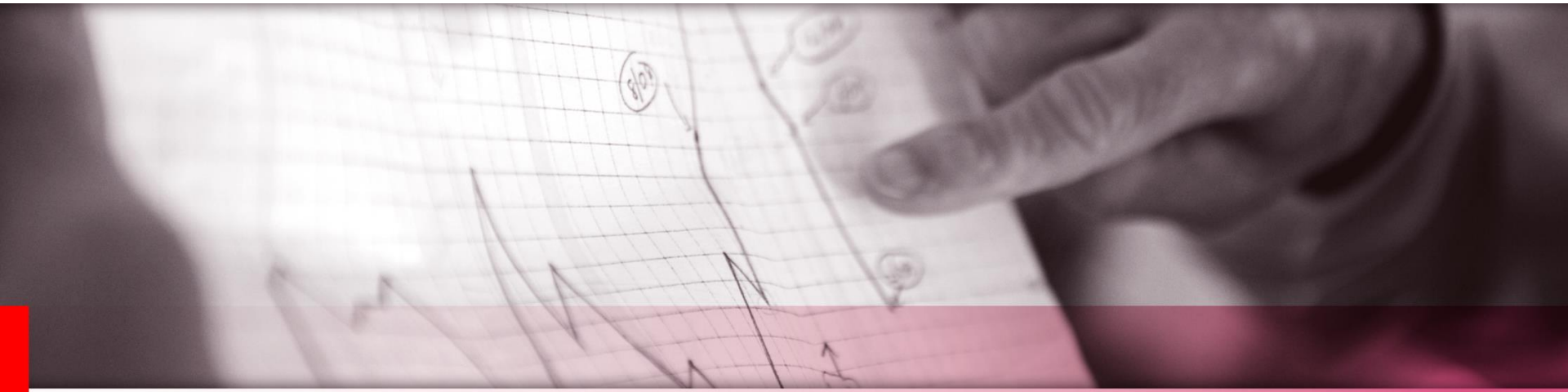




- In combinations, “MTD” is not unique
- RP2D[2] finding = toxicity constrained efficacy optimization problem
- Successfully applied to PIKTOR
- Model predicts mono > PIKTOR combo after accounting for tox
- Further validation on other combos recommended

Special thanks to:

- PIKTOR team
- Michael Bargfrede
- Qunli Xu
- Christopher Zopf (CJ)
- Doug White
- Ryan Hooper



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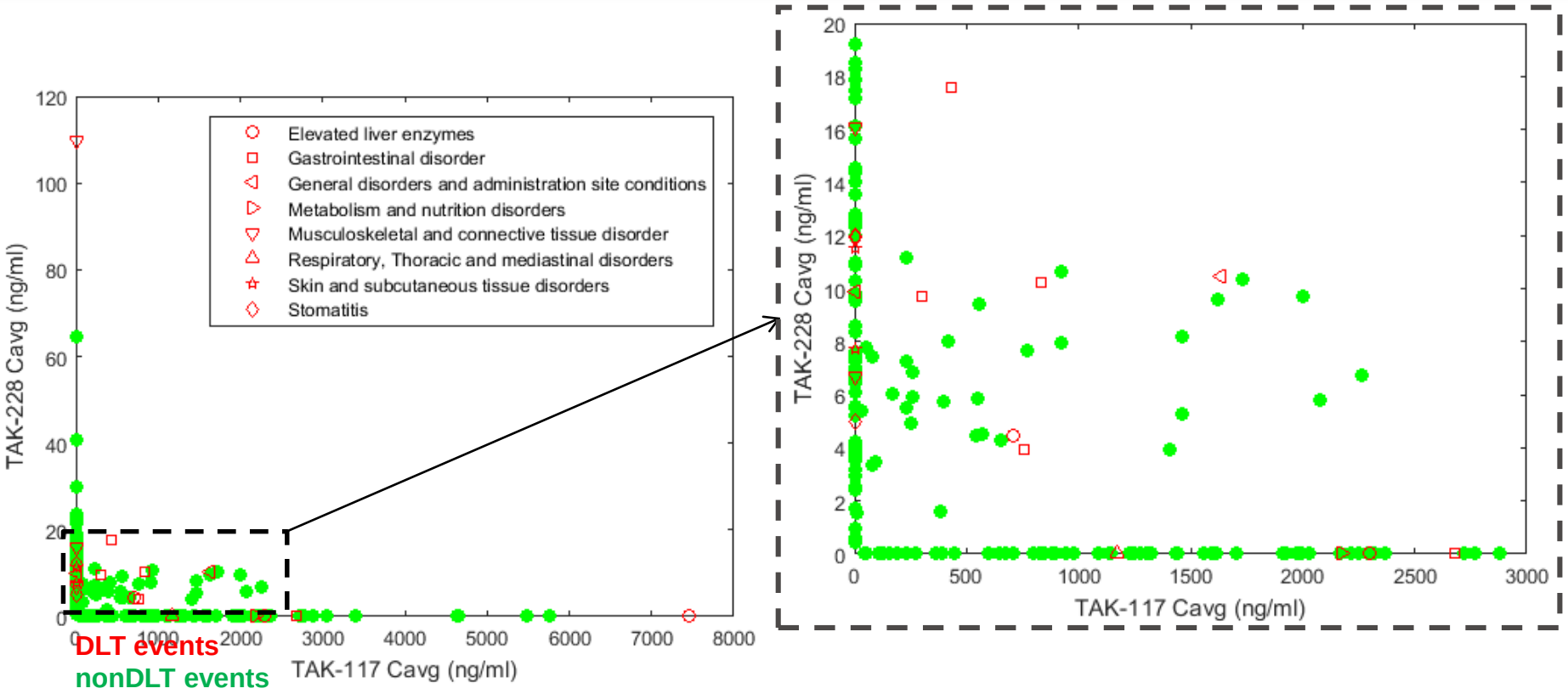
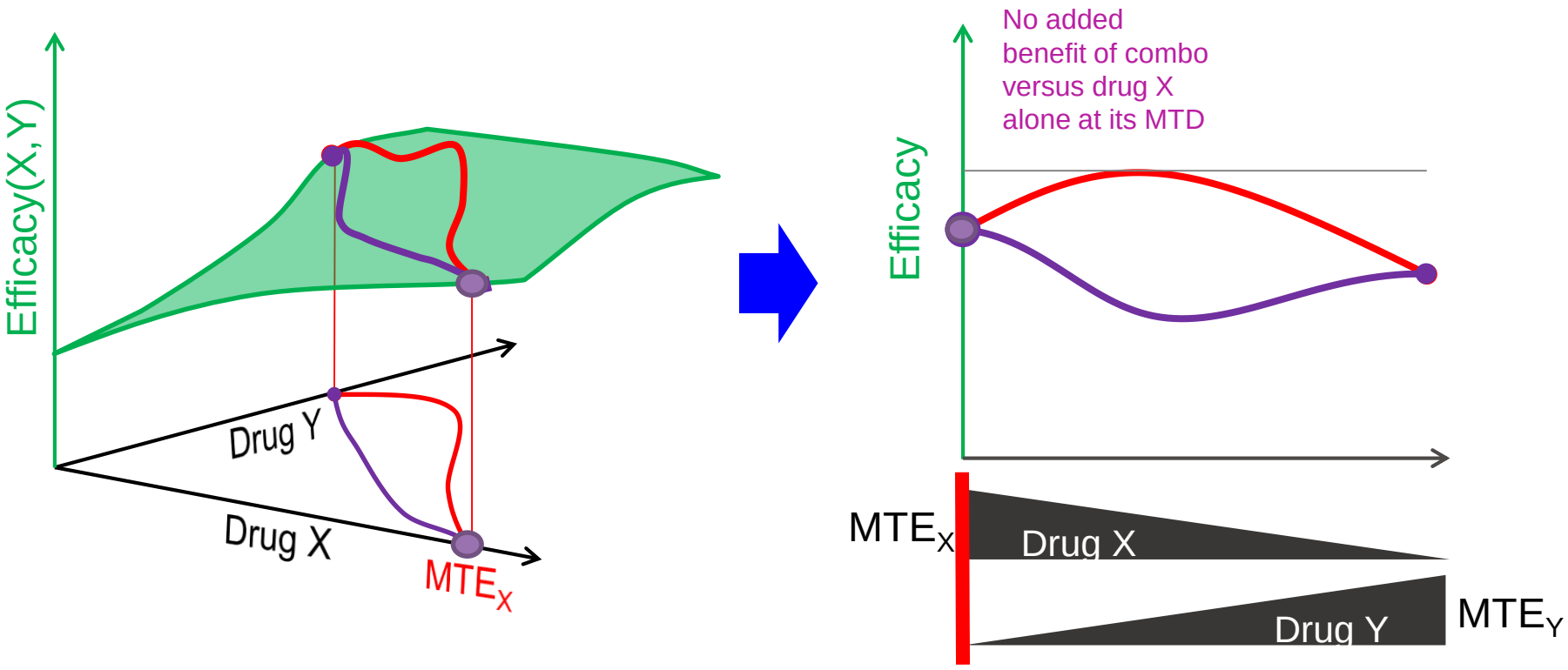
Dose-Limiting-Tox events plotted as function of TAK117 & TAK228 exposures



- Toxicity data grouped using CTCAE guideline
- Data is plotted (and modeled) as a binary readout
- 6/44 patients (combo arm) were associated with a DLT

*Common Terminology Criterion for Adverse Events (CTCAE) ver 4.03- JUNE 14 2014

What is the predicted efficacy as we walk along the max tolerated exposure “fence”? (Illustrating no added benefit)



If toxicity is “more synergistic” than efficacy, we can see on the right that one of the monotherapies is more efficacious than any attainable combination