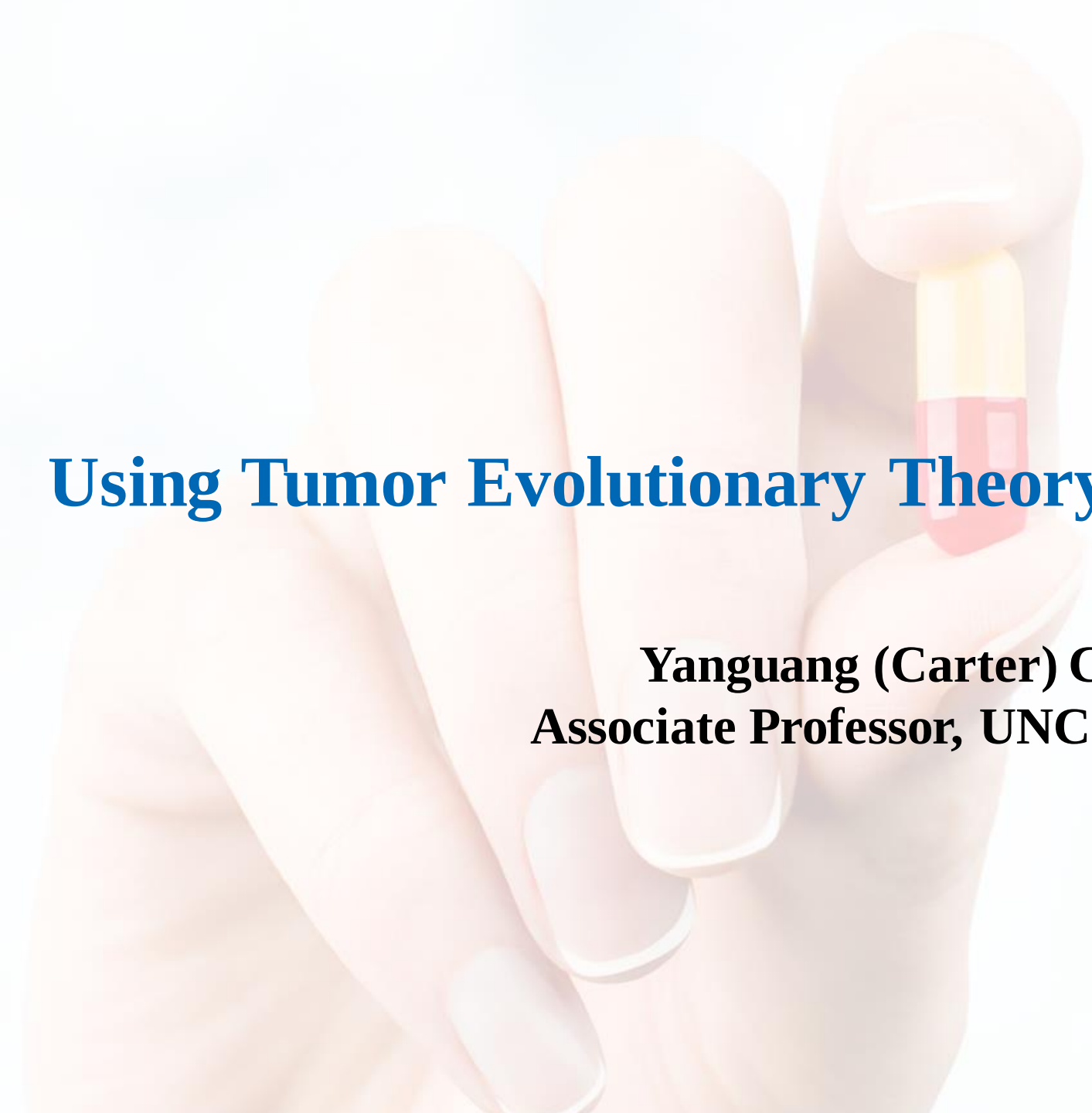


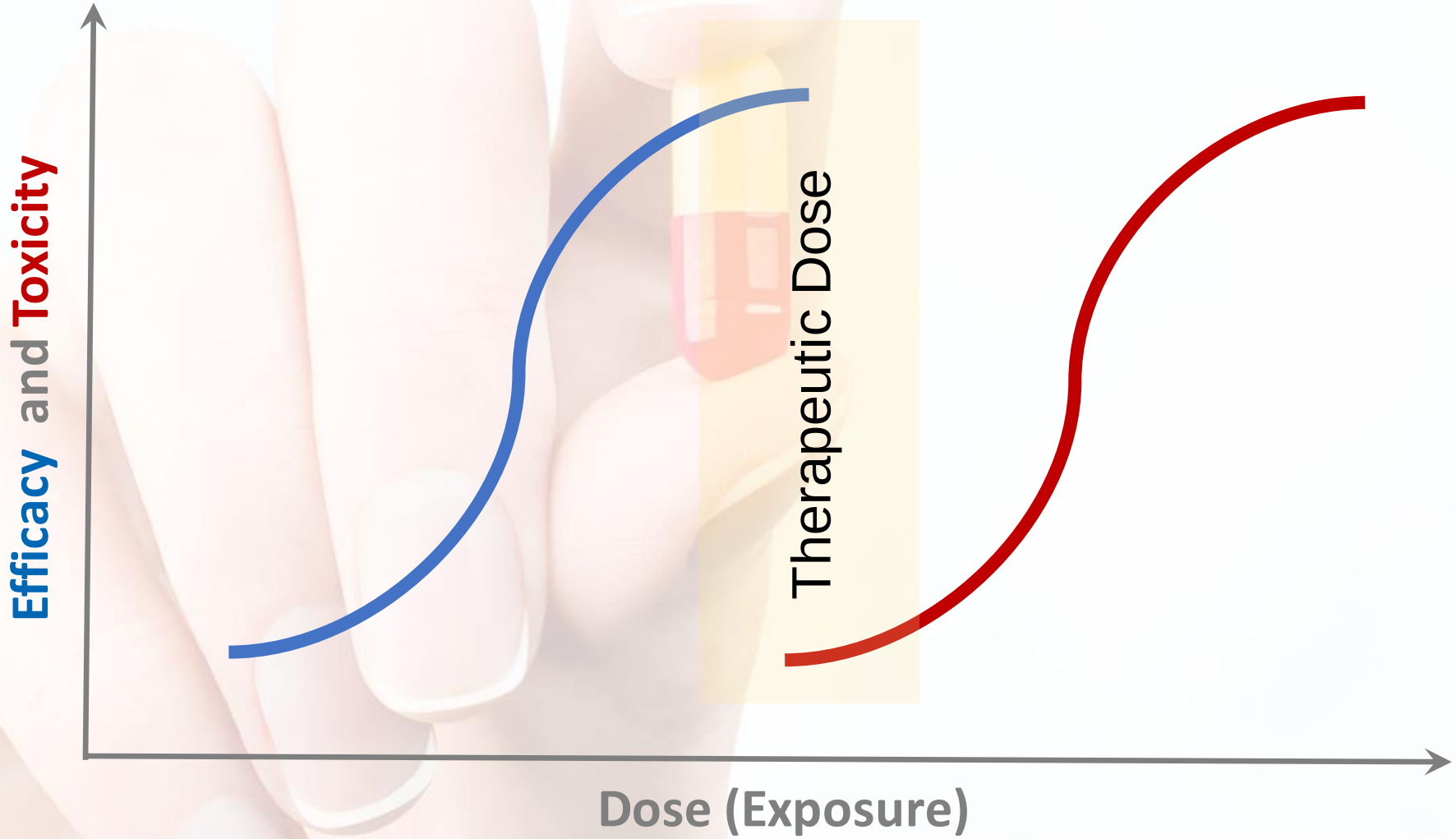
Using Tumor Evolutionary Theory to Inform Optimal Doses

Yanguang (Carter) Cao, Ph.D.
Associate Professor, UNC at Chapel Hill

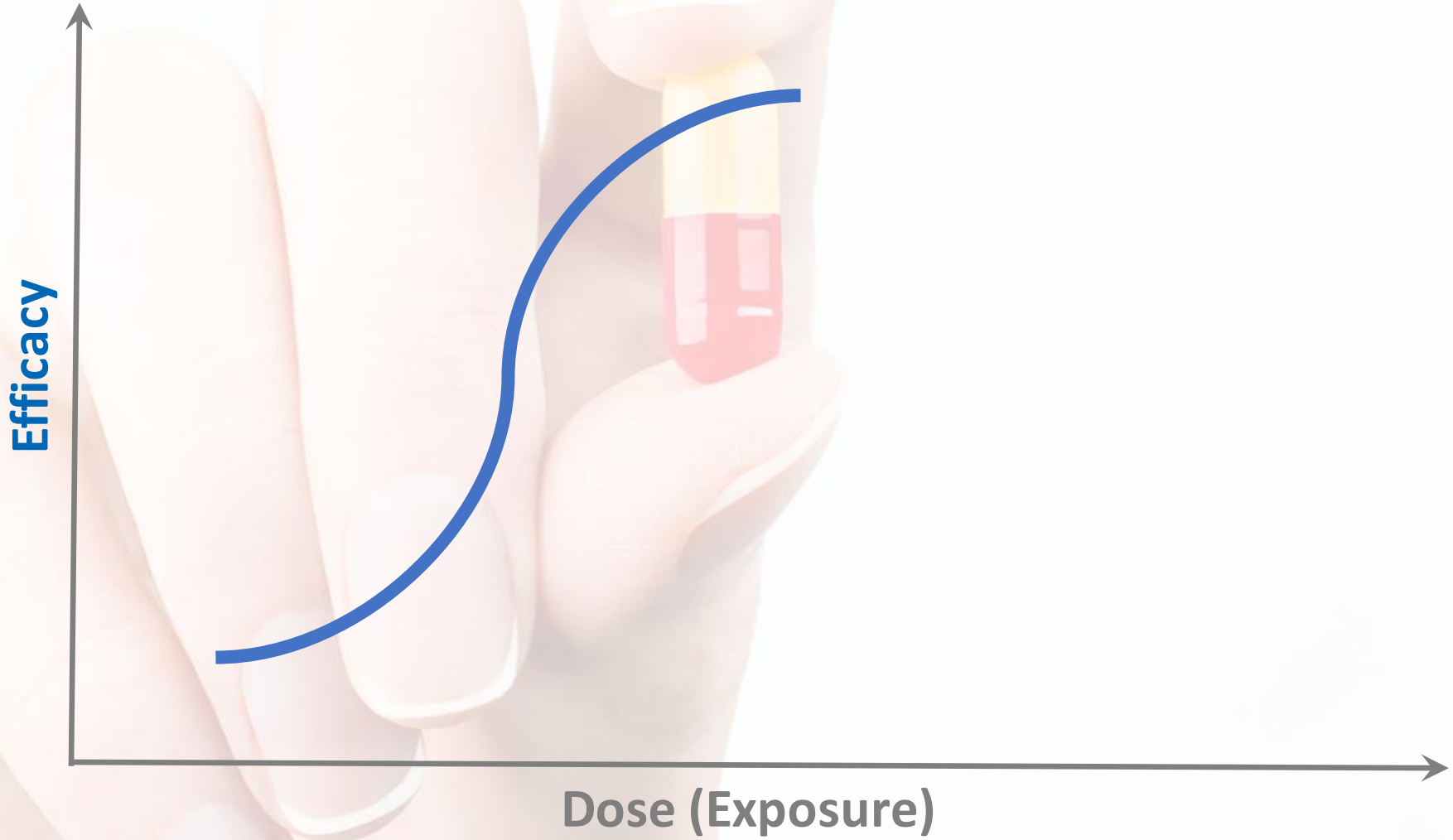
Disclaimer

Consultant for pharmaceutical companies, including Johnson and Johnson, I-Mab, 23andMe, Lundbeck.

Efficacy/Toxicity Balance

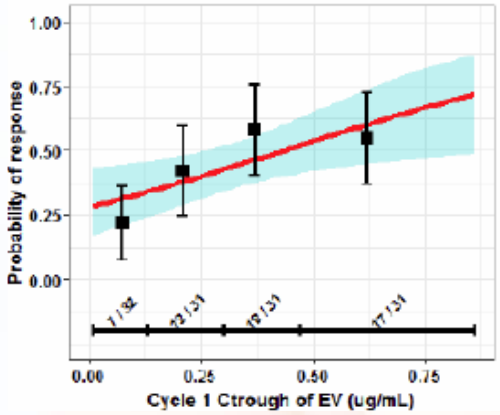


For a patient, do you think “the more E, the higher R”?

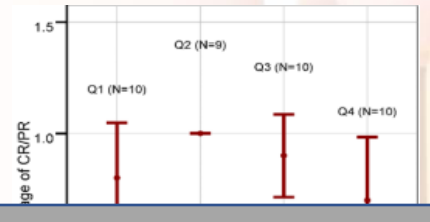


E-R: “flat”, “saturated”, “unclear”, or “inverse”?

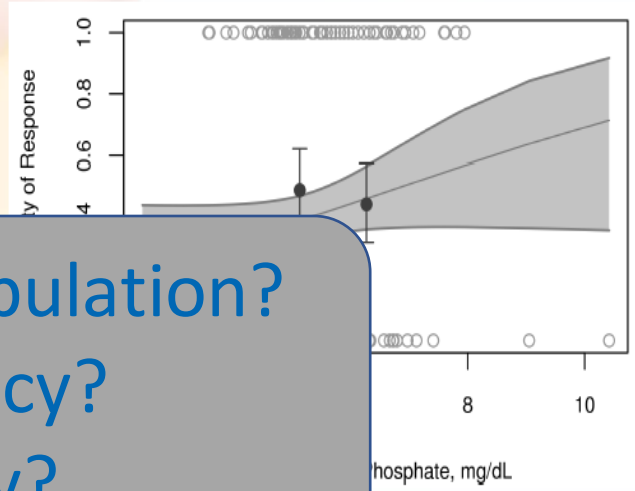
Enfortumab vedotin



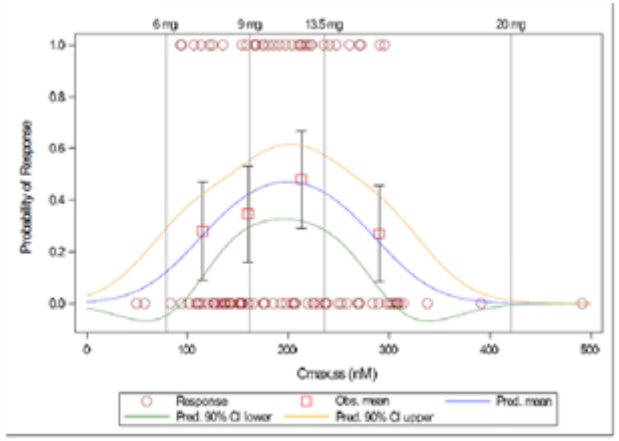
Entrectinib (NSCLC)



Erdafitinib (UC)



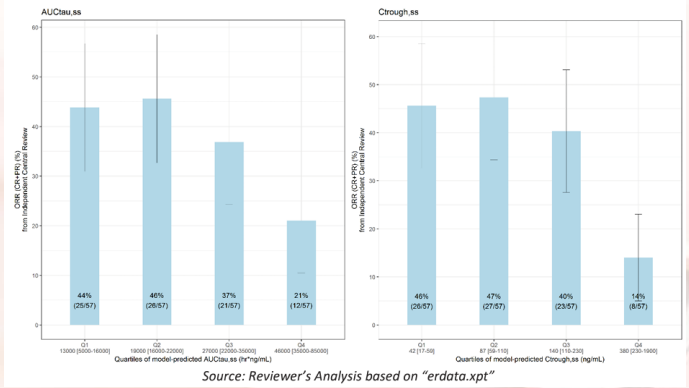
Pemigatinib (CCA)



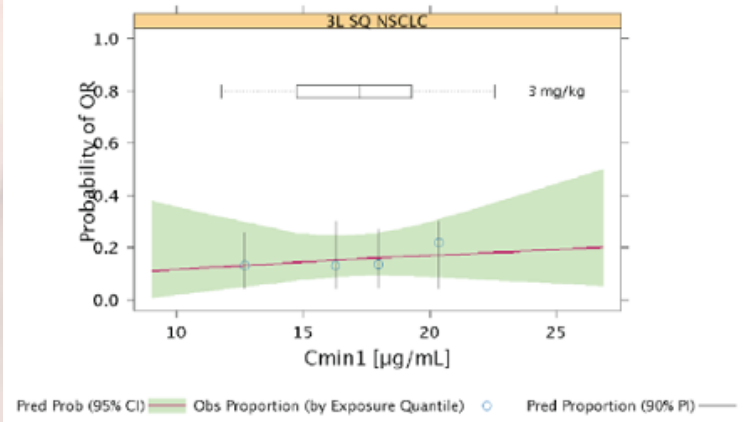
1. Unbalanced population?
2. Saturated efficacy?
3. Other possibility?

Sotorasib (N

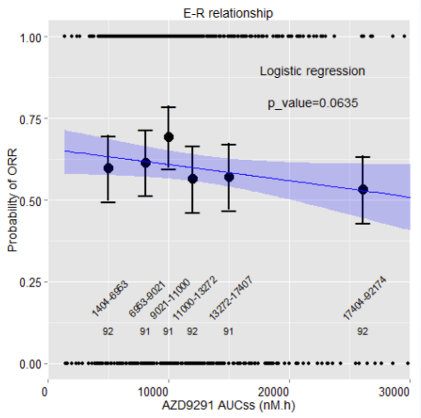
Figure 26. Relationship between Sotorasib Exposure and ORR
mutation.



Source: Reviewer’s Analysis based on “erdata.xpt”

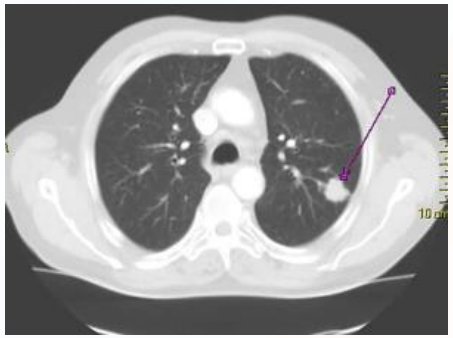


Osimertinib (NSCLC)

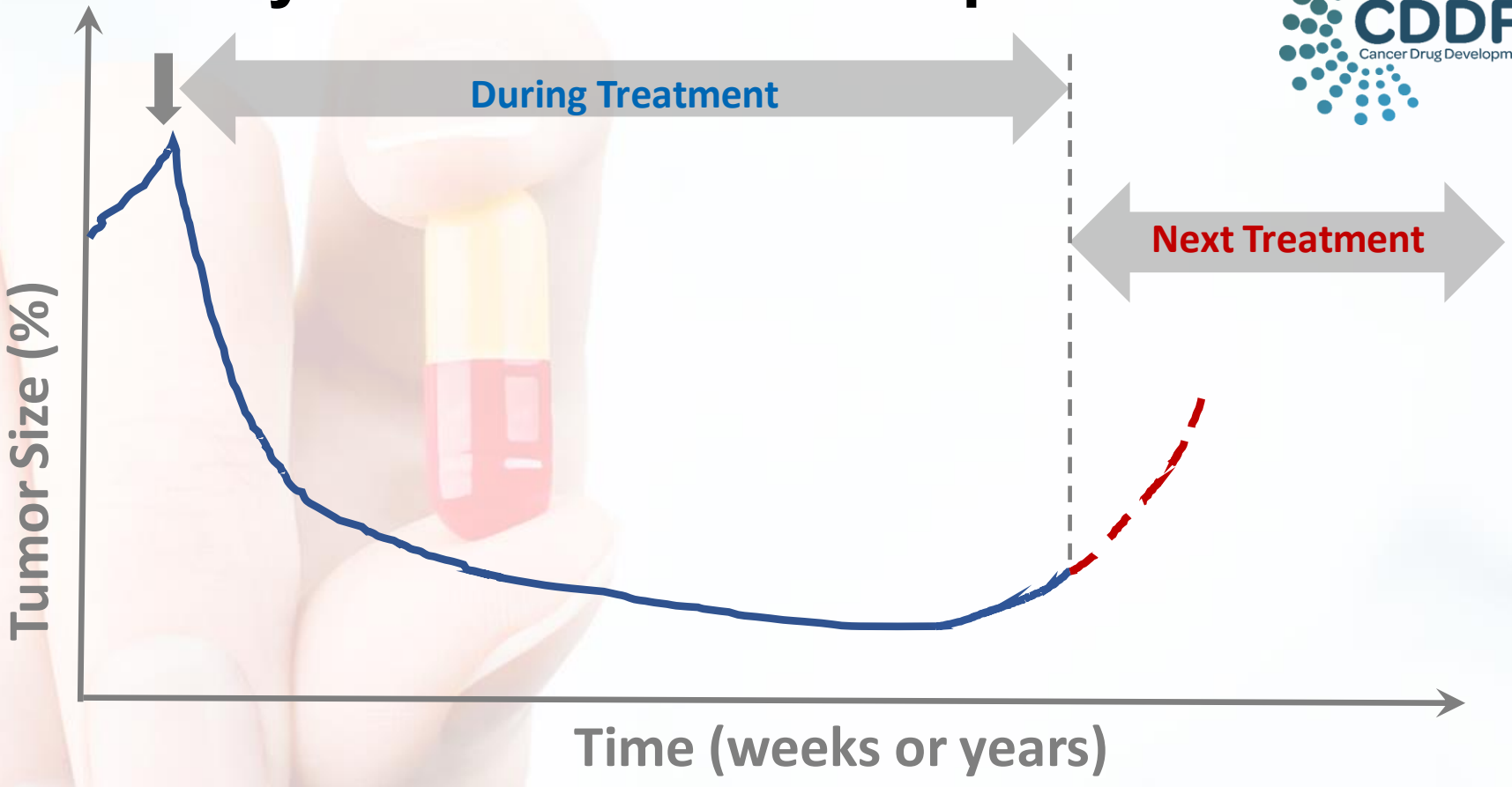


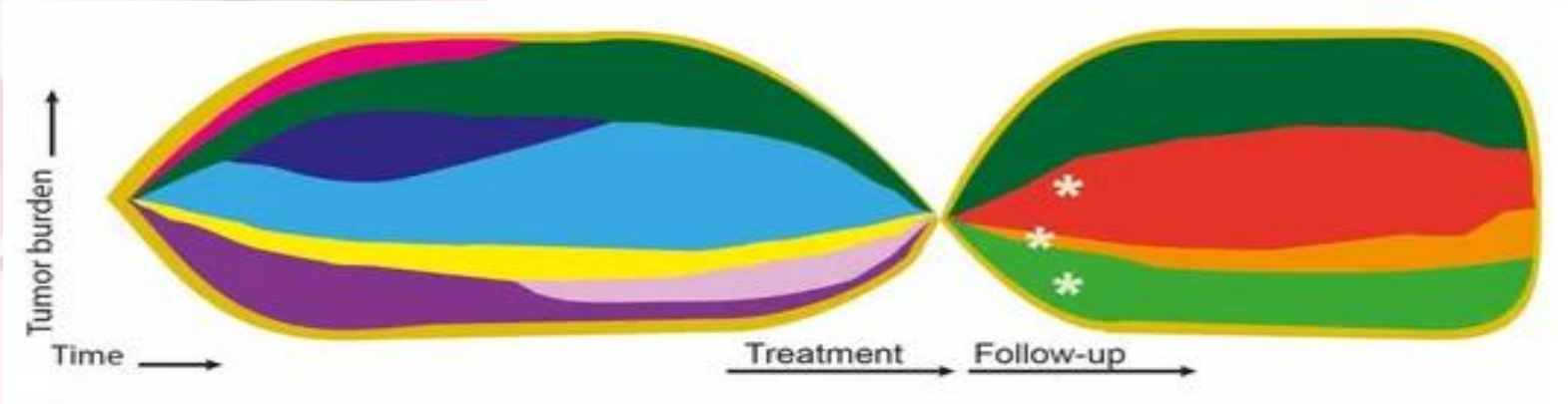
FDA approved materials

A patient's disease history: a clone war in the process

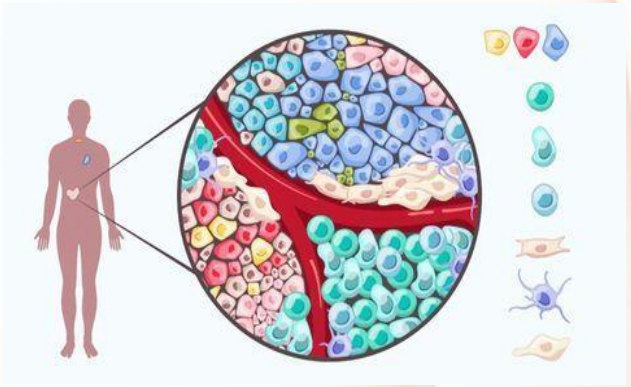


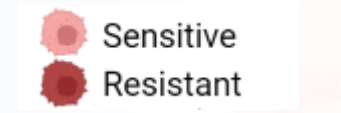
NSCLC

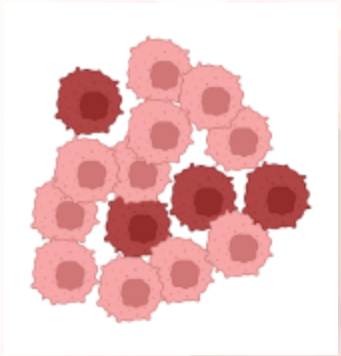




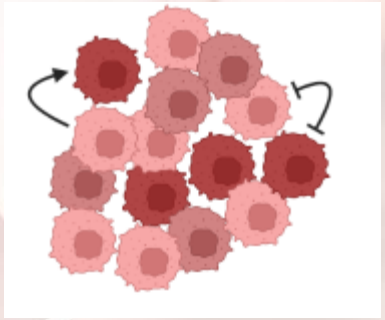
A proposal:



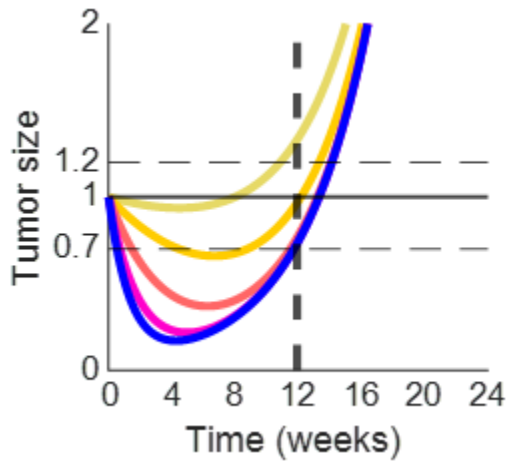


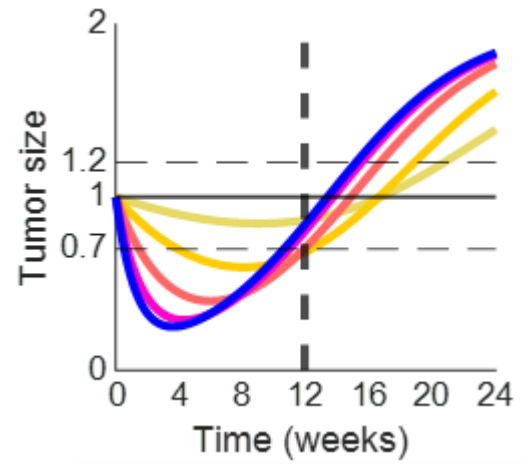


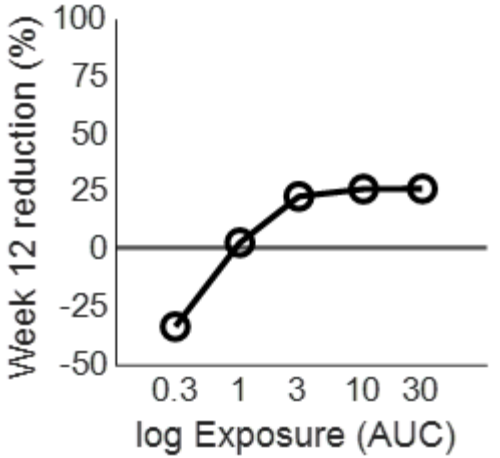
Independent

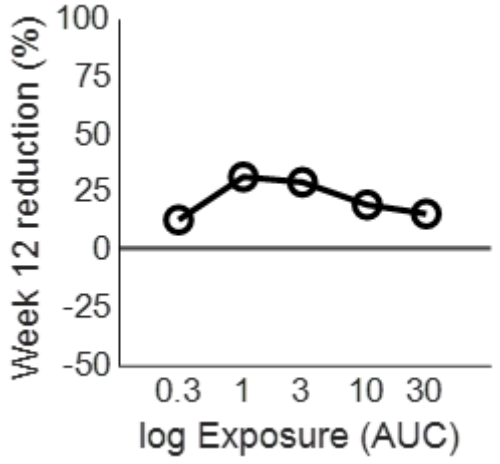


Competition

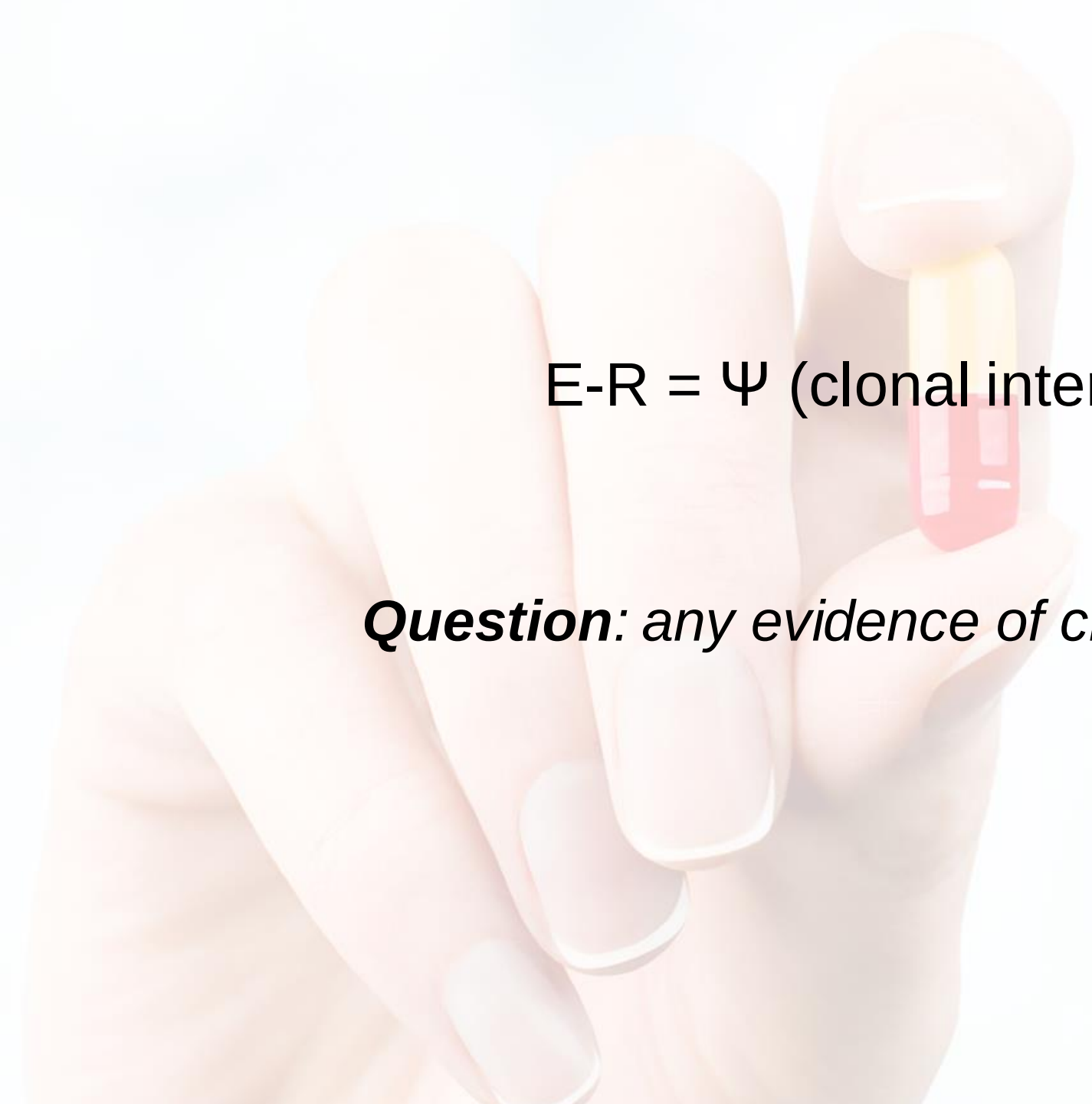








Qi, et al., *(2022) Pharm Res*

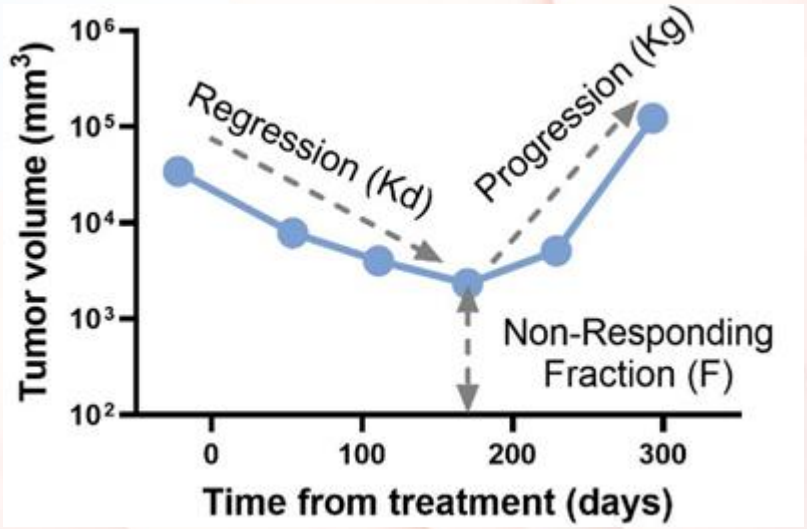


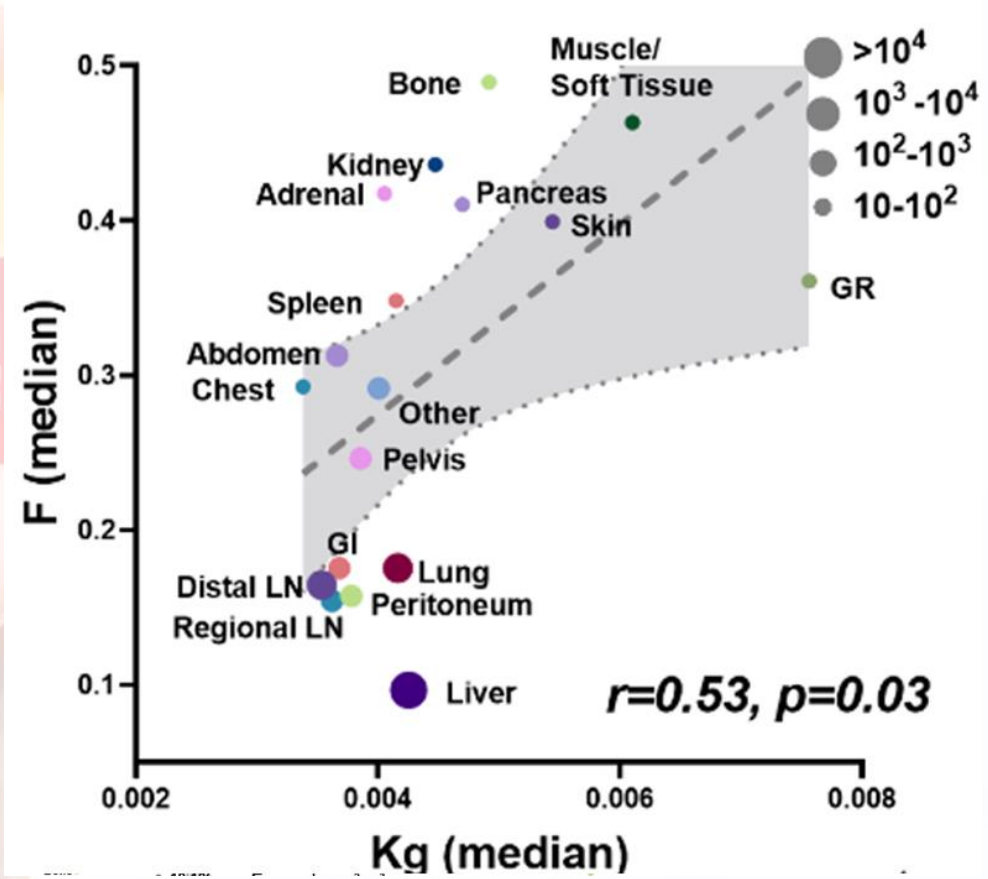
E-R = Ψ (clonal interactions)

***Question**: any evidence of clonal interactions?*

Metastatic Colorectal Cancer
(4,308 patients/40,612 lesions)

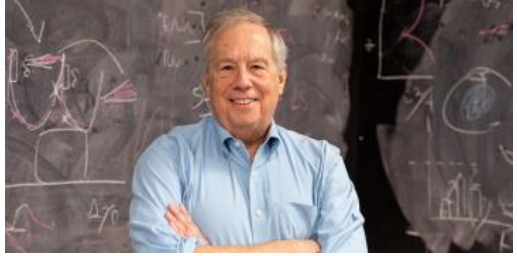
$$V = V0 \cdot [(1 - F) \cdot e^{-Kd \cdot t} + F \cdot e^{Kg \cdot t}]$$





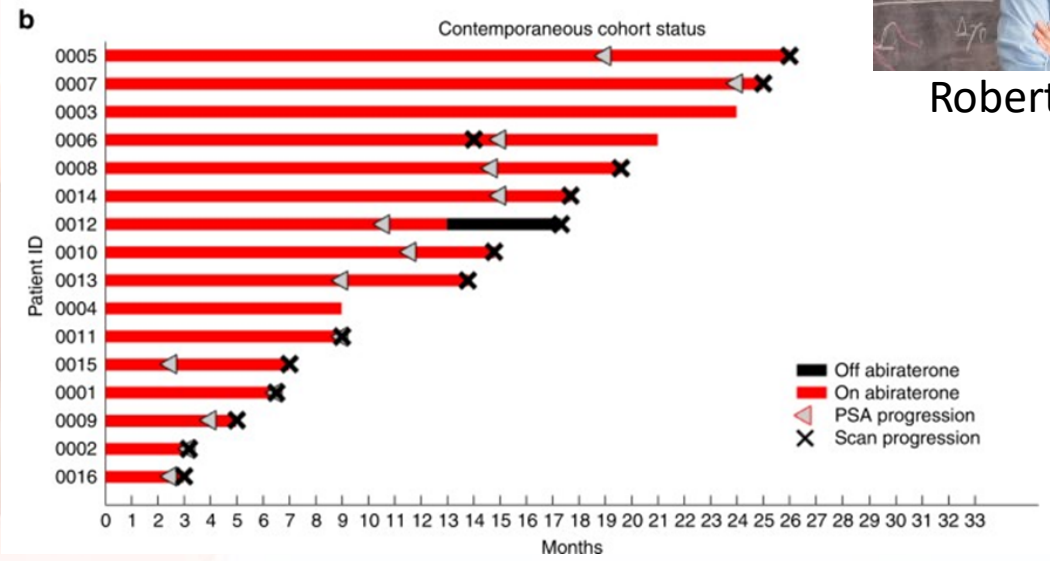
Zhao, et al., (2023) ***Nat Commun***

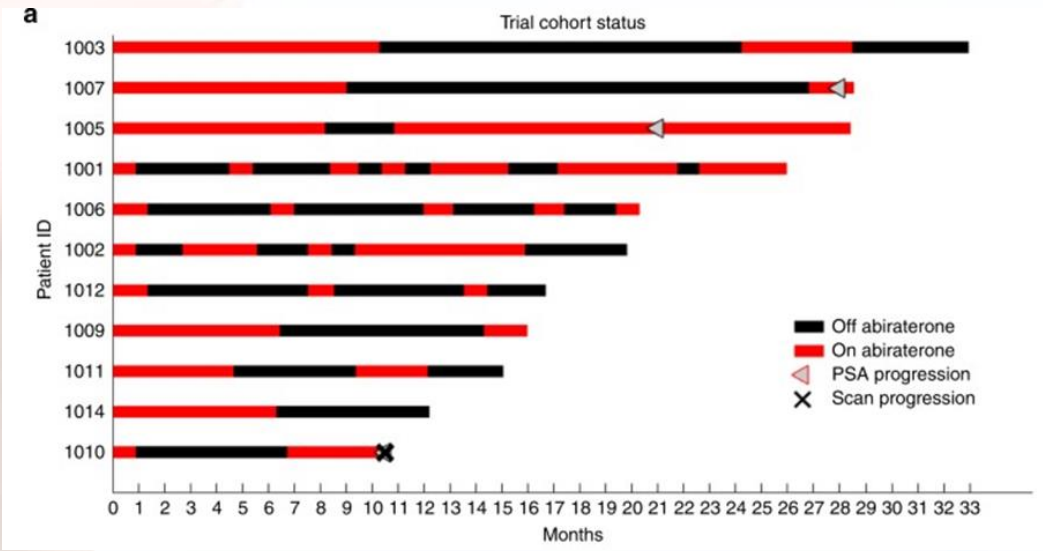
Metastatic Prostate Cancer (adaptive therapy)



Robert Gatenby, M.D.

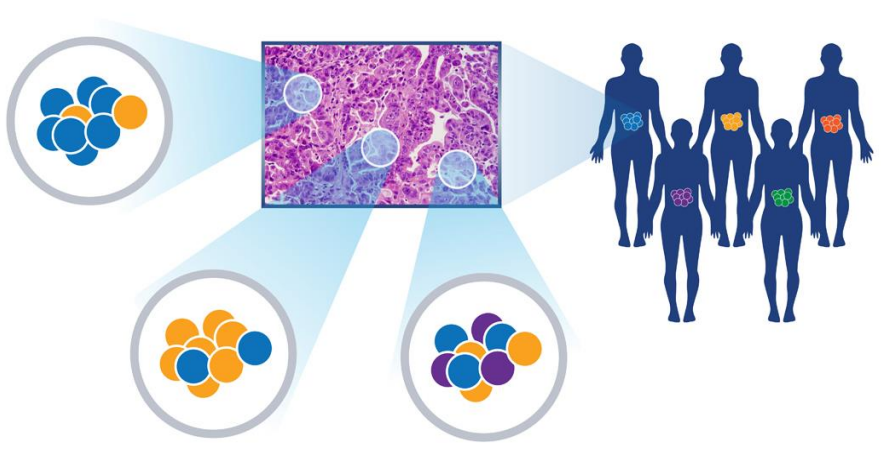
“competitive release”





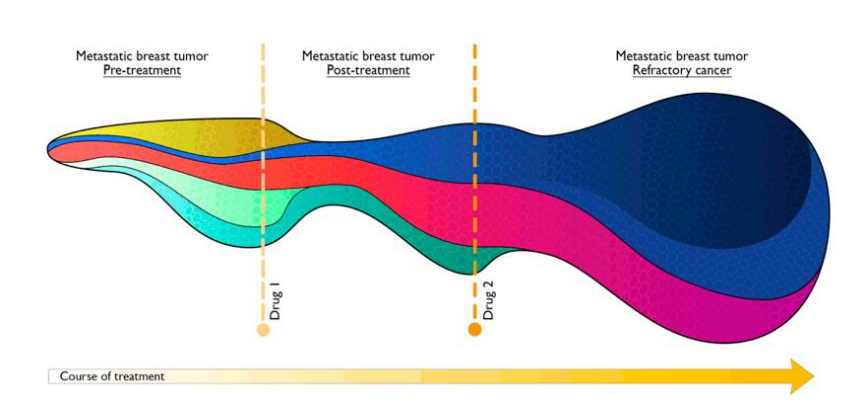
Nat Commun. 2020;11(1):1750
Nat Commun. 2017;08(1):1816.

How can we do better in our trials?



Patient Stratification:

- Subclonal composition
- Interaction types



Longitudinal Evaluation:

- Early metrics (ORR/PFS) often not sufficient
- Evolution index (e.g., ctDNA) needed

Qi, et al., *(2022) Pharm Res*

Summary:

- **Tumor evolution invariably leads to therapeutic failure.**
- **Tumor heterogeneity and clone interactions largely shape E – R relationships and influence the dose selection.**
- **Tumor evolutionary theory could be applied to help our dose selection process.**

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Tyler Dunlap, Pharm.D.

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Pilot Computation Medicine Program
NIGMS MIRA GM119661