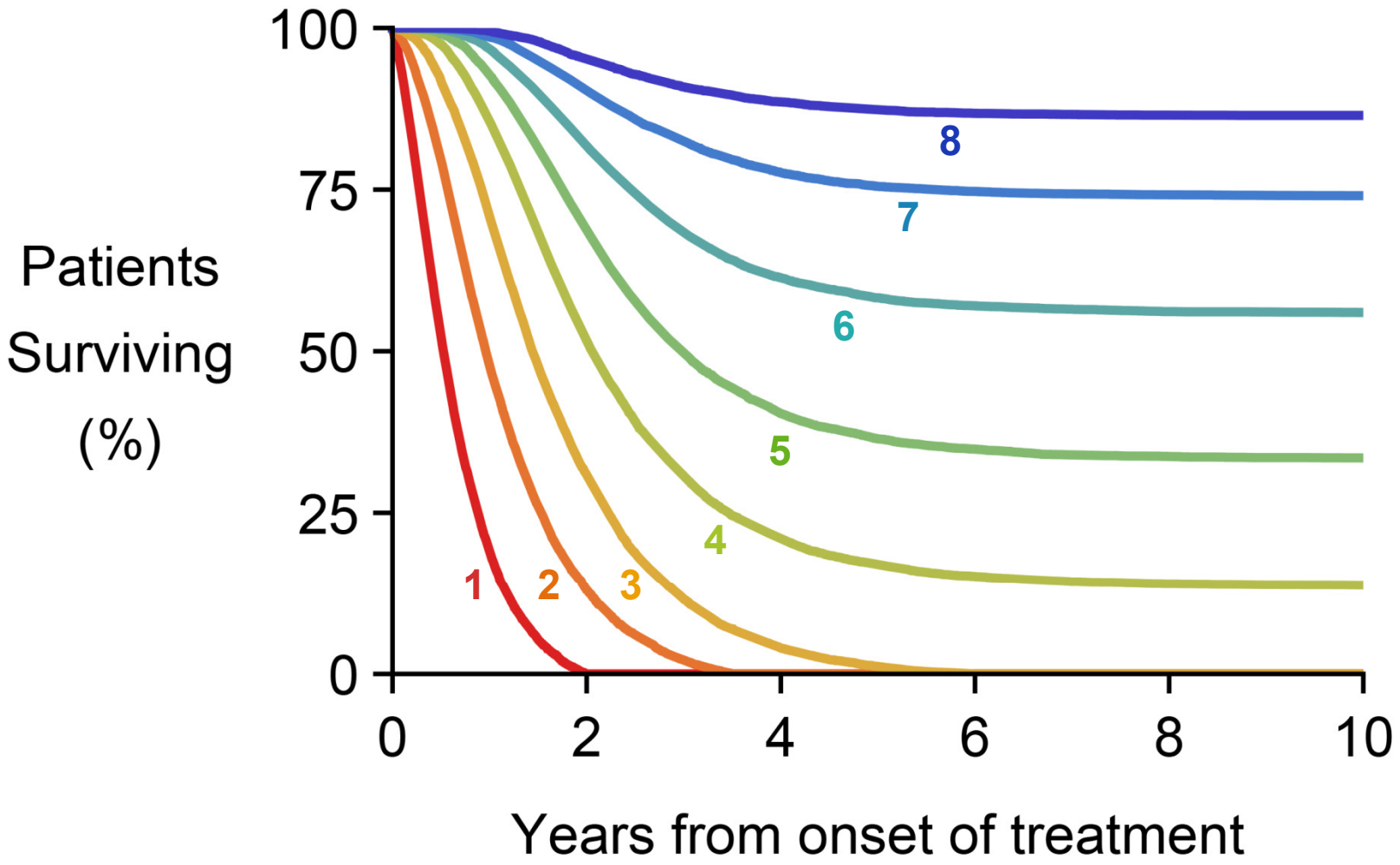
Models to understand and predict the clinical efficacy of combination cancer therapy

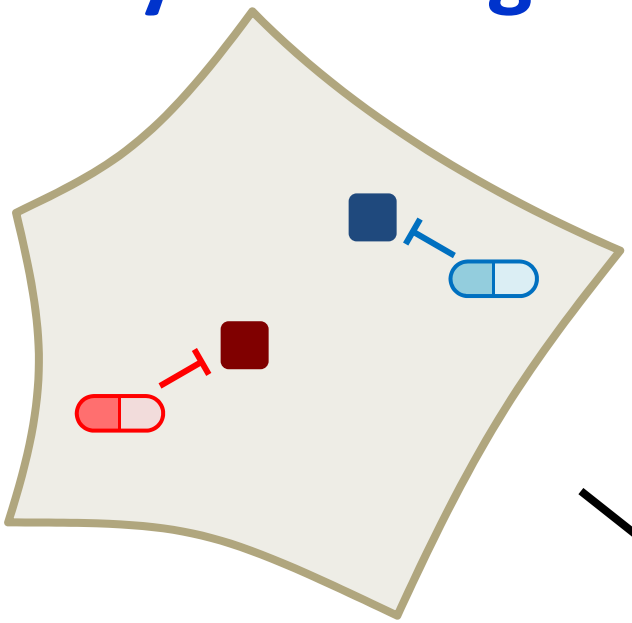
Adam Palmer

Assistant Professor of Pharmacology
Computational Medicine Program
UNC Lineberger Cancer Center
UNC Chapel Hill

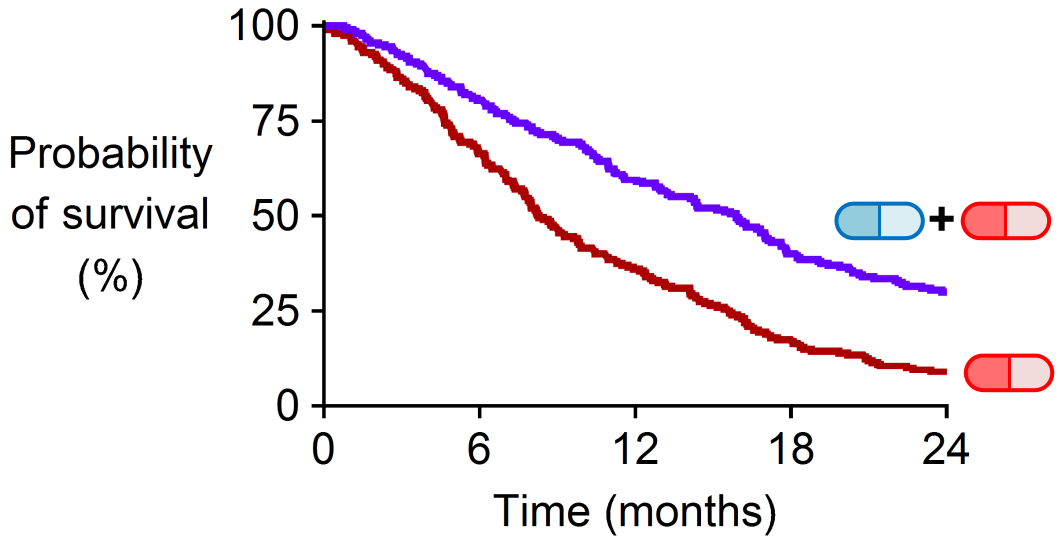
A case study of successful cancer treatment: Childhood Acute Lymphocytic Leukemia



Why are drug combinations clinically effective?



Translation



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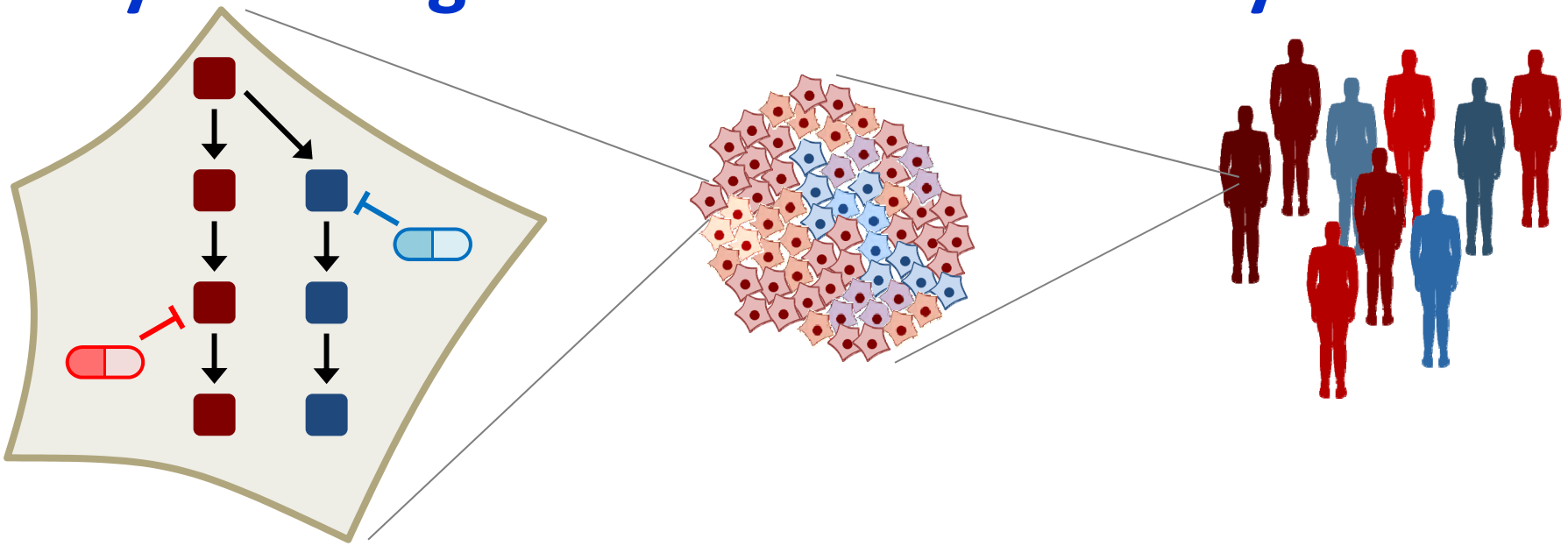

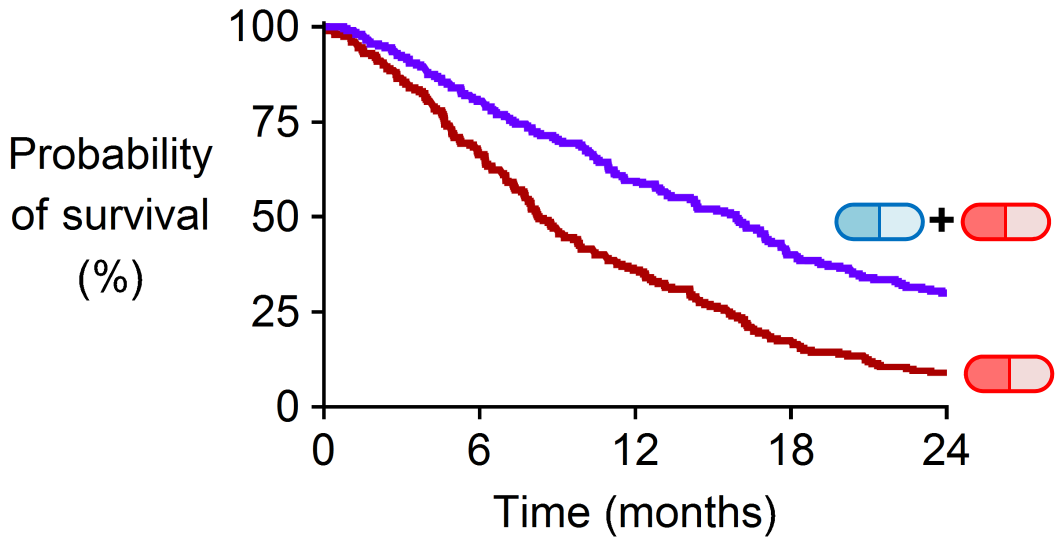

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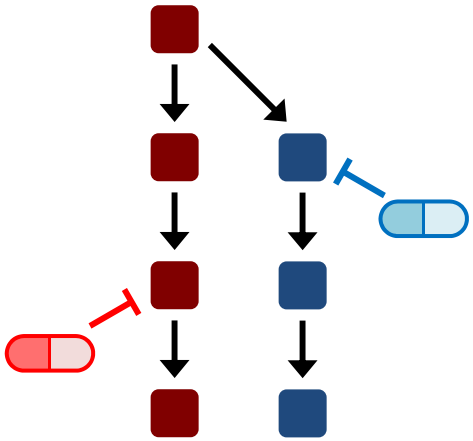
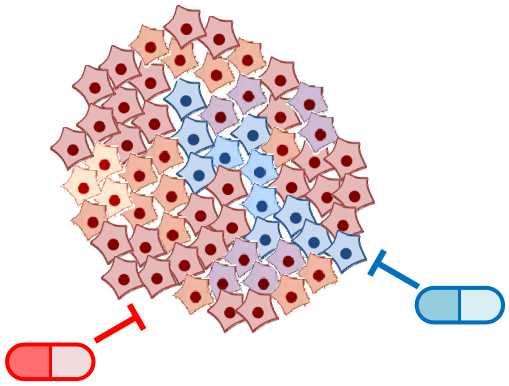
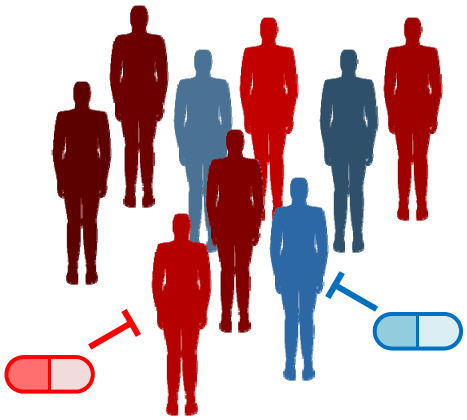


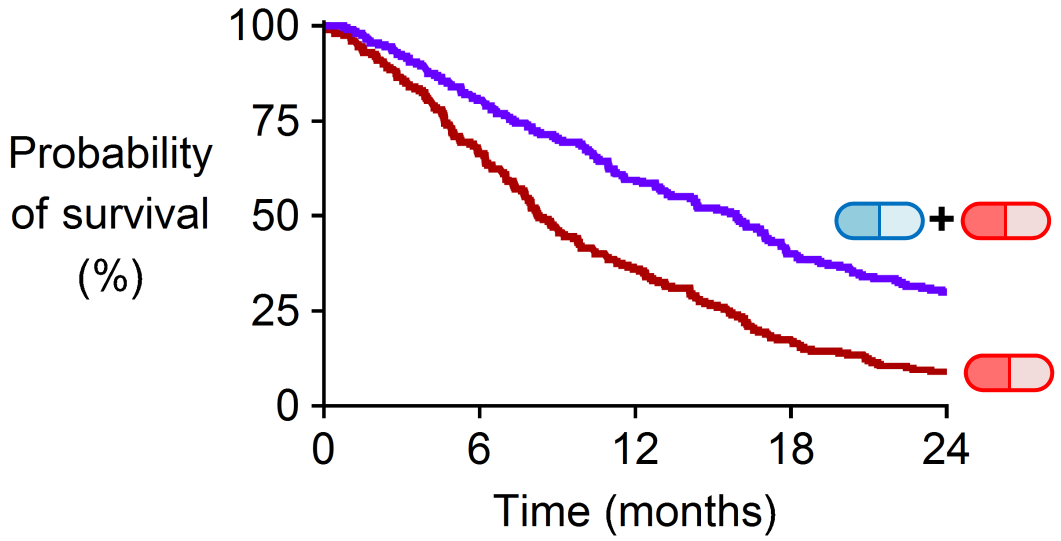
Additive or synergistic interactions



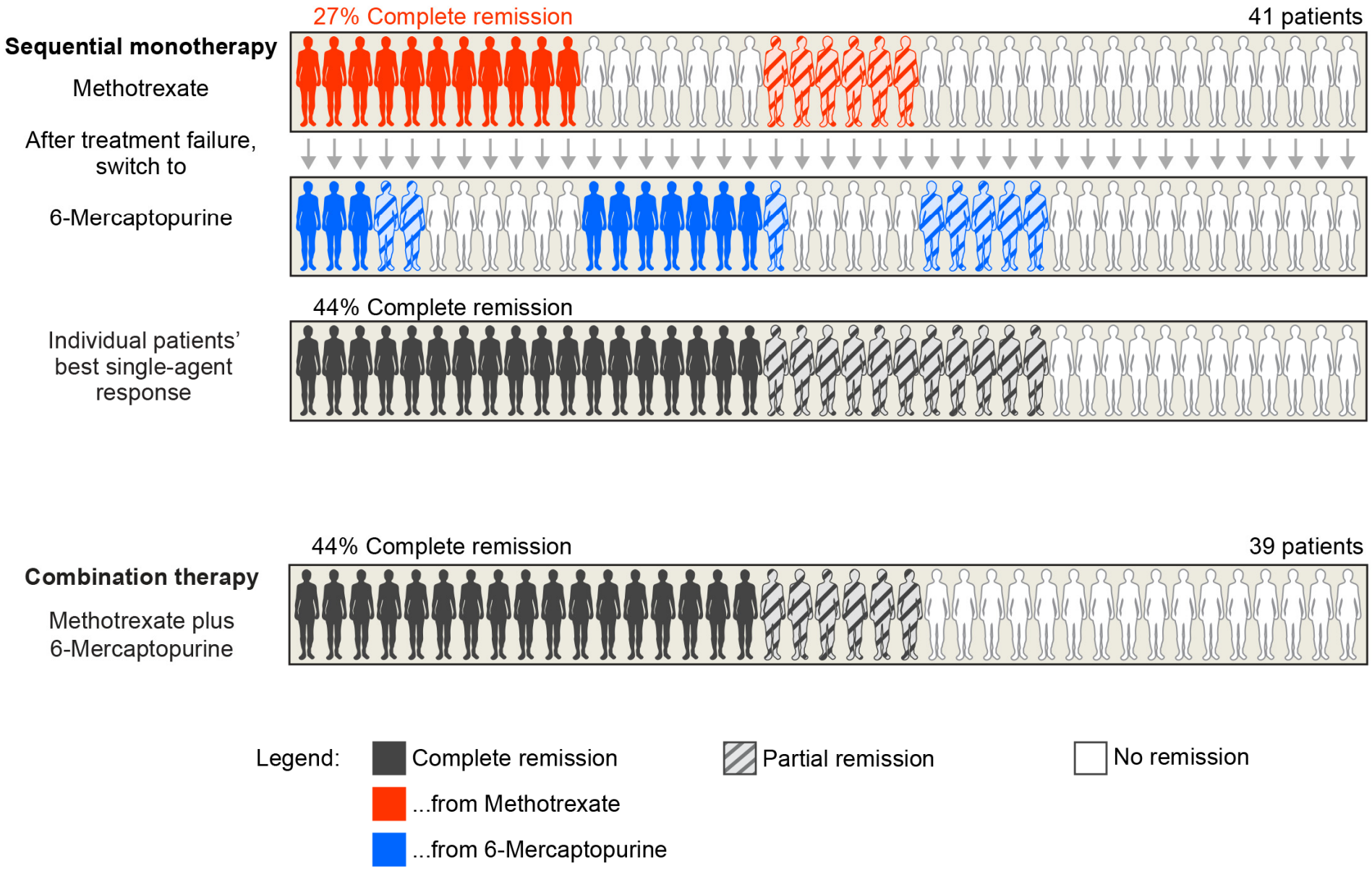
Within-tumor heterogeneity



Between-tumor heterogeneity

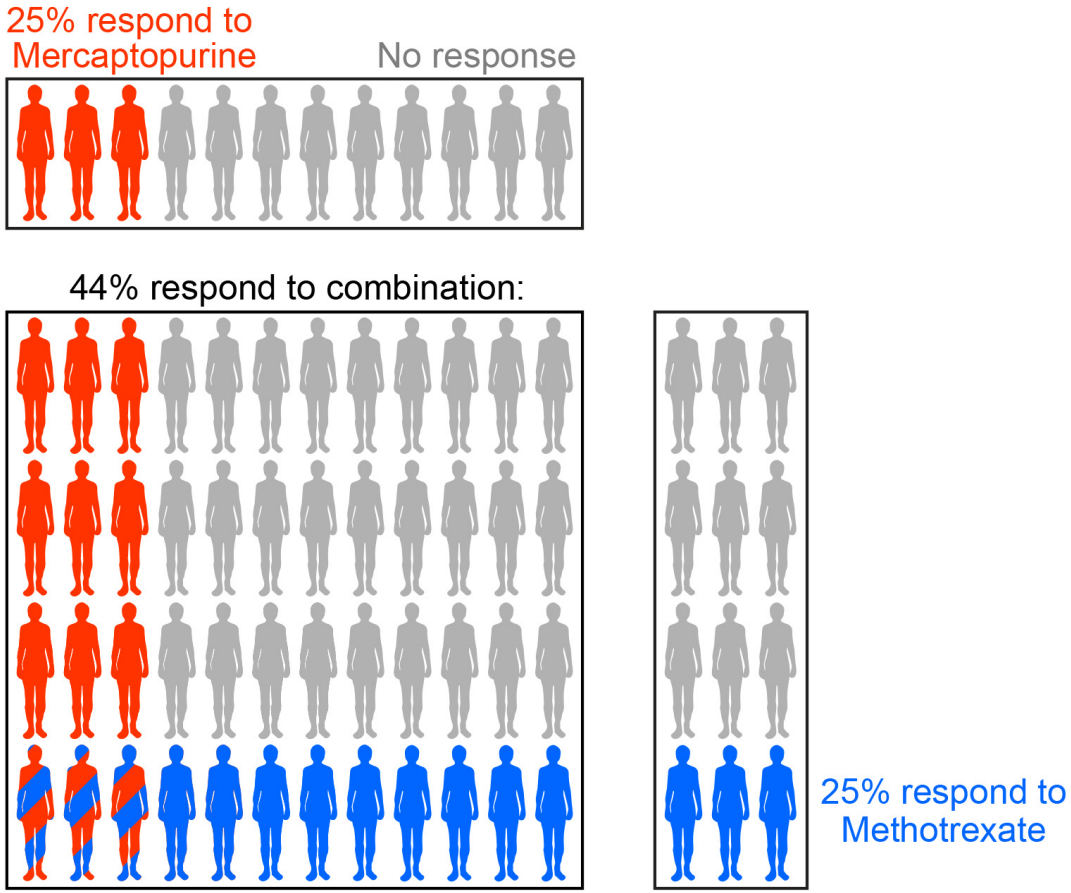


Different therapies are best for different patients



E. Frei 3rd, *et al.* (1961) *Blood* www.bloodjournal.org/content/18/4/431

Different therapies are best for different patients …and the benefit of drug combinations is calculable

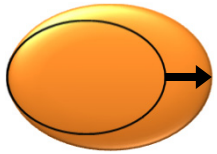


$$RR_{AB} = RR_A + (1 - RR_A) \times RR_B$$

(RR = response rate)

E. Frei 3rd, *et al.* (1961) *Blood* www.bloodjournal.org/content/18/4/431
E. Freireich *et al.* (1963) *Blood* www.bloodjournal.org/content/21/6/699
E. Frei 3rd, *et al.* (1965) *Blood* www.bloodjournal.org/content/26/5/642

Extracting clinical trial data with image processing



≥ 25%

Published clinical trial figure

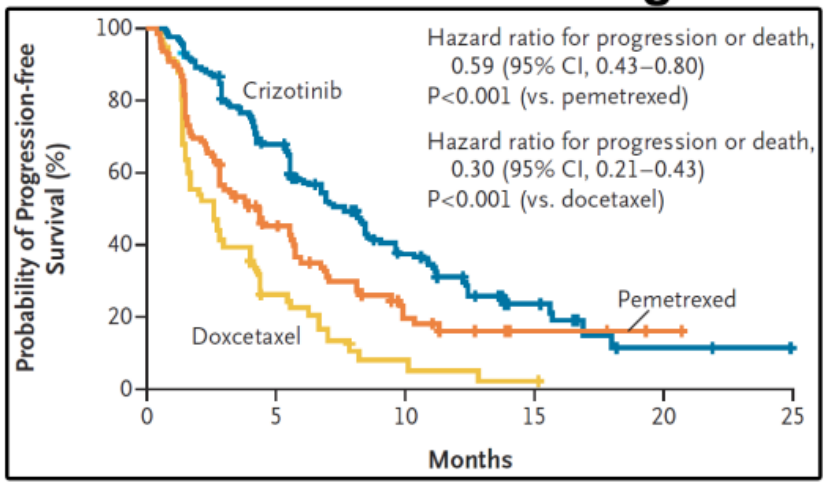
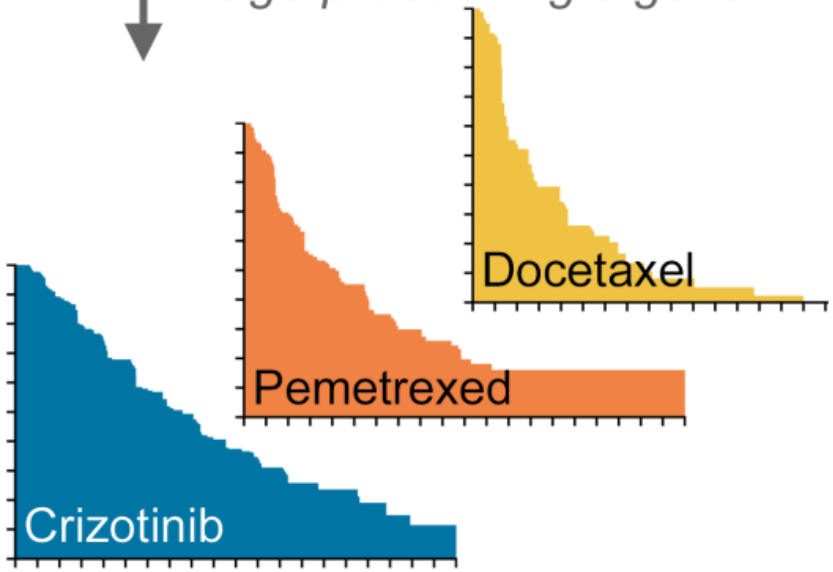


Image processing algorithm



Digitized survival distributions

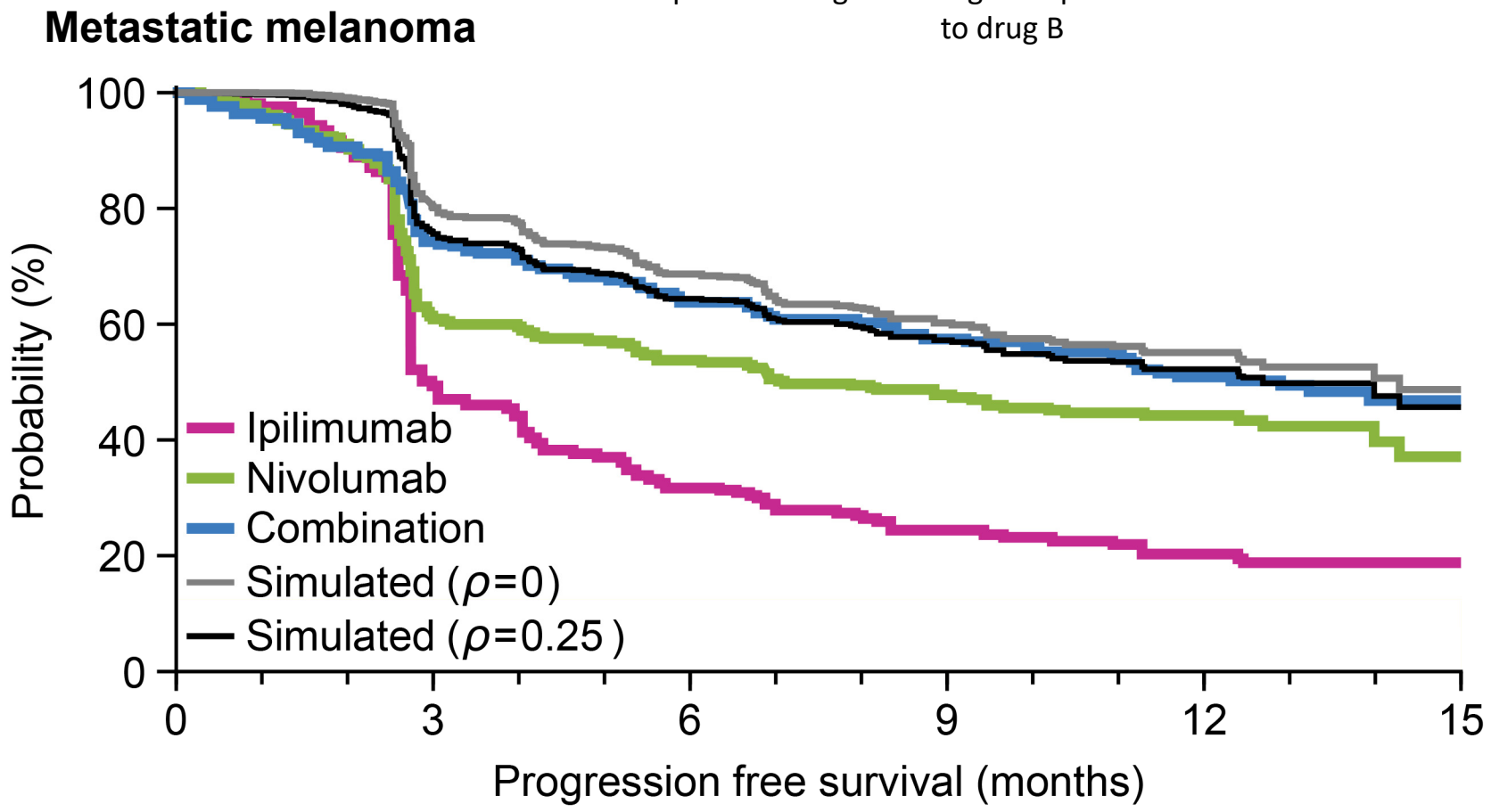
Independent action explains the activity of combination immunotherapy

Expected survival distribution:

$$PFS_{AB}(t) = PFS_A(t) + (100 - PFS_A(t)) \times PFS_B(t) \times (1 - \rho)$$

Cross-resistance ⇒ smaller benefit

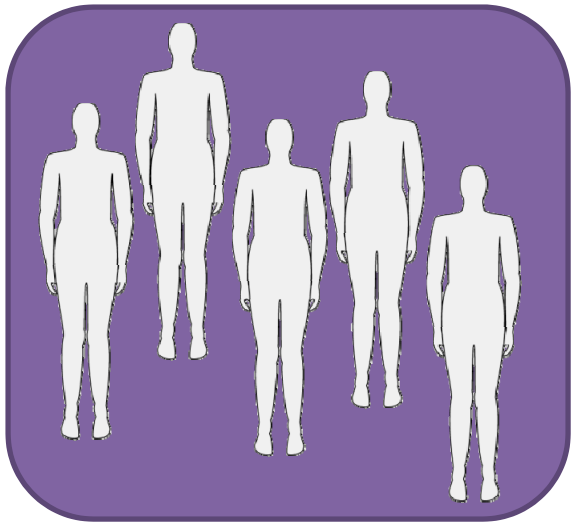
Patients who do not respond to drug A… …might respond to drug B



Palmer & Sorger (2017) *Cell*

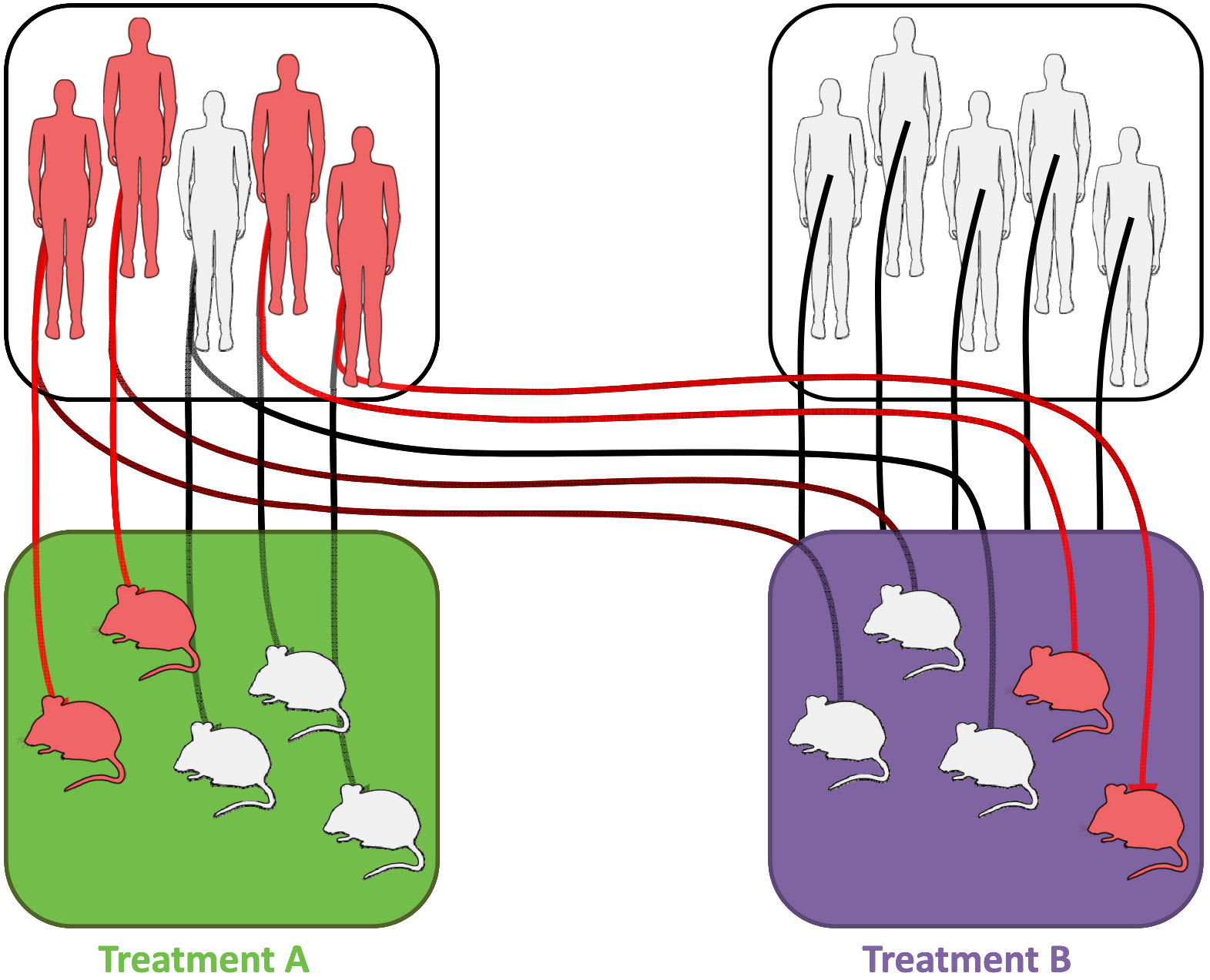
Analysis of data from Larkin *et al* (2015) *New England Journal of Medicine*

Treatment A



Treatment B

Patient-Derived-Xenograft trials reveal response correlations



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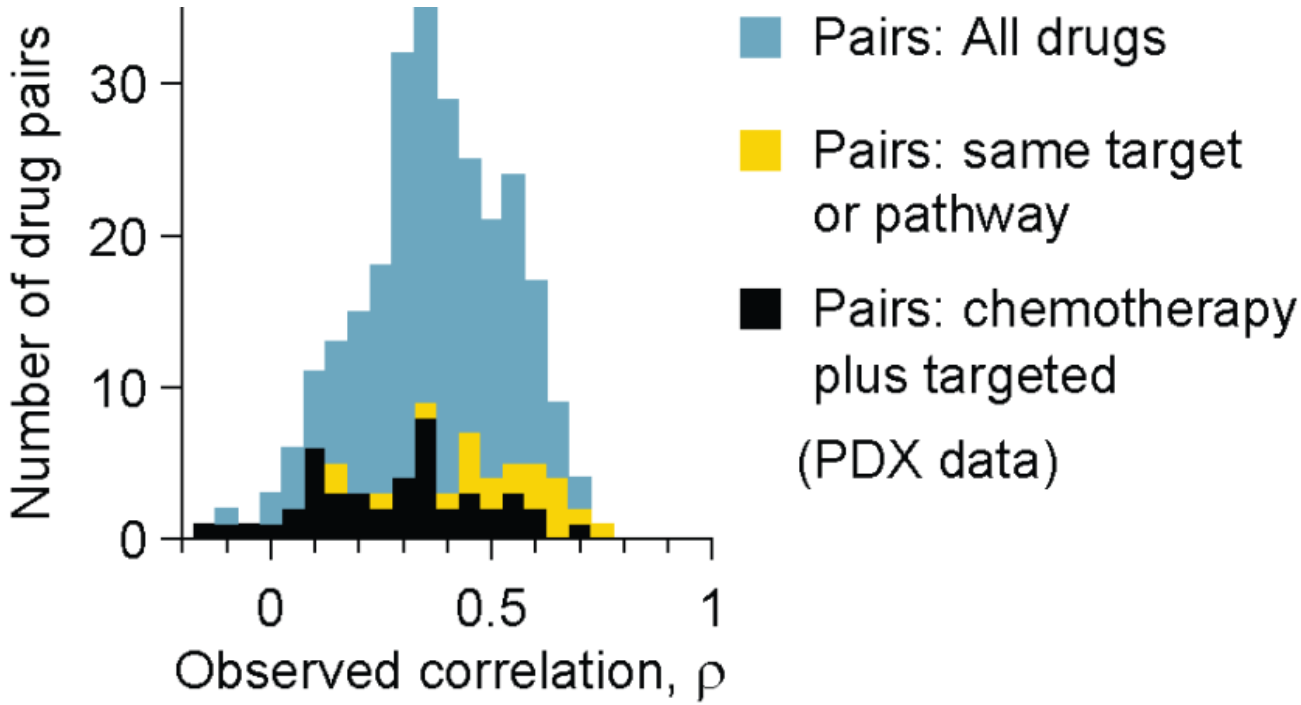
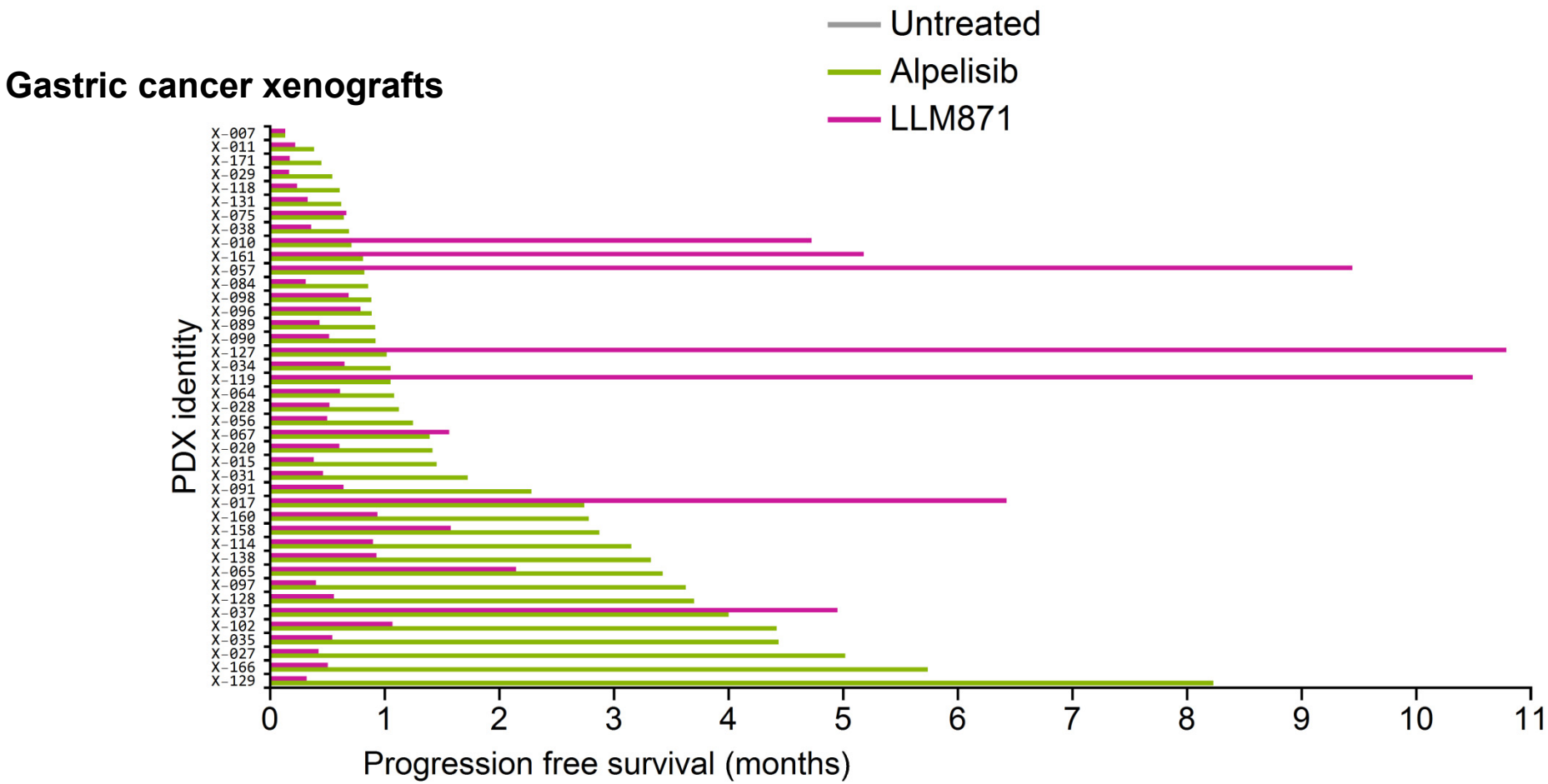


Palmer & Sorger (2017) *Cell*
Analysis of data from Gao *et al* (2015) *Nature Medicine*

Different tumors can respond to different therapies



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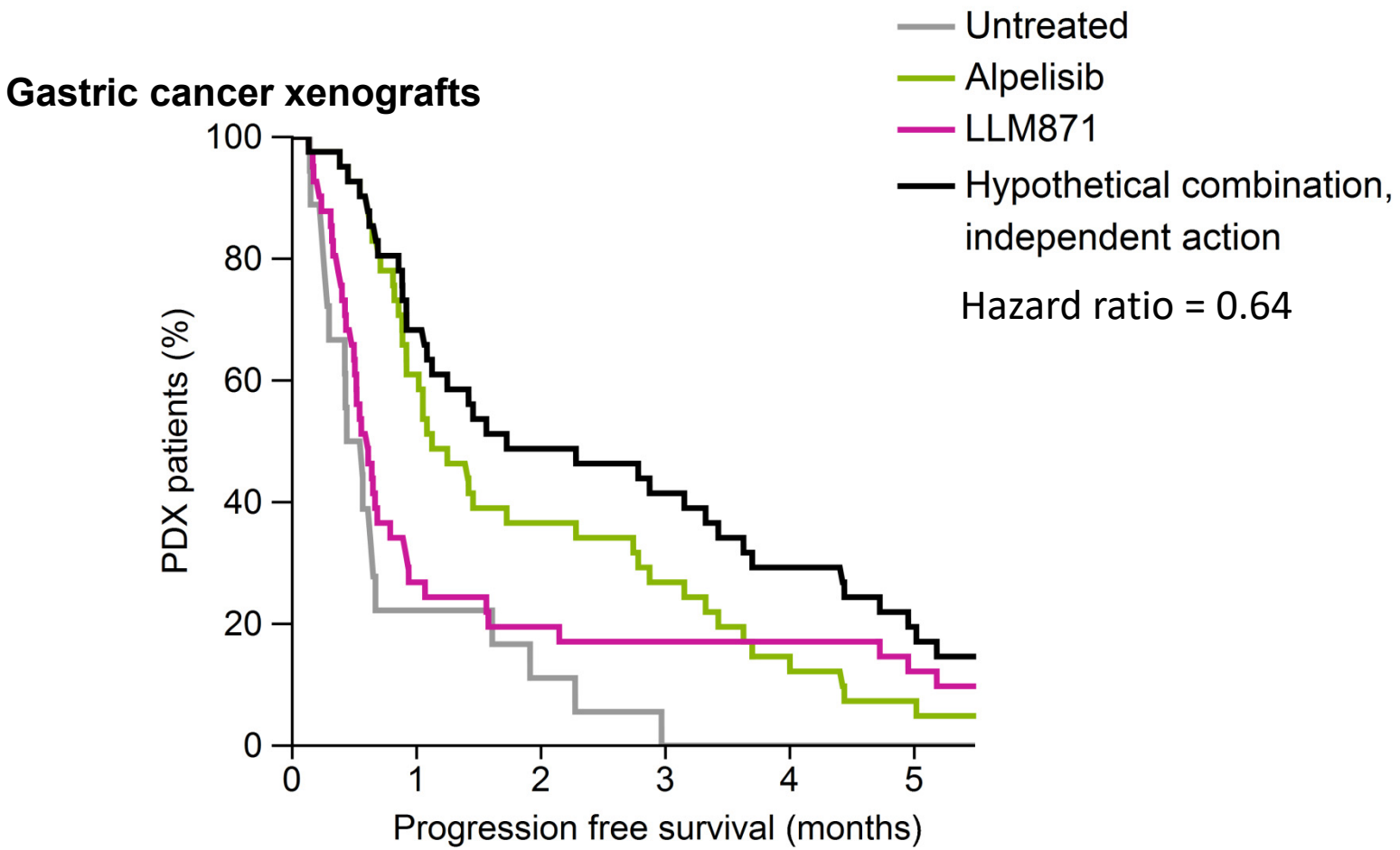
Different tumors can respond to different therapies

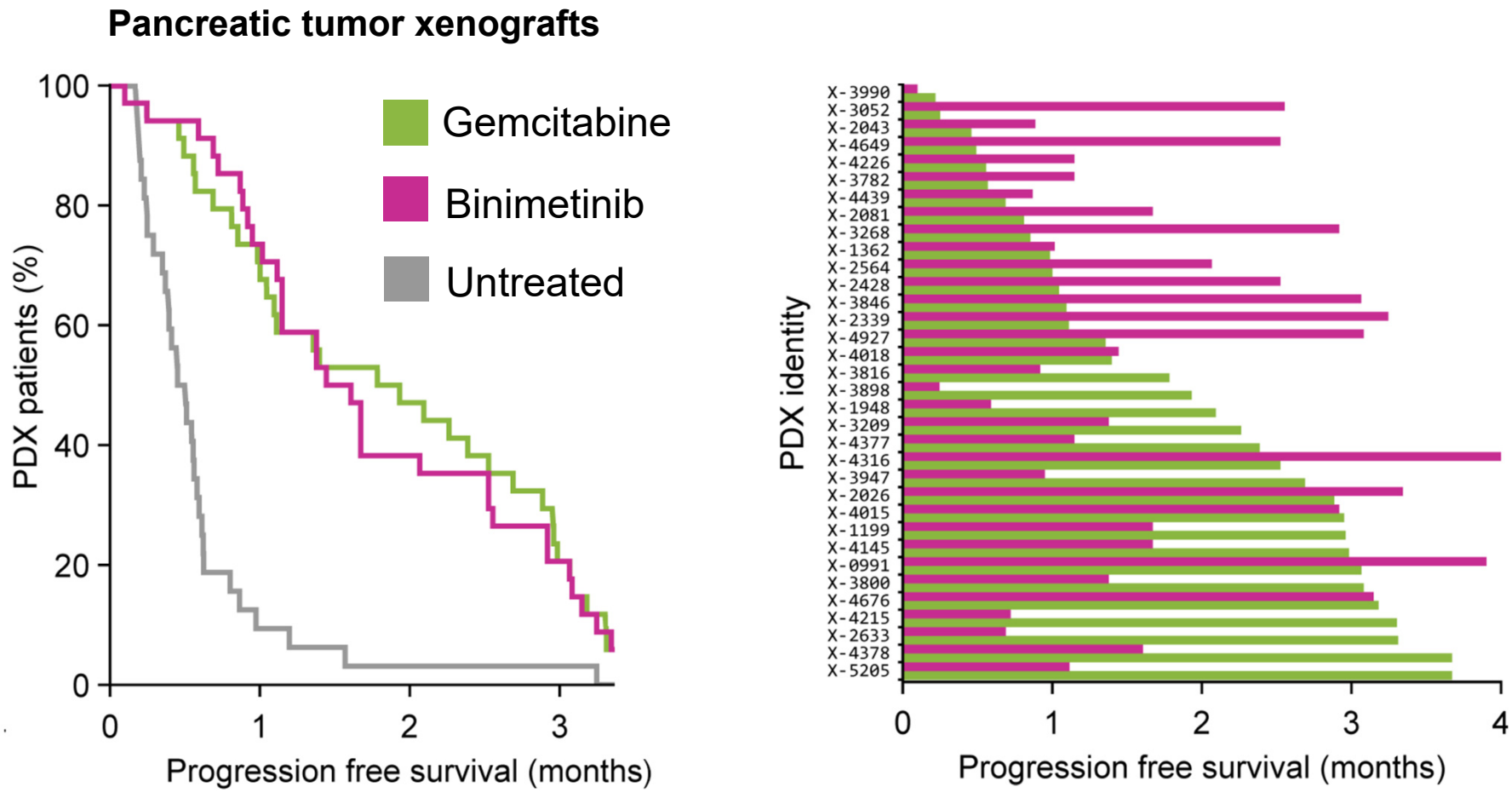
⇒ combinations can improve response rates *without* additivity



Palmer & Sorger (2017) *Cell*

Analysis of data from Gao *et al* (2015) *Nature Medicine*

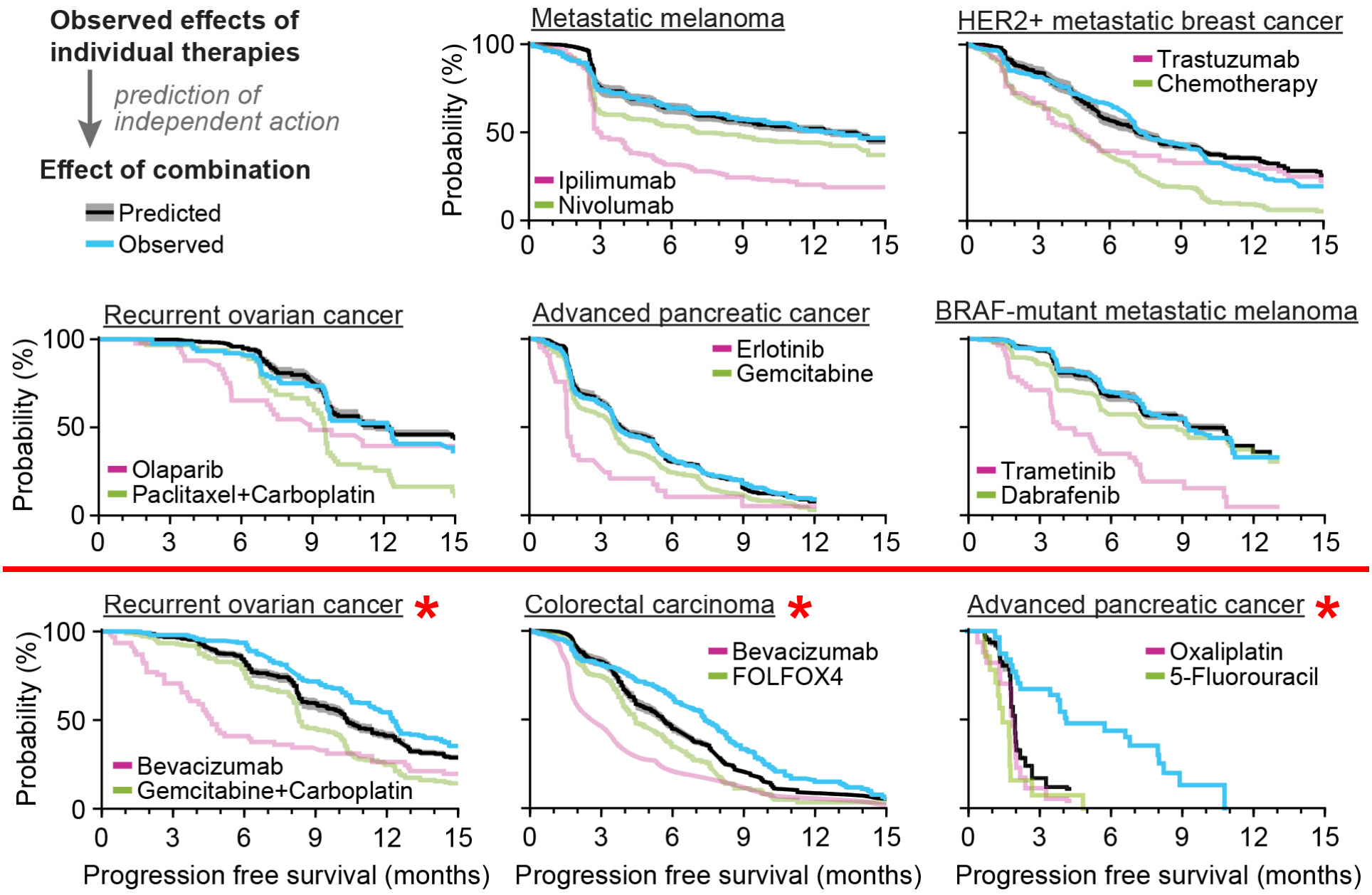
Comparative trials can fail to see benefits in different patient groups



Palmer & Sorger (2017) *Cell*

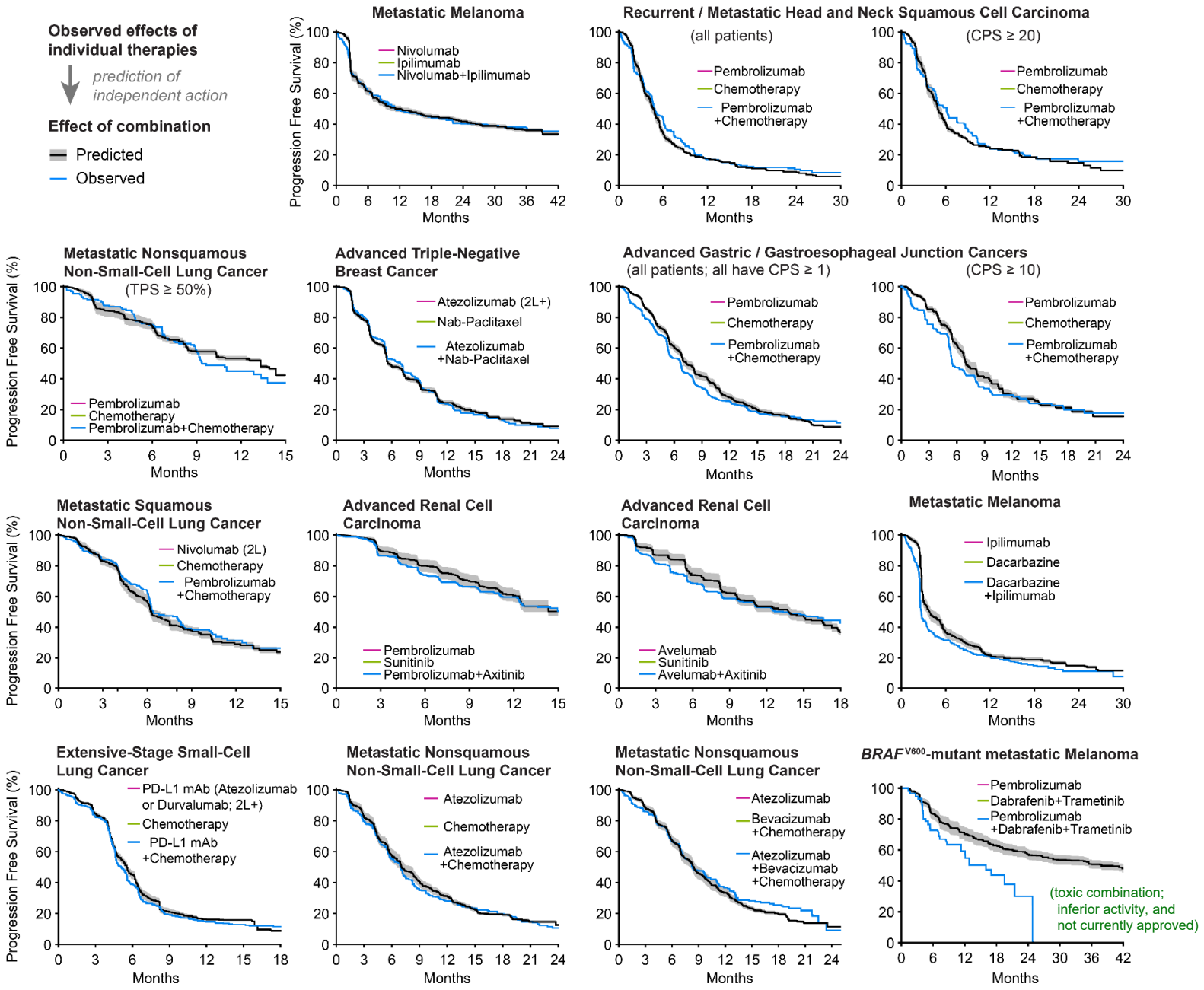
Analysis of data from Gao *et al* (2015) *Nature Medicine*

Many combination therapies are consistent with independent drug action



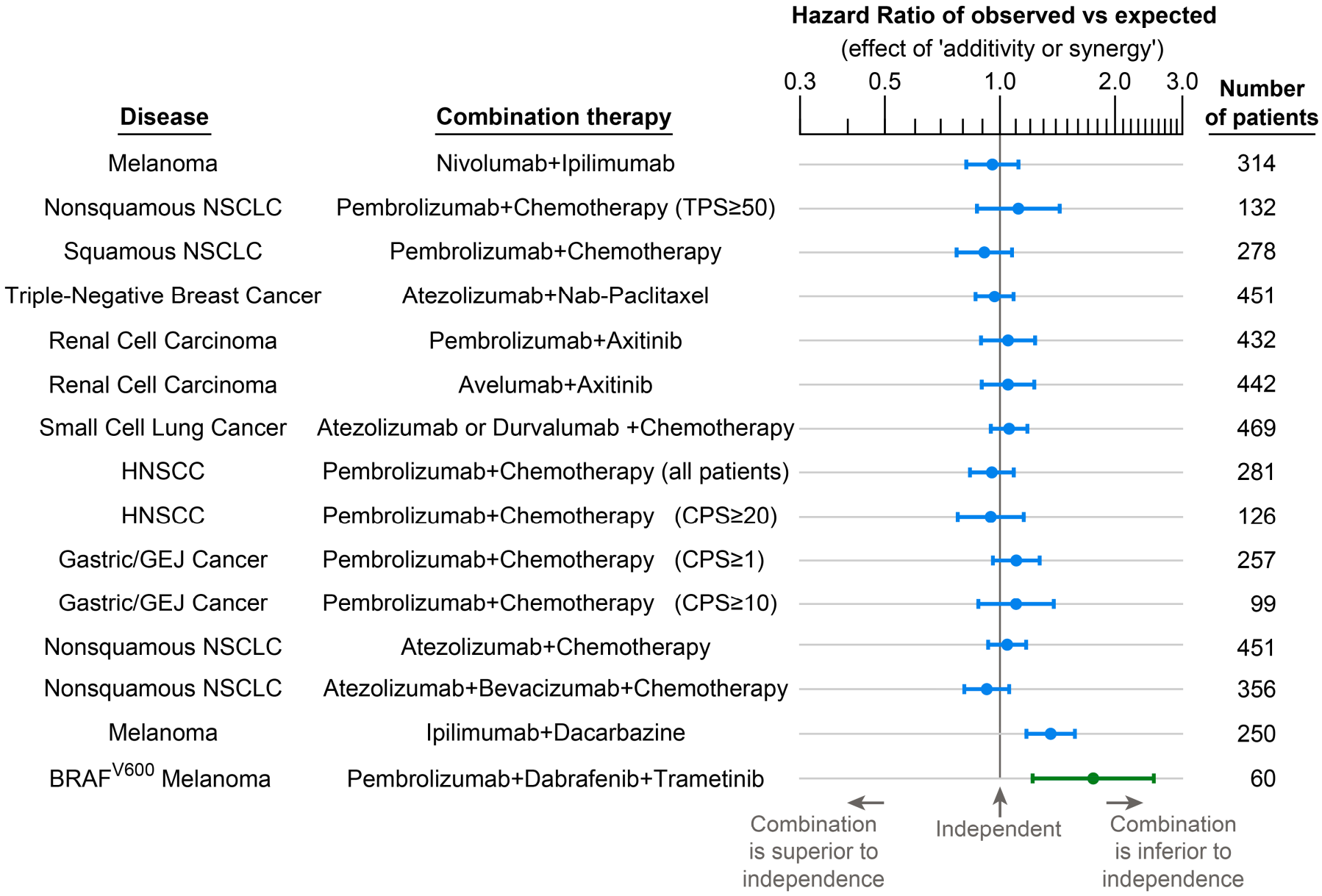
Palmer & Sorger (2017) *Cell*

*** Independent action is a reference to find *clinical* superiority**



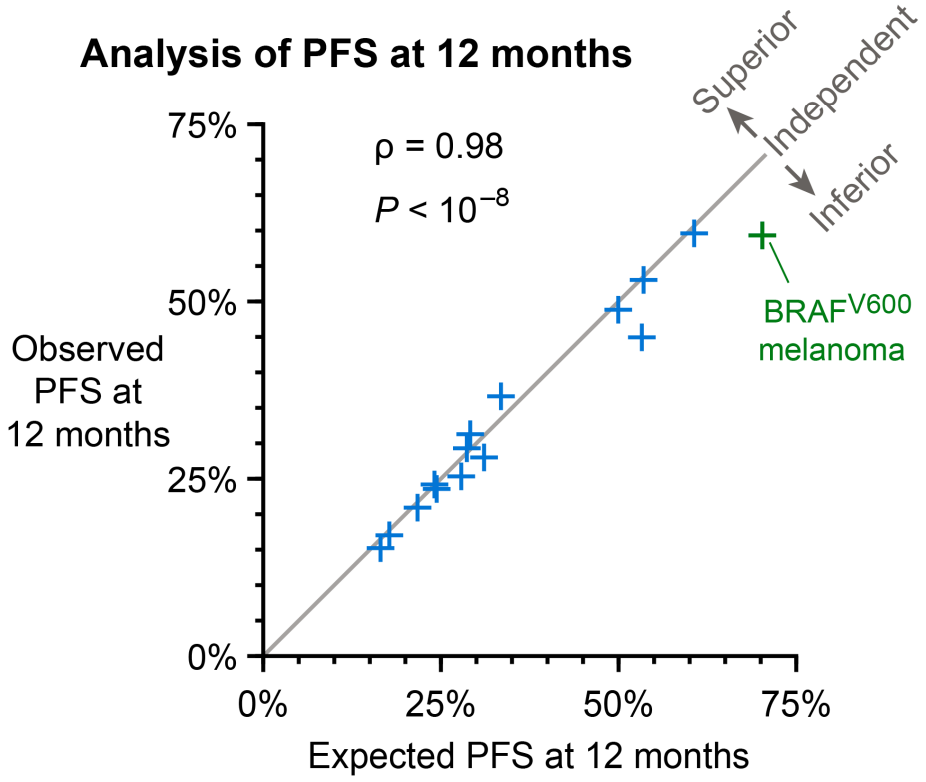
Palmer, Izar, Hwangbo, Sorger (2020) *medRxiv 2020.01.31.20019604*

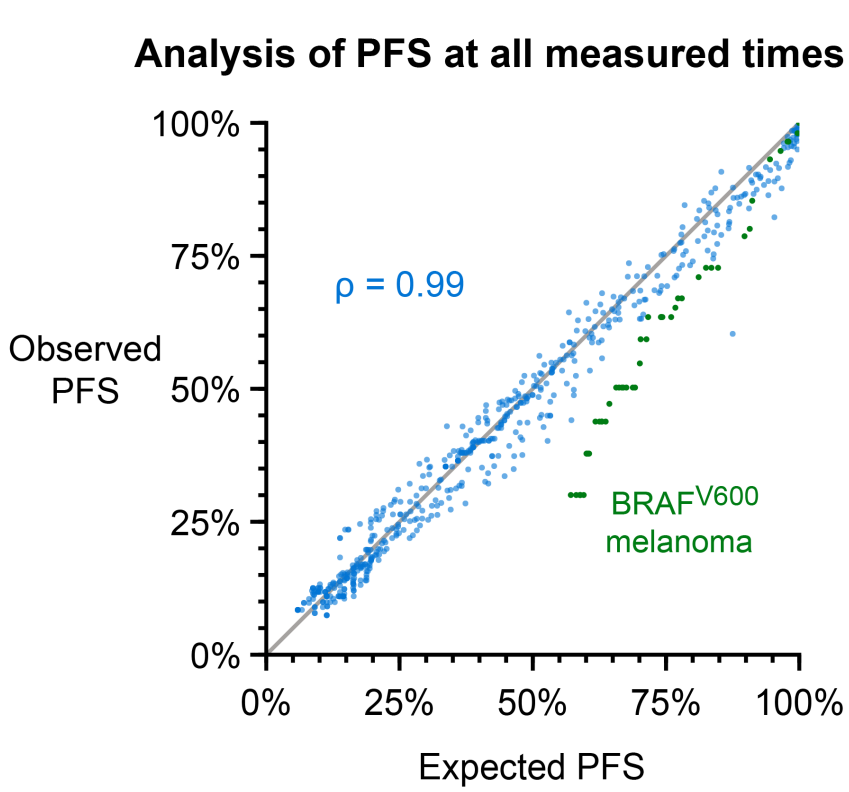
Combinatorial benefit with no statistically significant evidence of additivity or synergy



Palmer, Izar, Hwangbo, Sorger (2020) *medRxiv 2020.01.31.20019604*

Predictable benefit of combination therapies with Immune Checkpoint Inhibitors





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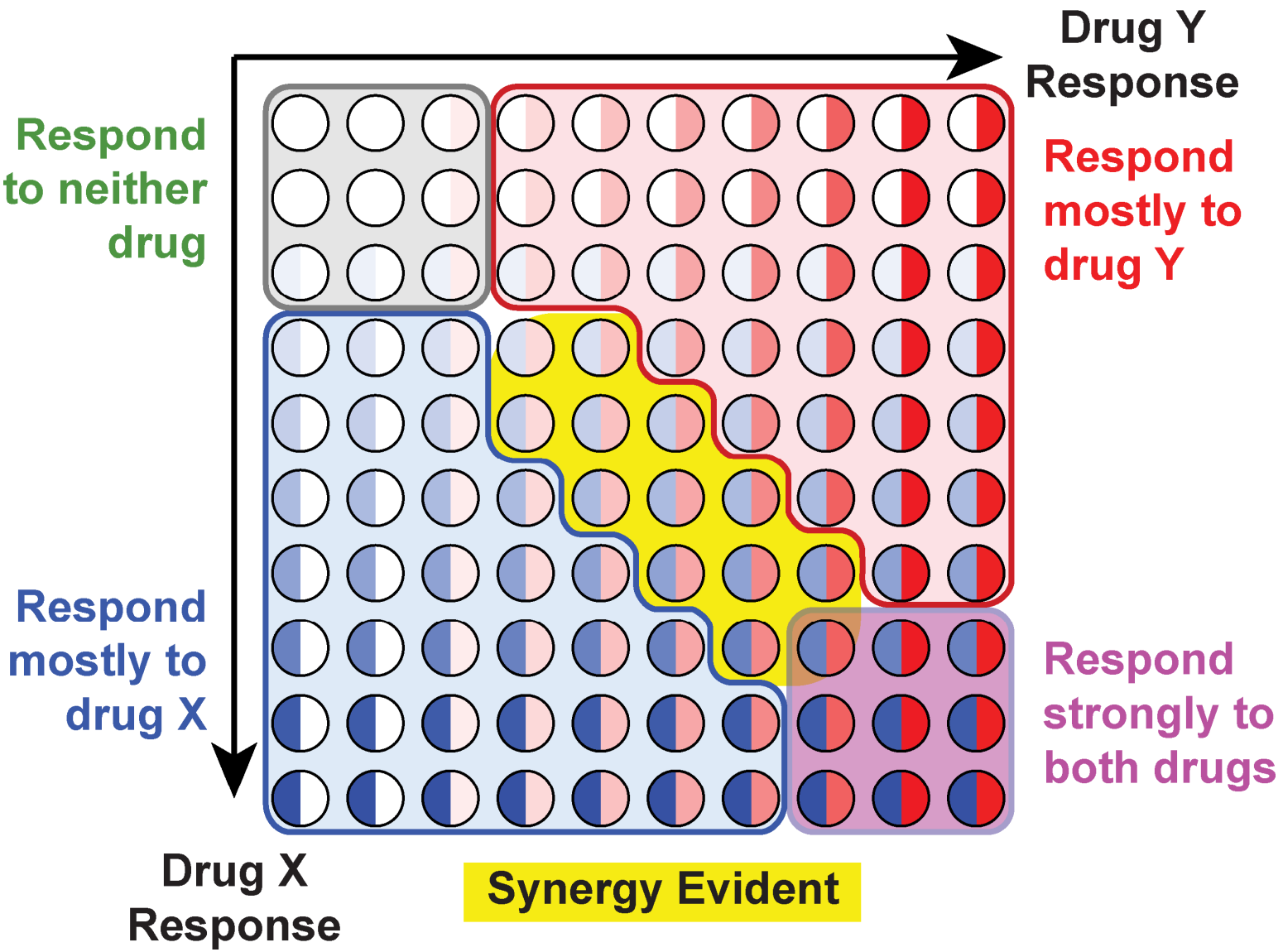
Why doesn't pre-clinical synergy translate?



Conclusions

Drug combinations give each patient more chances to receive one effective drug.

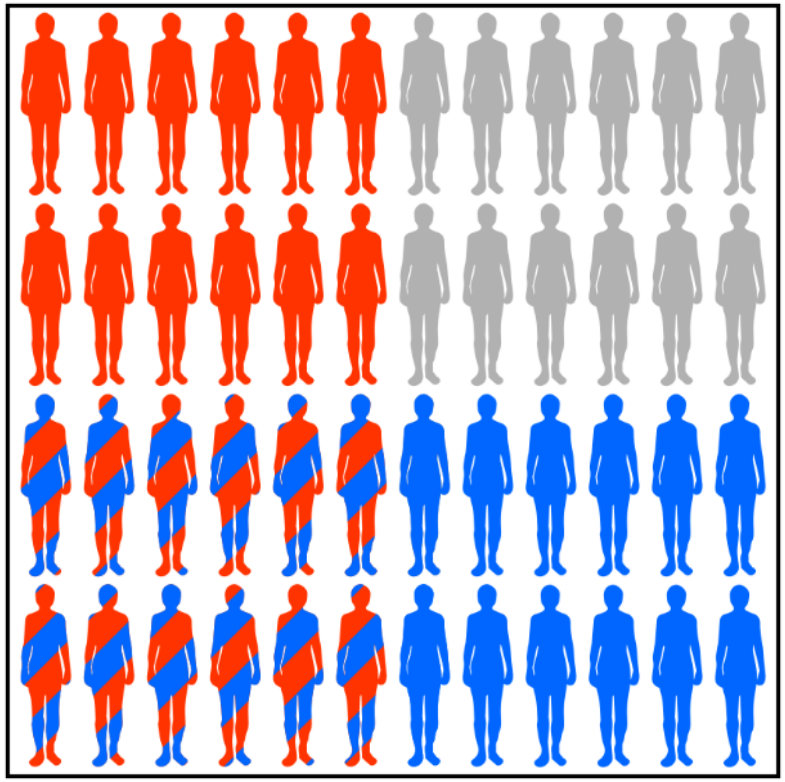
When cross-resistance is low, this can substantially improve survival.

Clinical activity of combinations can be often predicted from monotherapy activities.

Drug independence model can identify additive or synergistic effect in clinical trials.

Combinations that lack additivity/synergy could instead be stratified

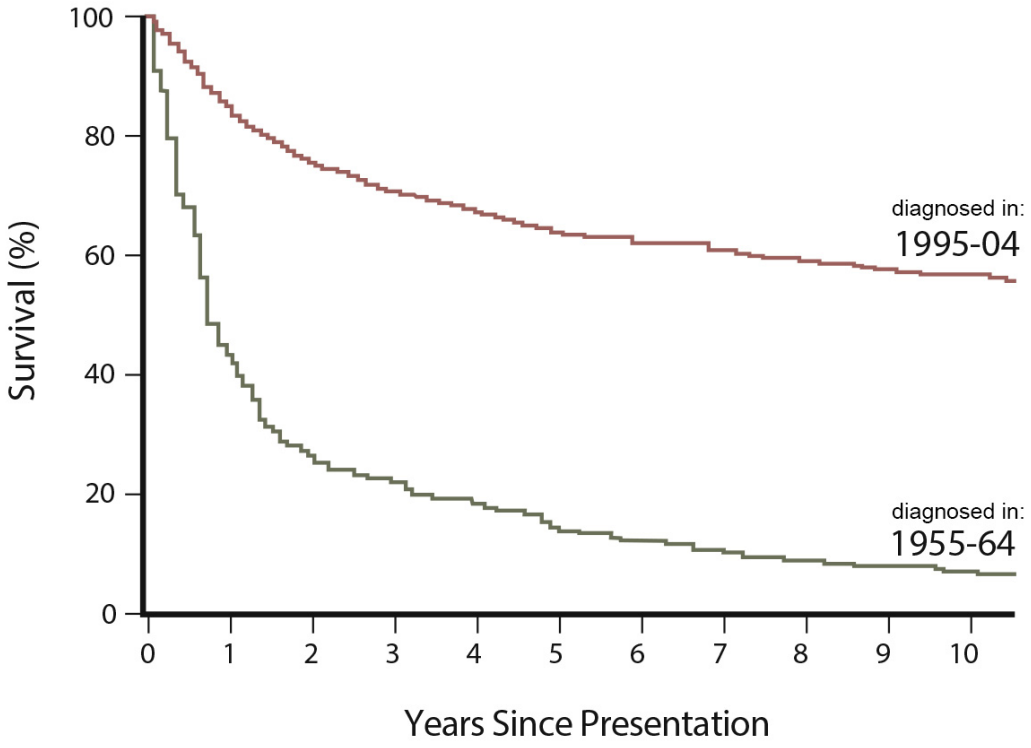
Mechanism of action of curative combinations



Multiple drug responses
MUST somehow add up

R-CHOP is a curative combination therapy for Diffuse Large B-Cell Lymphoma

R – Rituximab ---------- monoclonal antibody against CD20, a protein expressed on B-cells
C – Cyclophosphamide ---- alkylating agent
H – Doxorubicin ---------- topoisomerase poison
O – Vincristine ---------- inhibitor of microtubule formation in mitotic spindle
P – Prednisone ---------- steroid



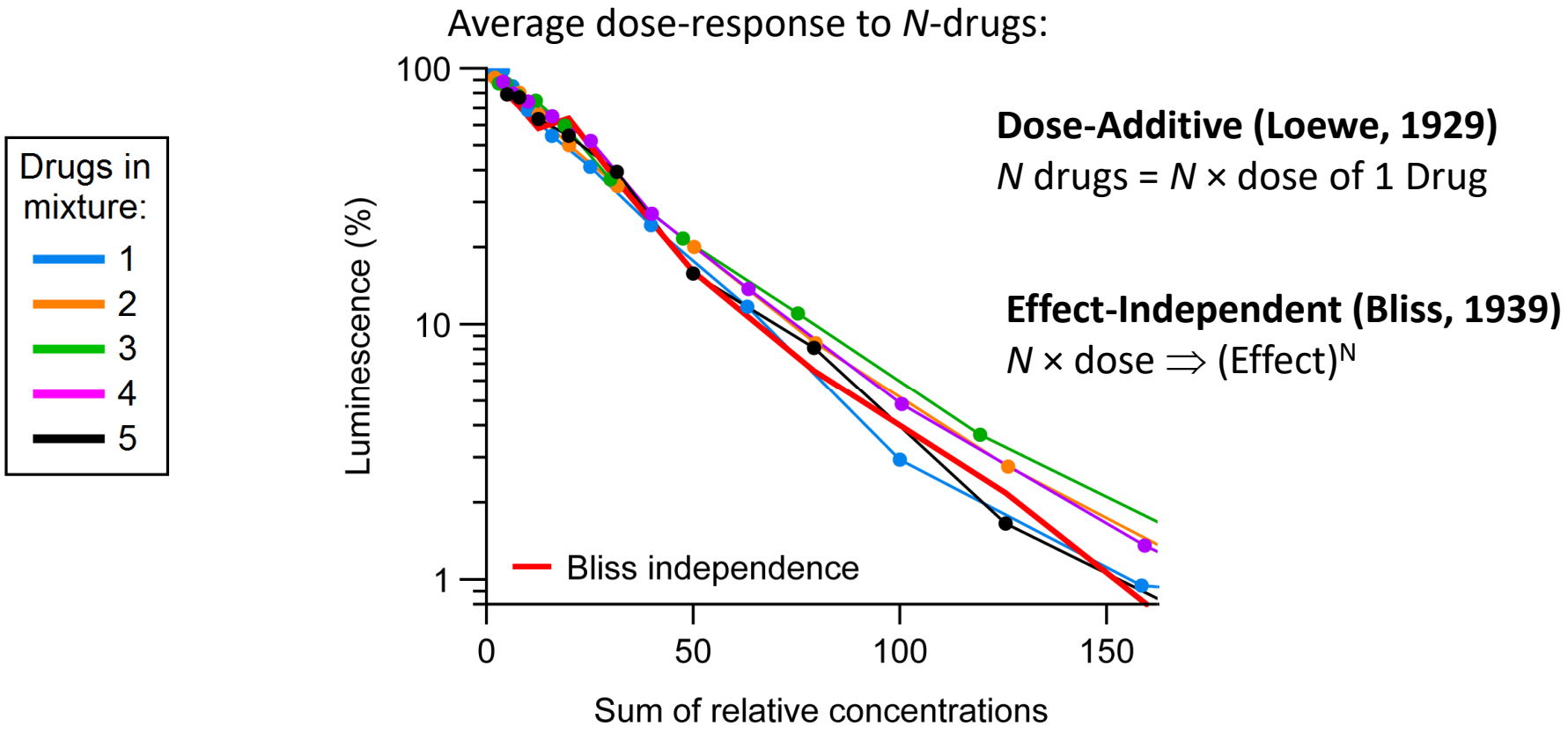
Treated with **R-CHOP**

Treated with alkylating drug

60 Years of Survival Outcomes at The University of Texas MD Anderson Cancer Center
Rodriguez, Walters, Burke, (Eds.), 2013

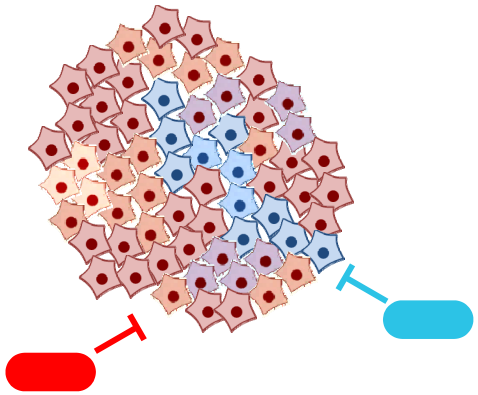
Is R-CHOP a *synergistic* combination?

The curative RCHOP combination is additive



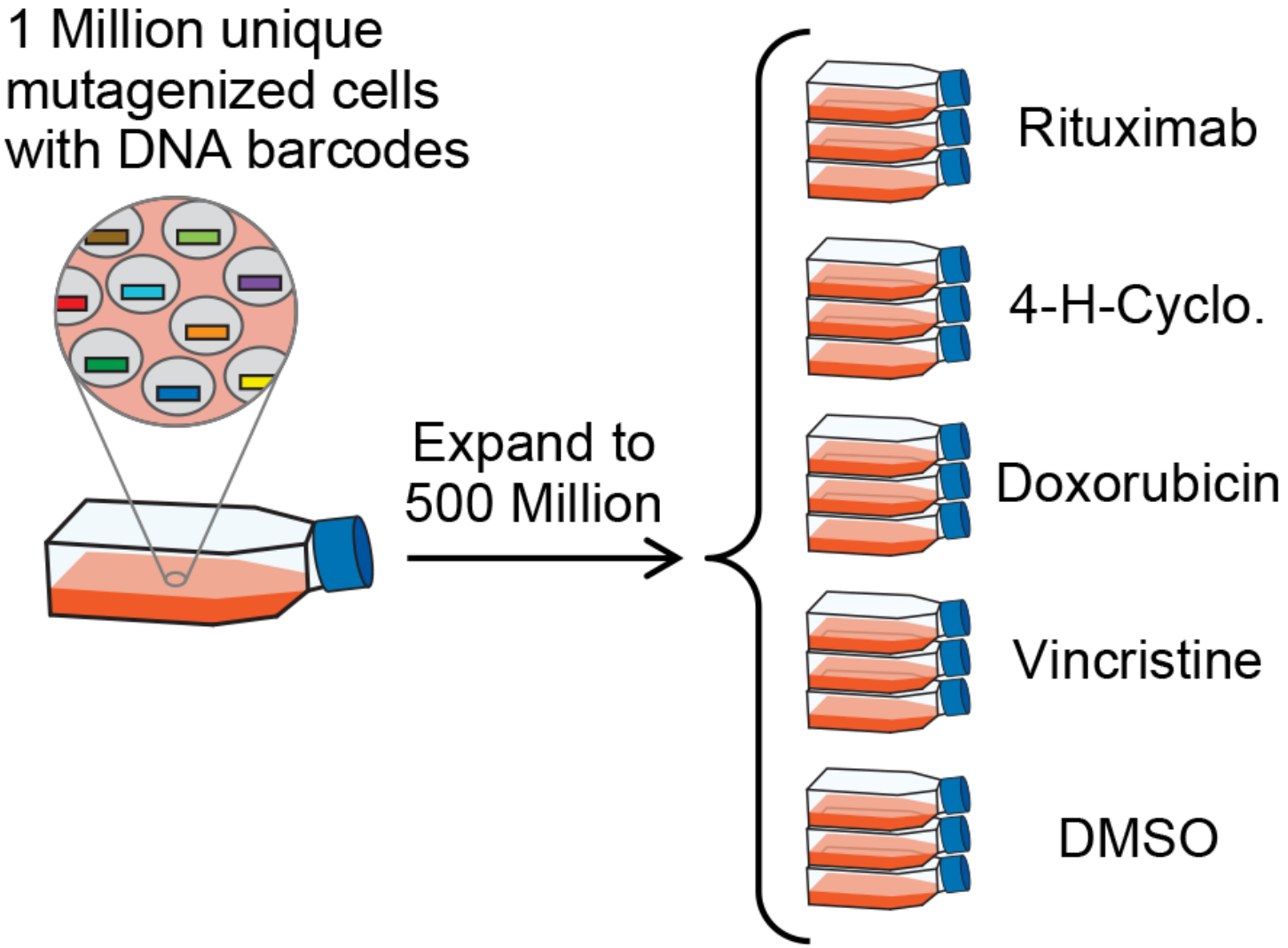
Palmer, Chidley, Sorger (2019) *eLife* 8:e50036

Tumor heterogeneity was the original rationale for drug combinations



L. Law (1952) *Cancer Research*

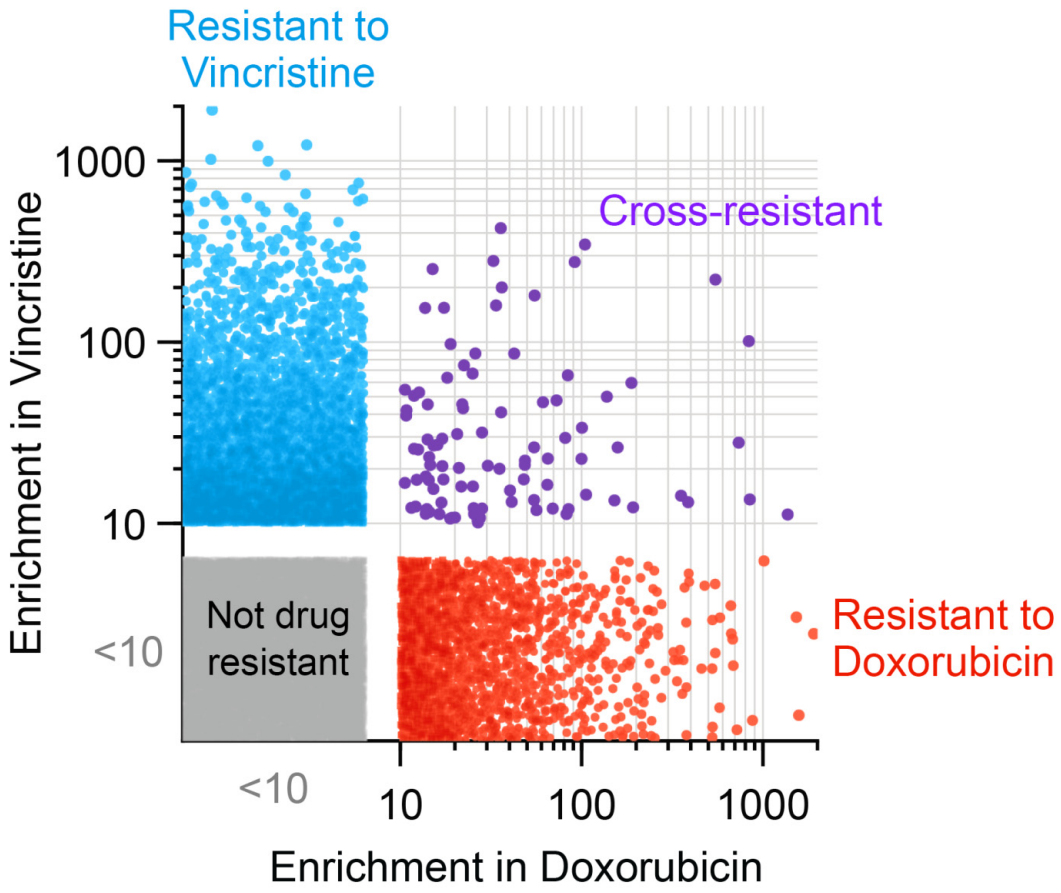
Measuring cross-resistance in RCHOP by clonal barcoding



Palmer, Chidley, Sorger (2019) *eLife* 8:e50036

Single-drug resistance is common, multi-drug resistance is rare

$$\text{Enrichment} = \frac{\text{Post-treatment barcode abundance}}{\text{Pre-treatment barcode abundance}}$$



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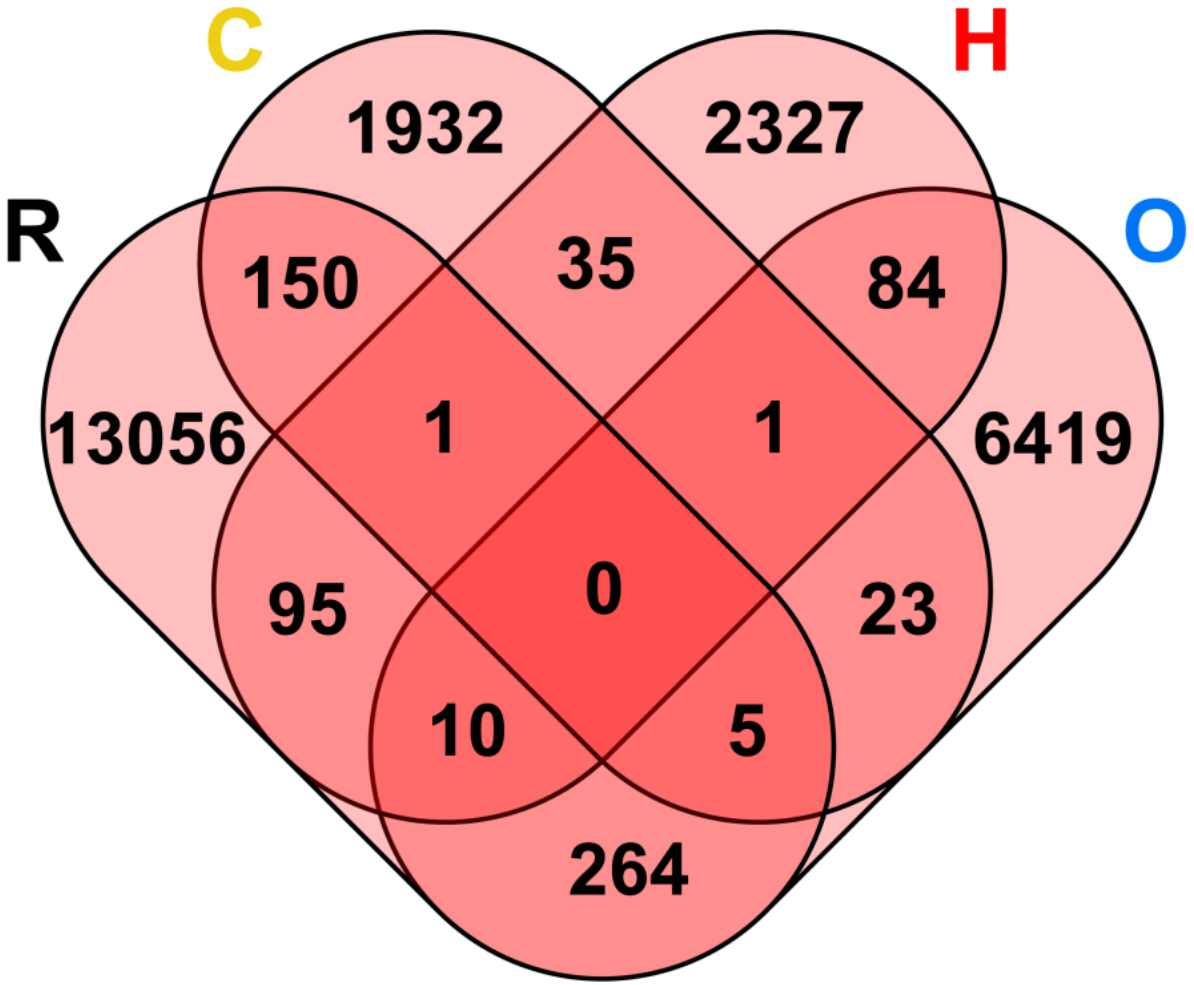
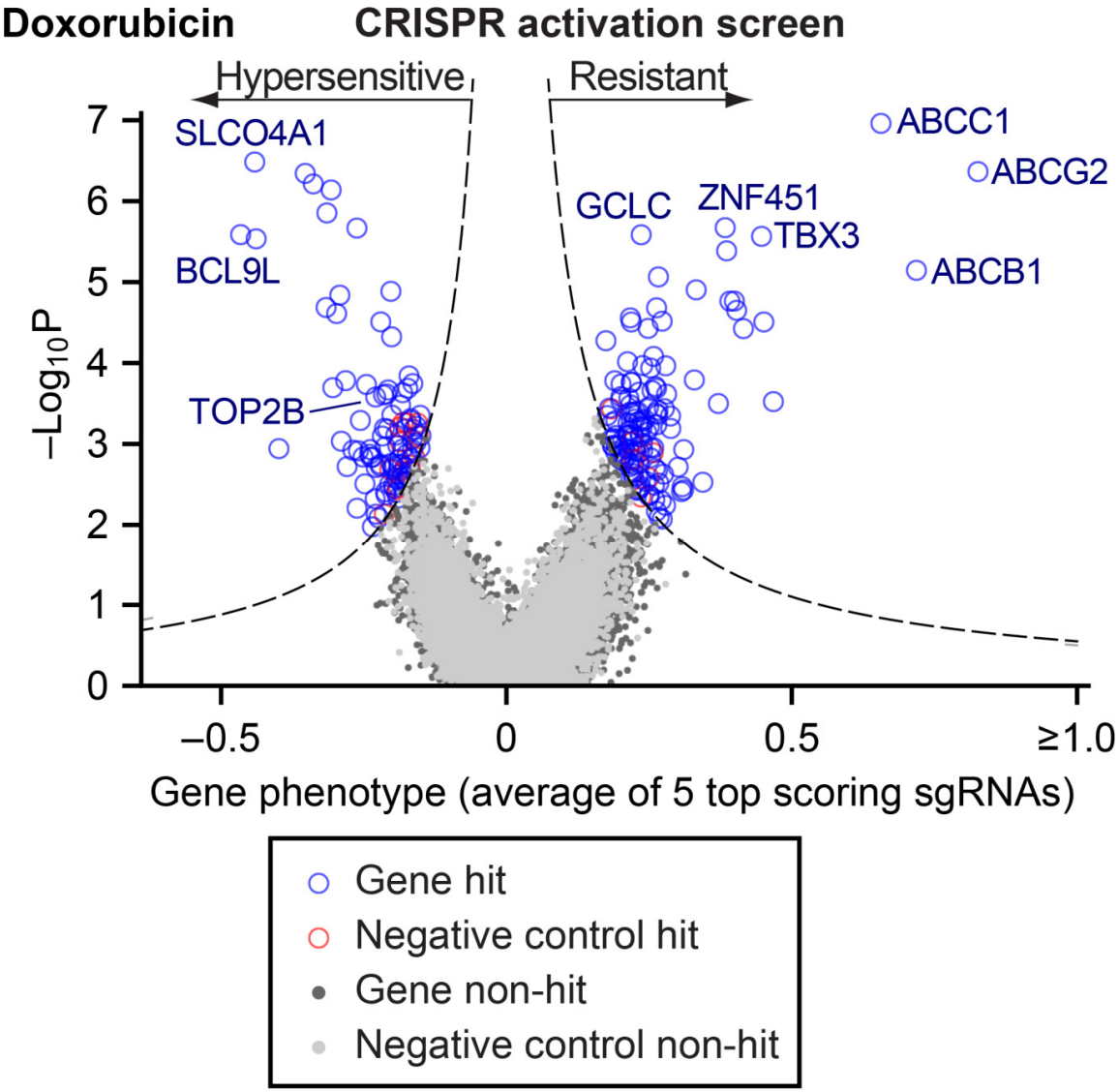


Palmer, Chidley, Sorger (2019) *eLife* 8:e50036

Many resistance mechanisms revealed by genome-wide CRISPR-i and CRISPR-a screens



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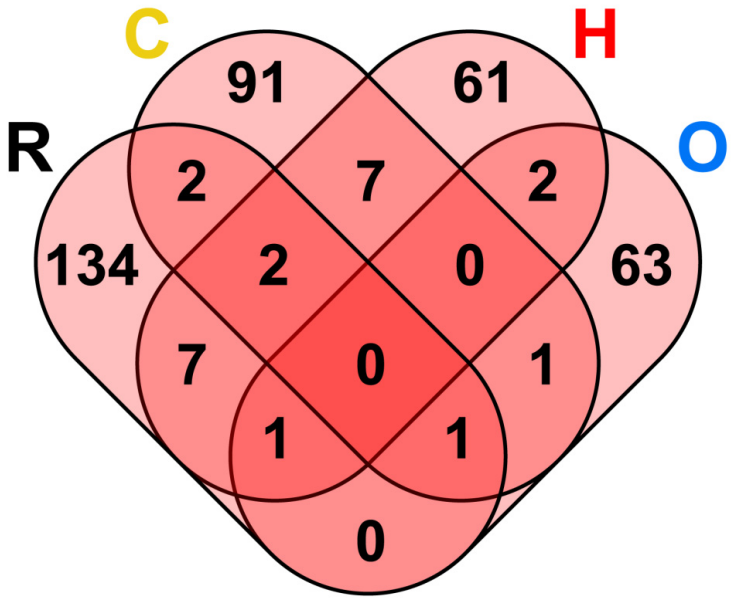
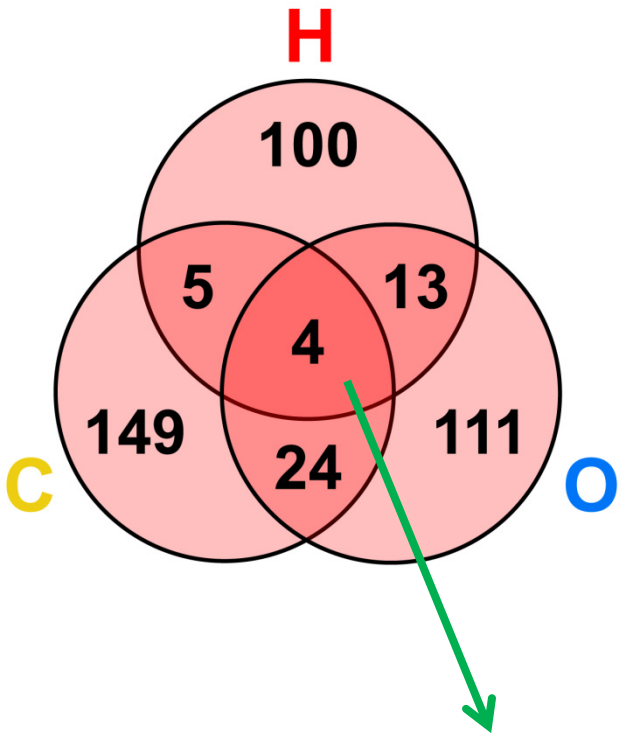
Gene knockdown



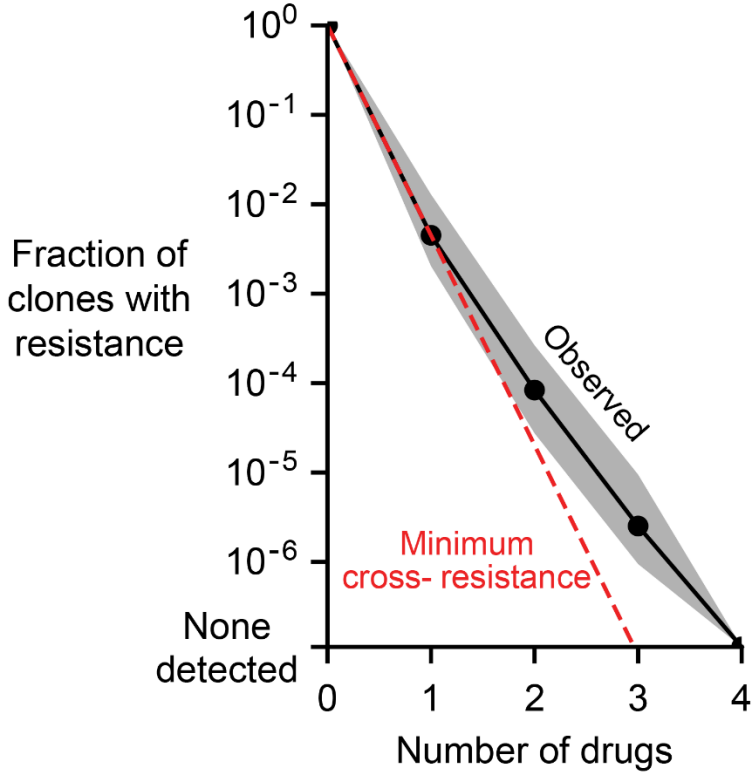
Gene activation



High expression of GCLC clinically associated with lower survival

Palmer, Chidley, Sorger (2019) *eLife* 8:e50036

The curative RCHOP combination is additive

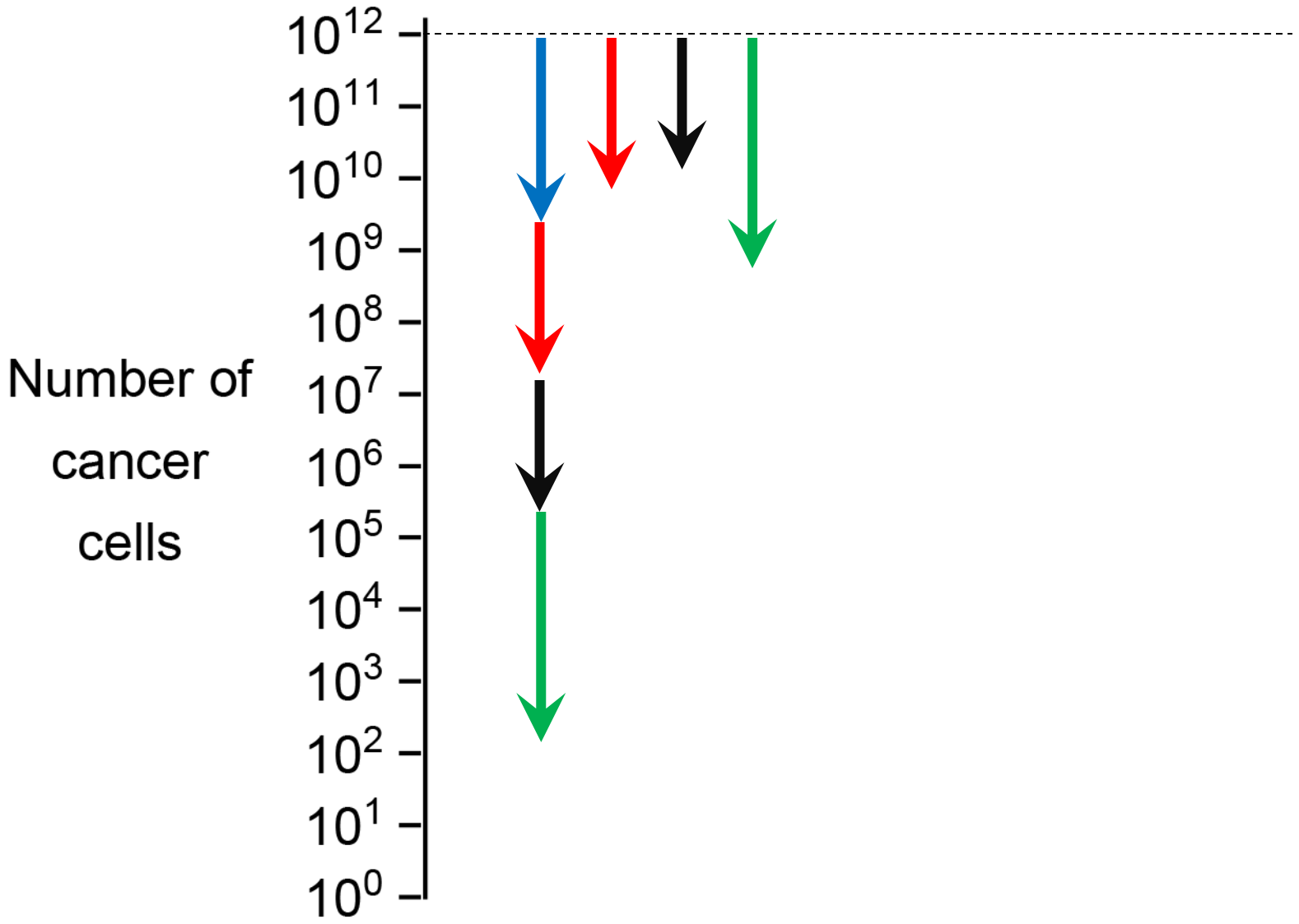


RCHOP is clinically effective but not because of synergistic interactions.

RCHOP can kill most resistant cells because its ingredients are
individually effective
with **low cross-resistance**

Palmer, Chidley, Sorger (2019) *eLife* 8:e50036

Log-kills add up, but response is variable among patients



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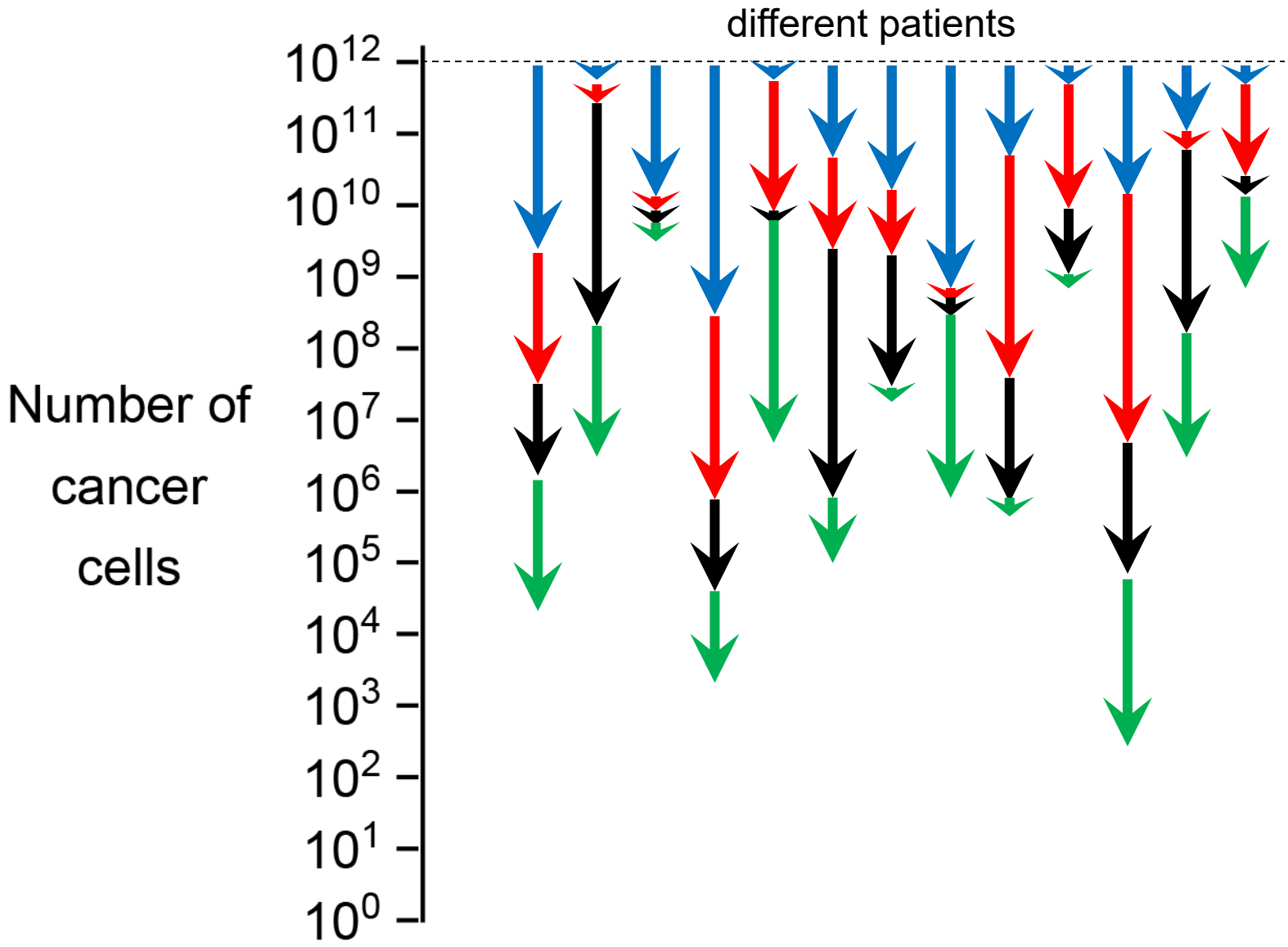
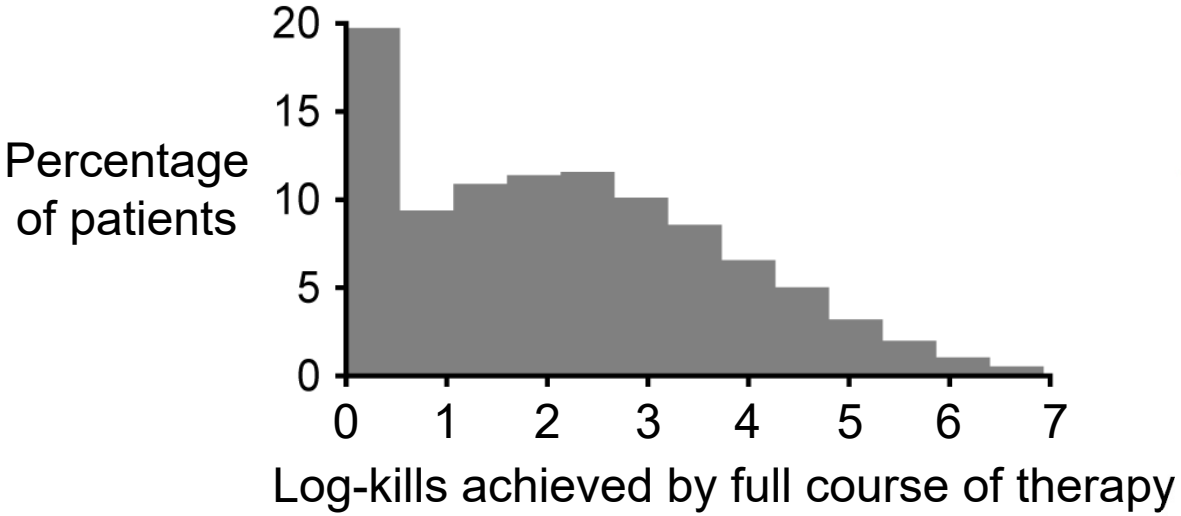
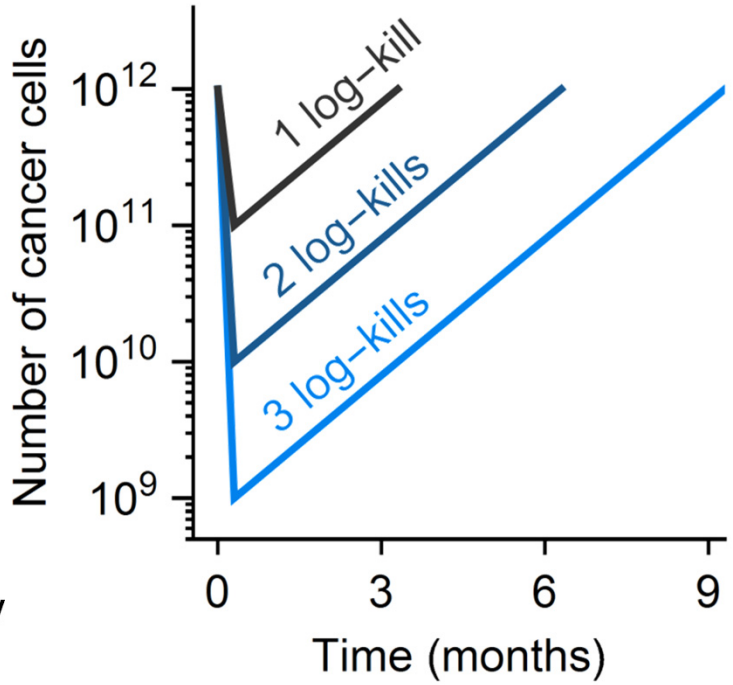


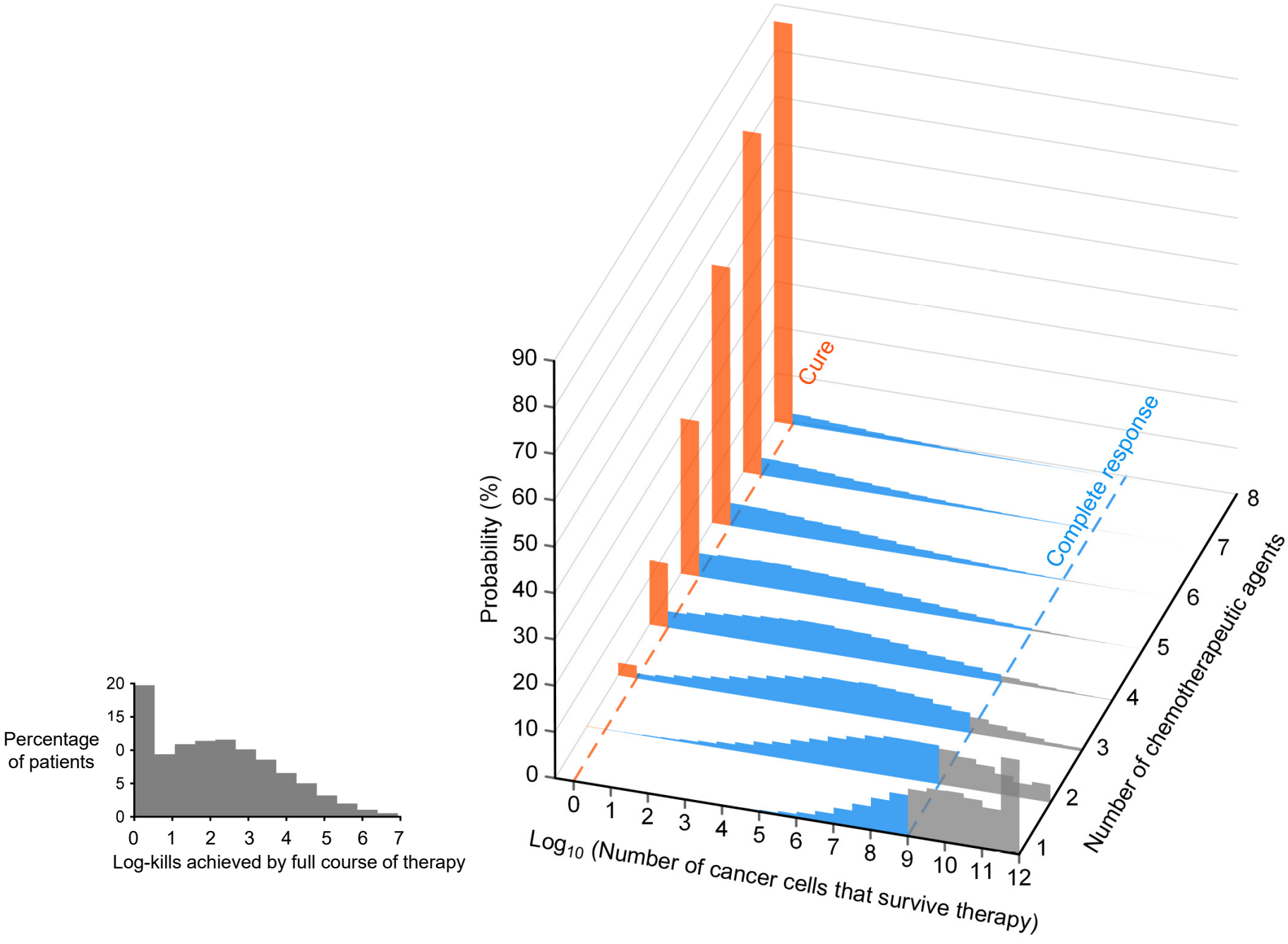
Single-drug efficacy measured in early clinical trials



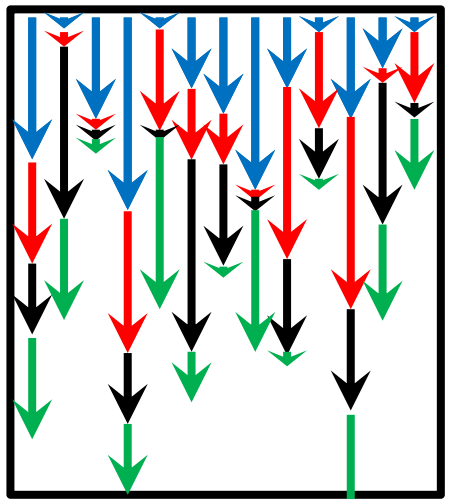


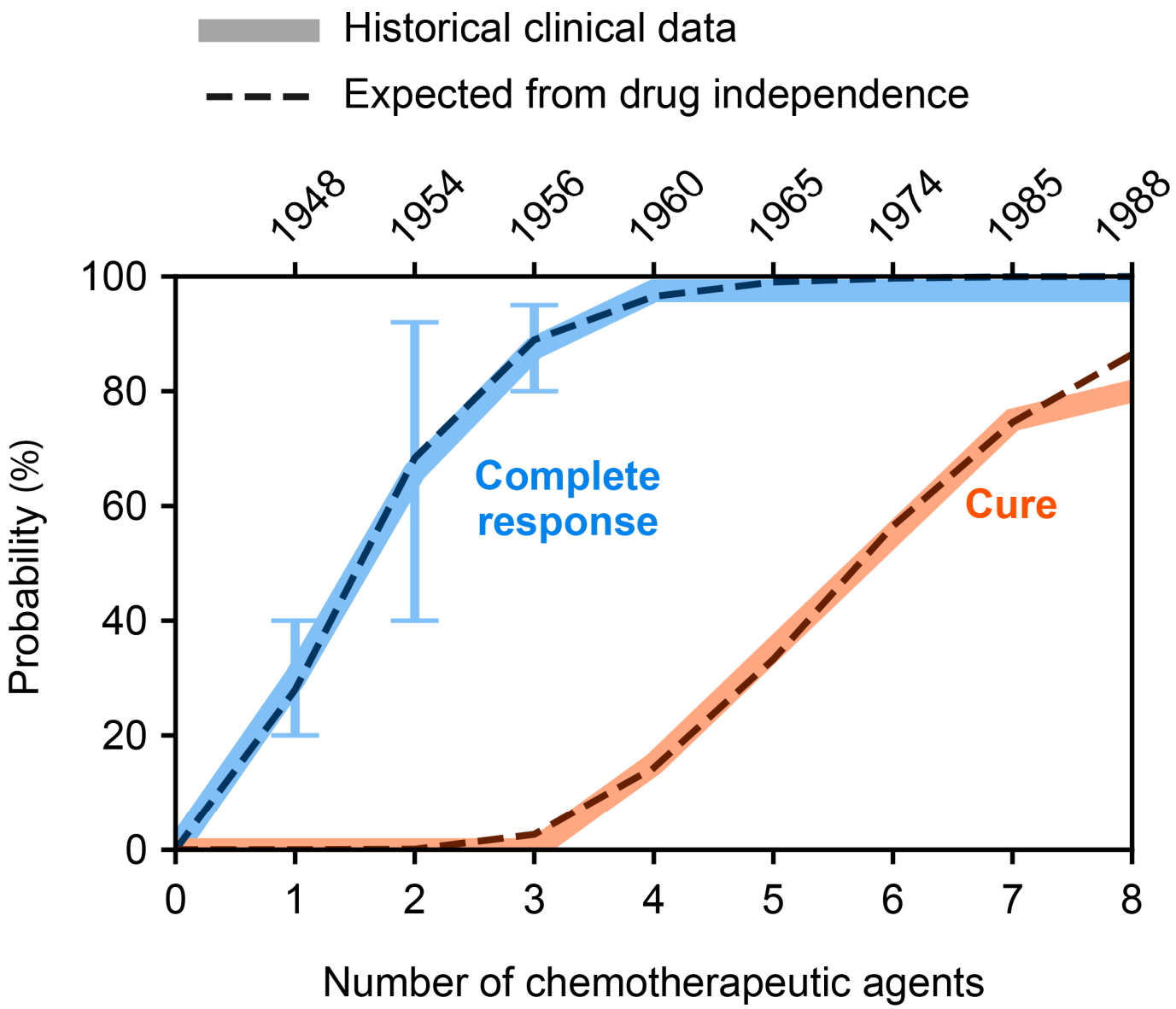
Survival distributions following treatment with Methotrexate or 6-Mercaptopurine, in trials of sequential regimens: E. Frei 3rd *et al.* (1961) Blood

Modeling independent drug action in childhood ALL

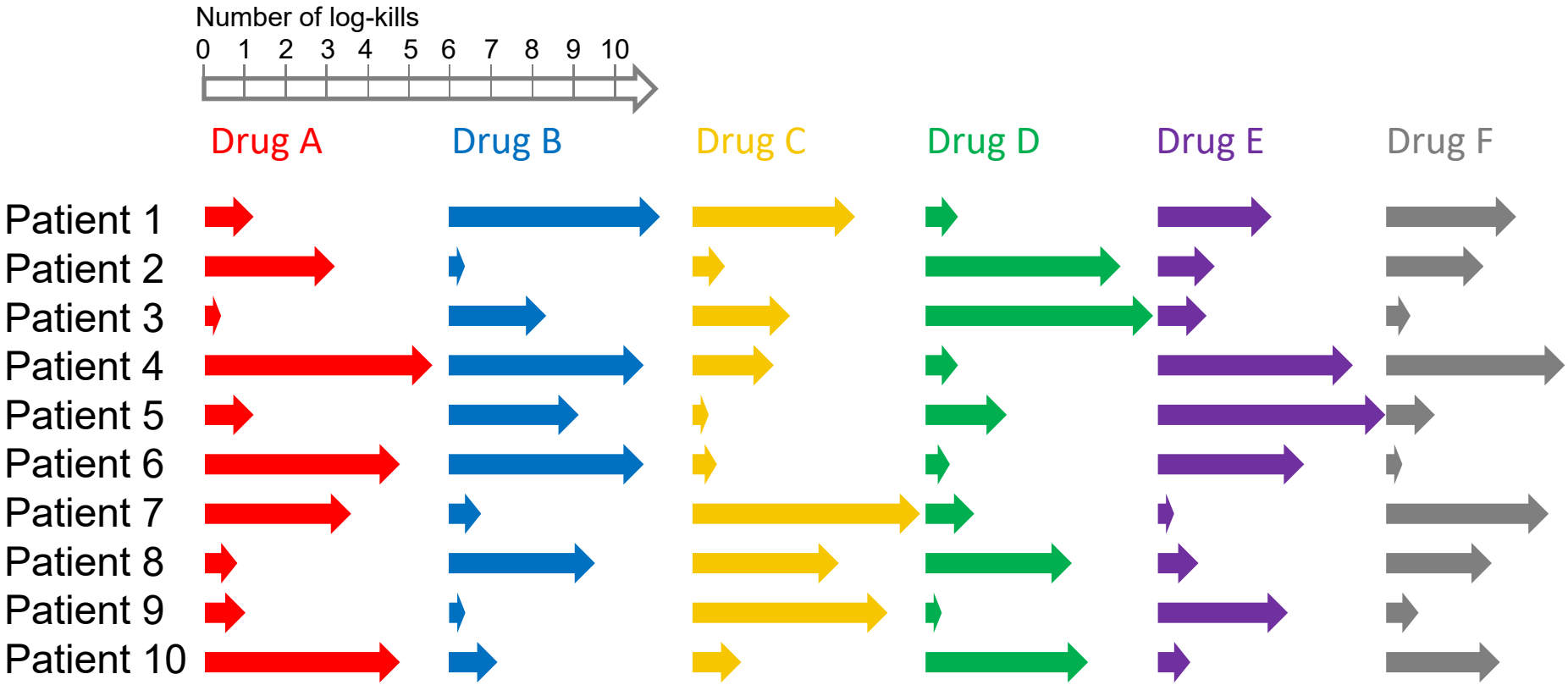


Cure rates are as expected by drug independence



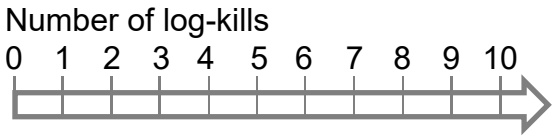


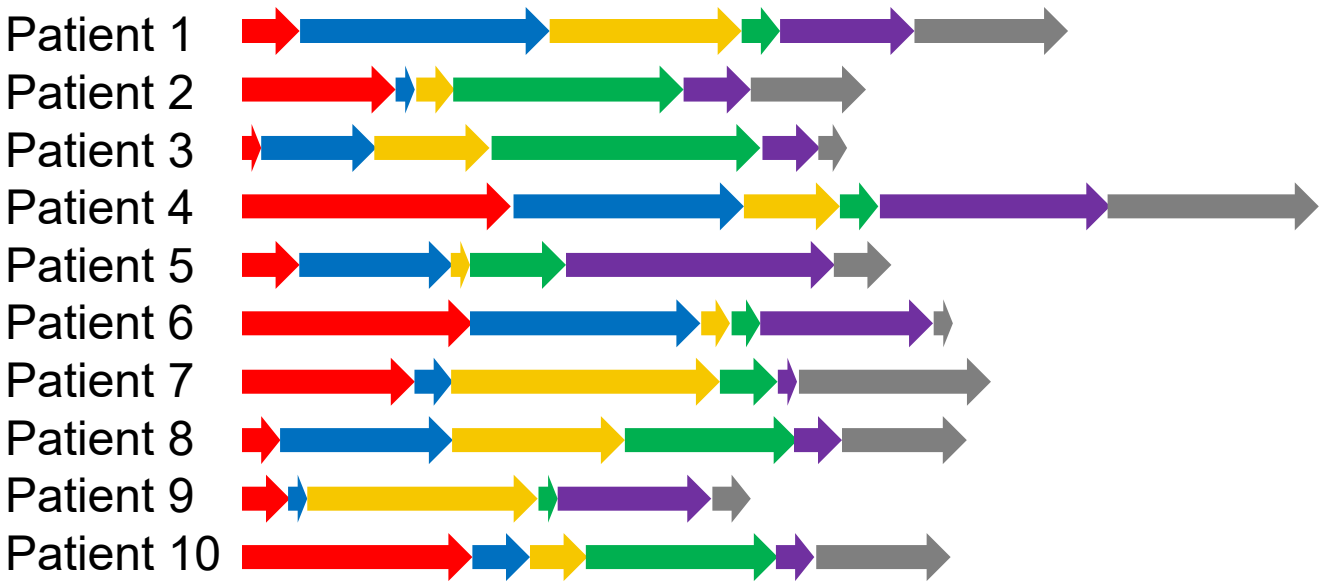
How should we design combinations?

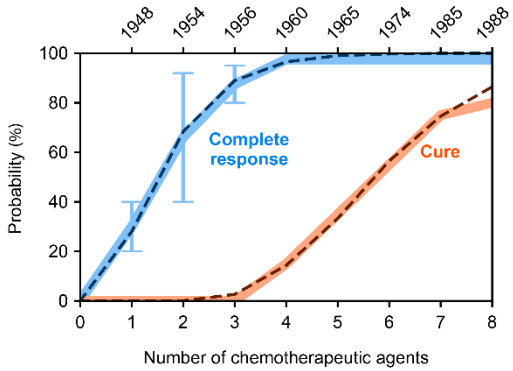


“Total therapy” = all drugs for all patients

applied to cure pediatric ALL, today with risk-stratification





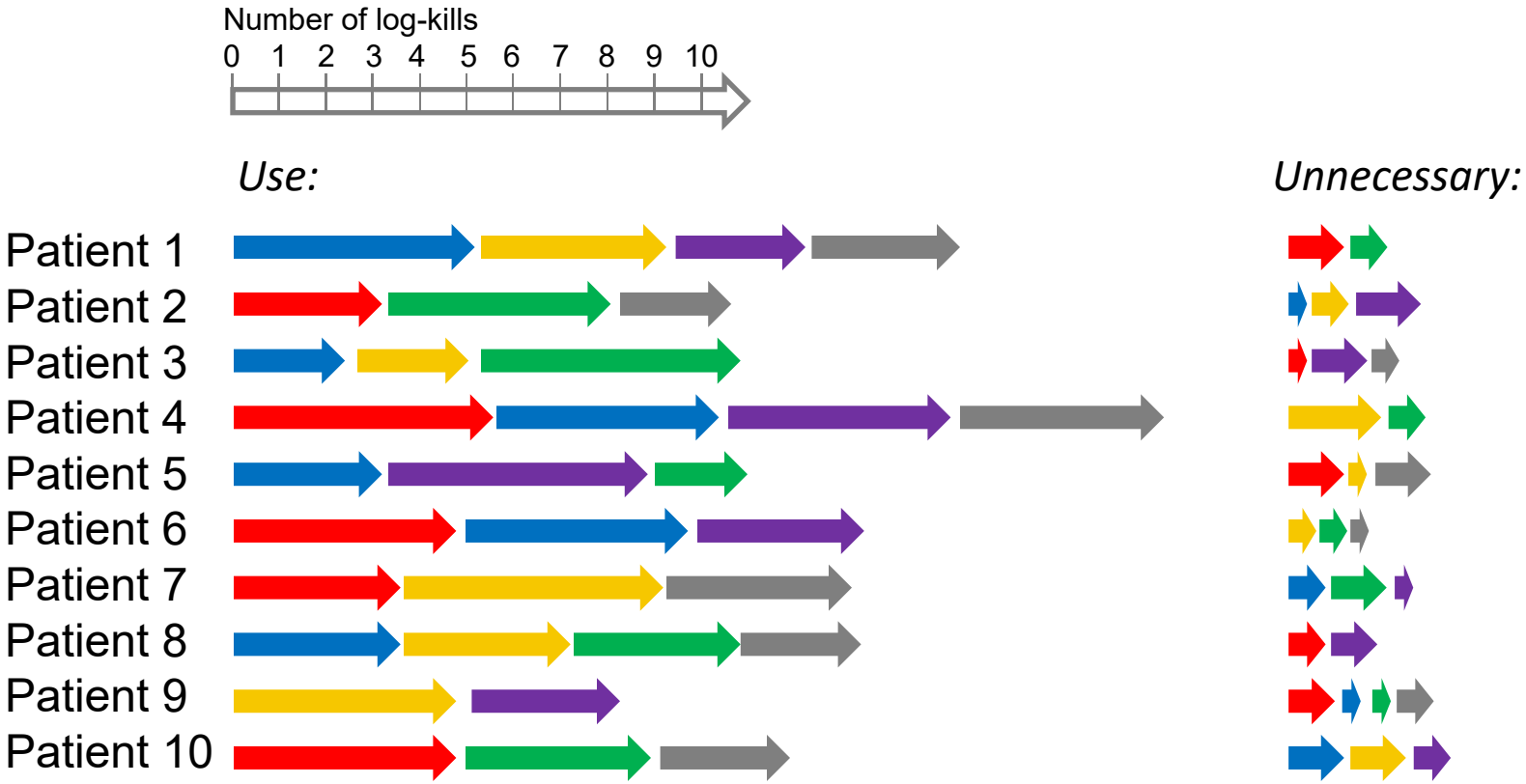


“We said, ‘**Let’s put it all together. Let’s attack the disease from different directions, all at once.**’ My hypothesis was that there were some leukemia cells that were sensitive to one drug and other cells that were sensitive to another. But if we use all these drugs at once and hit them along different pathways, we would permanently inhibit the development of resistant cells.”

- Donald Pinkel (inventor of Total Therapy)
  Smithsonian Magazine, 2016

Total therapy tempered by precision:

Maximize the sum of single-drug activities in each patient.

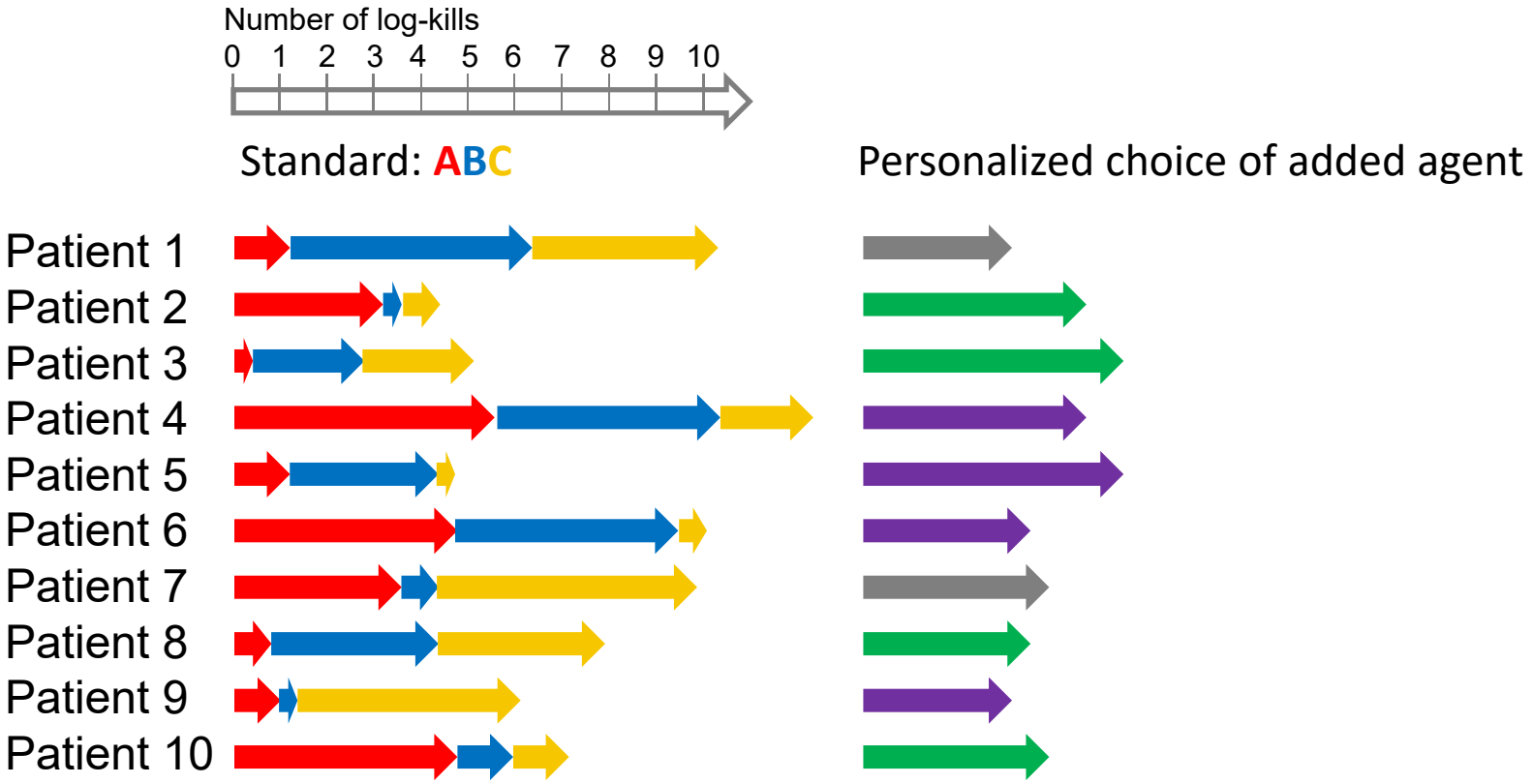


⇒ Maximally-effective combinations depend on choosing the ingredients with precision.

Exceedingly difficult to apply in practice, but possible via functional precision medicine

proof of principle: Kornauth et al, 2021, *Cancer Discovery*

Personalized consolidation:
Use precision methods to select an additional agent



Toxicity could be avoided with sequential consolidation.

E.g. in DLBCL,
CHOP + Rituximab
is equally effective as
CHOP → Maintenance Rituximab

(Haberman, *Journal of Clinical Oncology*, **24**:3121)

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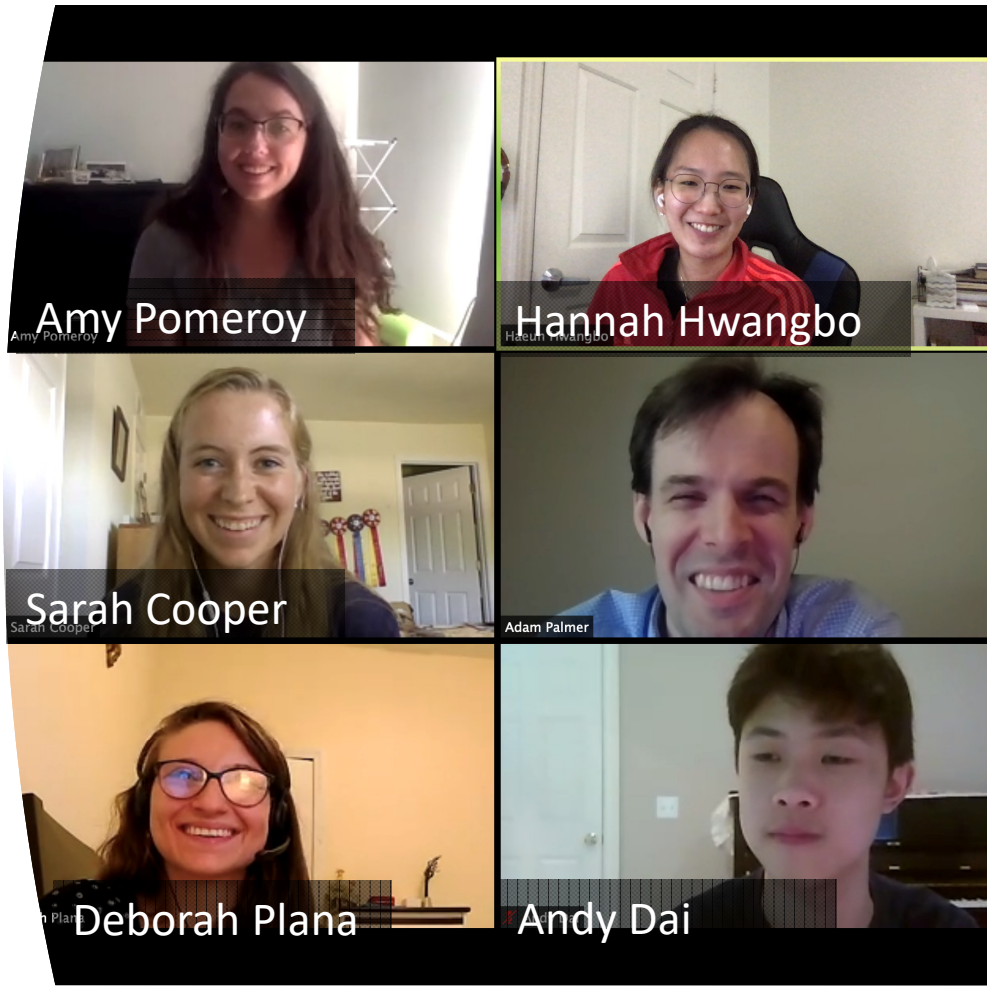

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