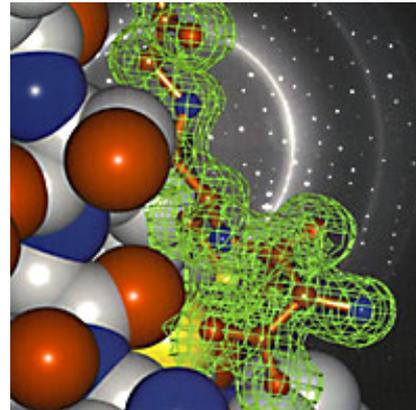
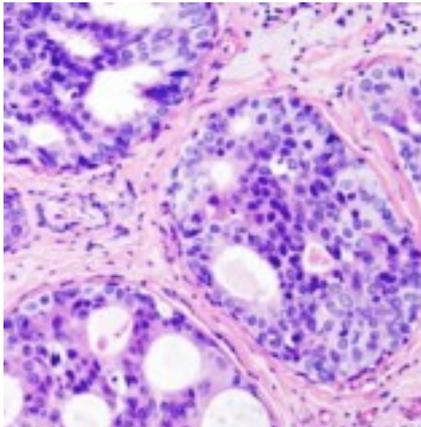


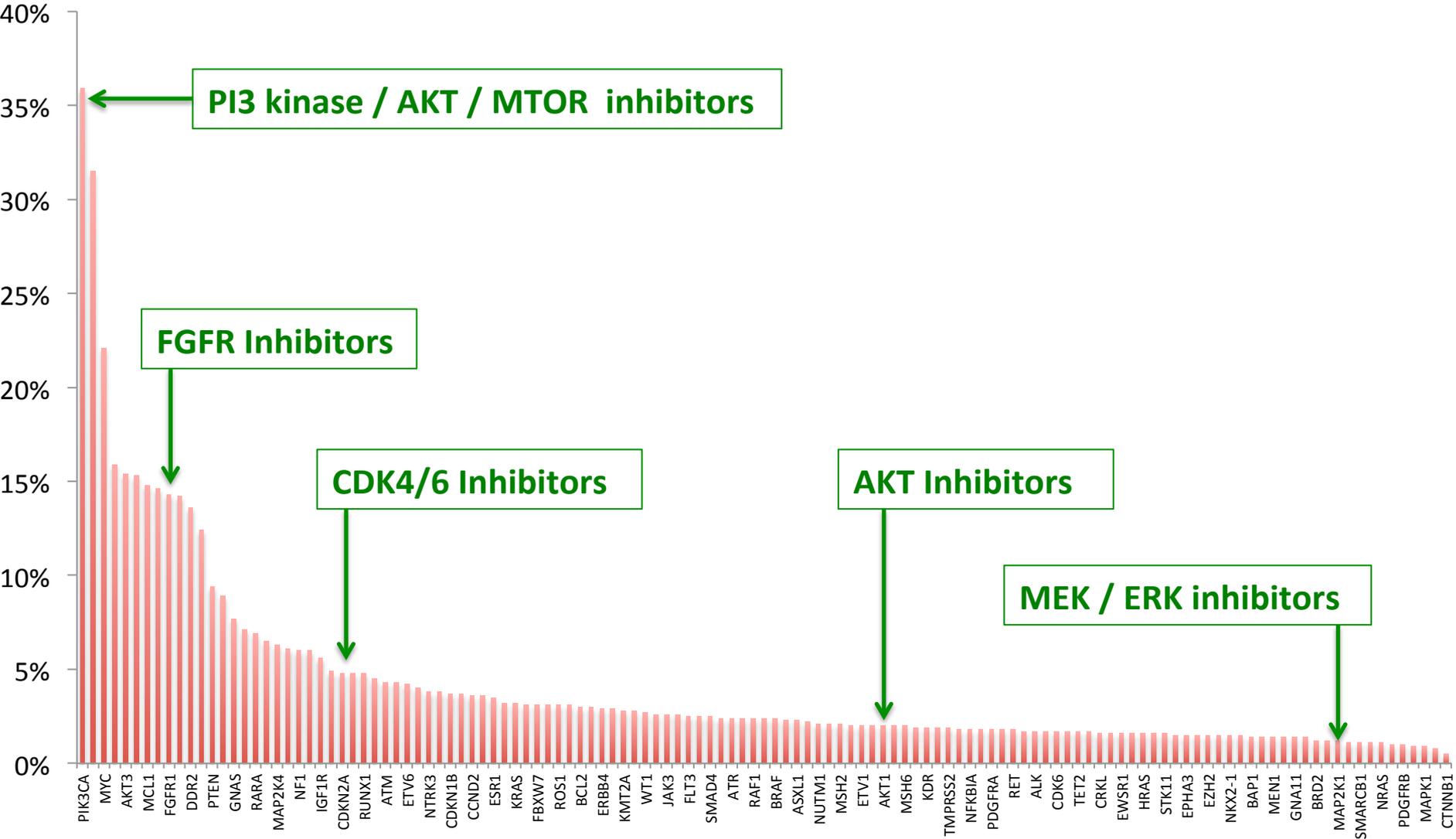
How Can We Move Forward With Combination Targeted Therapies In A Breast Cancer Genomically-Driven Trial?

Nikhil Wagle, MD

October 21 2014



Genomic Alterations in 128 Clinically Relevant Genes in 962 TCGA Breast Cancer Samples



Potential Genomic Targets in Breast Cancer

Selected genes with Mutations, Amplifications/Deletions, Rearrangements in Breast Cancer

ERBB2

PIK3CA
PTEN
AKT1
AKT2
AKT3
PIK3R1
INPP4B
MTOR
TSC1
TSC2

KRAS
NRAS
BRAF
MAP2K1
MAP3K1
NF1

FGFR1
FGFR2
FGFR3

CDKN2A
CDKN1B
CCND1
CCNE1
CDK4
RB1

BRCA1
BRCA2
ATM

EGFR

TP53
MDM2

MYC

KIT
NTRK3
NOTCH1

Anti-Her2 Therapies

FGFR Inhibitors

EGFR Inhibitors

Anti-p53 Strategies

PI3k / AKT / MTOR Inhibitors

CDK Inhibitors

Nutlins

Anti-MYC Strategies

RAF / MEK / ERK Inhibitors

PARP Inhibitors

Platinums

Others

Most Breast Tumors Harbor Multiple Targets

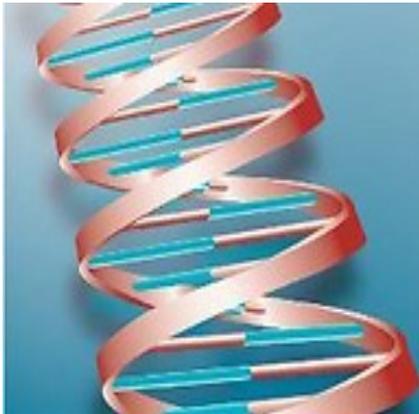
TCGA SAMPLE	POTENTIALLY CLINICALLY RELEVANT GENOMIC ALTERATIONS
A8-A06U	HER2 Amplification PIK3CA H1047R CyclinD1 Amplification CDKN2A/B Deletion TP53 R209fs
A2-A0D1	HER2 Amplification PIK3CA E545K EGFR Amplification MYC Amplification TP53 Q331*
A8-A08B	HER2 Amplification PIK3CA E545K AKT3 Amplification MYC Amplification BRCA2 V1270del

TCGA SAMPLE	POTENTIALLY CLINICALLY RELEVANT GENOMIC ALTERATIONS
D8-A1XT	HER2 Amplification FGFR1 Amplification CDKN2A/B Deletion TP53 A276P
E9-A1NG	KRAS G12V PIK3CA E545K AKT2 Amplification
E2-A159	PTEN Deletion RB1 L550fs MEK1 E203K TP53 V216M
A1-A0SI	PIK3CA H1047R RB1 S829* TP53 R175H

How should we decide what to target?



The goal of combination targeted therapies is to target the key genomic and molecular dependencies as well as overcome/prevent the emergence of resistance mechanisms



Nodes to Target with Combination Therapies

- 1) Primary Dependencies (ER, HER2)
- 2) Secondary / Additional Alterations (PIK3CA, FGFR1)
- 3) Mechanisms of Intrinsic/Adaptive Resistance
- 4) Mechanisms of Acquired Resistance

Overcoming Intrinsic/Adaptive Resistance with Combinations

- PI3Ki alone not usually highly effective in PIK3CA-mut breast cancer
- Mechanisms of intrinsic/adaptive resistance include MYC amplification, mTORC activation, others
- Combination **PI3Ki + mTORi** or **PI3Ki + CDK4/6i** effective *in vitro* and *in vivo* in overcoming PI3Ki-resistance

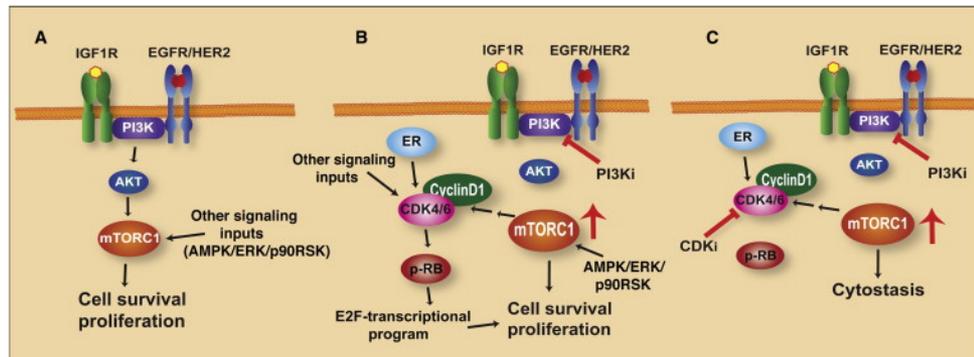


Image from Muranen, Meric-Bernstam, Mills, *Cancer Cell* 2014

Elkabets, Vora, et al, Science Trans Med, 2013

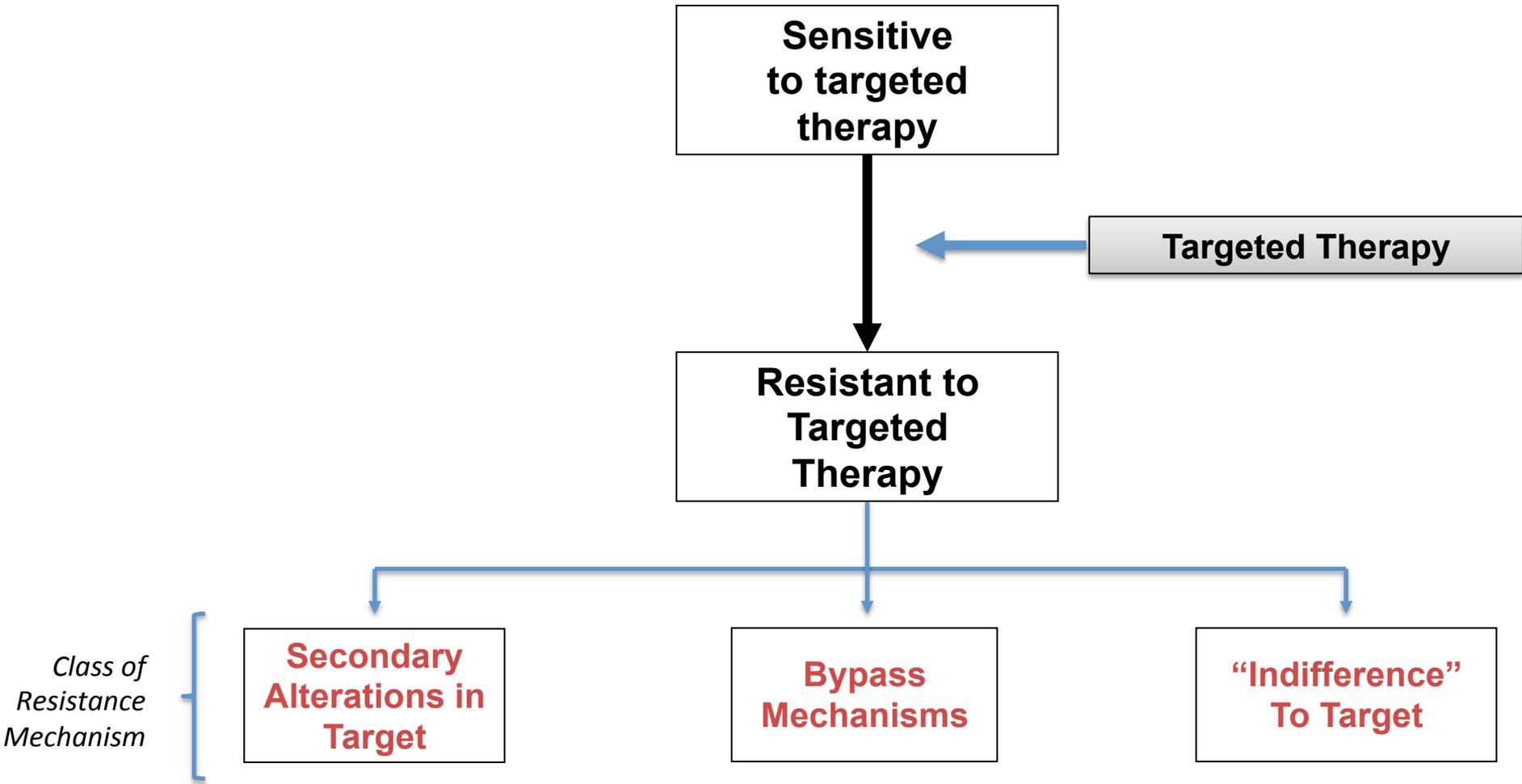
Vora et al, Cancer Cell, 2014

- Genomic profiling alone wouldn't dictate this combination – need to incorporate knowledge of intrinsic/adaptive resistance for specific alterations (e.g. PIK3CA)
- **Develop alteration-based rules** linking specific genomic alterations to rational combos

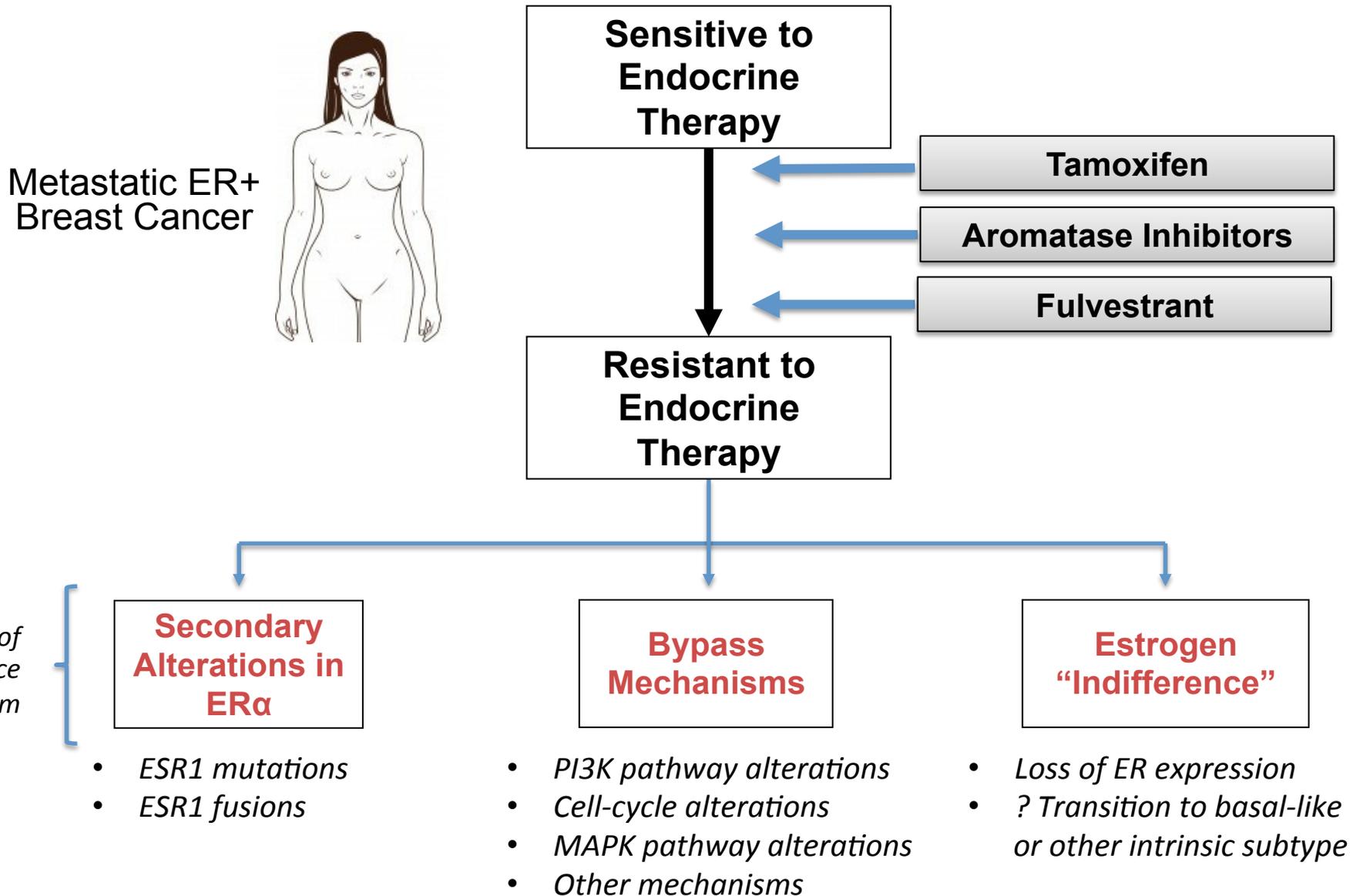
Addressing Acquired Resistance

- Following a response to single-agent targeted therapy, resistance almost invariably occurs
- **Option #1: Re-biopsy and profile a tumor at the time of resistance and target resistance mechanisms**
 - However, addressing one resistance mechanism at a time allows the tumor to continue to evade
 - Tumor heterogeneity makes it likely that other simultaneous resistance mechanisms won't be detected
- **Option #2: Predict the resistance mechanisms and address as many as possible up front to preempt resistance**

A Model for Resistance to Targeted Therapies

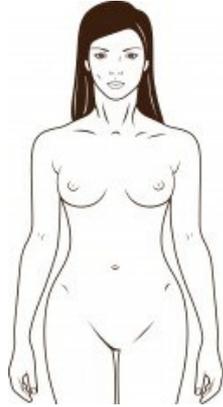


Proposed Classes of Endocrine Resistance



Proposed Classes of Resistance to HER2 Inhibition

Metastatic ER+
Breast Cancer



**Sensitive to
Anti-HER2
Therapy**

Anti-HER2 Therapies

**Resistant to
Anti-HER2
Therapy**

**Secondary
Alterations in
HER2**

- *HER2 mutations*

**Bypass
Mechanisms**

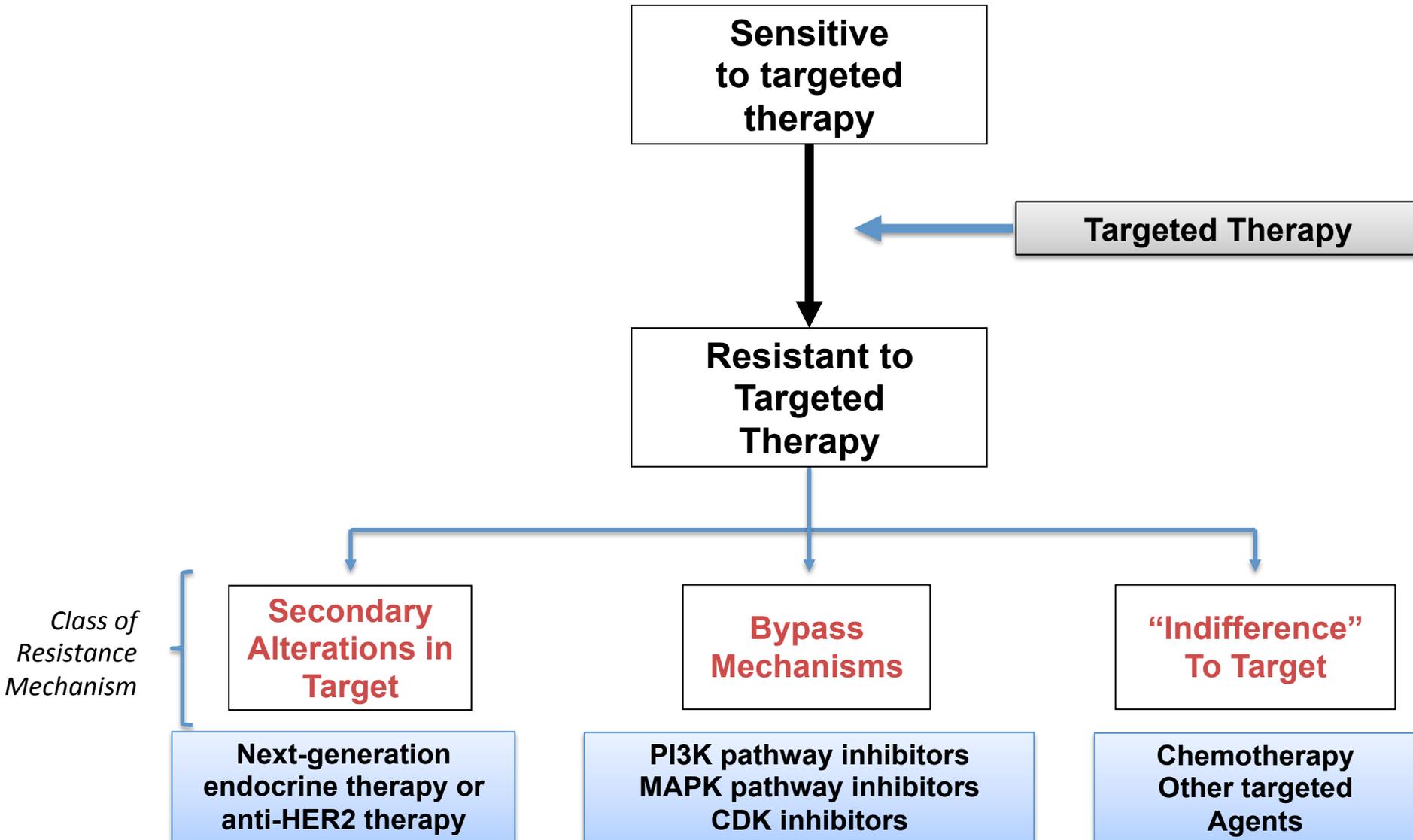
- *PI3K pathway alterations*
- *MAPK pathway alterations*
- *Other mechanisms*

**HER2
“Indifference”**

- *Loss of HER2 expression*
- *? Transition to basal-like or other intrinsic subtype*

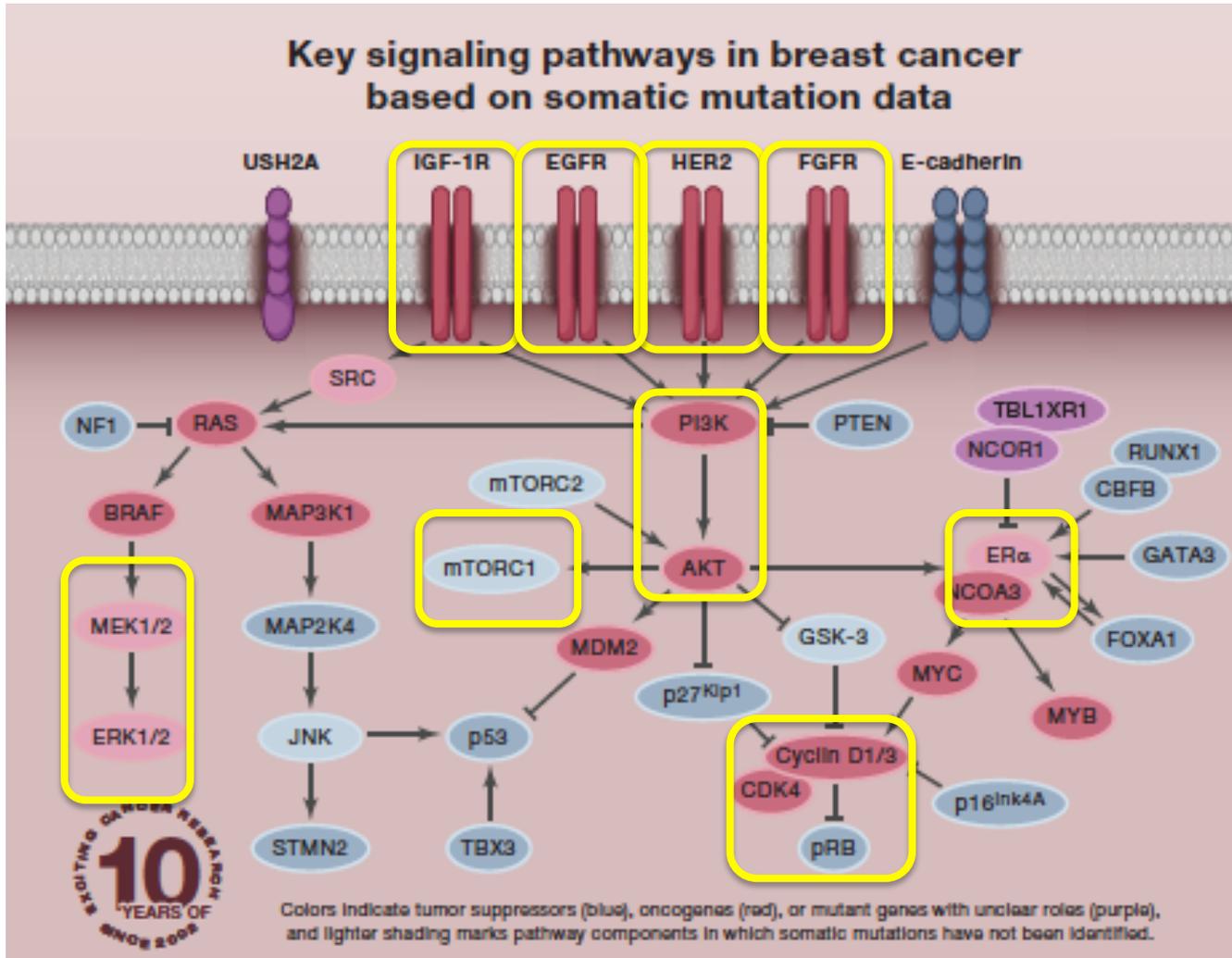
*Class of
Resistance
Mechanism*

Targeting Multiple Modes of Acquired Resistance



Targeting Multiple Nodes with Combination Therapies

Key signaling pathways in breast cancer based on somatic mutation data



Anti-HER2 therapy
Endocrine therapy

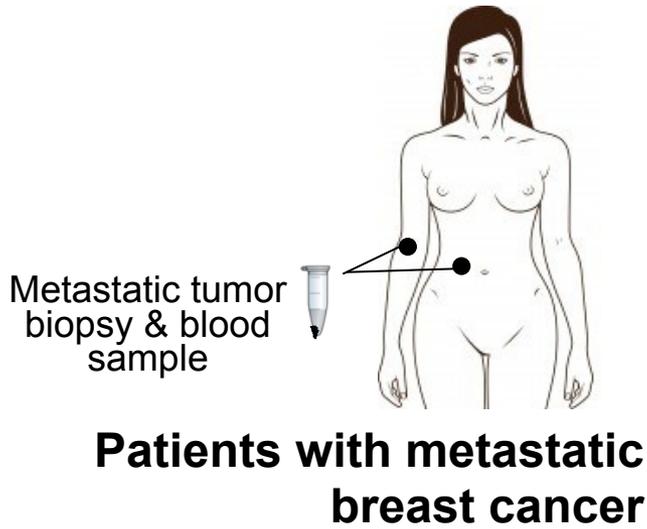
PI3K-pathway inhibitors
CDK inhibitors
mTOR inhibitors
IGF1-R antibodies

EGFR inhibitors
FGFR inhibitors
MAPK-pathway inhibitors

PARP inhibitors
Chemotherapy

Image from Polyak and Filho, Cancer Cell, 2012

GENOMIC AND MOLECULAR PROFILING



Clinical Trials of Combinations Specific to Base Genotypes

**ER+
HER2-**

**ER-
HER2+**

**TNBC
PIK3CA mut**

**TNBC
MAPK mut**

Additional Targetable Alterations

**Combo #1
(e.g. SERM/AI/
SERD, PI3Ki,
CDK4/6i)**

**Combo #2
(e.g. anti-HER2,
PI3Ki, CDK4/6,
IGF1-R)**

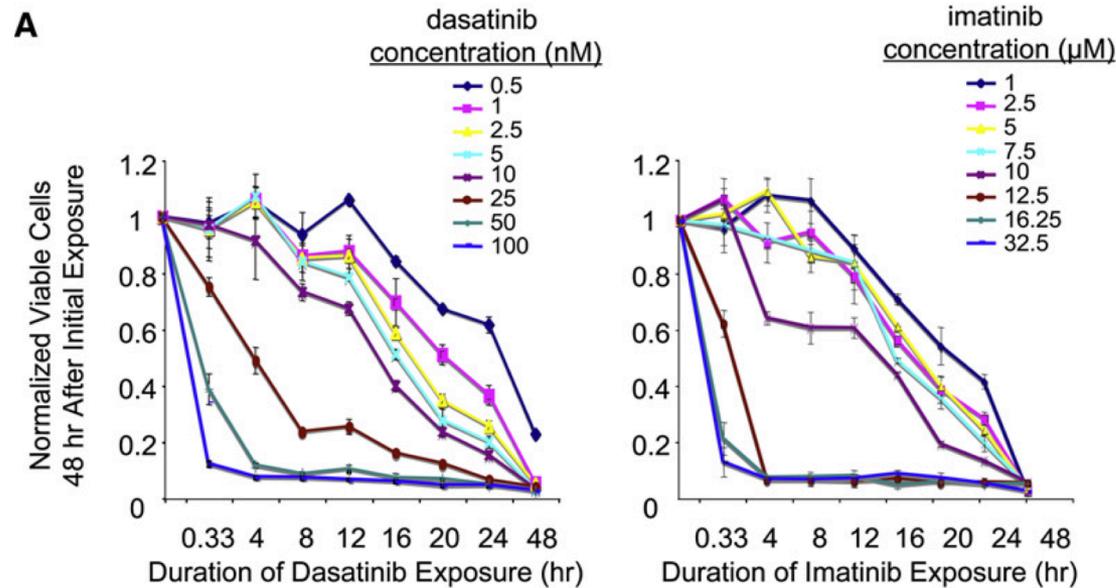
**Combo #3
(e.g. PI3Ki,
CDK4/6, mTOR,
IGF1-R)**

**Combo #4
(e.g., MAPKi
combinations)**

**Basket Trials
(e.g. MEKi, mTORi,
or combinations)**

Creating Combination Targeted Therapy *Regimens*

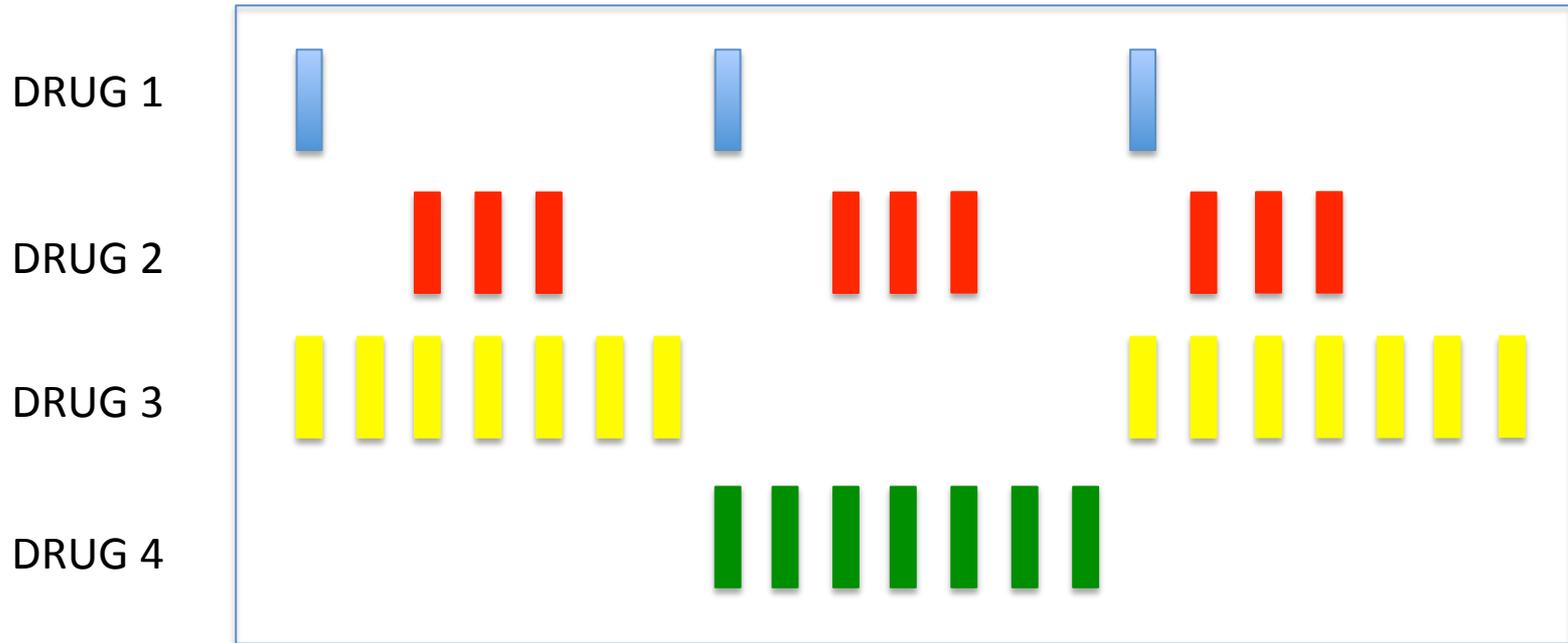
- Major issue for combining targeted therapies is additive & overlapping toxicities
- Pre-clinical and clinical evidence that for some agents (dasatinib, erlotinib), high dose over shorter interval may be as effective as continuous dosing



Shah et al., Cancer Cell, 2008

- Such windows *off therapy* may provide opportunities for intercalating other therapies and offsetting toxicities
- Preclinical experiments can be designed to take advantage of drug half-life and knowledge of intrinsic and acquired resistance to assemble rational regimens that don't require continuous dosing of 3+ agents

Creating Combination Targeted Therapy *Regimens*



- MTDs of individual agents will need to be determined at intermittent schedules
- Combinations of multiple intermittent drugs can then be tested

Monitoring and Translational Science

- Trials would benefit from serial monitoring with blood draws and periodic tumor sampling (biopsies, CTCs, cfDNA, etc)
- **Timepoints:**
 - Baseline
 - Early On-Treatment (before response)
 - Late On-Treatment (after response)
 - Resistance / Progression
- **Testing:**
 - **Genomics** (WES, RNASeq) to monitor emerging resistance mechanisms
 - **Pharmacology** studies for drug and drug metabolite levels
 - **Pharmacodynamic testing** using protein levels, IHC, RNASeq, single-cell RNASeq

*Initially would focusing on improving regimens, understand resistance
In the future, real-time monitoring could directly inform regimen*

Summary

- Our knowledge of mechanisms of therapeutic resistance informs our choice of agents to use in combination trials
- Upfront genomic and molecular profiling may help us understand which combination regimen(s) to give – though heterogeneity and simultaneous resistance mechanisms might require fewer, more “universal” regimens
- To develop the effective and tolerable combination regimens, we will need to identify optimal doses and schedules
- Continuous monitoring and translational science will help to refine and improve combination regimens – and might ultimately be useful in *real time* to adjust regimens over the course of therapy