

# **Molecular mechanisms of endocrine resistance and new scenarios for personalizing treatment in patients subpopulation**

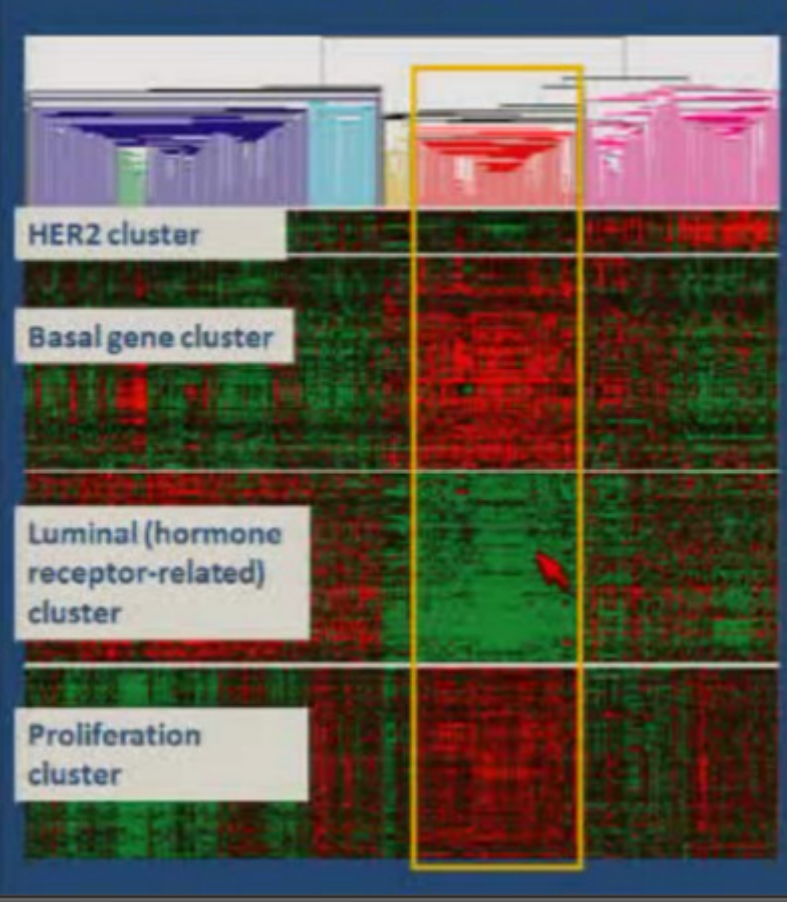
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# Drug Development

One drug for the whole

Angiogenesis inhibitors  
 Biphosphonates  
 Stroma-targeting drugs  
 New chemotherapies  
 Modulation of drug sensitivity (incl IGF1r inh)  
 Cancer vaccines



Low benefit for the whole

Expected effect

Subtype-specific  
 First-in class

Second-in class  
 In a specific subtype:  
*To do better*  
*To reverse resistance*

Trastuzumab  
 T-DM1

mTOR inhibitors  
 small TKI  
 Pertuzumab/trast

PARP inh ?  
 Cisplatin?

CHK1 inh ?

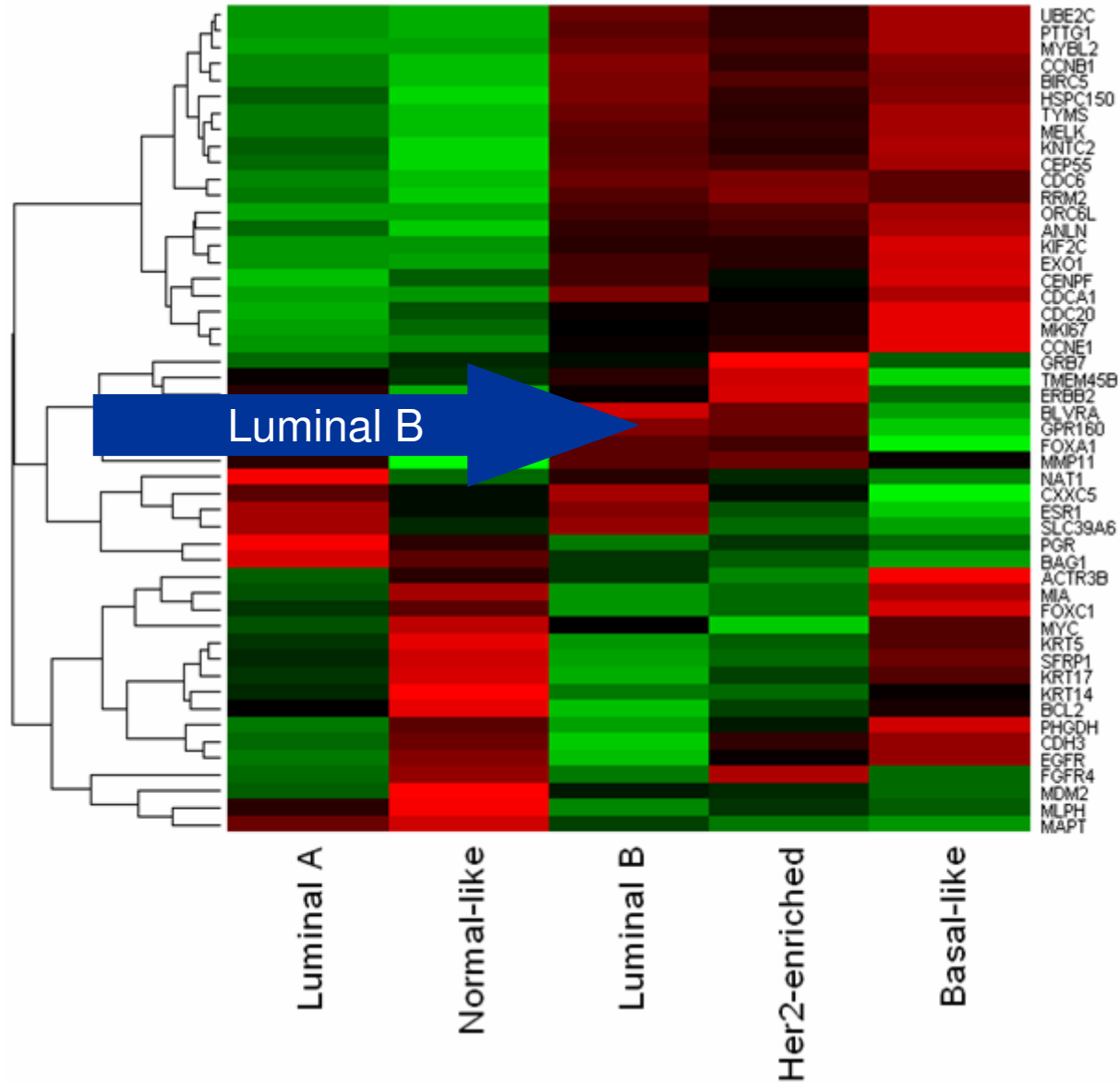
TAM

AI +  
 everolimus? TKI ?  
 or  
 new subdivision  
 according to  
 molecular events

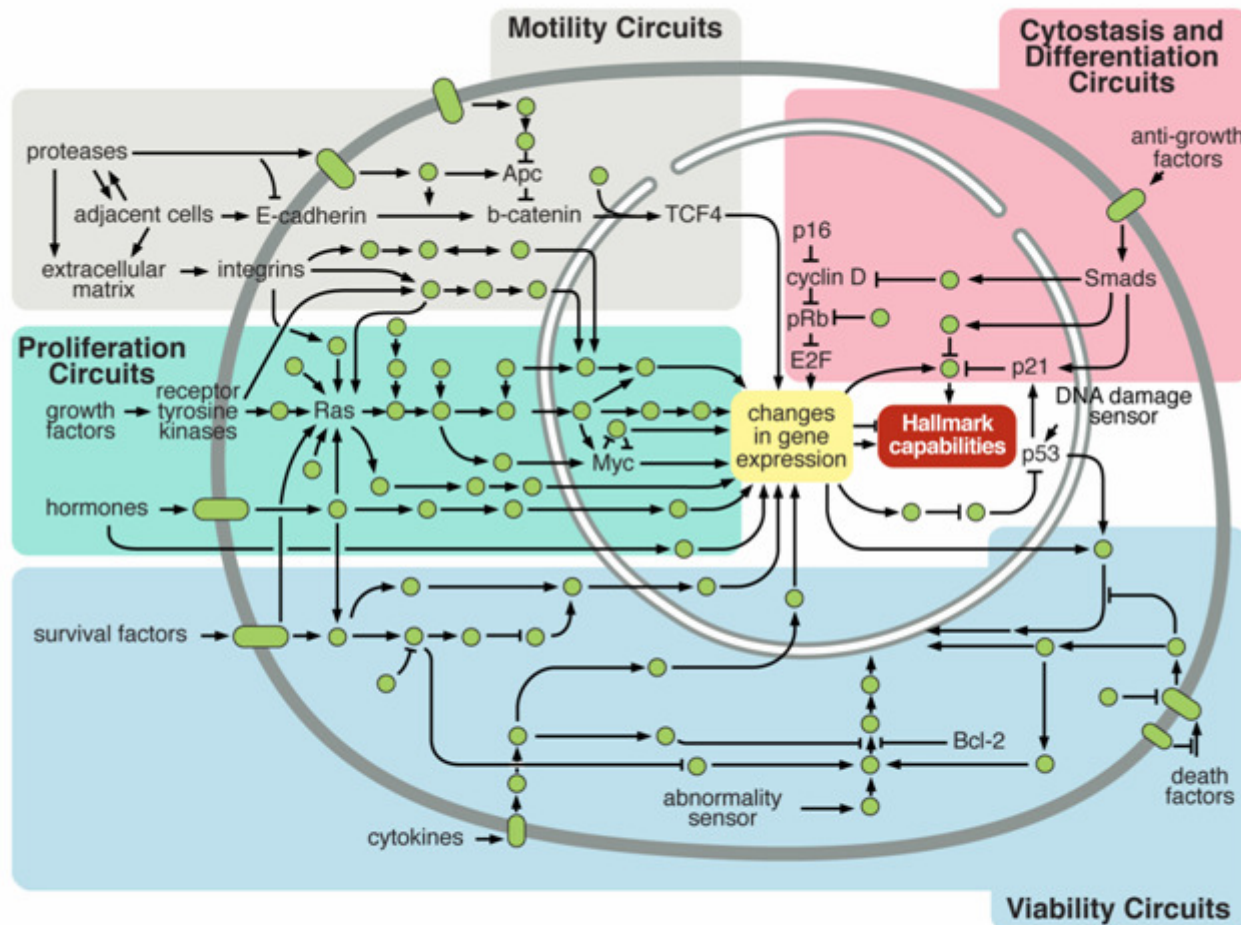
Small population  
 High sensitivity

Molecular Niche  
 Global trials

# Drug Development

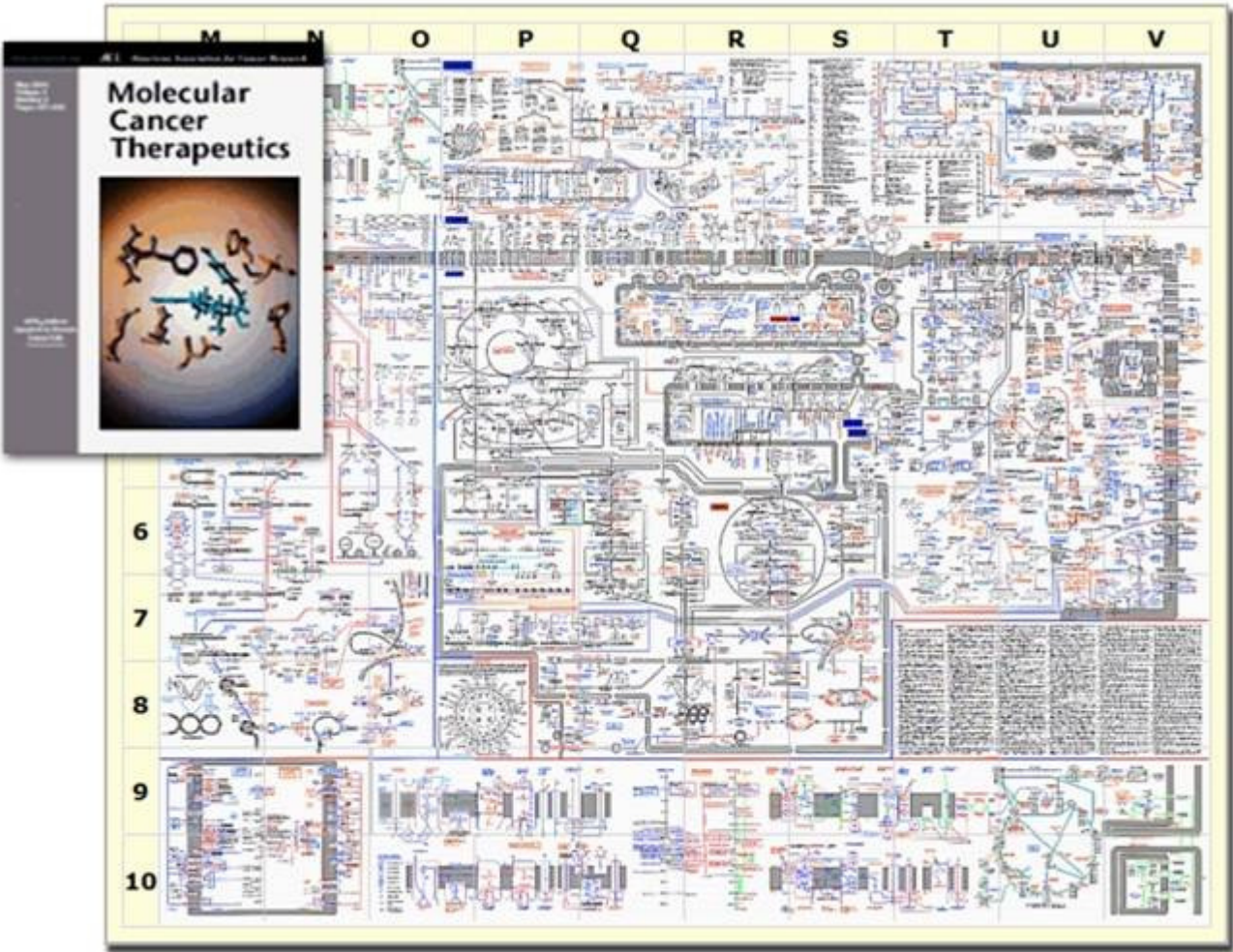


# Overcoming Endocrine Resistance



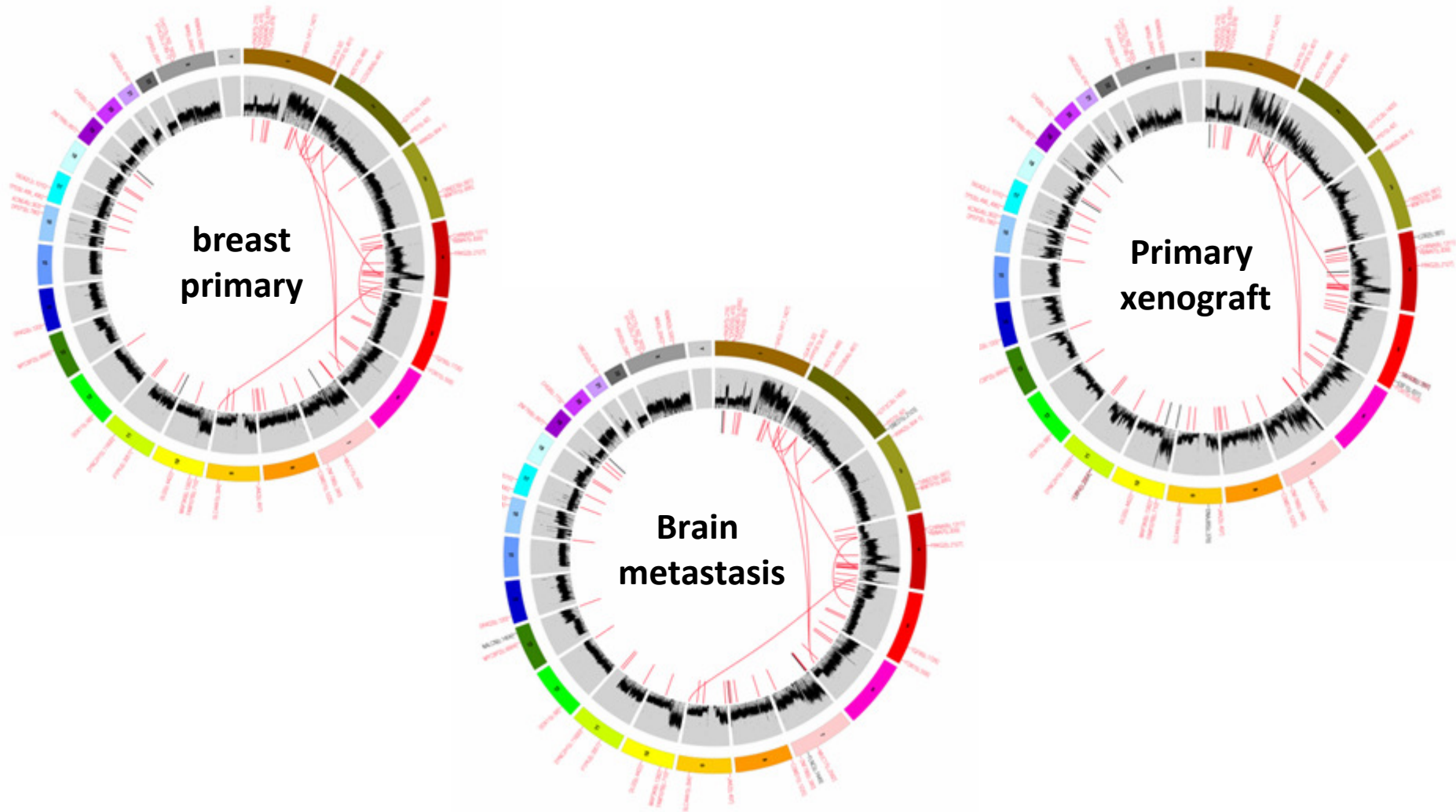
Hanahan and Weinberg, 2011

# Understanding the wiring diagram



# Genome Remodeling in a Basal-like Breast Cancer Metastasis and Xenograft

L. Ding, M. J. Ellis, .... and E.R. Mardis, Nature Vol 464, 2010



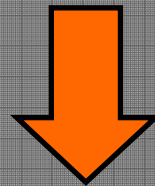
Three genomes, 50,000,000 billion base pairs of sequence  
50 somatic mutations in the primary, with 2 new mutations in the brain metastasis

**Luminal-B Breast Cancer:  
Who will be the First-in-class?**

# New drugs in Luminal B Breast cancers

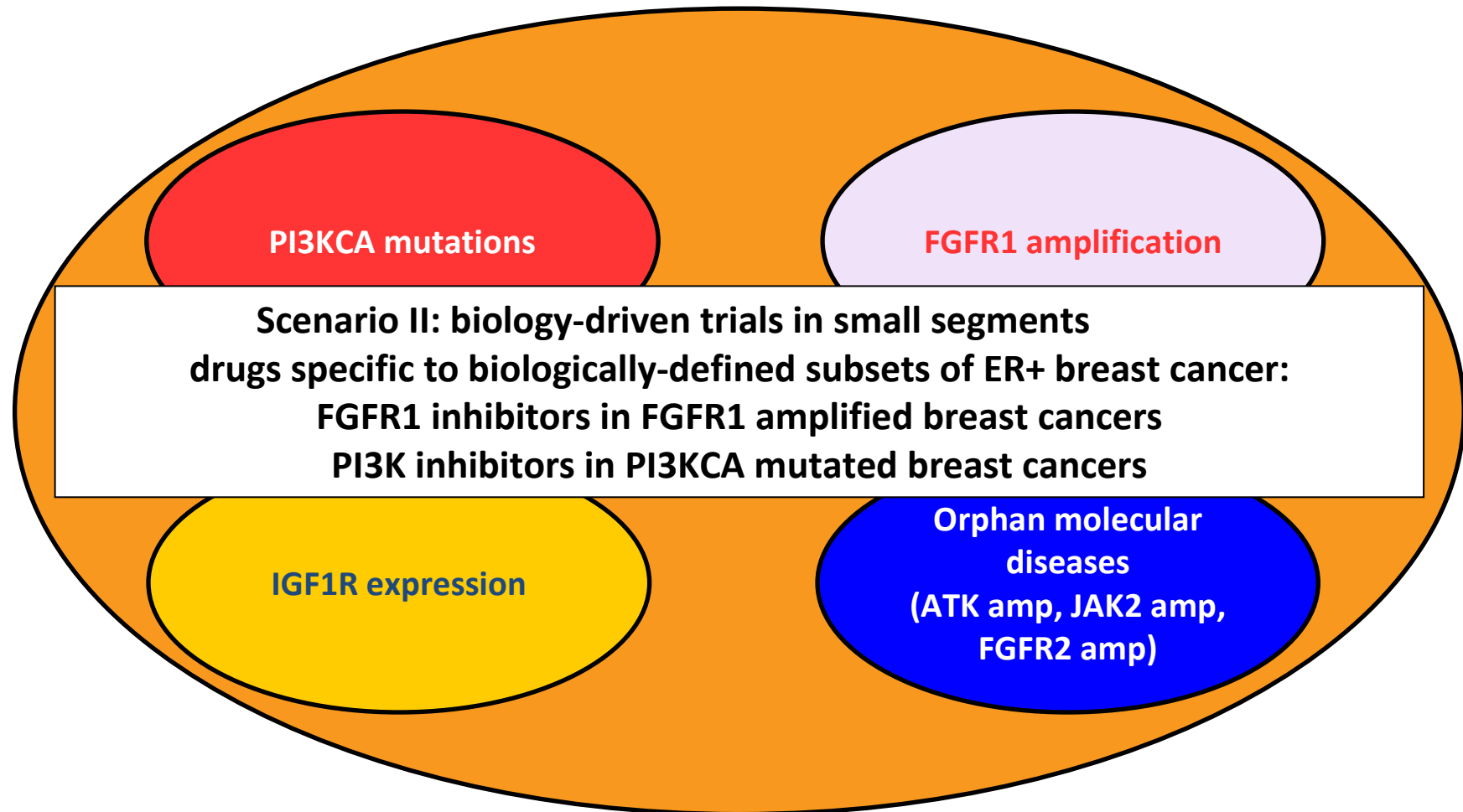
Scenario I:

First-in-class drug for the whole luminal B breast cancer:  
Intracellular kinase inhibitors: mTOR inhibitors (everolimus)  
Tyrosine kinase inhibitors: EGFR, IGF1R inhibitors



Retrospective identification of predictors

# New drugs in Luminal B Breast cancers



# Overcoming Endocrine Resistance

1. Develop more effective ways to antagonize estrogen.
2. Understand mechanisms of resistance and develop strategies to overcome them.
3. Develop better biomarkers to predict estrogen dependence (response to therapy).
4. Will require serial tumor biopsies.
5. Understand genetic makeup of the patient and tumor.

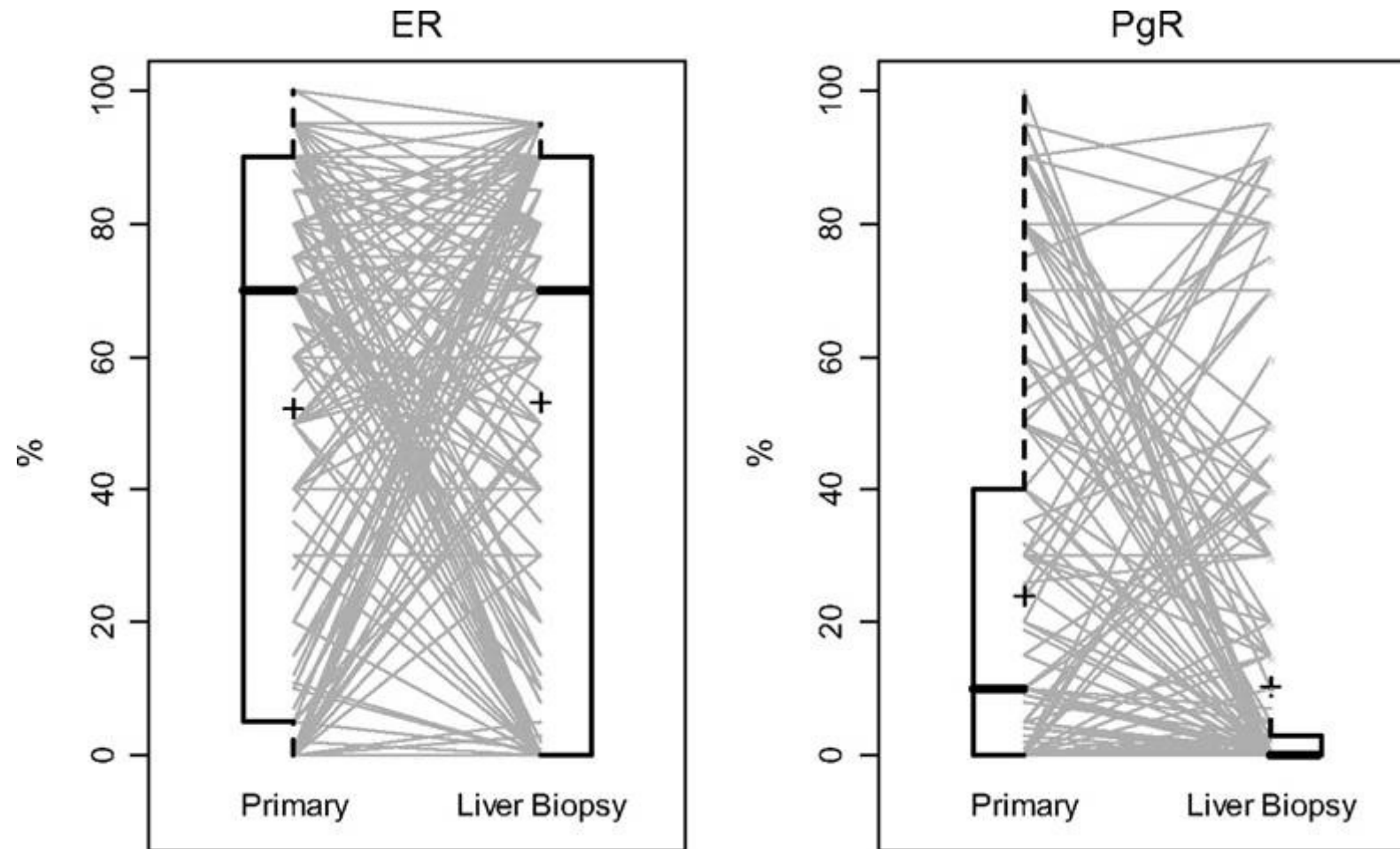
# Clinical Clues to Mechanisms of Resistance

- Loss of ER expression.
- Multiple responses to sequential endocrine therapies over time; “drug” resistance but not loss of E dependence.
- ER level decreases over time; gradual loss of E dependence; responses are shorter and less frequent.
- Tumors with high HER2 or EGFR have lower ER and PR and less responsiveness to endo therapy.
- Eventual loss of E dependence even though ER is still present.

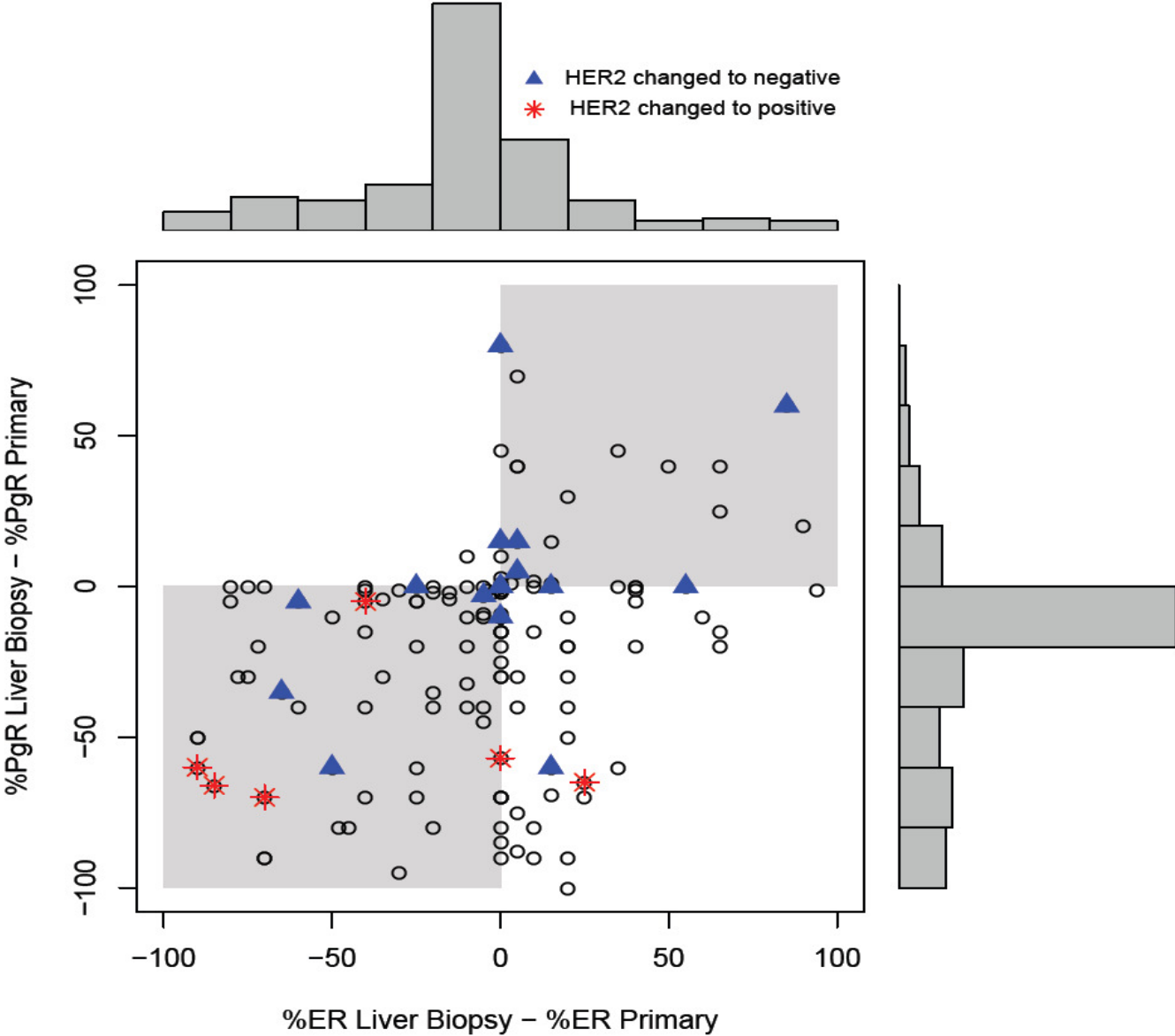
# Clinical Clues to Mechanisms of Resistance

<b>ER</b>	<b>Liver biopsy</b>		<b>Total</b>
	<b>Negative</b>	<b>Positive</b>	
<b>Primary</b>			
<b>Negative</b>	43 (74.1%)	15 (25.9%)	58 (100%)
<b>Positive</b>	22 (11.2%)	175 (88.8%)	197 (100%)
<b>Total</b>	67	188	<b>255</b>

# Clinical Clues to Mechanisms of Resistance



# Clinical Clues to Mechanisms of Resistance



# Clinical Clues Conclusion

- The tumor evolves and activates other survival pathways (**escape pathways**) to bypass the E block.
- What are these escape pathways and can we target them for better treatment?

# Endo Therapy Plus EGFR TKI

- Delay in resistance in mouse models but no tumor eradication when HER2 is not amplified
- Some patients may benefit from this approach
- Benefit is modest
- May be more than one escape pathway functioning
- Other escape pathways?

# Potential Escape Pathways

1. Growth factors: EGF, HER2, IGFR
2. Integrins: FAK, SRC
3. PI3K/AKT
4. MEK/MAPK
5. Stress kinases: p38MAPK; HIF1,2a; JNK/AP-1

# Oxidative Stress and Endocrine Resistance

- Tamoxifen can alter the redox status of the cell both as an oxidant and as an antioxidant
- Resistance to endocrine treatment is associated with oxidative stress (Schiff R *et al.*, JNCI, 2000)
  - increased antioxidant enzymes
  - increased lipid peroxides
  - increased p-JNK
  - increased p-cJun
  - increased AP-1 transcriptional activity

# Conclusions

- **Multiple** survival pathways can potentially cause resistance to endo therapy.
- Stress pathways (**AP-1**) are important in preclinical models.
- AP-1 inhibition **potentiates** the effect of endocrine treatment and circumvents endocrine resistance.
- The AP-1 TF plays a key role in endocrine resistance, presumably via its role in redirecting ER-DNA binding and gene transcription.
- Drugs **targeting AP-1** deserve study in this setting.
- Overcoming endo therapy resistance may require **inhibition of multiple escape pathways** for optimal treatment.
- **Biopsies of endocrine resistant tumors** from patients are needed to confirm mechanisms of resistance.

**Thank you**