Drilling Down on Molecular Targeted Approaches to Therapy

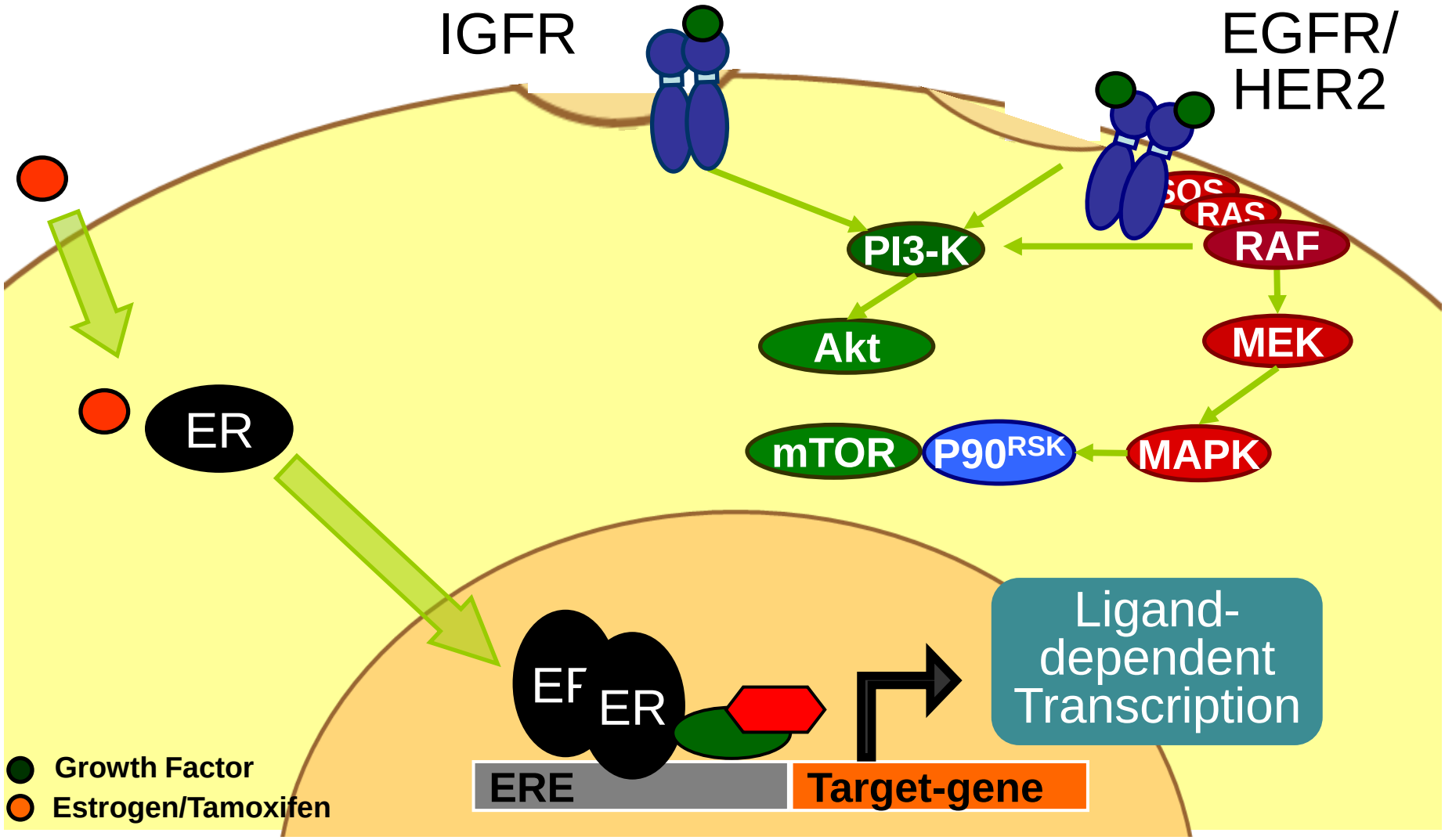
Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine
Barts Cancer Institute, St Bartholomew's Hospital
Queen Mary University of London

Molecular Targeted Approaches to Therapy in MBC

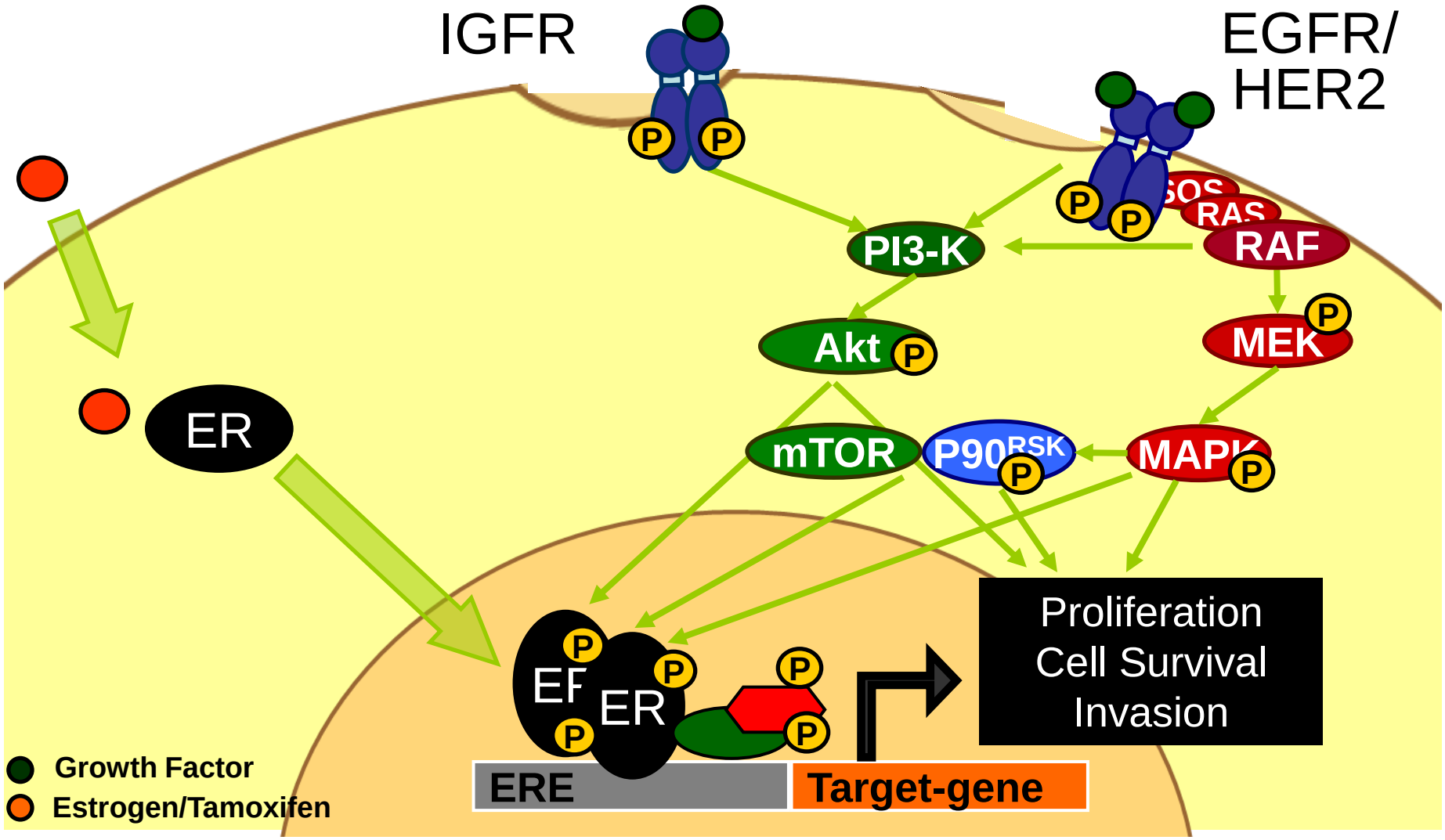
- Key molecular pathways in MBC
  - ER signaling, PI3K/mTOR, cyclin D/CDK4/6
  - HER2 and HER3
  - DNA damage repair
  - Immune checkpoints
- Pathway adaptation over time and therapeutic implications
- Mutation analysis and biomarkers to select targeted treatments

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



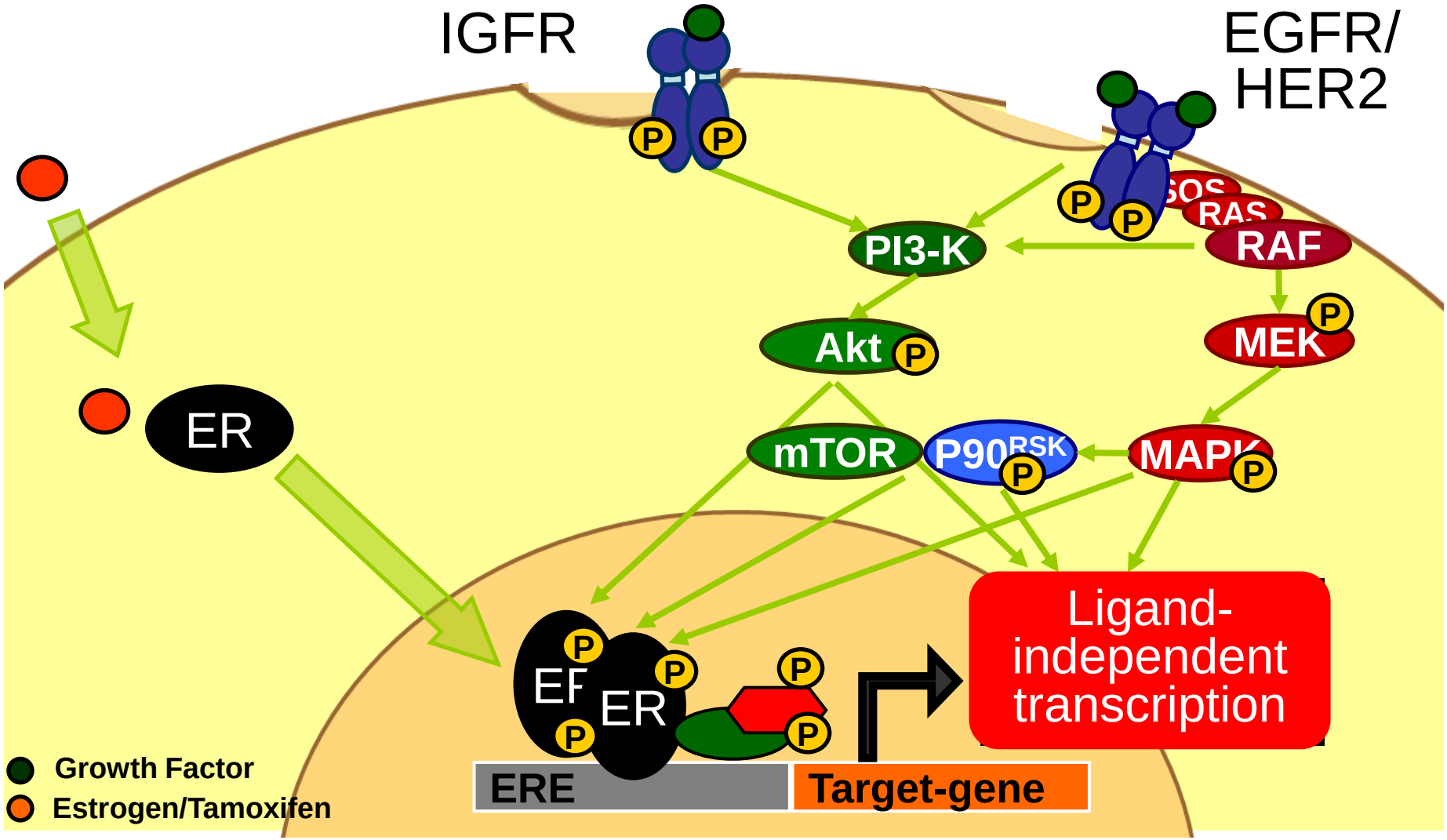
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



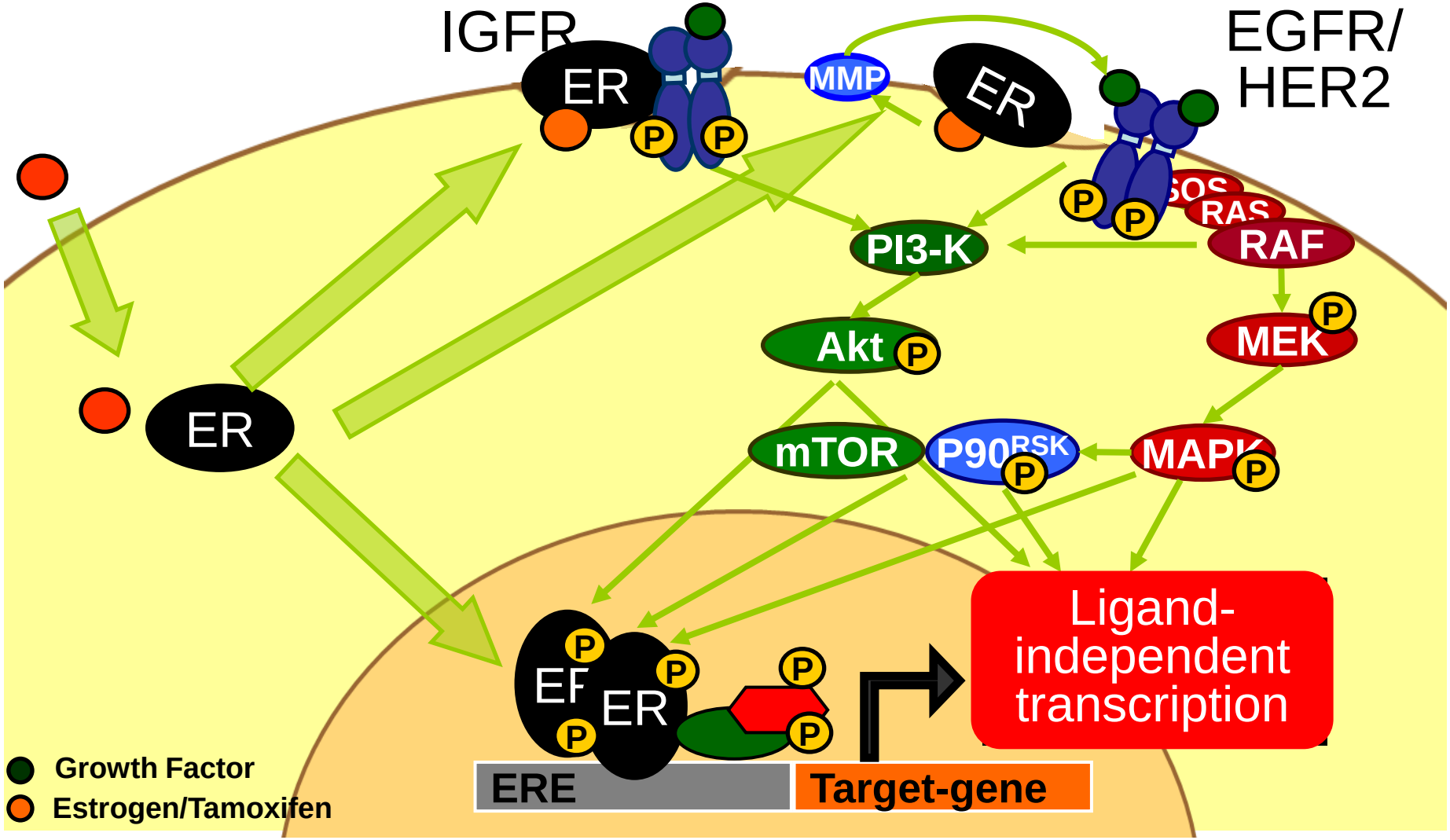
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



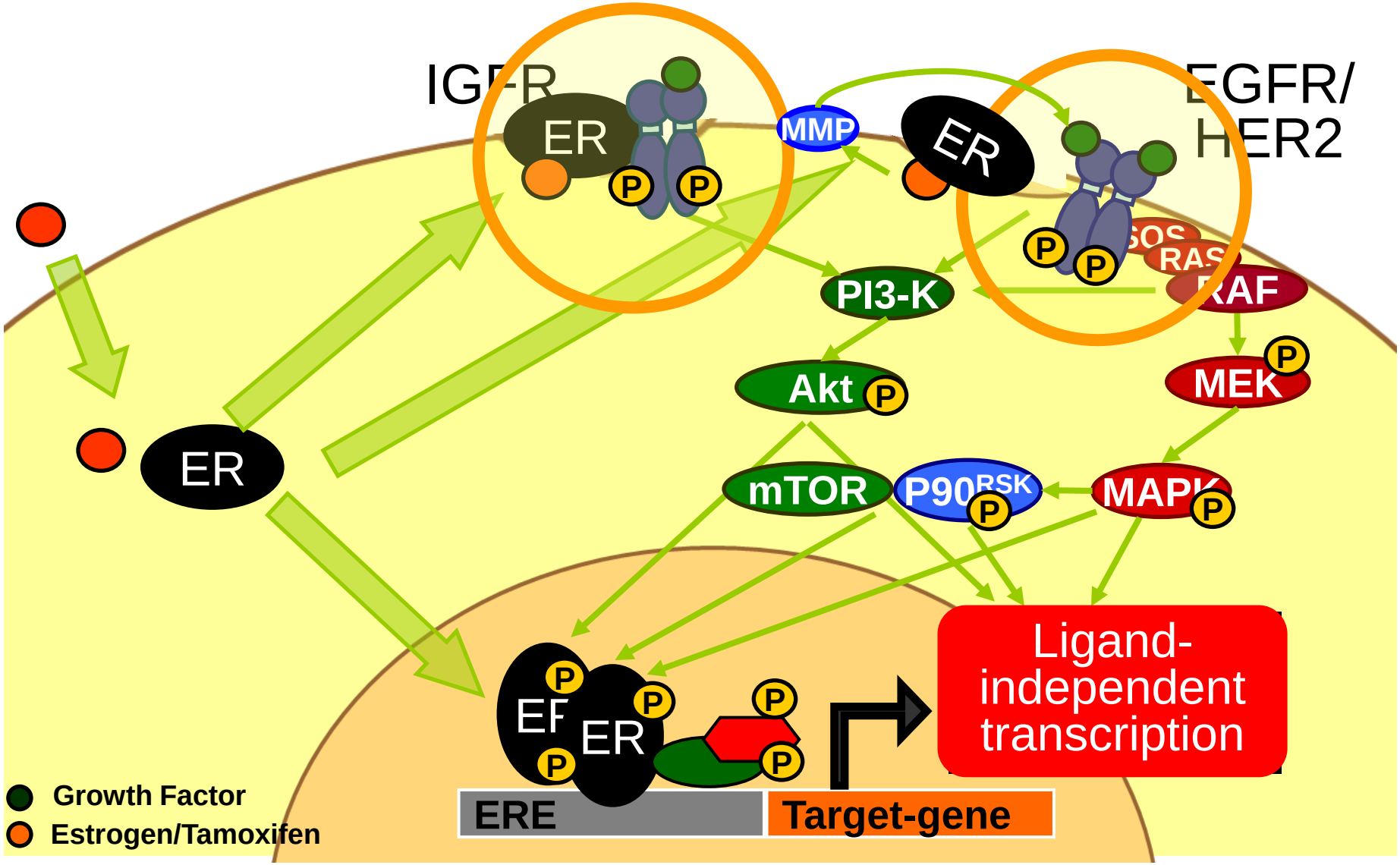
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



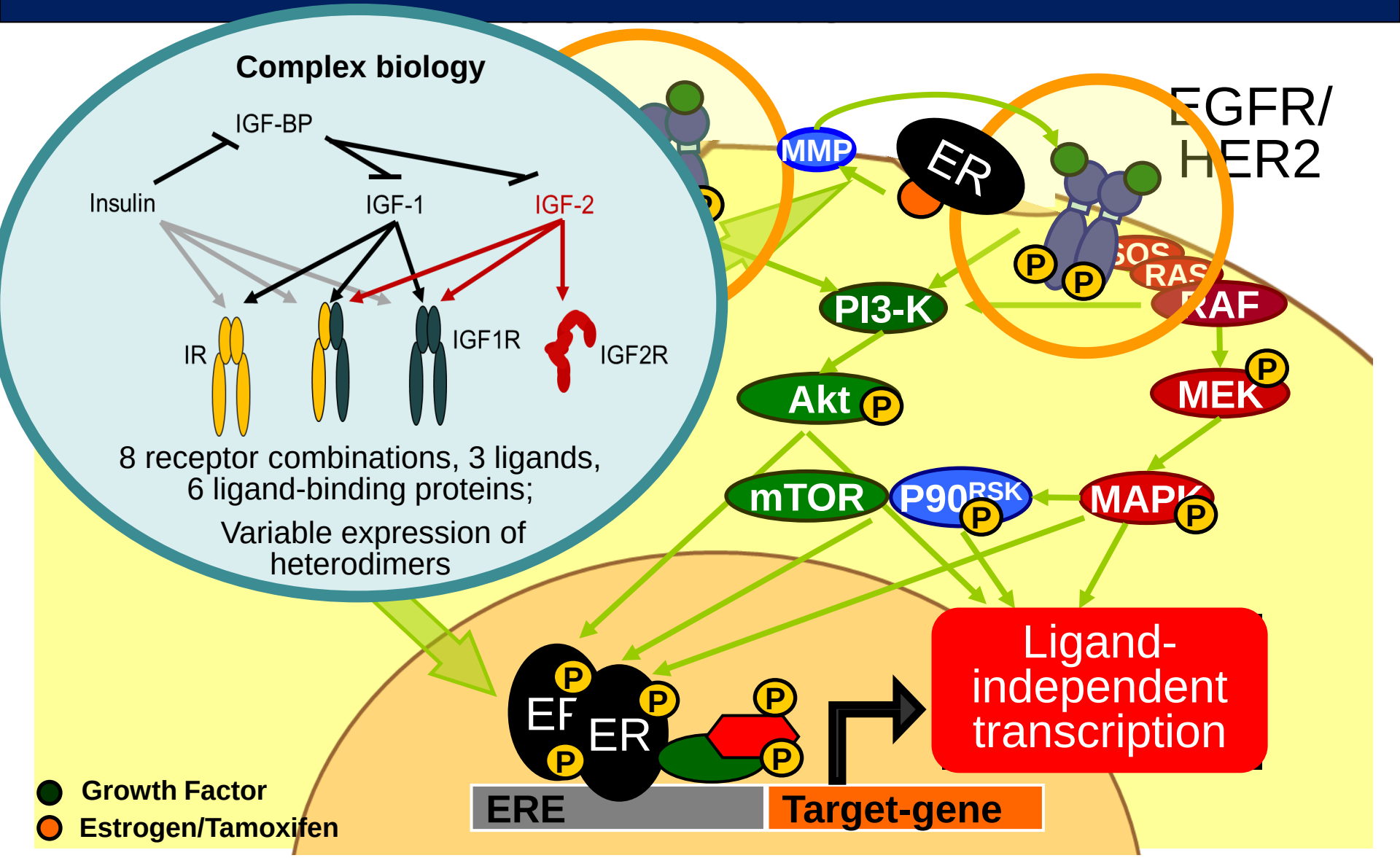
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



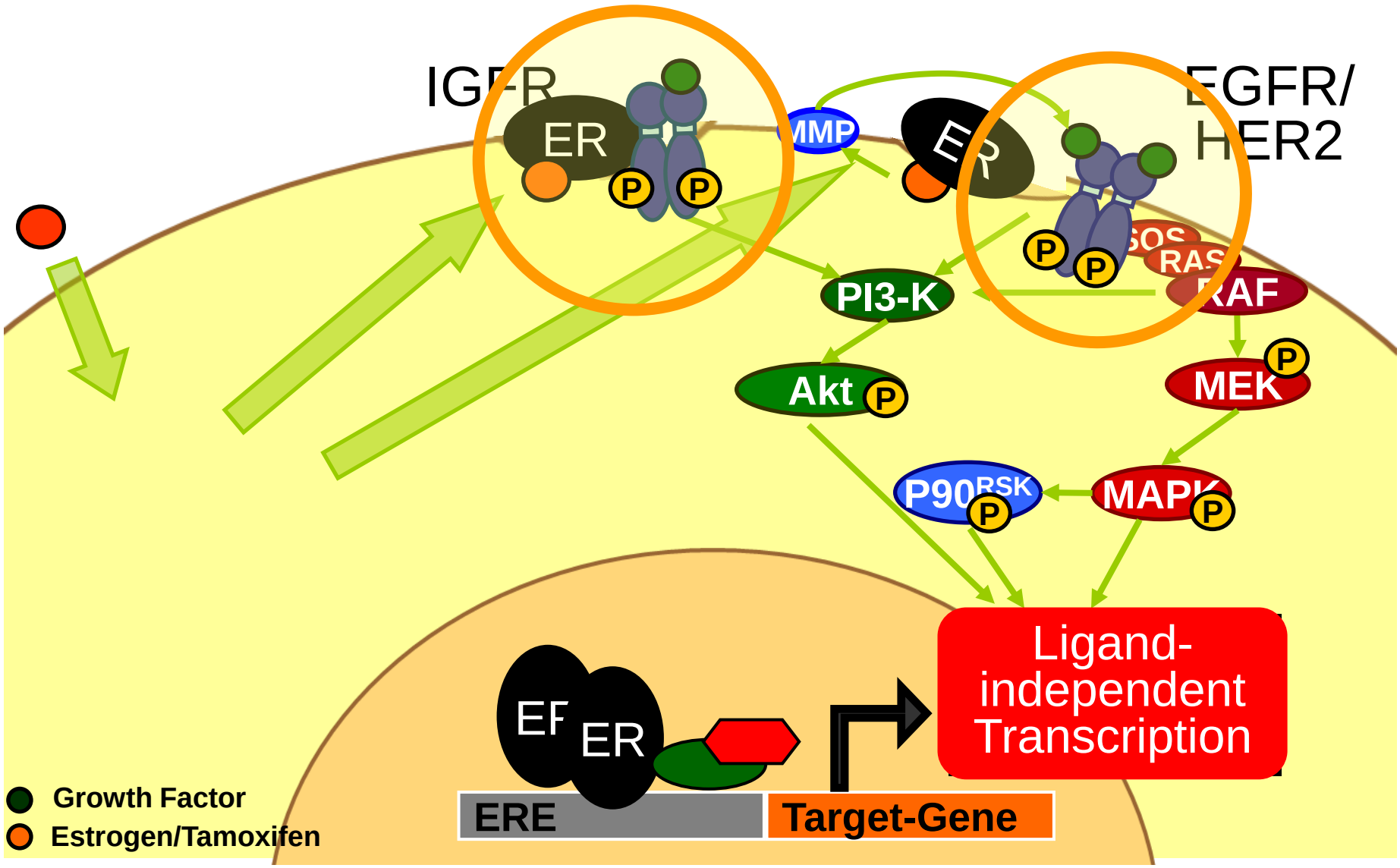
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



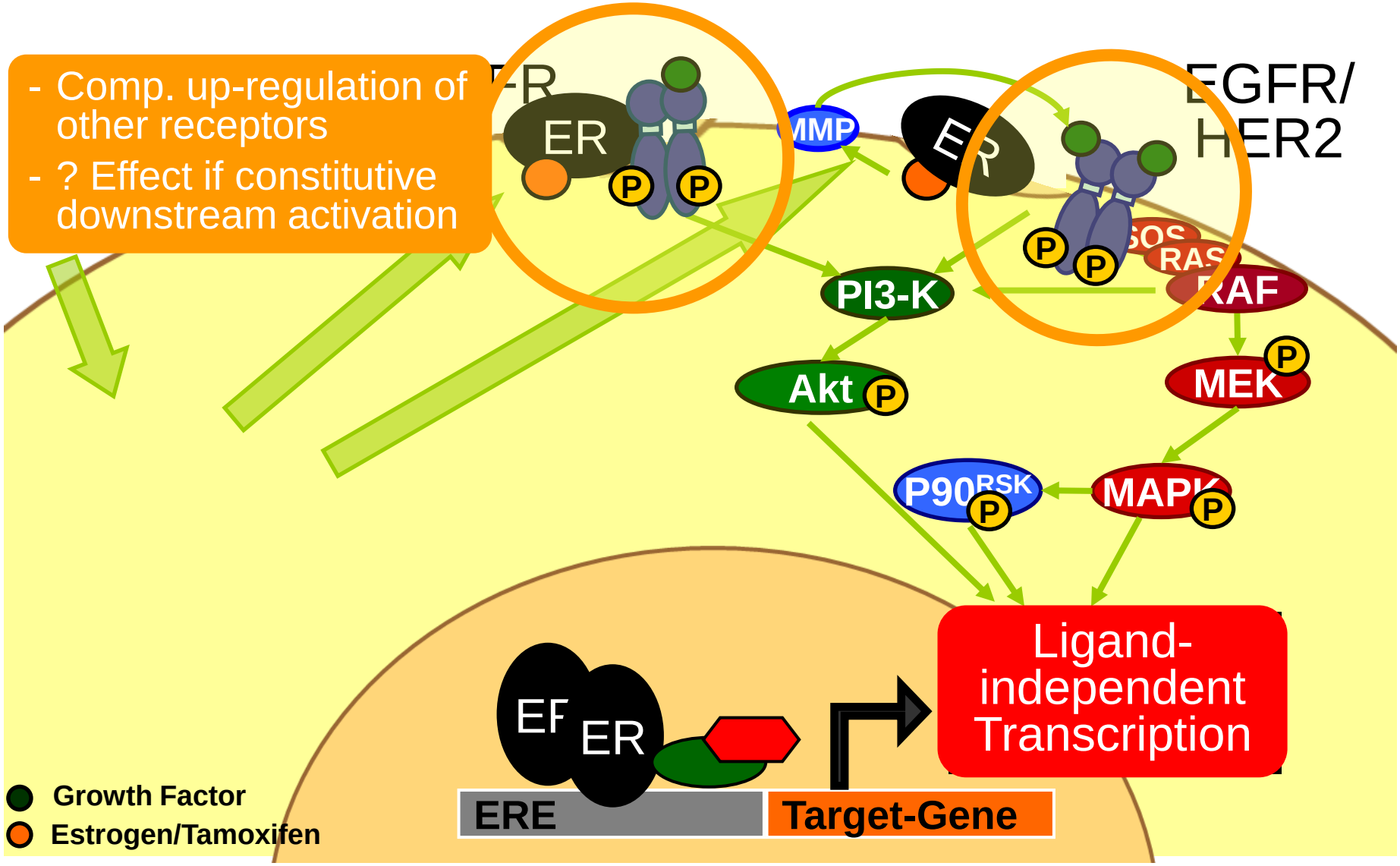
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



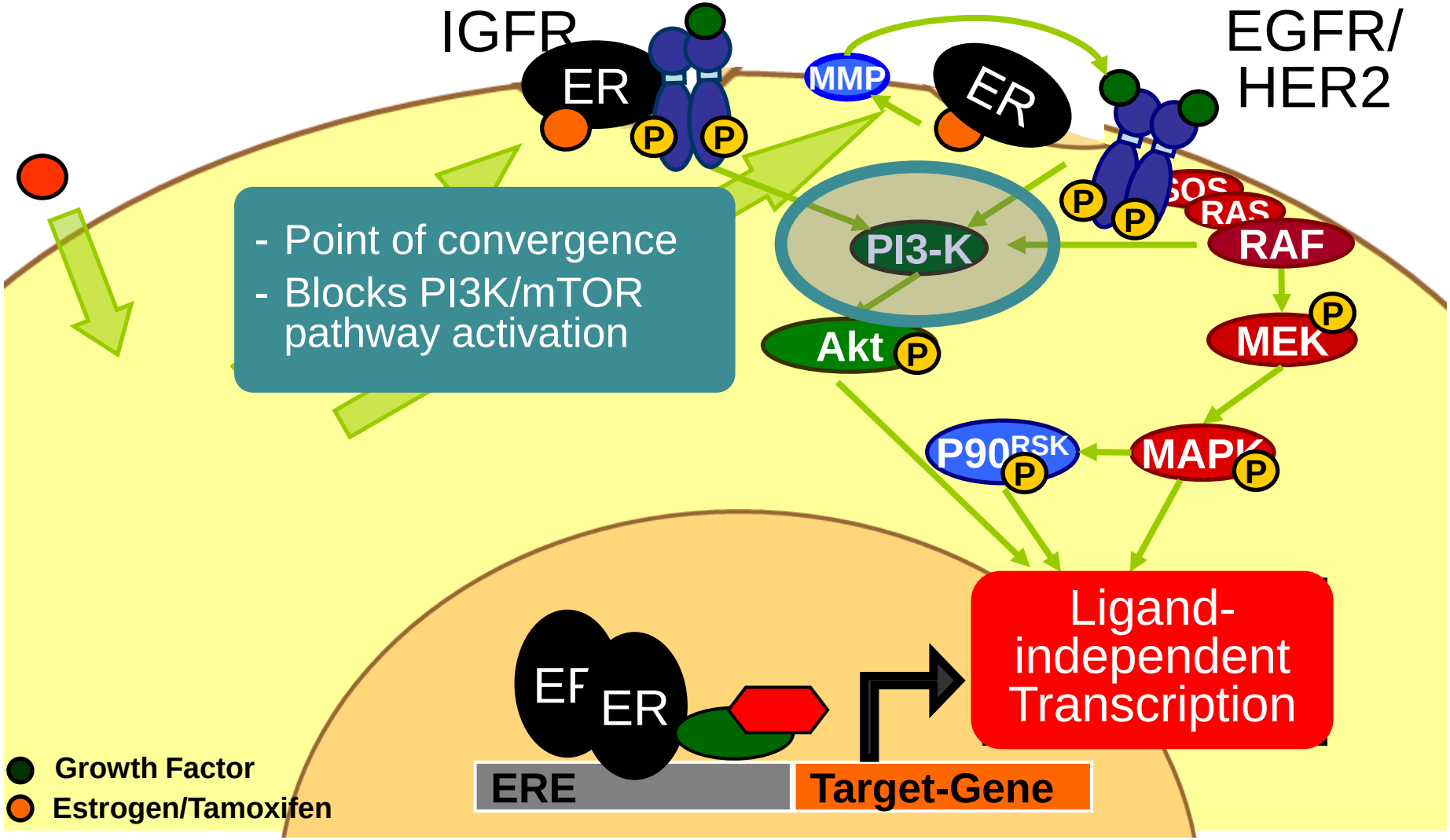
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



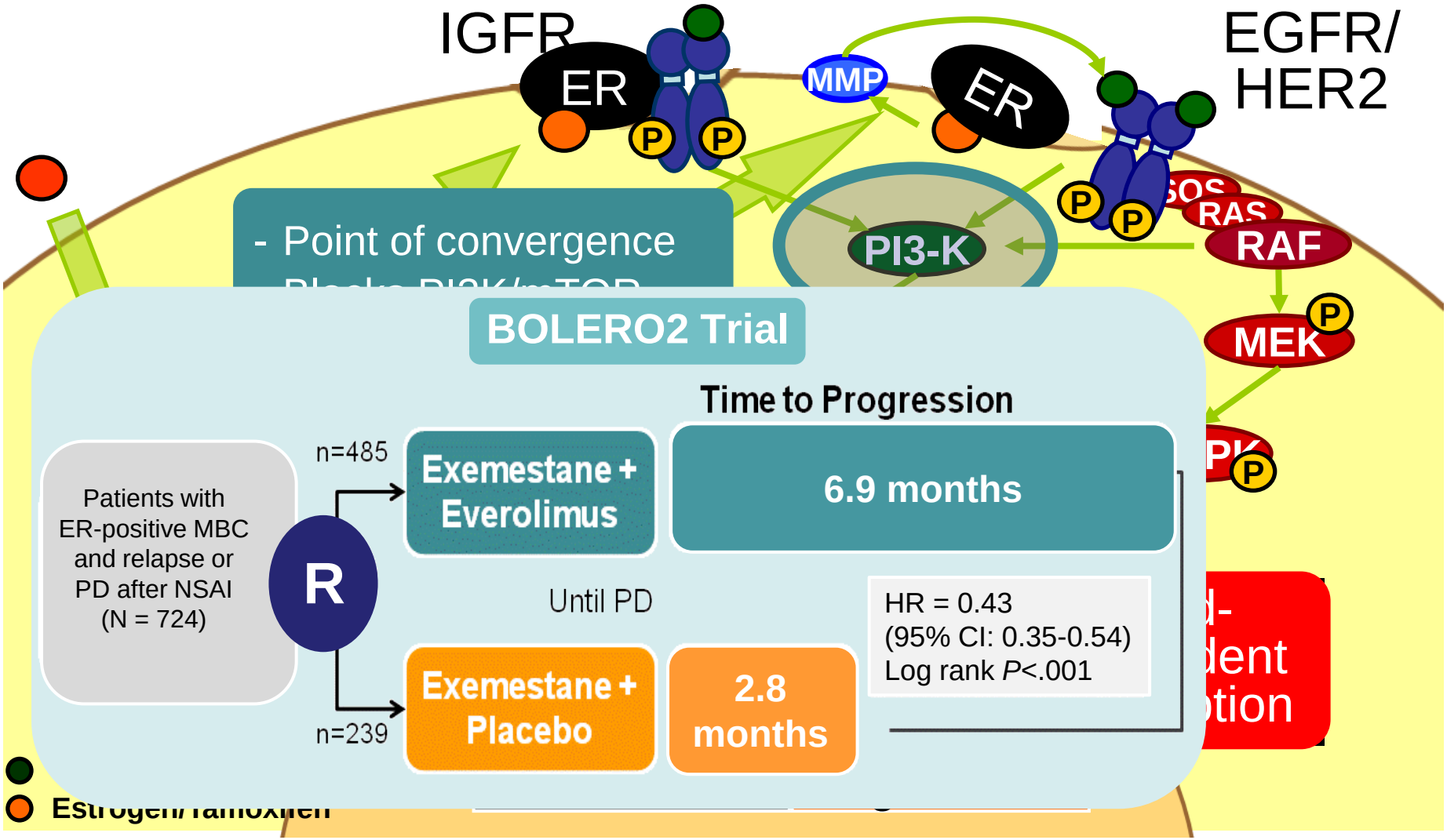
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



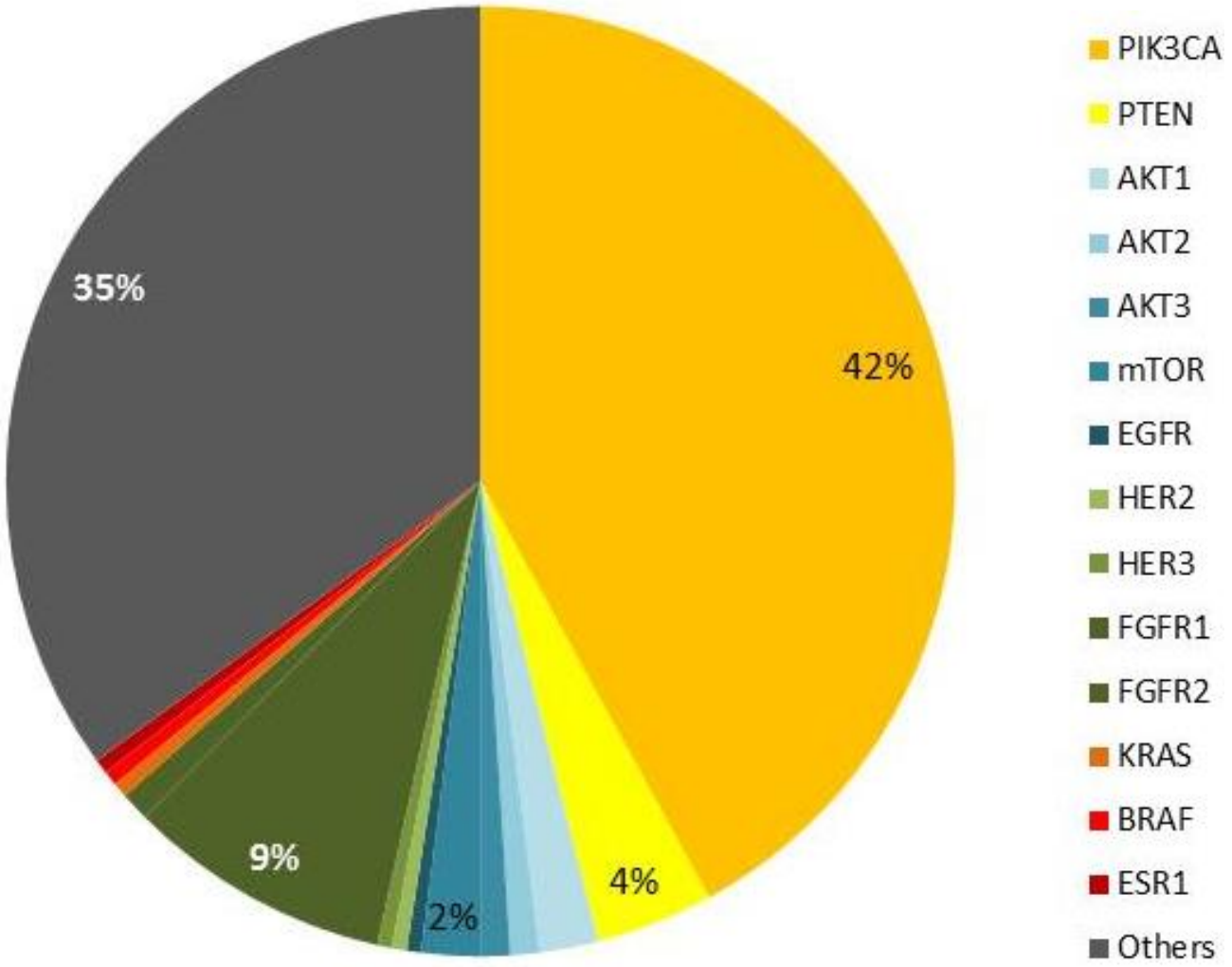
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

ER-Signaling and Anti-oestrogen Therapy
Understanding the Cellular Signaling Network



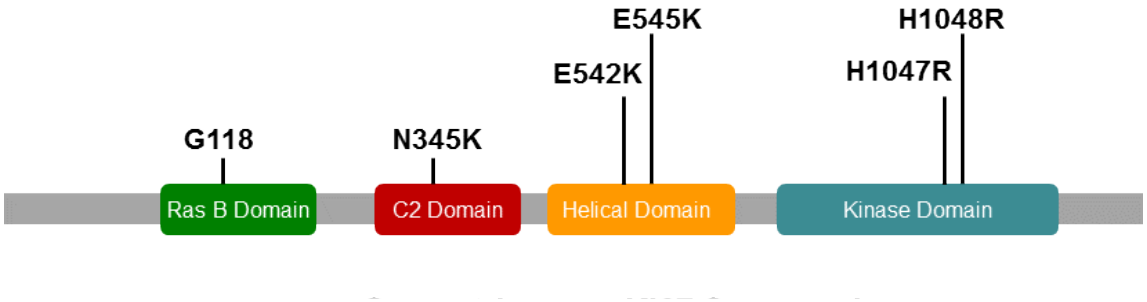
Adapted from Johnston SR. *Clin Cancer Res*. 2005;11(2 Pt 2):889s-899s.

Genetic Aberrations in Signaling Pathways in Luminal Tumors
Target-Focused Classification



TGCA, database (www.cbioportal.org)

Genetic Aberrations in Signaling Pathways in Luminal Tumors
Target-Focused Classification

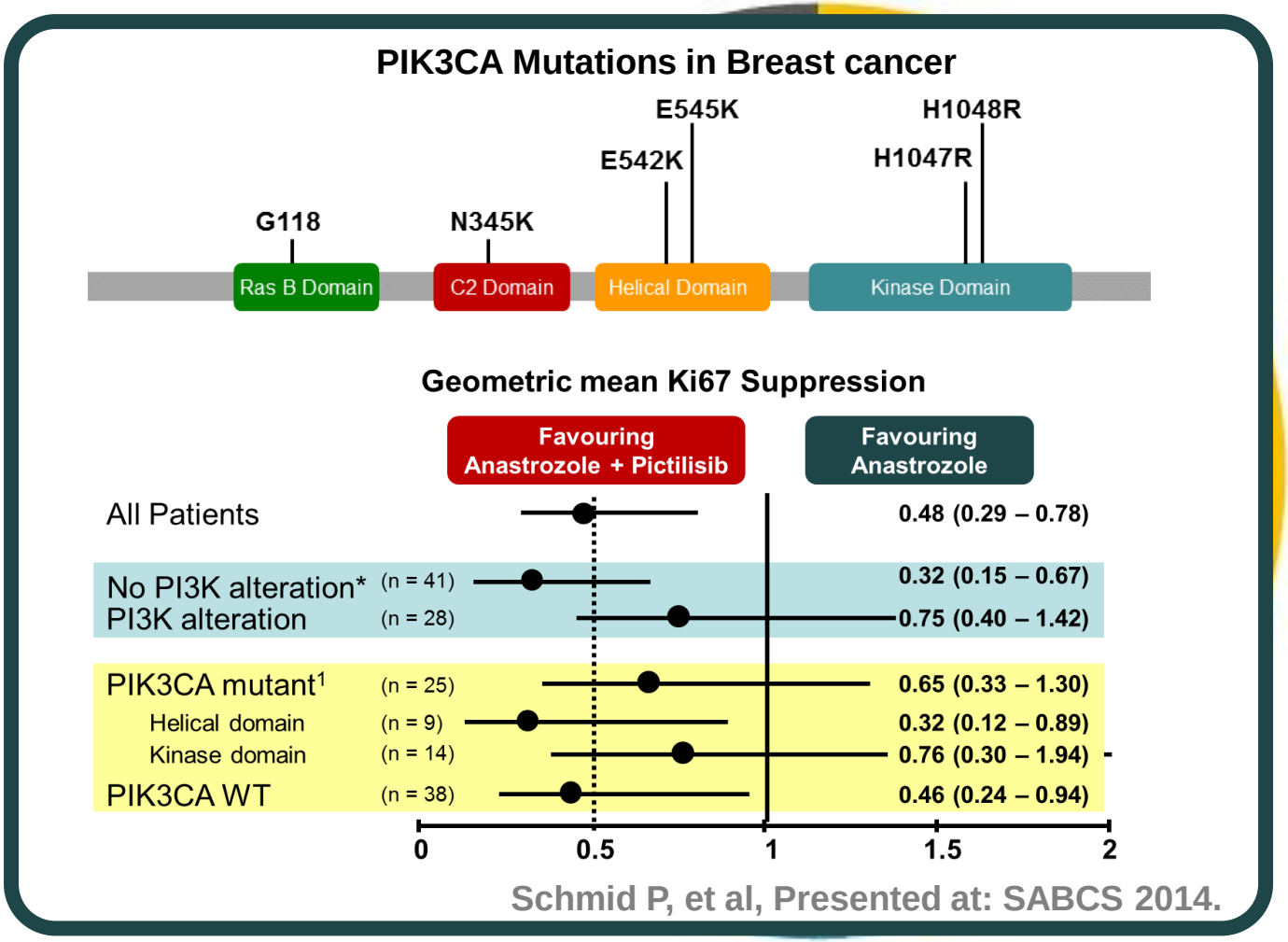


- **Activating PI3KCa mutations occur in 30-40% of ER+ BC**
- **Are PIK3CA the best biomarker for benefit from PI3K/mTOR inhibition?**

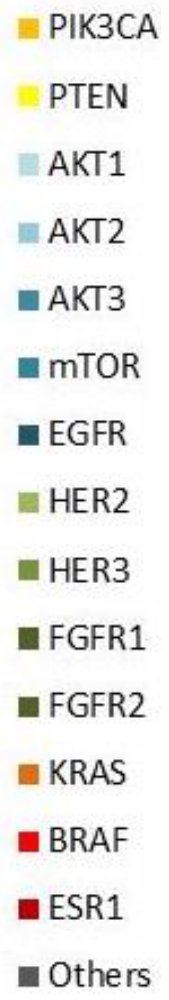
Schmid P, et al, Presented at: SABCS 2014.

TGCA, database (www.cbioportal.org)

Genetic Aberrations in Signaling Pathways in Luminal Tumors
Target-Focused Classification



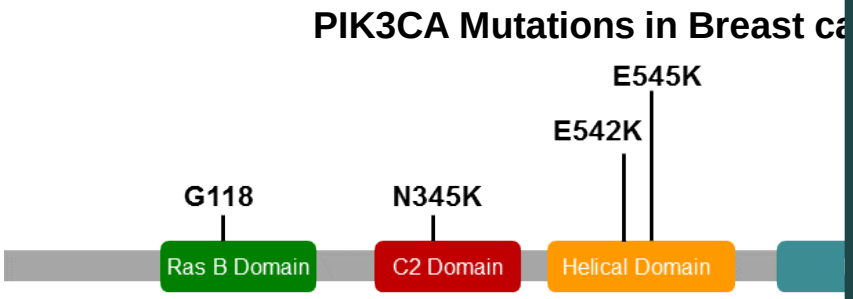
Schmid P, et al, Presented at: SABCS 2014.

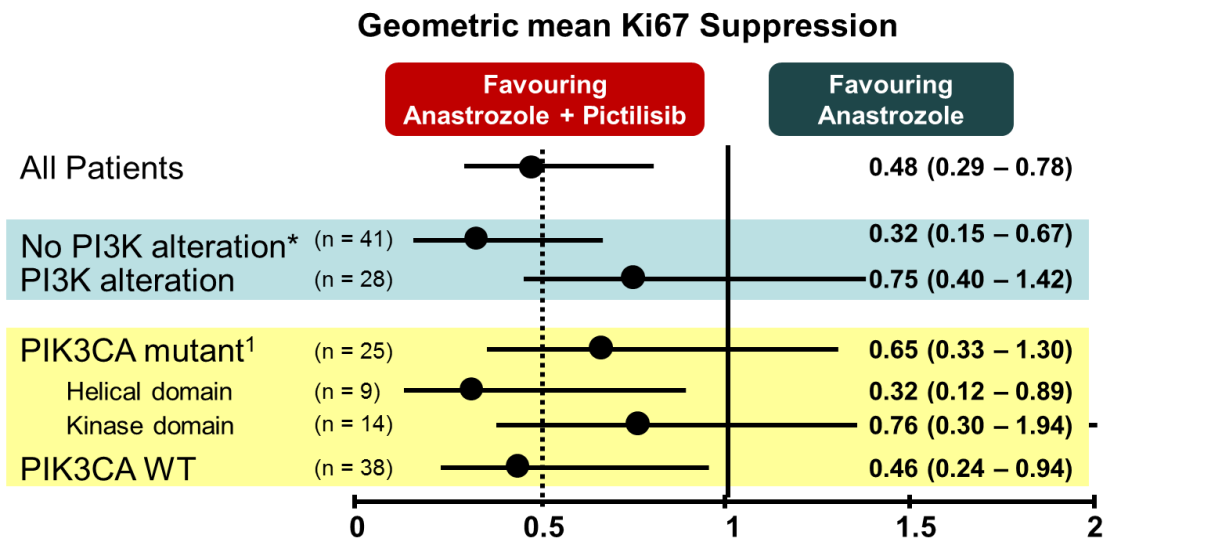


TGCA, database (www.cbioportal.org)

Genetic Aberrations in Signaling Pathways in Luminal Tumors
Target-Focused Classification

Isolated genetic analysis often fails to define functional relevance and cellular dependence of aberrant target

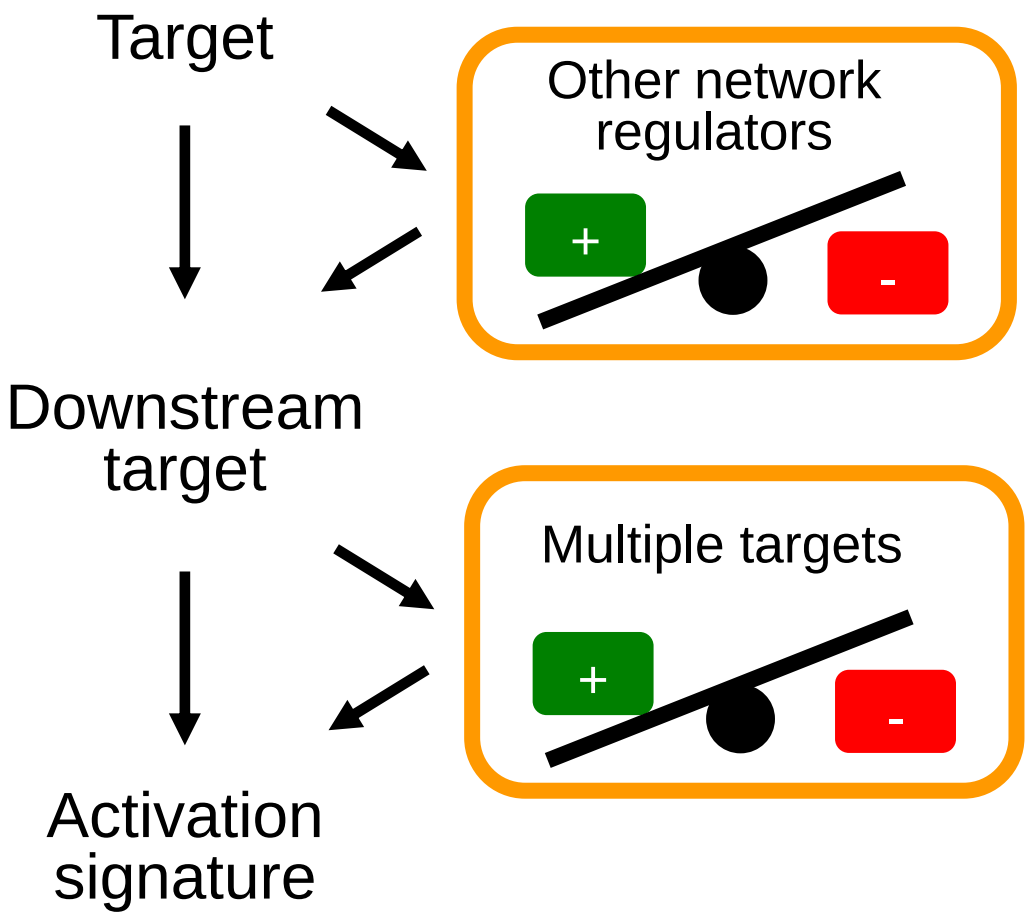




Schmid P, et al, Presented at: SABCS 2014.

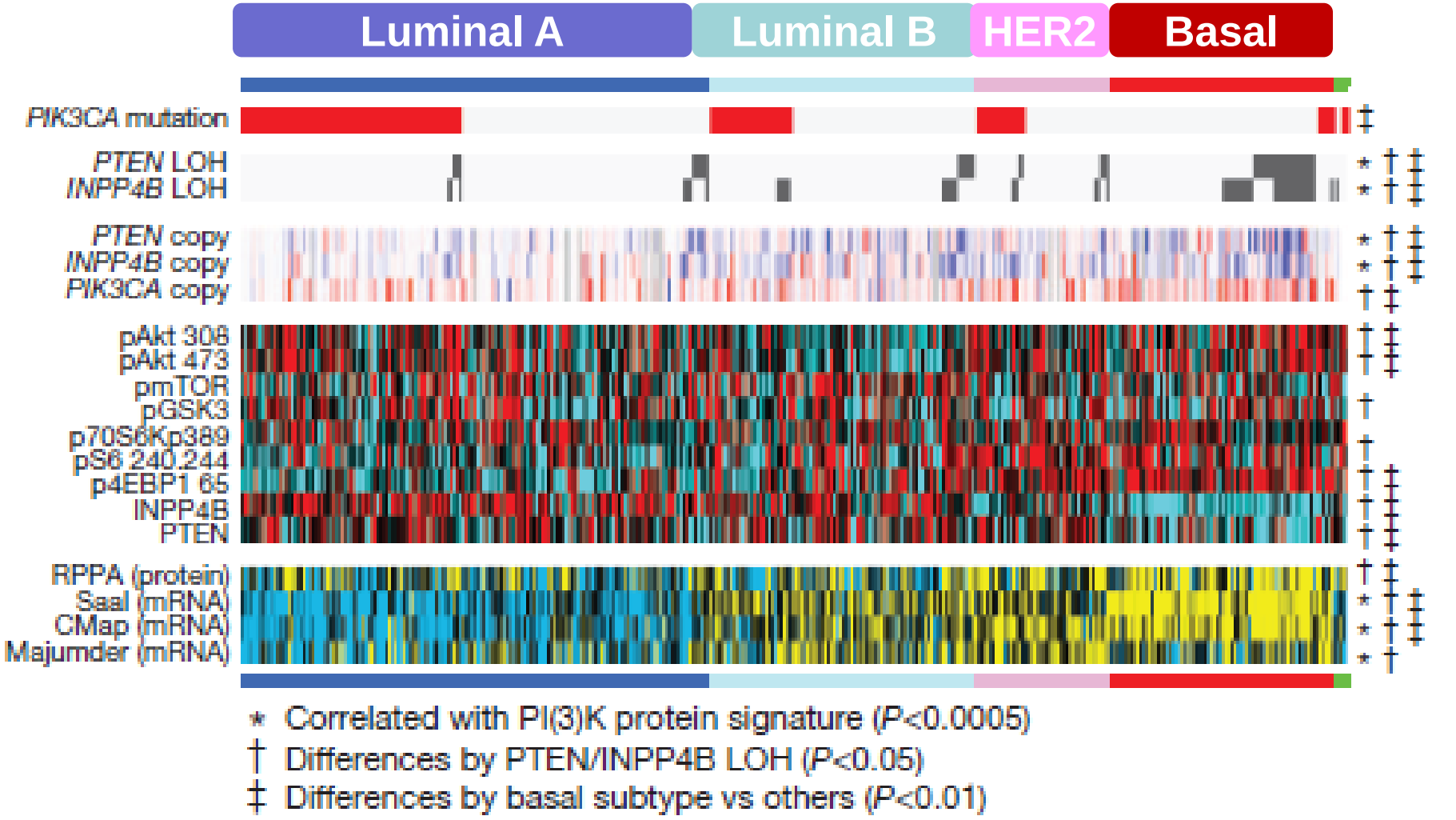
TGCA, database (www.cbioportal.org)

Challenges Around Identifying Biomarkers



Understanding Cellular Signaling Networks: PI3K/mTOR Pathway

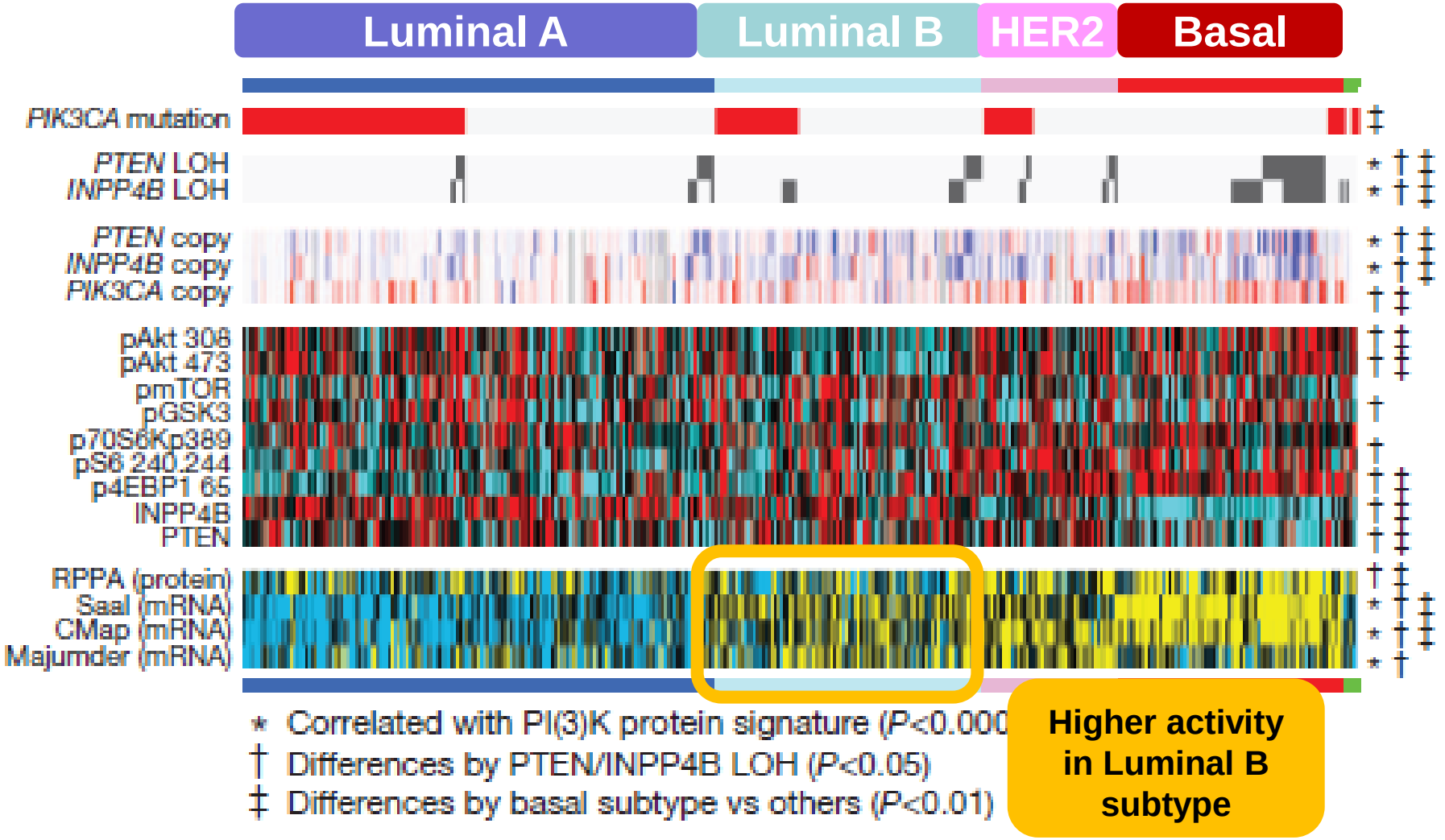
Challenges Around Identifying Biomarkers



Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70.

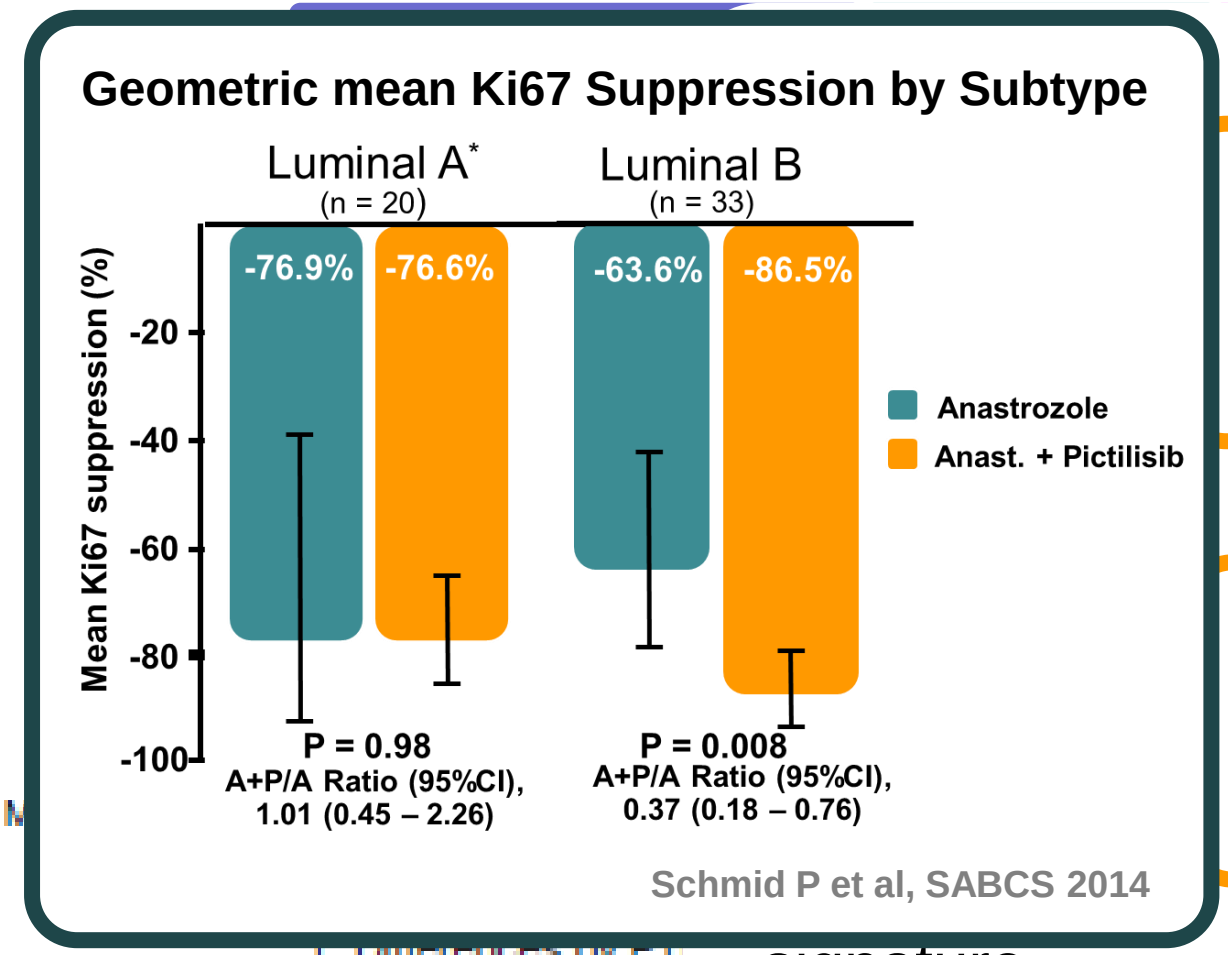
Understanding Cellular Signaling Networks: PI3K/mTOR Pathway

Challenges Around Identifying Biomarkers



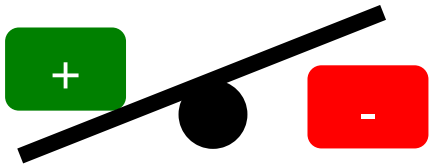
Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70.

Understanding Cellular Signaling Networks: PI3K/mTOR Pathway
Challenges Around Identifying Biomarkers

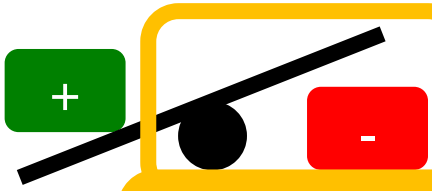


signature

Other network regulators



Multiple targets

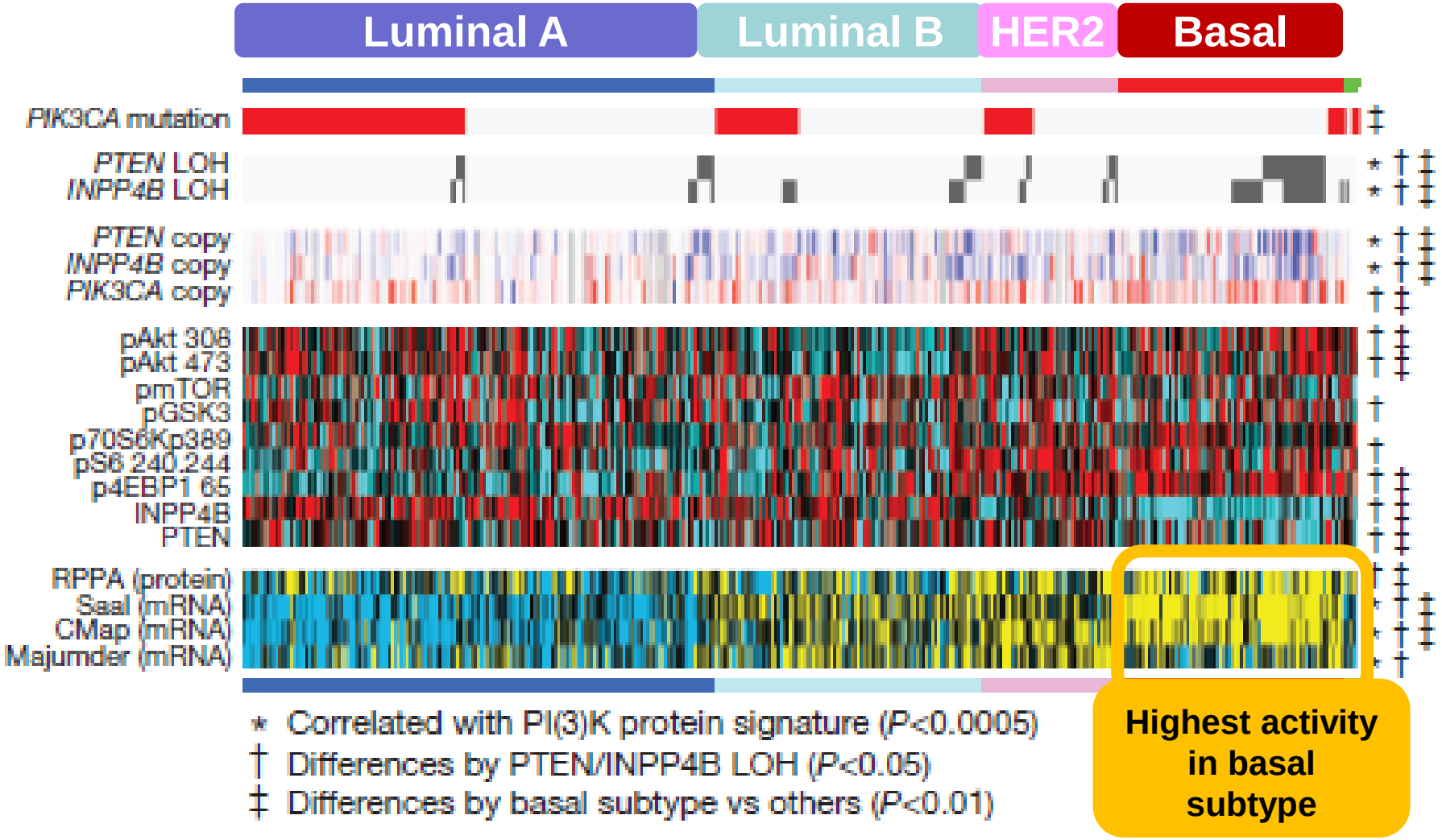


Highest activity in basal subtype

Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70.

Understanding Cellular Signaling Networks: PI3K/mTOR Pathway

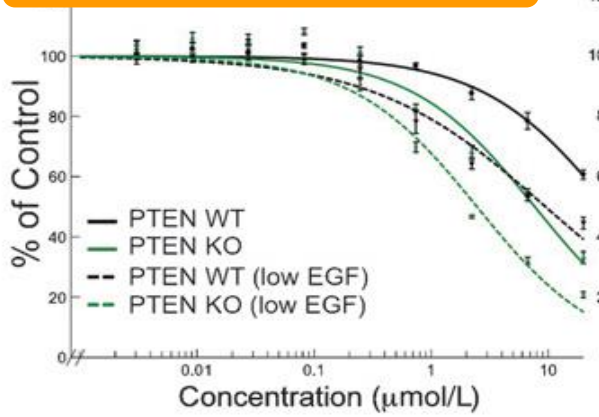
Challenges Around Identifying Biomarkers



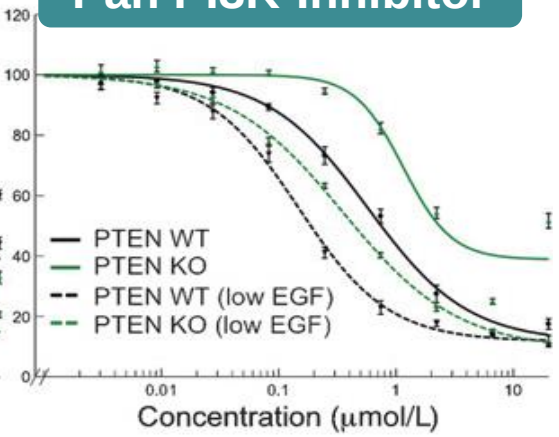
Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70.

Understanding Cellular Signaling Networks: PI3K/mTOR Pathway
Challenges Around Identifying Biomarkers

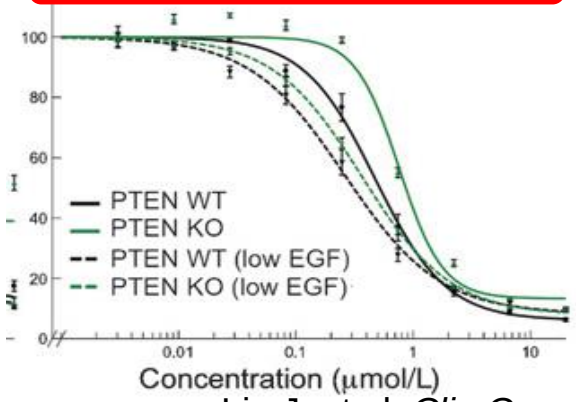
AKT-Inhibitor



Pan PI3K-Inhibitor



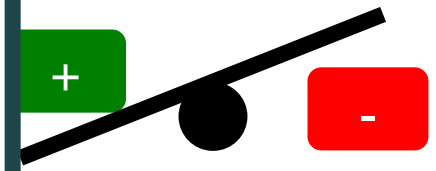
PI3K/mTOR-Inhibitor



Cancer with PTEN loss may be particularly sensitive to AKT inhibitors

Lin J, et al. *Clin Cancer Res*. 2013;19(7):1760-1772.

Other network regulators

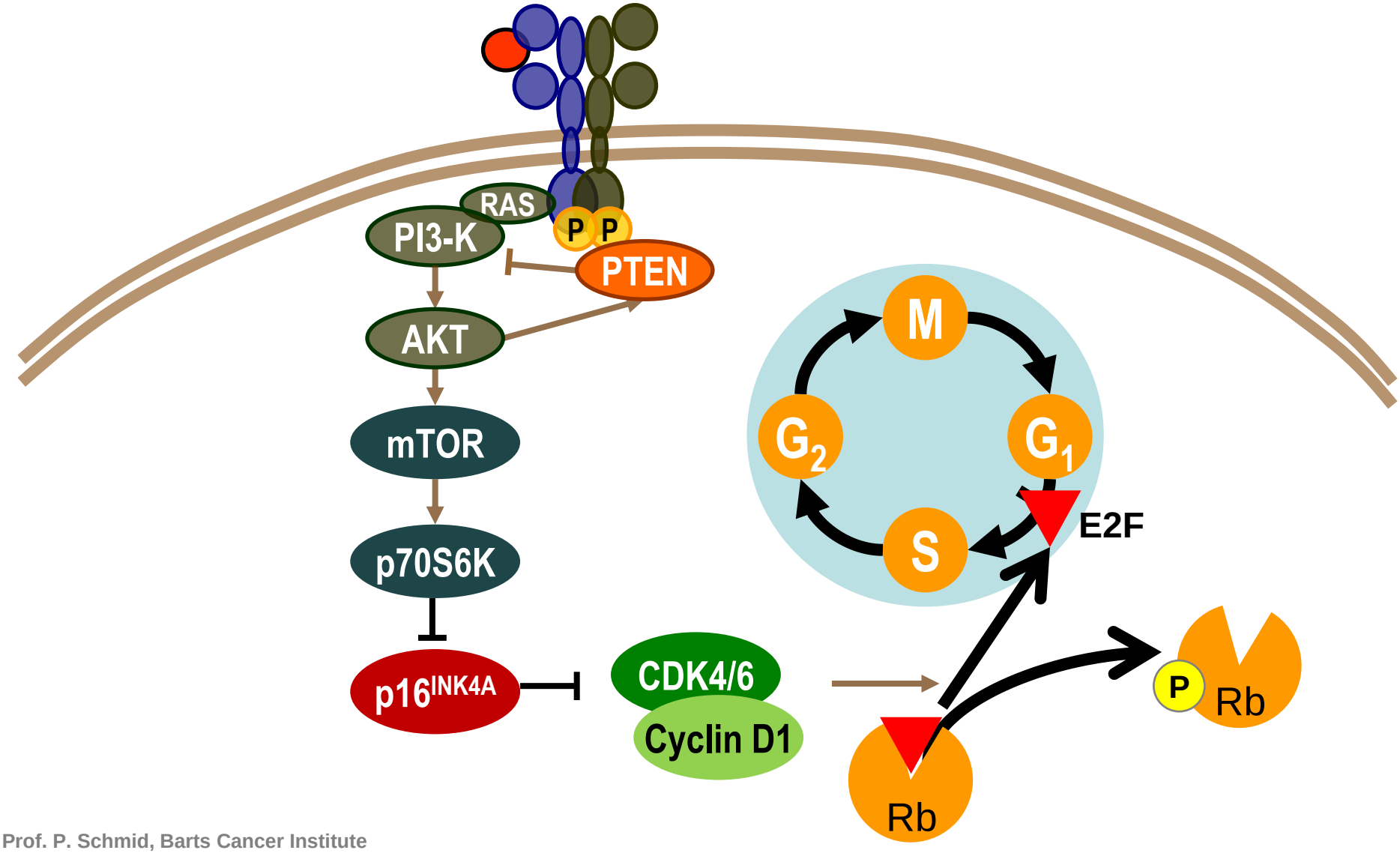


Multiple targets

Highest activity in basal subtype

Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70.

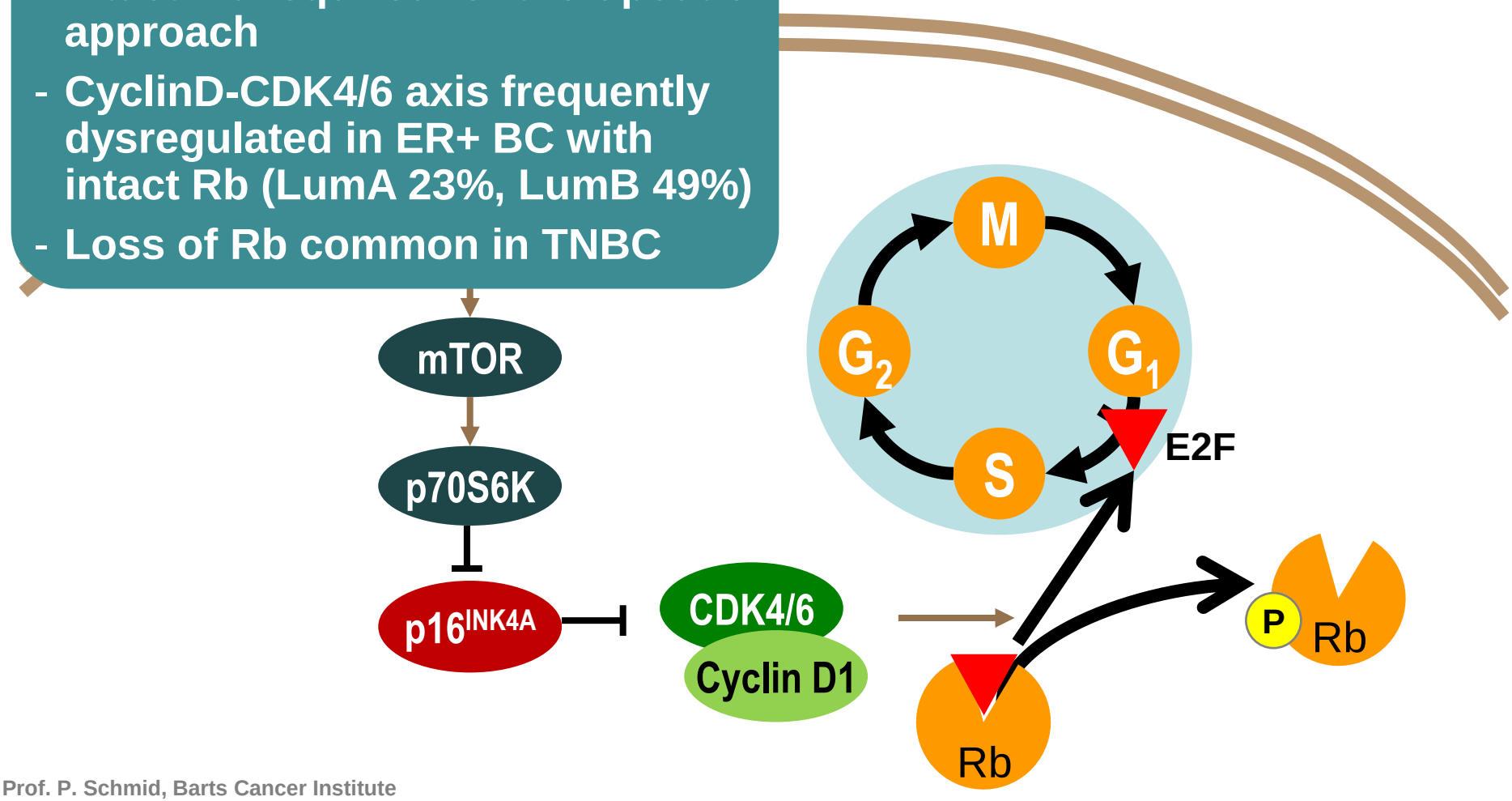
Targeting Cell Cycle Control (CDK4/6)



Targeting Cell Cycle Control (CDK4/6)

Targeting CDK4/6:

- Intact Rb required for therapeutic approach
- CyclinD-CDK4/6 axis frequently dysregulated in ER+ BC with intact Rb (LumA 23%, LumB 49%)
- Loss of Rb common in TNBC

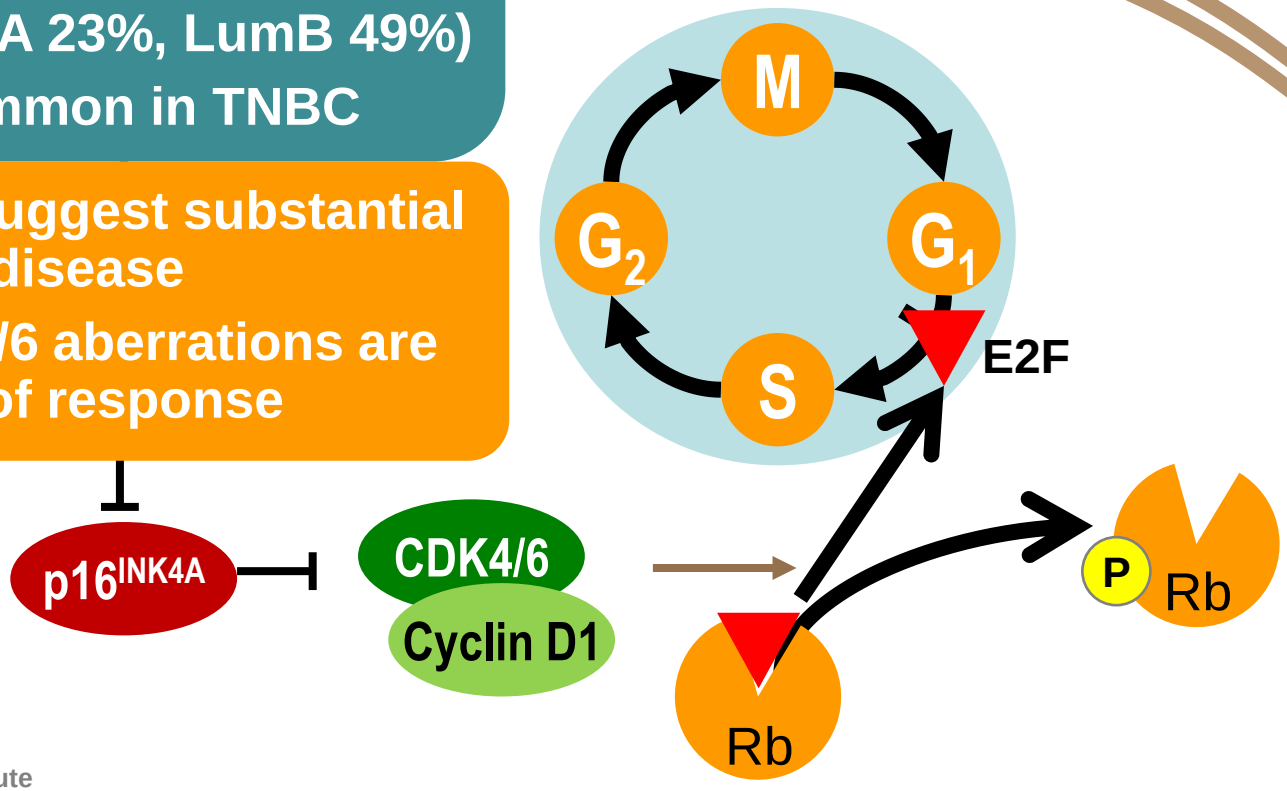


Targeting Cell Cycle Control (CDK4/6)

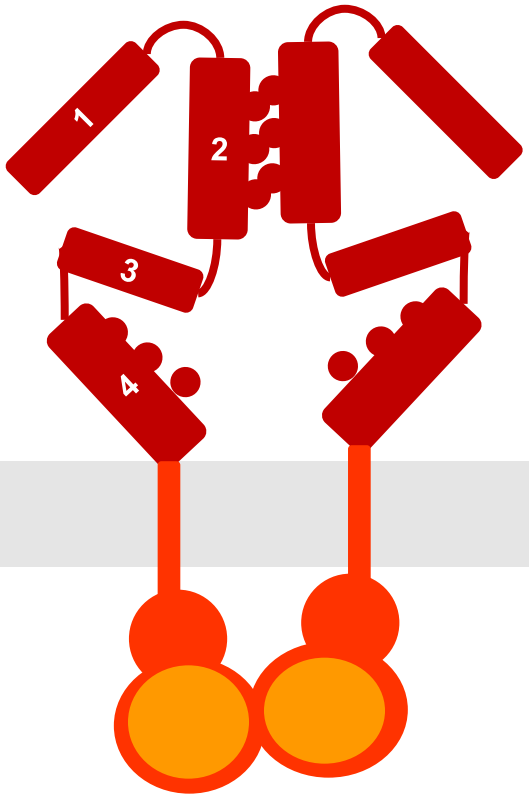
Targeting CDK4/6:

- Intact Rb required for therapeutic approach
- CyclinD-CDK4/6 axis frequently dysregulated in ER+ BC with intact Rb (LumA 23%, LumB 49%)
- Loss of Rb common in TNBC

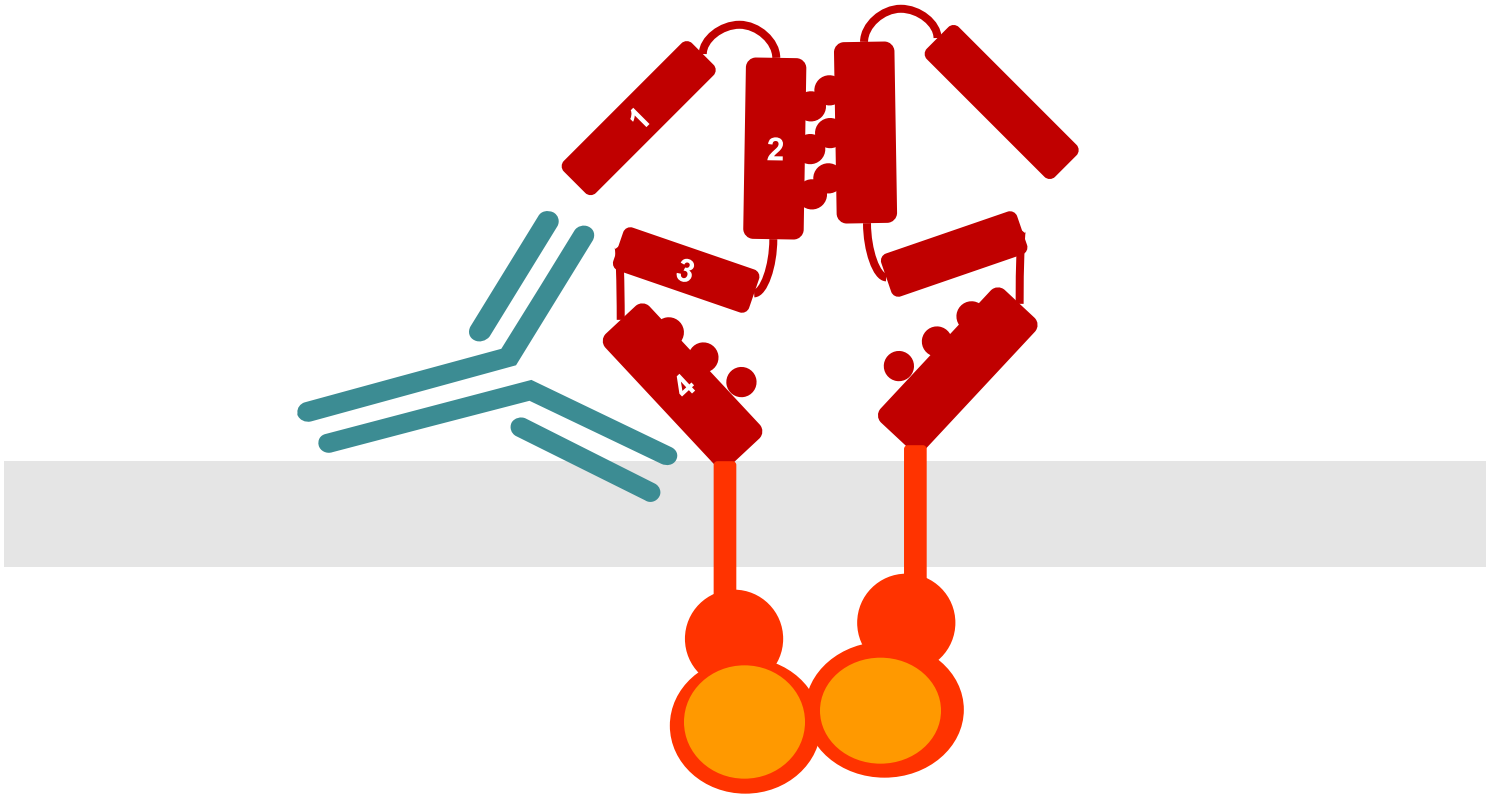
- Early studies suggest substantial benefit in ER+ disease
- Cyclin D-CDK4/6 aberrations are not predictive of response



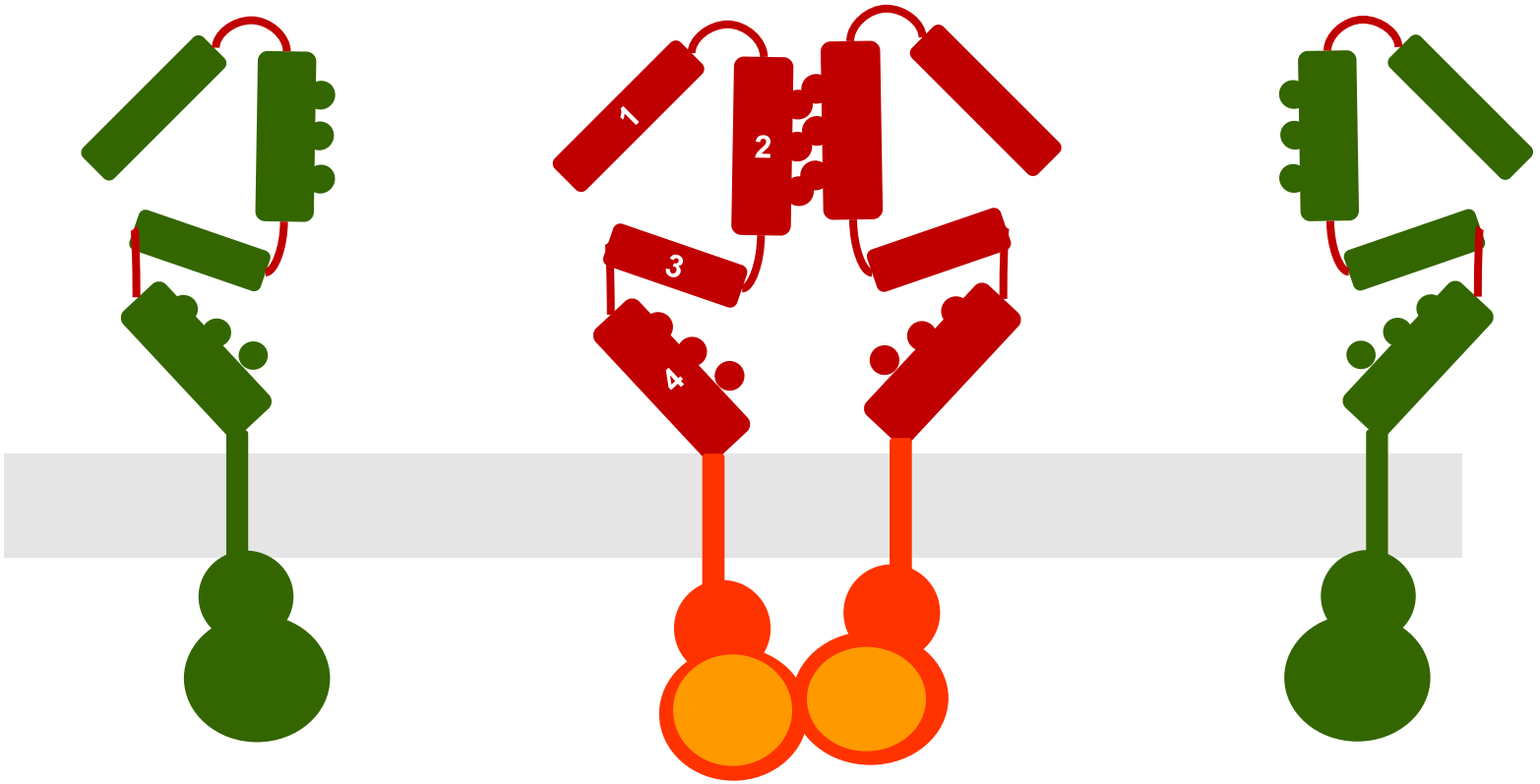
Targeting HER2+ Disease



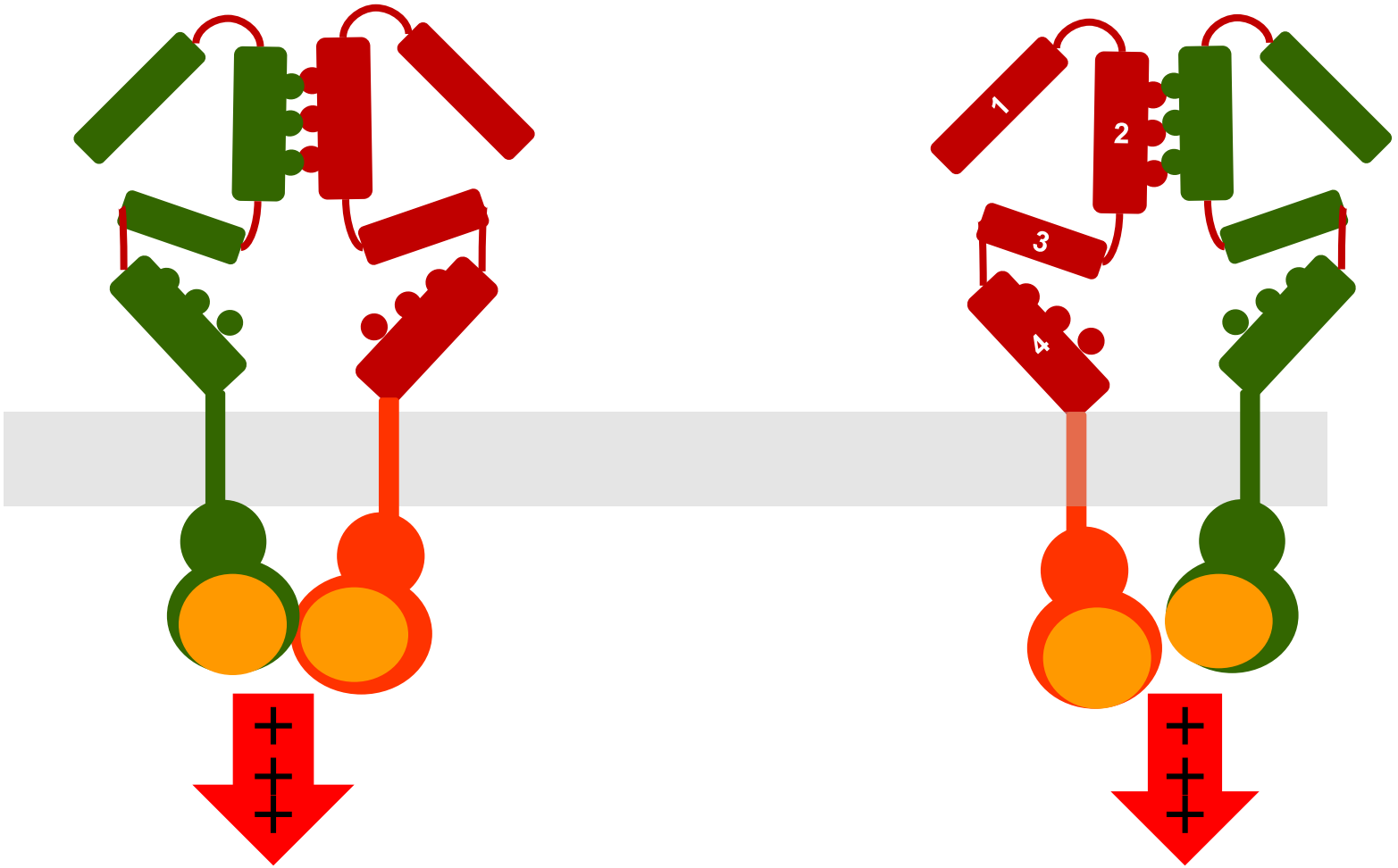
Targeting HER2+ Disease



Targeting HER2+ Disease

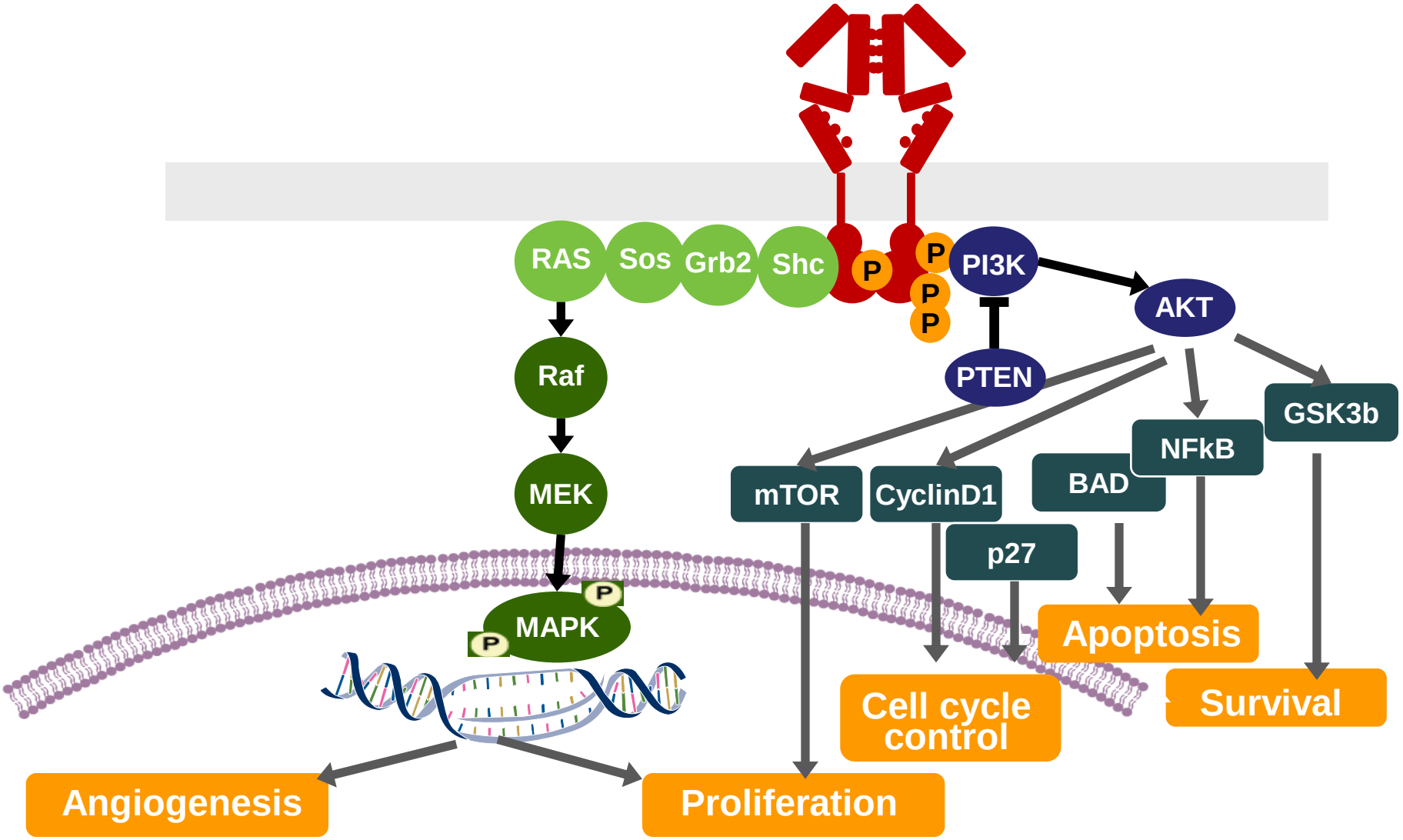


Targeting HER2+ Disease

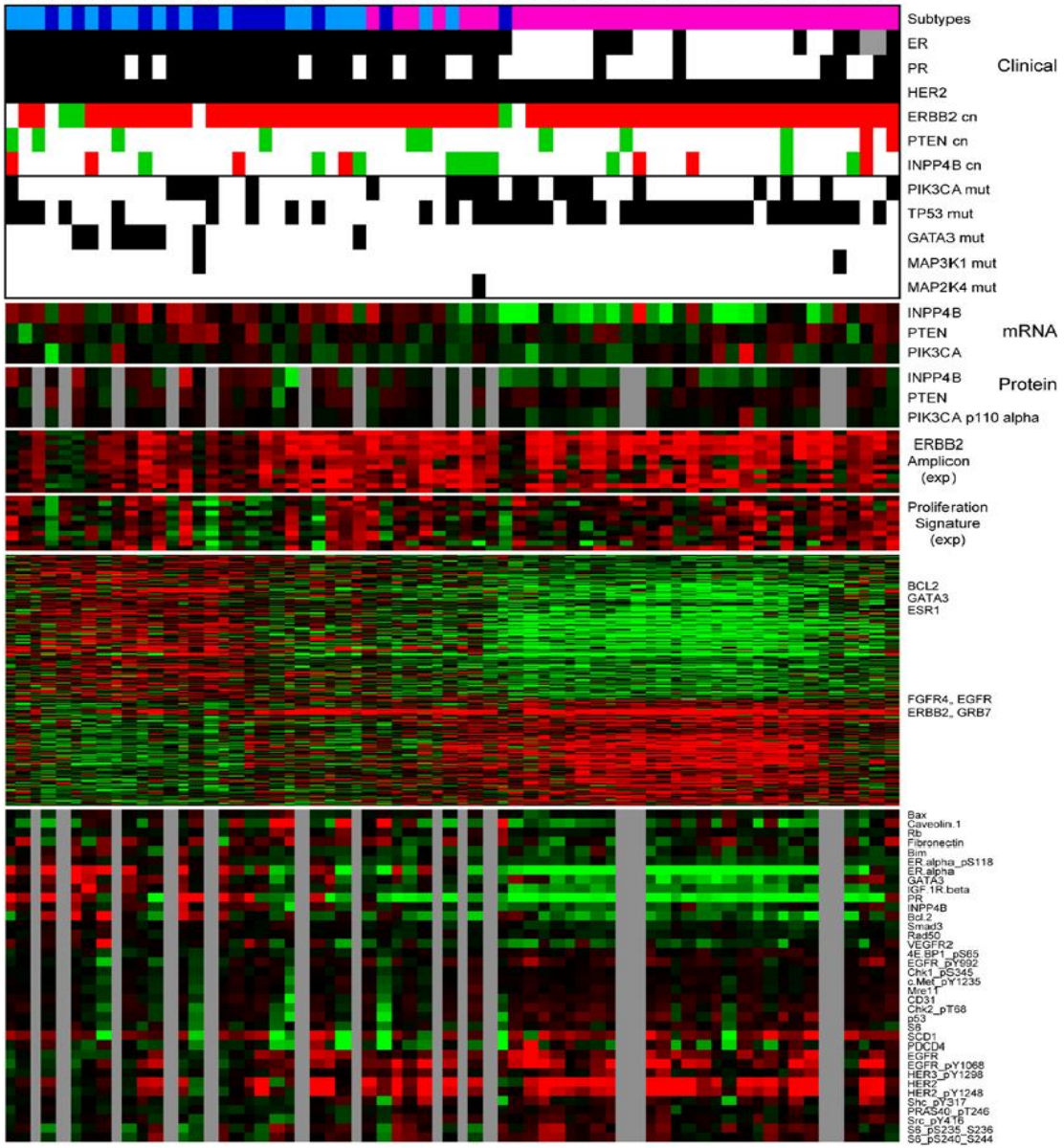


Targeting HER2+ Disease

Intracellular Signaling Network

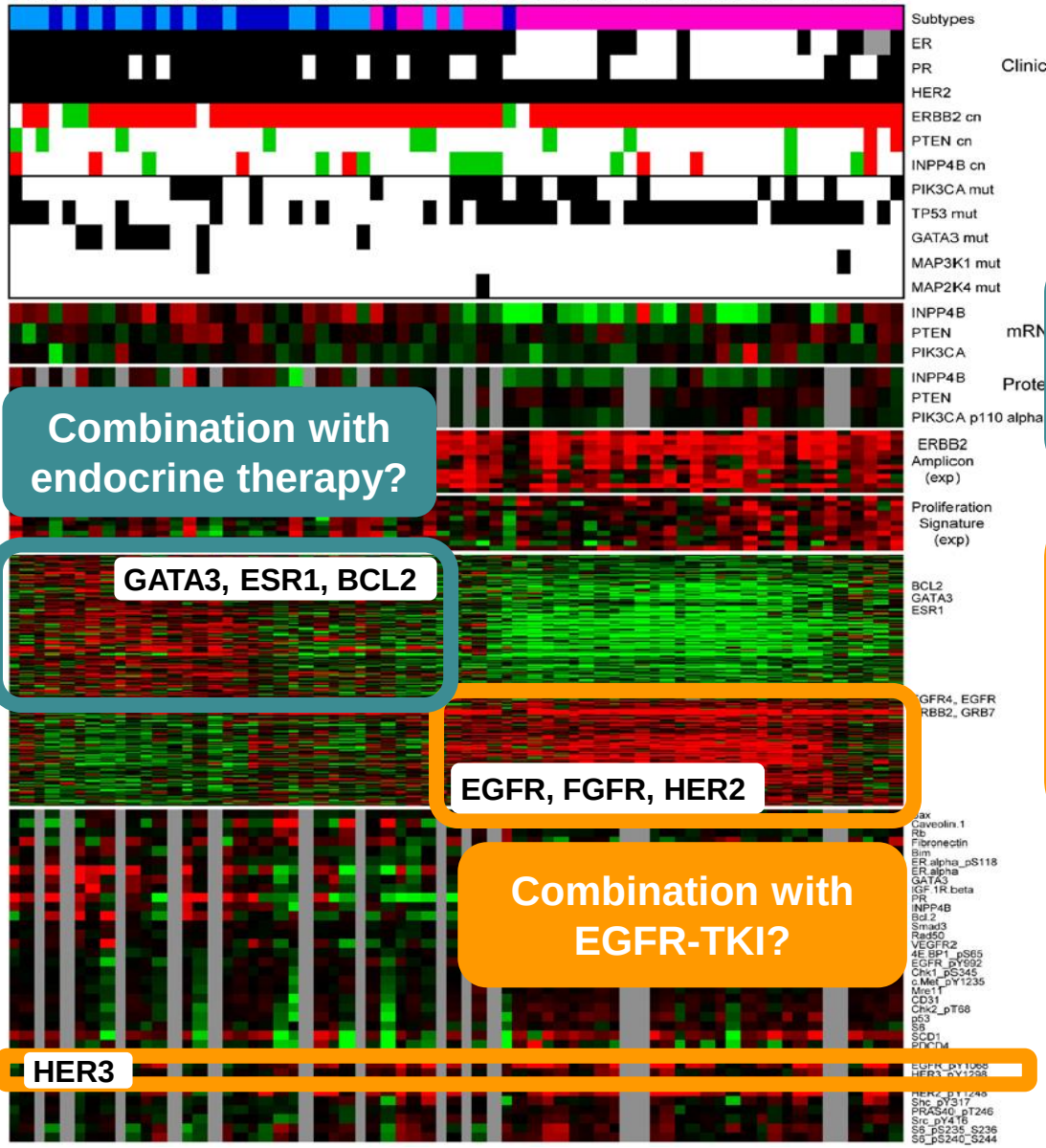


Targeting HER2+ Disease
Luminal vs HER2 Subtype & Potential Co-Targets



Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70.

Targeting HER2+ Disease
Luminal vs HER2 Subtype & Potential Co-Targets



HER2+/Luminal:

- **Strong signal for luminal cluster GATA3, BCL2, ESR1**

HER2+/HER2E :

- **Strong signal for EGFR, FGFR4, HER2 amplicon, pS6;**
- **Amplification of CDK4, cyclin D1, EGFR, FGFRs**

Positive / mut
Negative / wt
NA

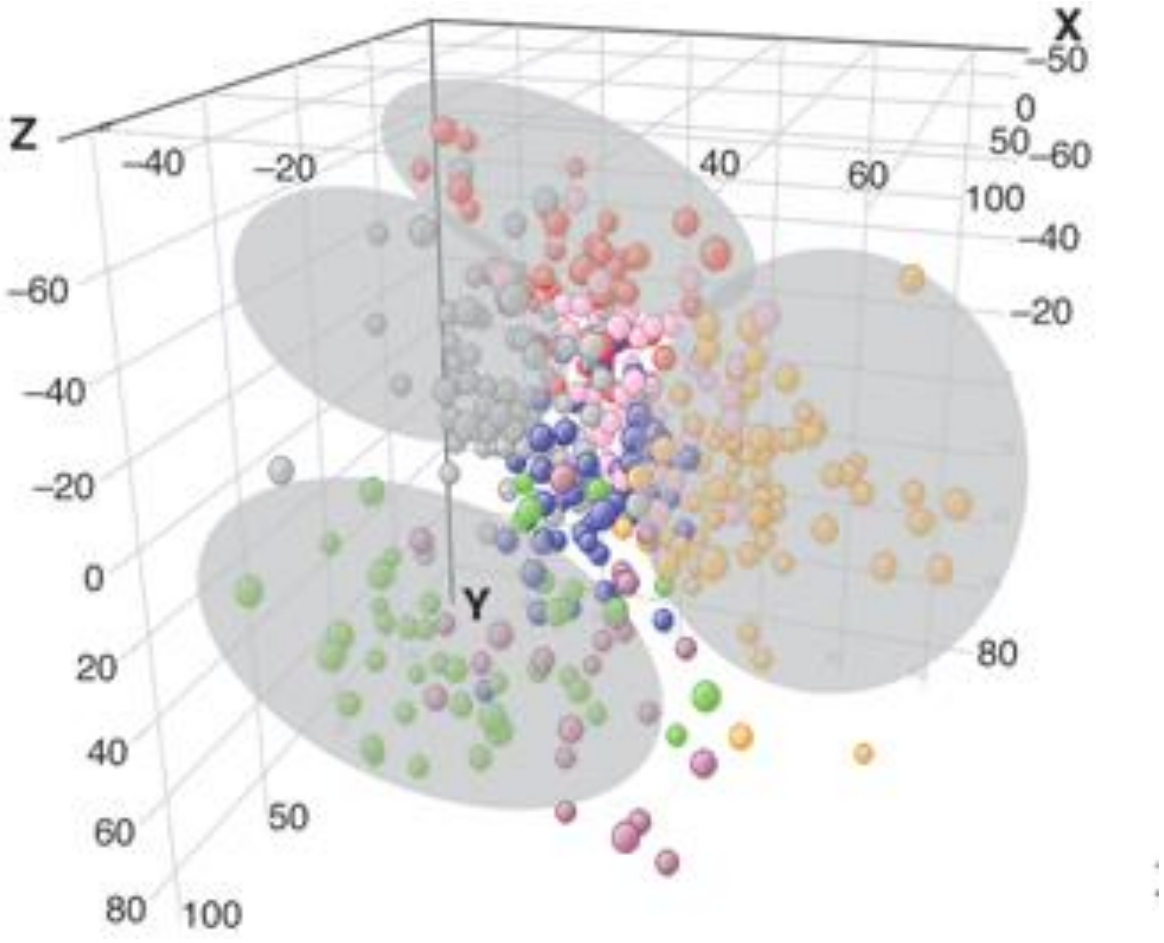
Amplified
CN Neutral
Deleted

HER2-enri
Luminal A
Luminal B

Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70.

Triple Negative Cancer: Potential Treatment Targets?
Heterogeneity Requires Different Strategies

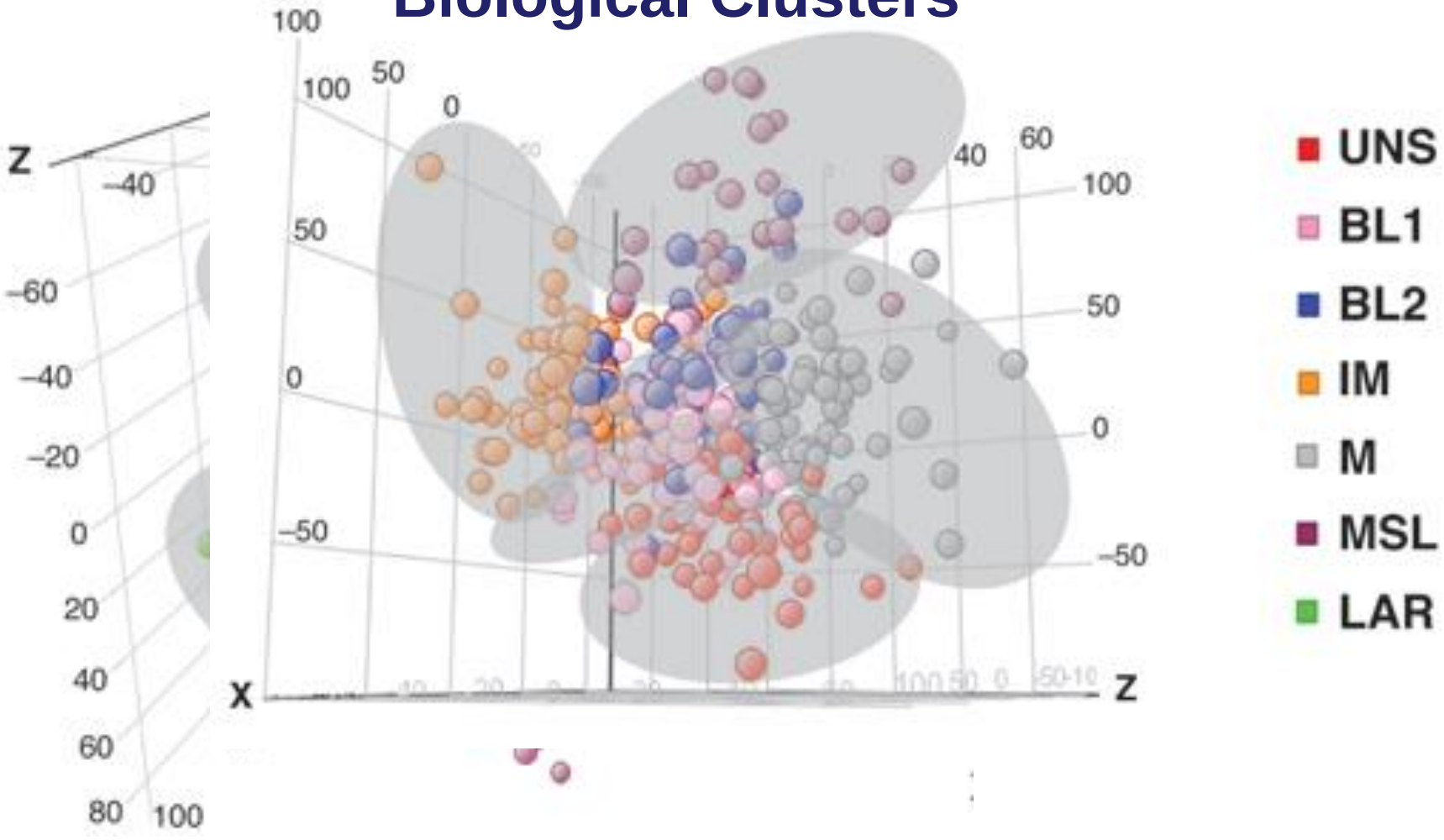
Biological Clusters



Lehmann BD, et al. *J Clin Invest*. 2011;121(7):2750-2767.

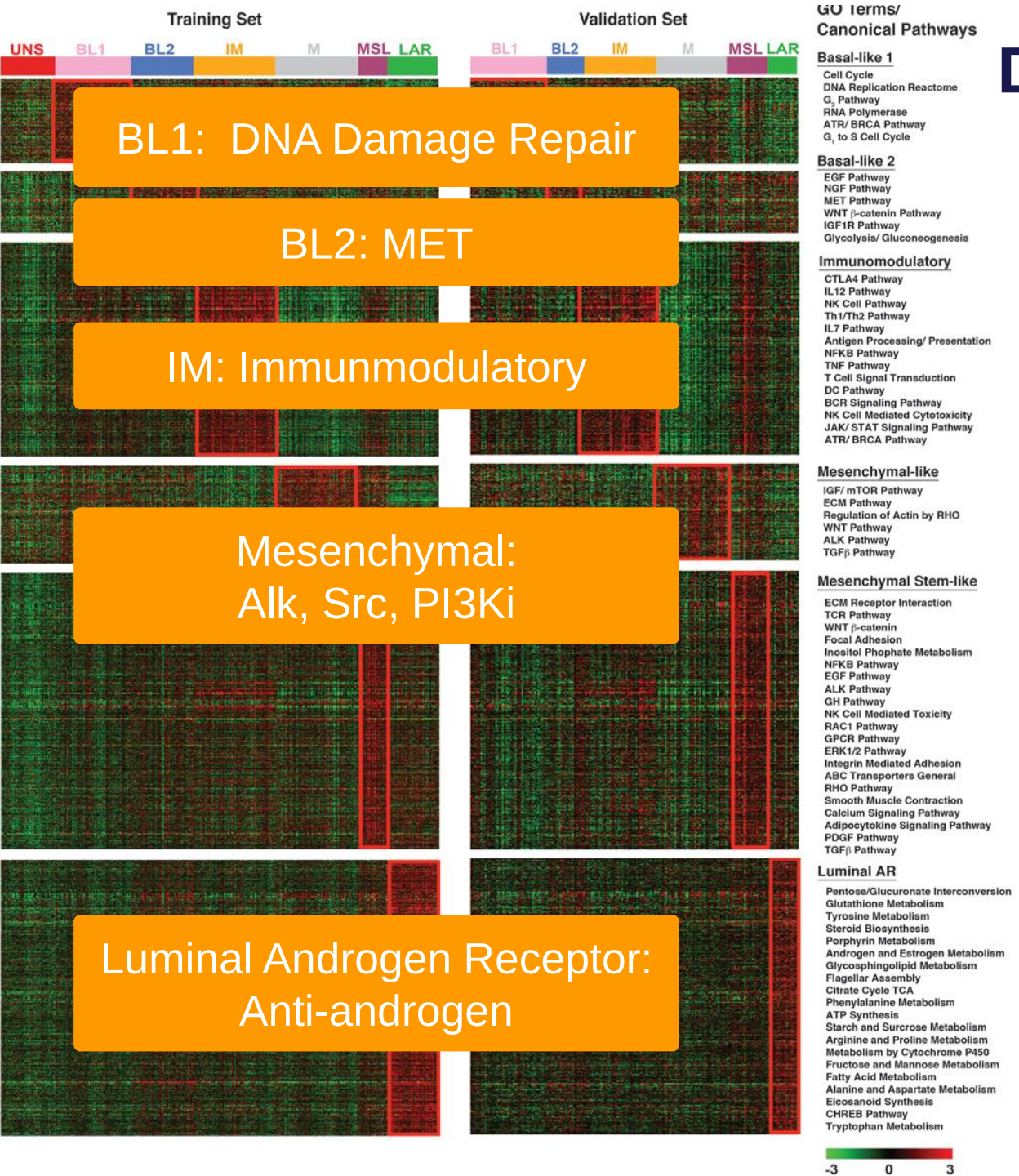
Triple Negative Cancer: Potential Treatment Targets?
Heterogeneity Requires Different Strategies

Biological Clusters



Lehmann BD, et al. *J Clin Invest*. 2011;121(7):2750-2767.

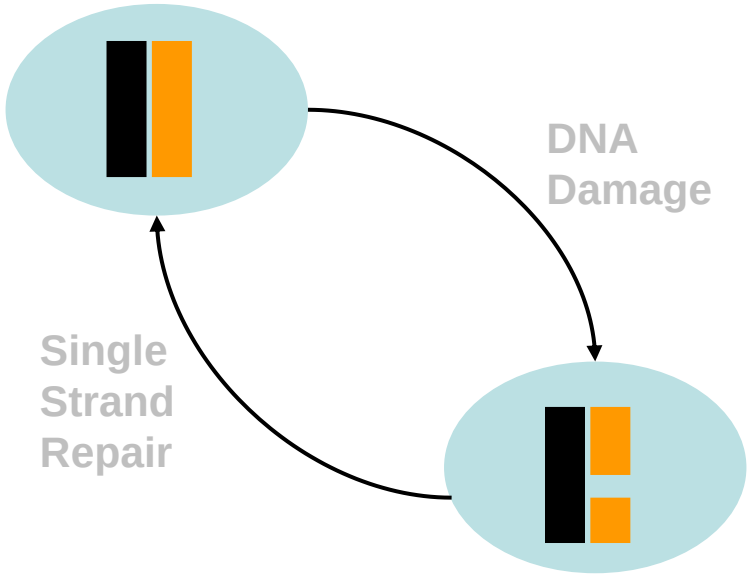
Different Targets for Biological Clusters



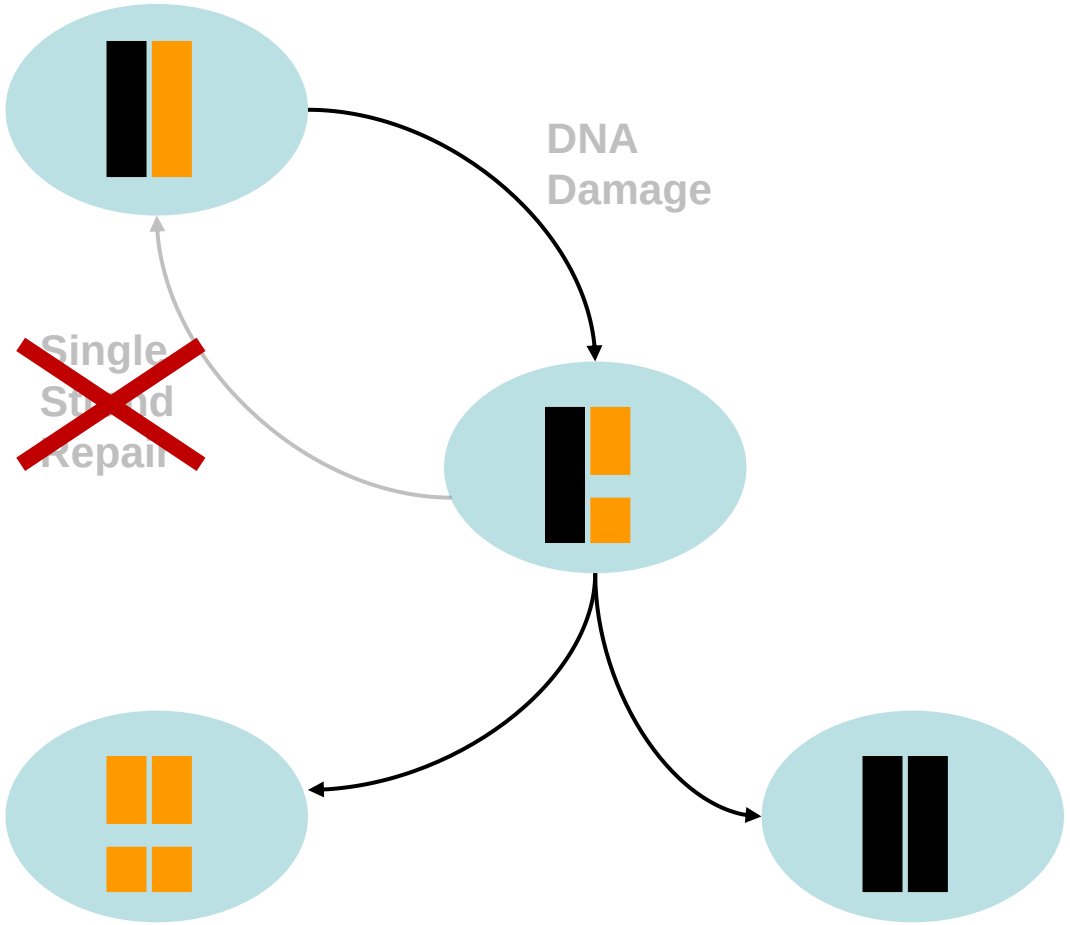
Lehmann BD, et al. *J Clin Invest*. 2011;121(7):2750-2767.

Utilizing Synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP

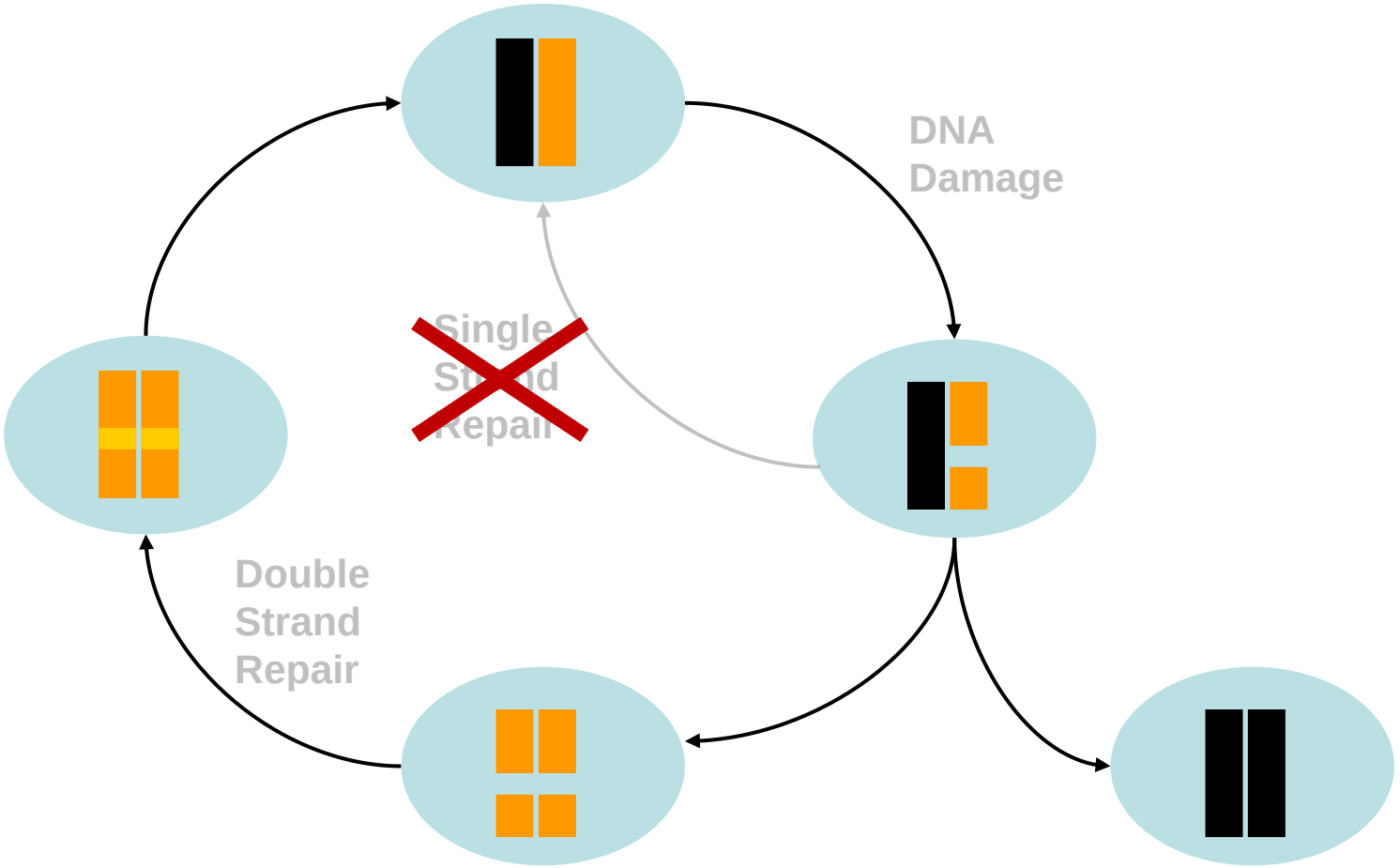
Utilizing Synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP



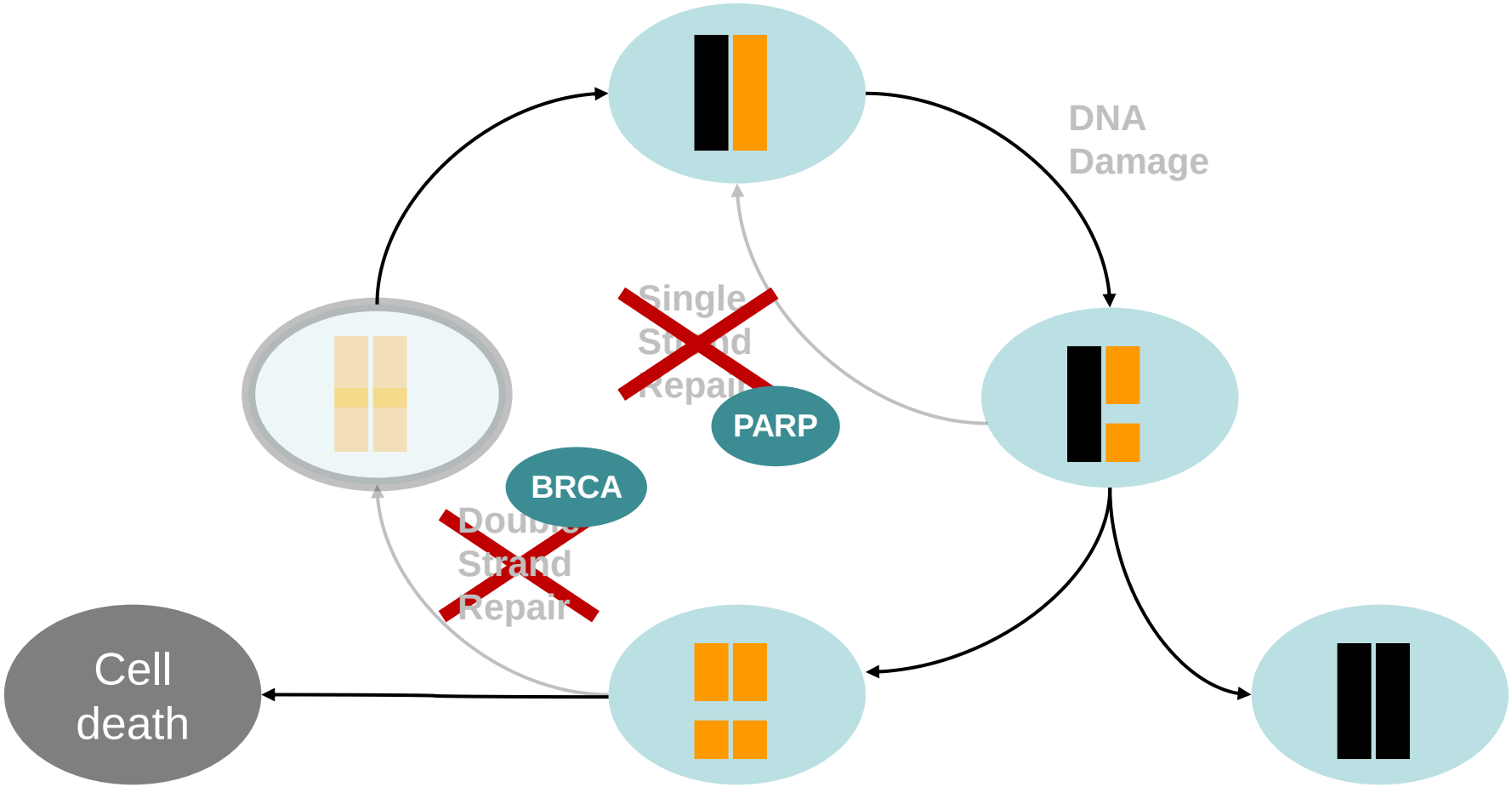
Utilizing Synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP



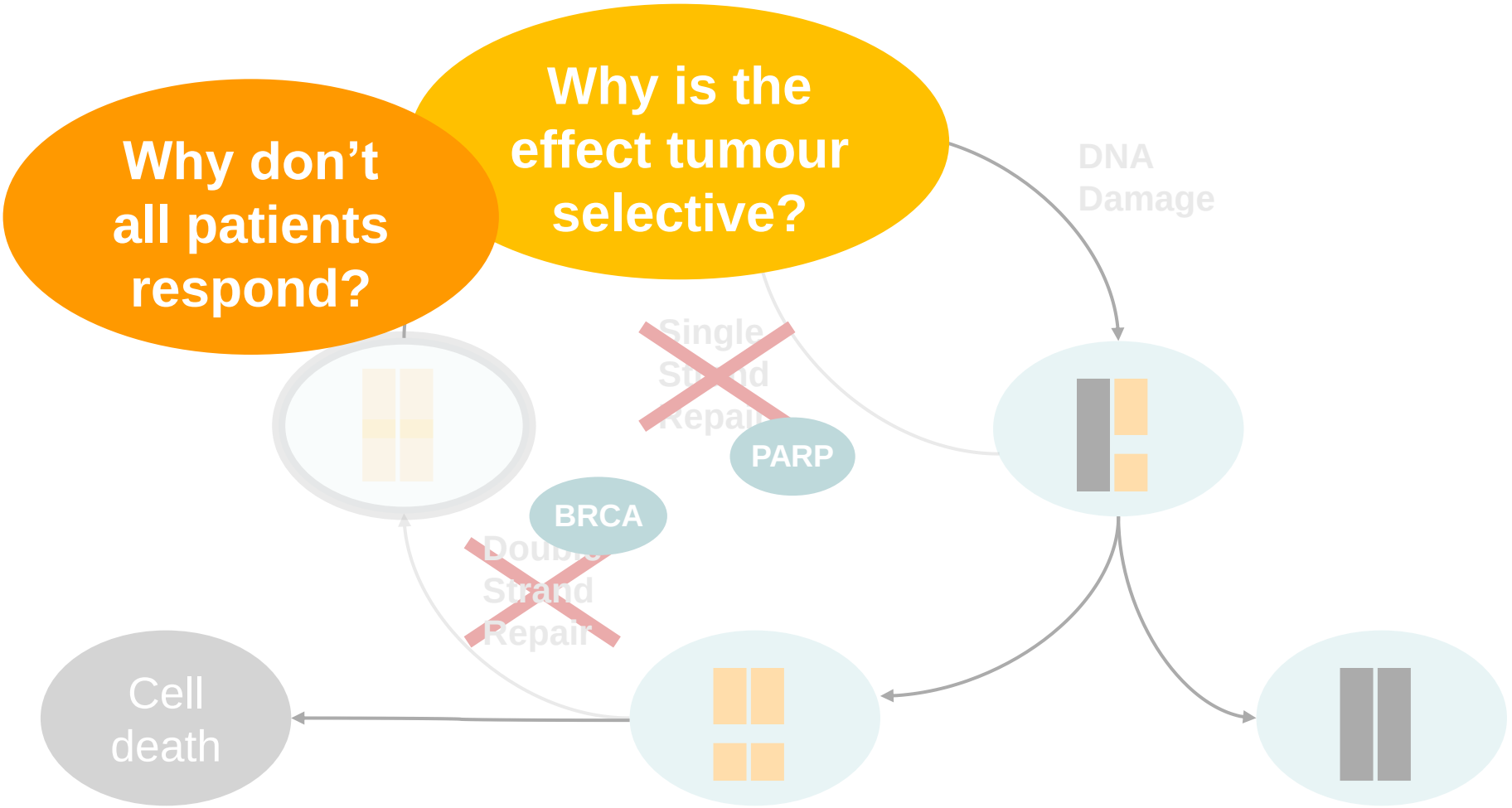
Utilizing Synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP



Utilizing Synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP



Utilizing Synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP



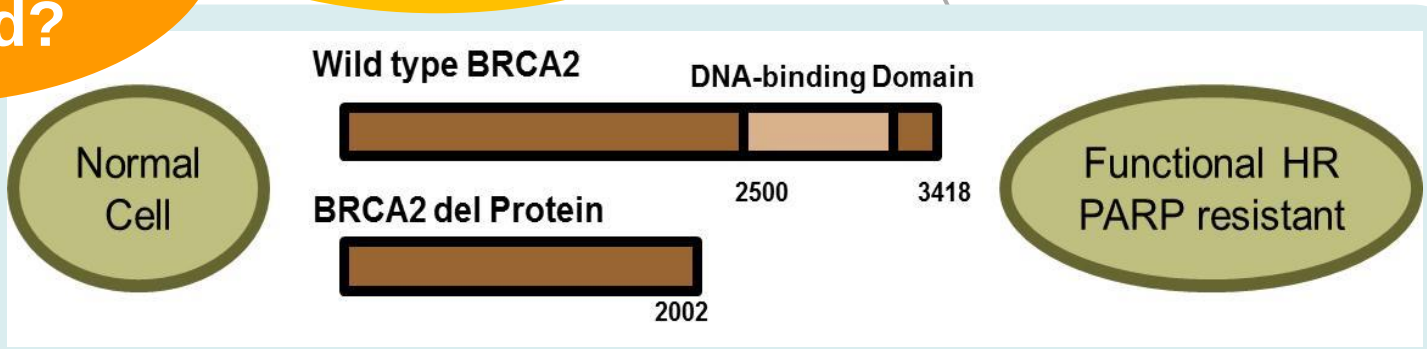
Utilizing Synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP

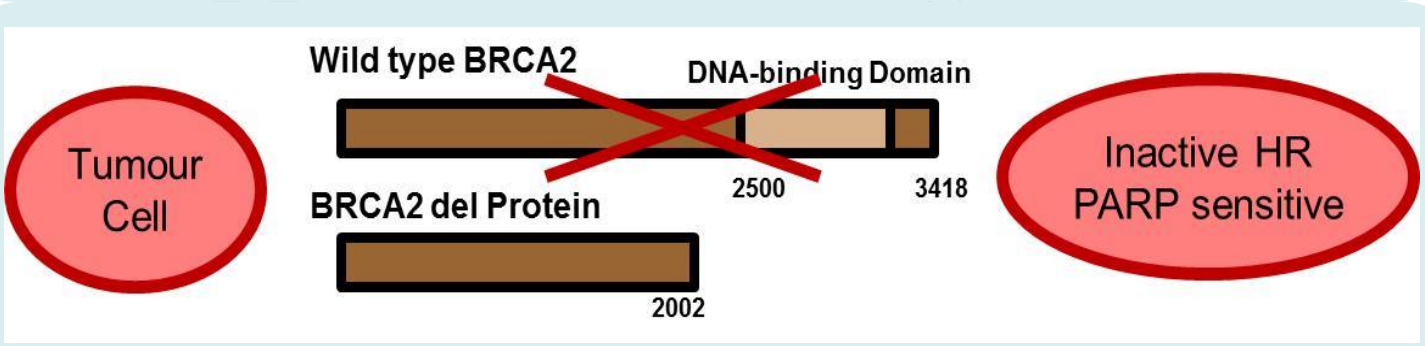
Why don't all patients respond?

Why is the effect tumour selective?

DNA Damage

Cell death





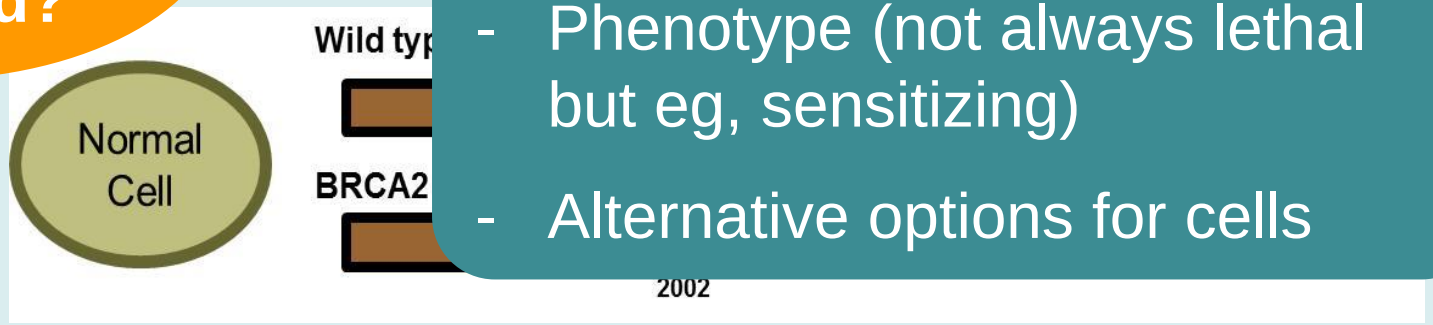
Utilizing Synthetic Lethality Strategies
DNA Damage Repair – BRCA & PARP

Why don't all patients respond?

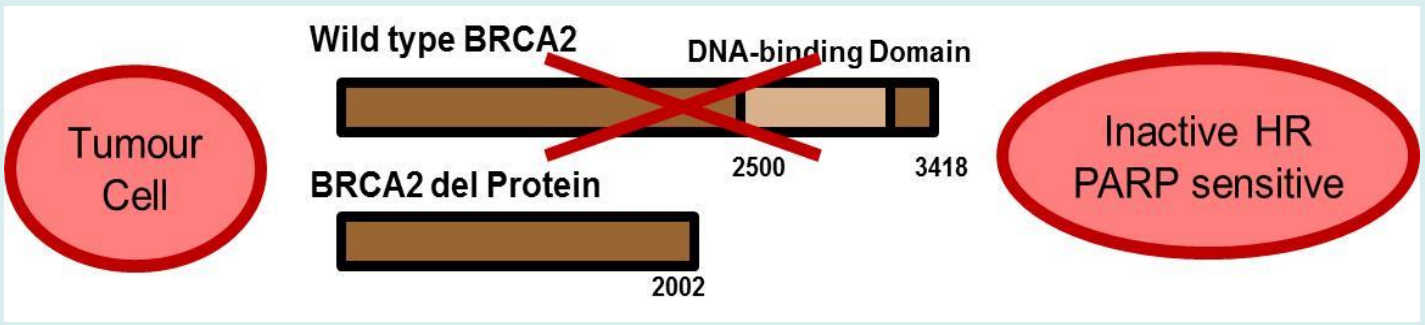
Why
effect
selec

Critical to understand biology

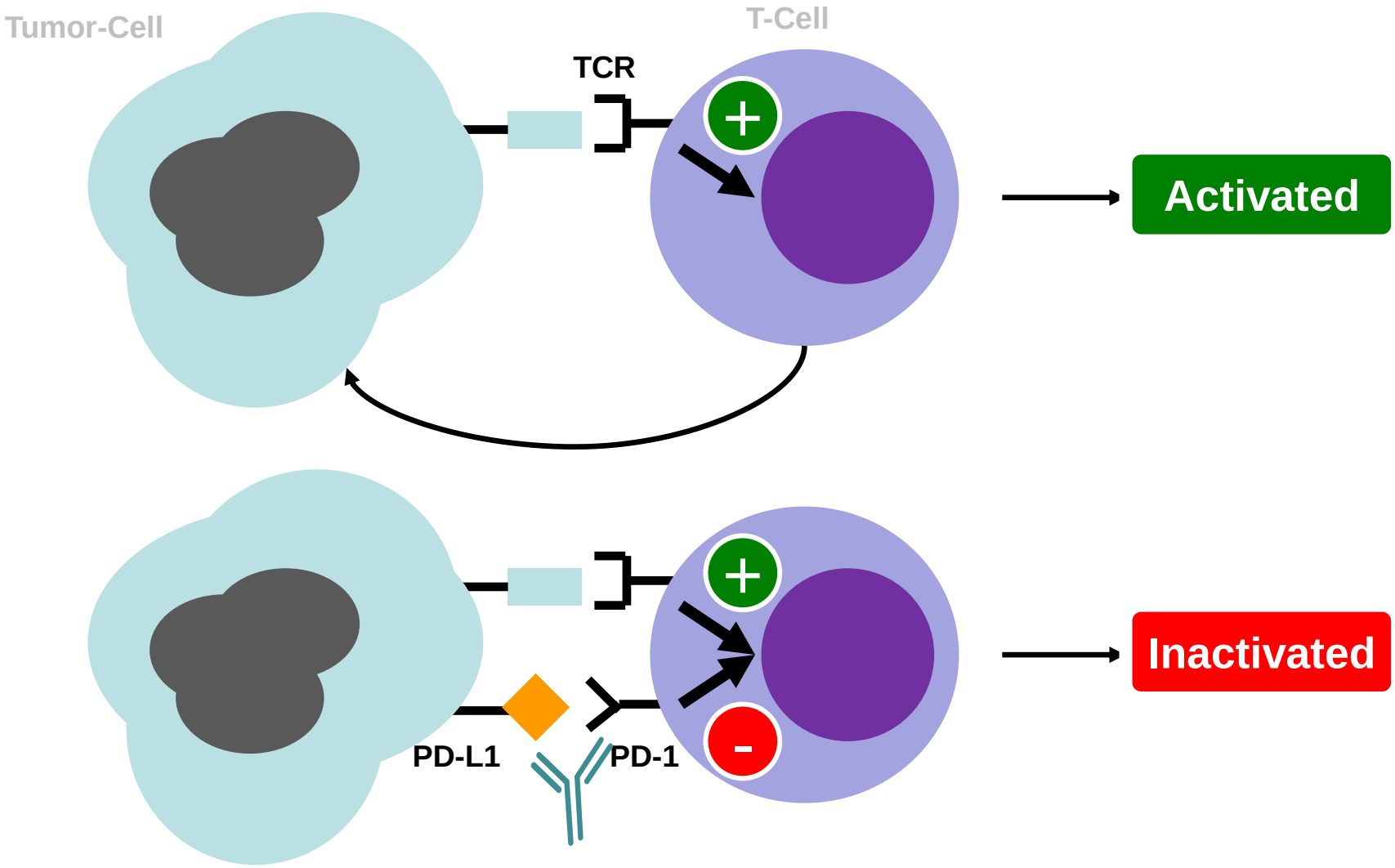
- (Epi) genetic background (eg, total vs partial loss of function)
- Phenotype (not always lethal but eg, sensitizing)
- Alternative options for cells



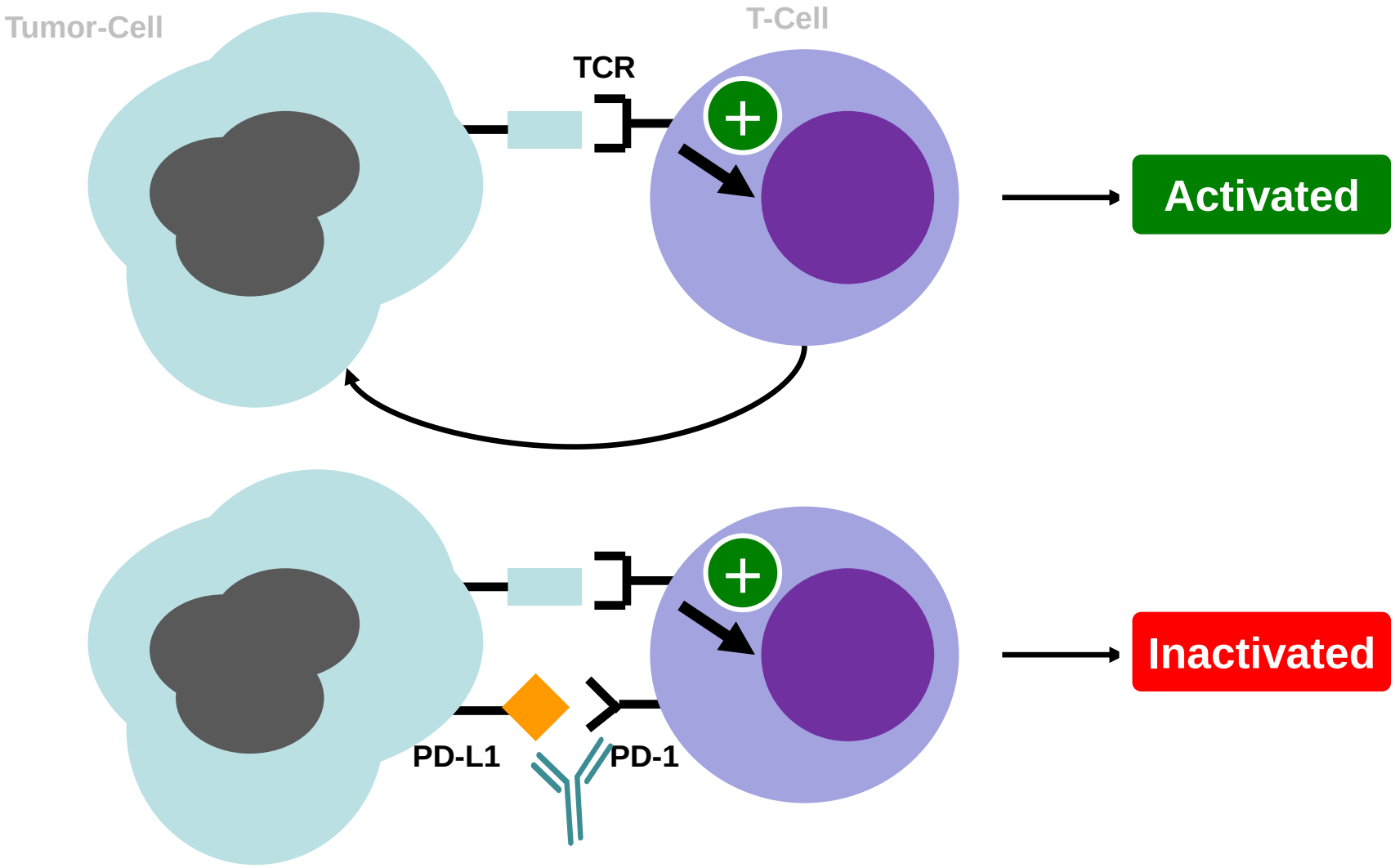
Cell death



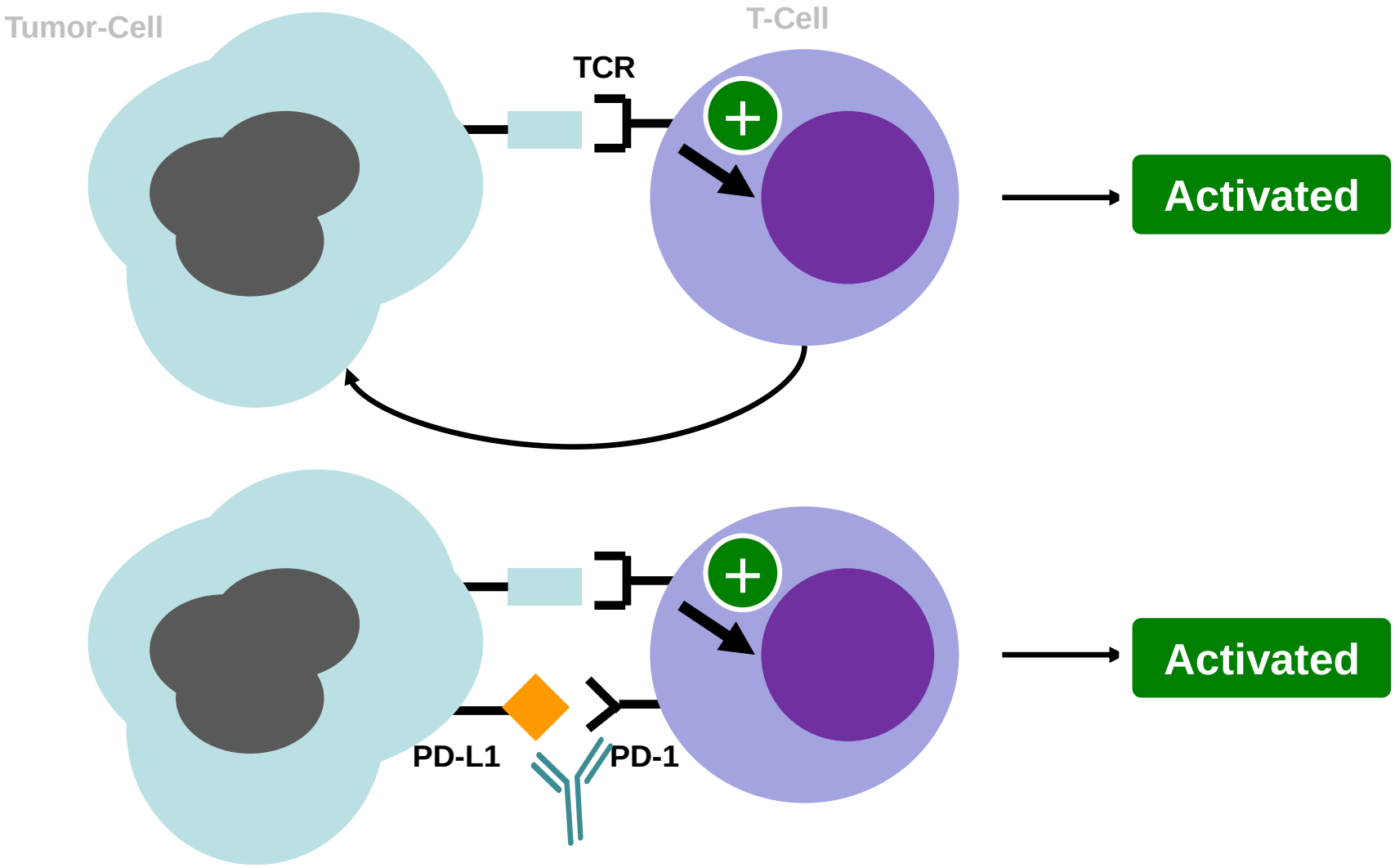
New Targets for TNBC
Targeting Immune-Checkpoints (PD-L1)



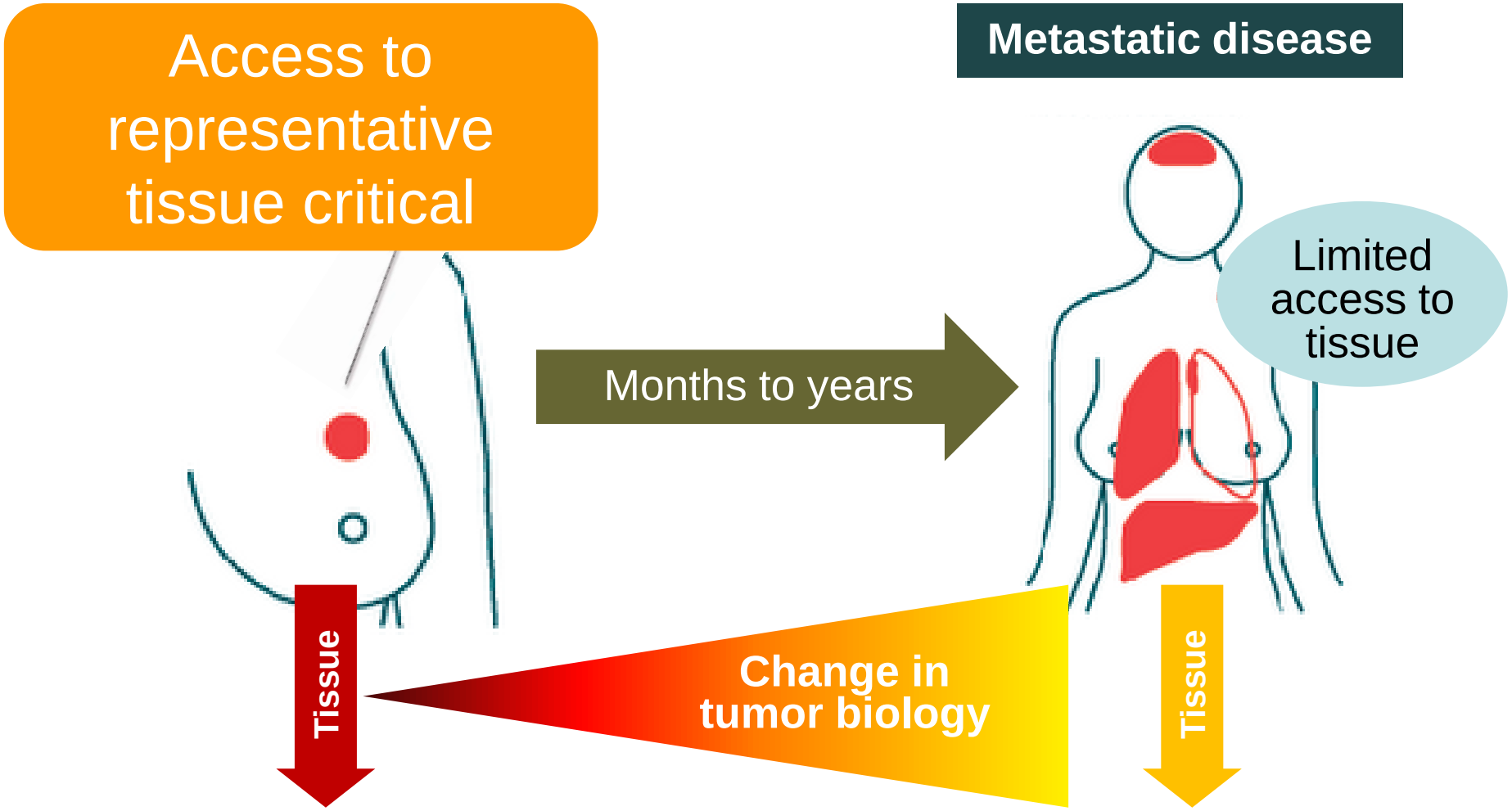
New Targets for TNBC
Targeting Immune-Checkpoints (PD-L1)



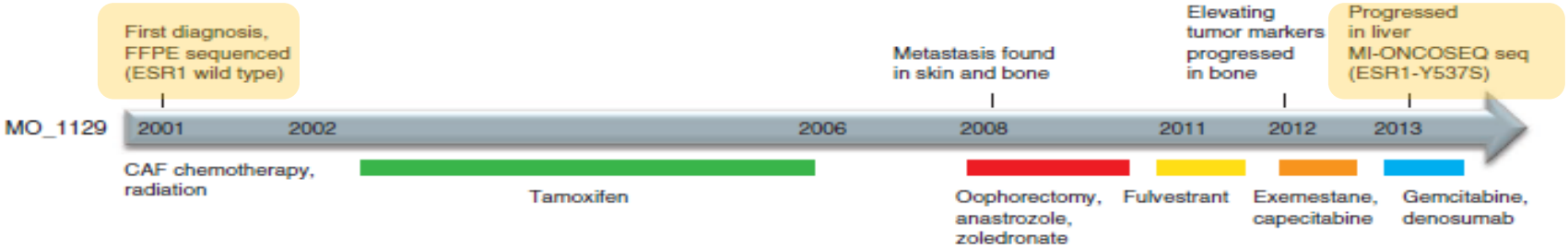
New Targets for TNBC
Targeting Immune-Checkpoints (PD-L1)



Novel Targeted Therapies and Patient Selection
Change of Tumor Biology Over Time

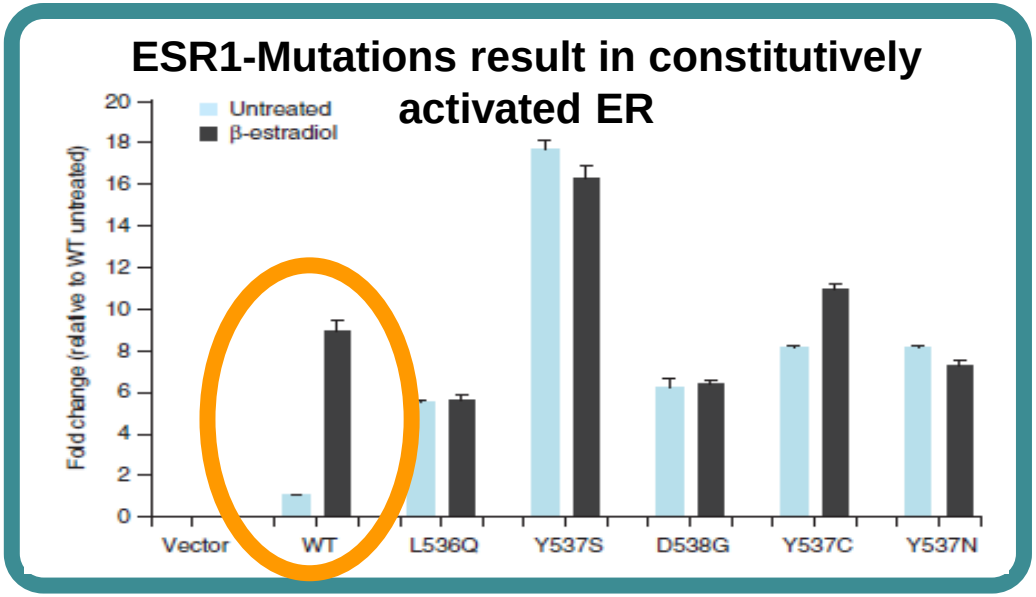


Change of Tumor Biology Over Time
Acquired ESR1 Mutations



Robinson DR, *Nat Genet.* 2013;45(12):1446-1451.

Change of Tumor Biology Over Time
Acquired ESR1 Mutations



Primary Tumor **ESR1 <1%**

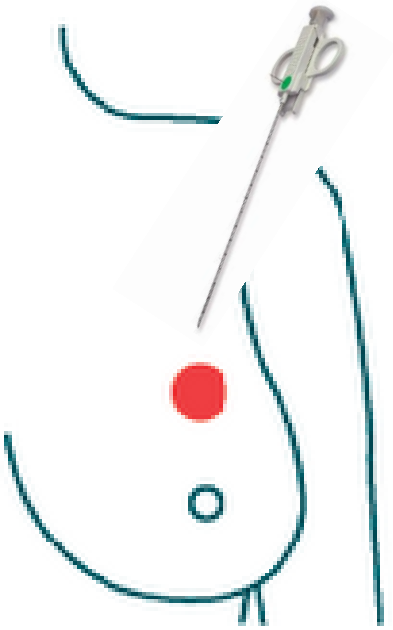
→

Metastatic disease **ESR1 10-20%?**

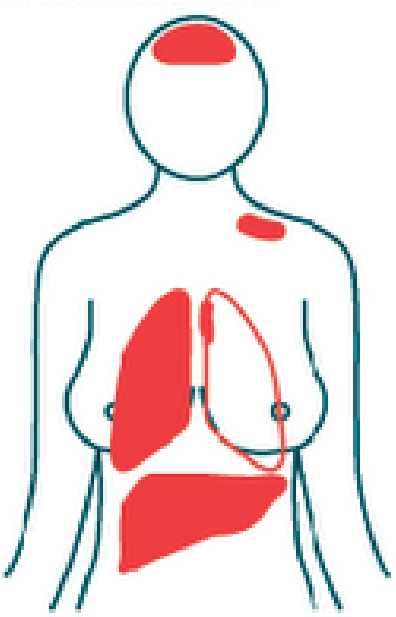
Robinson DR, *Nat Genet.* 2013;45(12):1446-1451.

Circulating Biomarkers to Assess Dynamic Changes Genetic Profiles From cfDNA

Early breast cancer

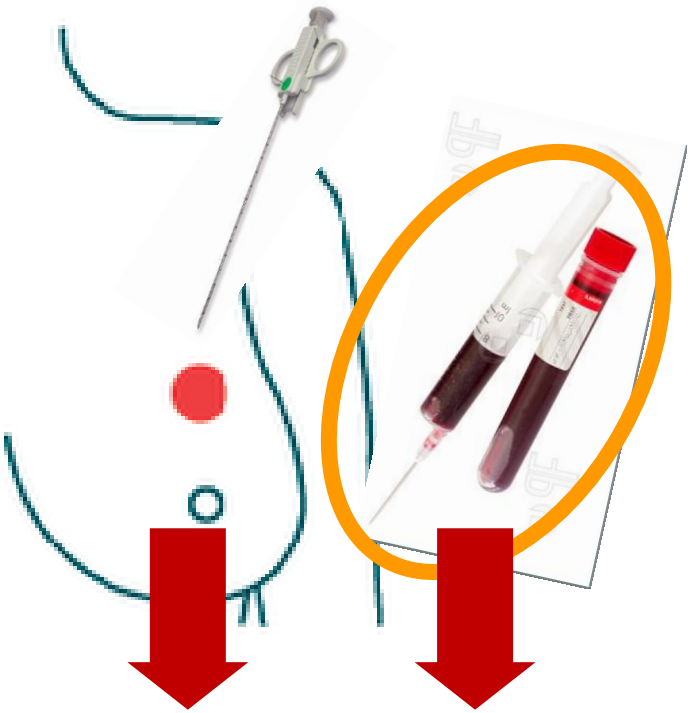


Metastatic disease

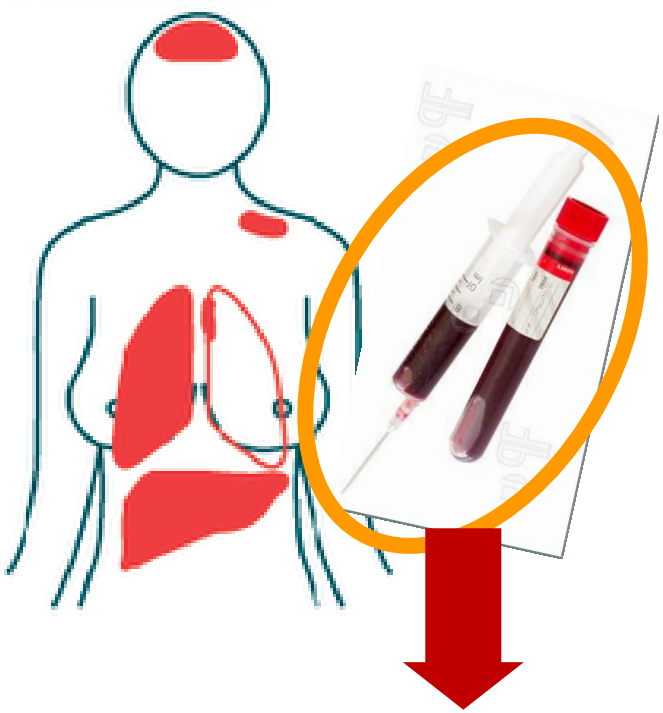


Circulating Biomarkers to Assess Dynamic Changes Genetic Profiles From cfDNA

Early breast cancer



Metastatic disease

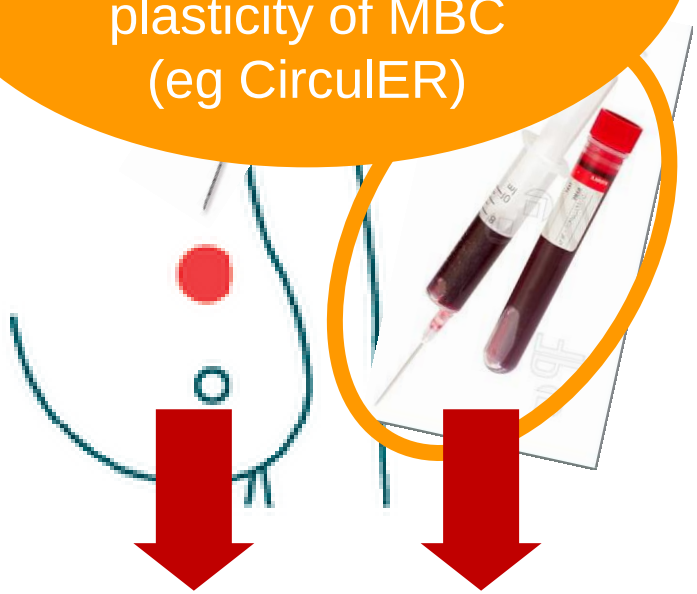


(Epi)genetic changes detectable in blood

Simple means for assessing changes

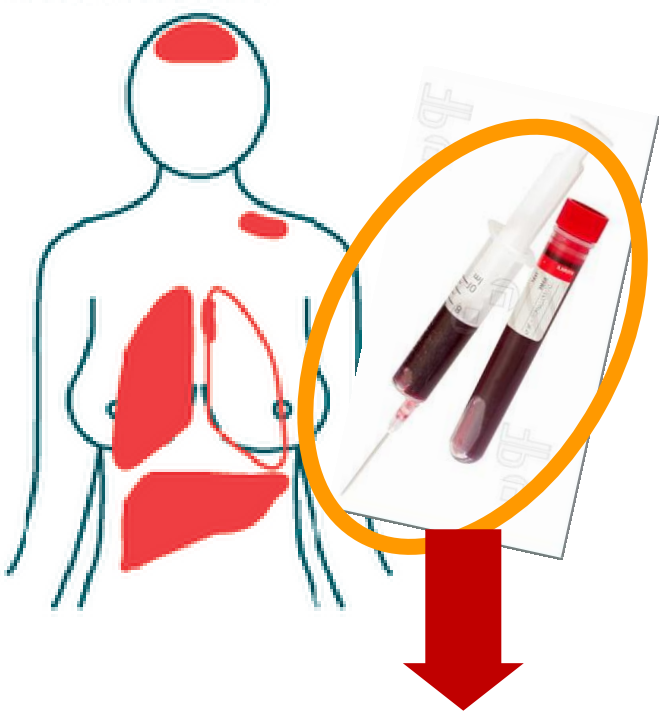
Circulating Biomarkers to Assess Dynamic Changes Genetic Profiles From cfDNA

Longitudinal studies of circulating biomarkers to study plasticity of MBC (eg CirculER)



(Epi)genetic changes detectable in blood

Metastatic disease



Simple means for assessing changes

Molecular Targeted Approaches to Therapy in MBC
Summary and Conclusions

- ER and HER2 remain the dominant pathways in MBC
- Crosstalk between ER or HER2 and signaling pathways is a key driver of endocrine resistance
- Combination treatment strategies (eg, with PI3K/mTOR pathway inhibitors or CDK4/6 inhibitors) can overcome resistance
- Increasing understanding of the heterogeneity of TNBC reveals new therapeutic targets (eg, DNA Damage repair, Immune checkpoints)
- Lack of biomarkers for patient selection remains challenging

Striking Success:

The Emergence of New Targeted Treatment Strategies for Advanced Breast Cancer