ATLAS OF MOLECULAR ONCOLOGY

BREAST CANCER PATHWAYS

Biology of HER2 Cell Signaling and Anti-HER2 Agents

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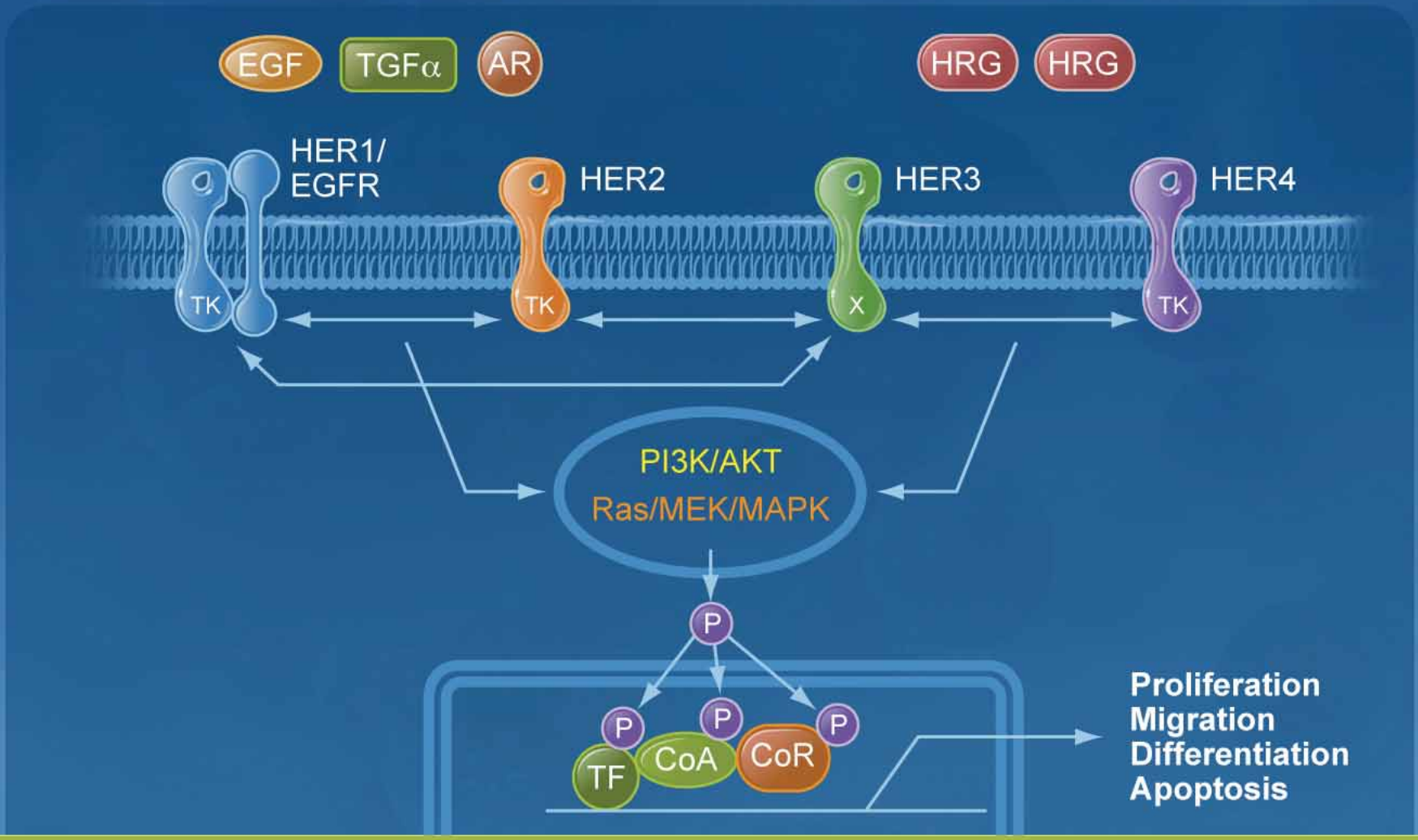
Disclosures for Jenny C Chang, MD

Consulting Agreement	Boehringer Ingelheim Pharmaceuticals Inc
Speakers Bureau	GlaxoSmithKline

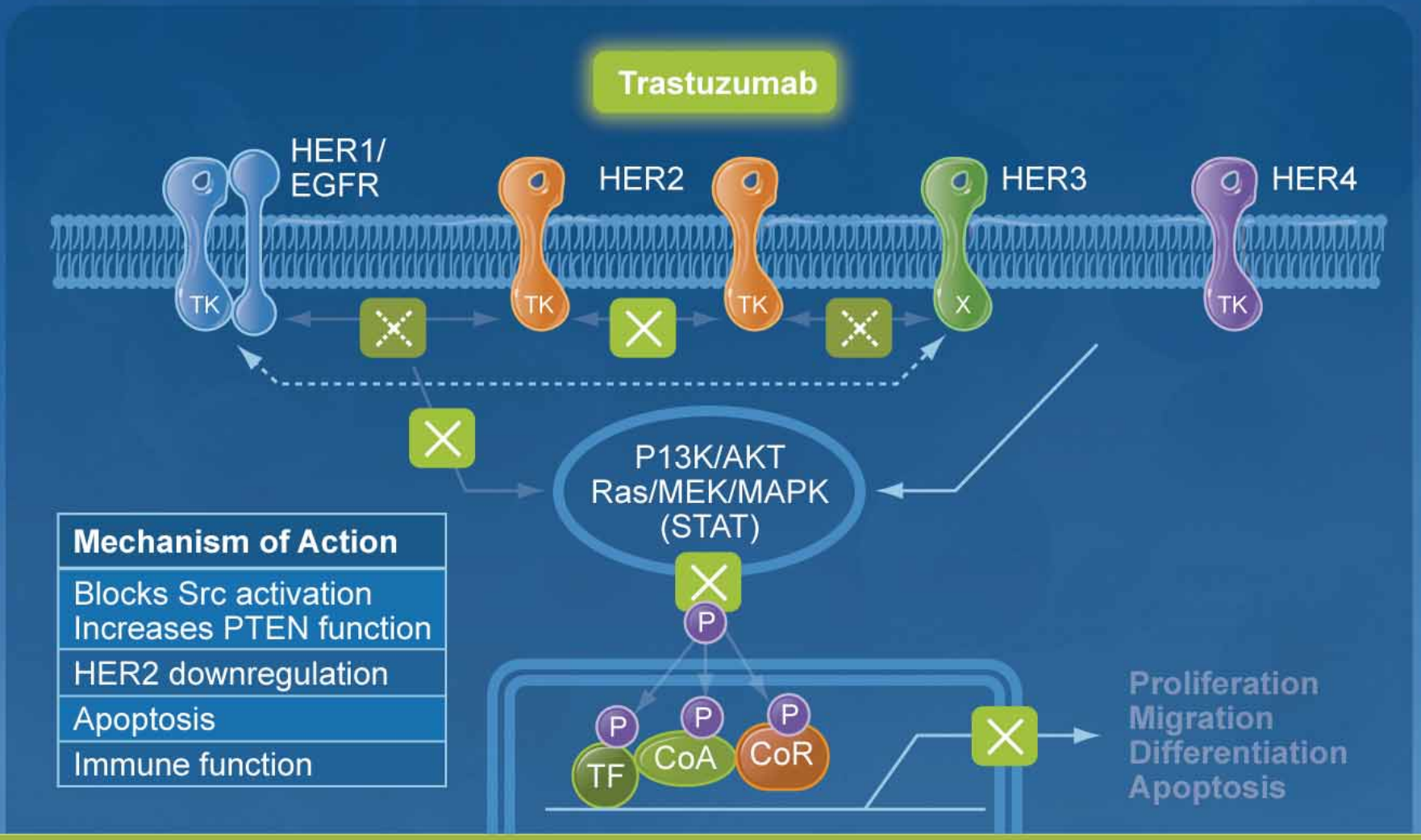
Optimal Targeted Therapy

- Identify key pathway(s)
- Block this pathway completely
- Anticipate escape (resistance) mechanisms and block them
- Combination therapy

Pathway Activation – HER Ligands



Pathway Inhibition



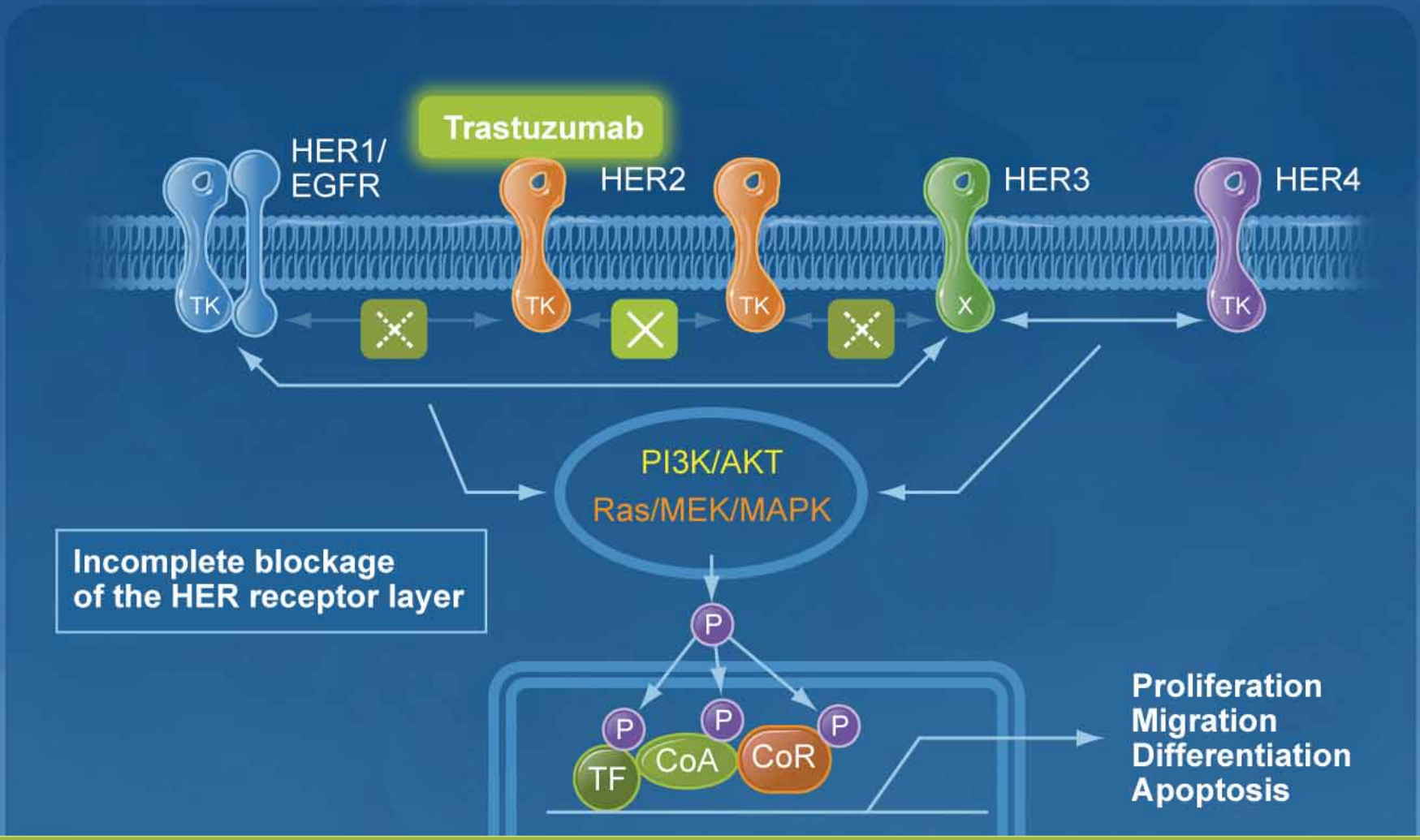
Mechanisms for Resistance to Trastuzumab

- Activation of the pathway downstream
  - PI3K mutations
  - pTEN loss
  - Cyclin E amplification
- Loss of the HER2 ext binding domain
  - p95
- Increased expression of HER ligands

Mechanisms for Resistance to Trastuzumab (continued)

- Redundant survival pathway
  - IGF, ER
- Activation by other kinases
  - Src, MET, integrins, stress kinases
- Upregulation of HER1 or HER3
- Incomplete blockade of the HER receptor layer

Mechanisms of Resistance to HER Targeted Therapy



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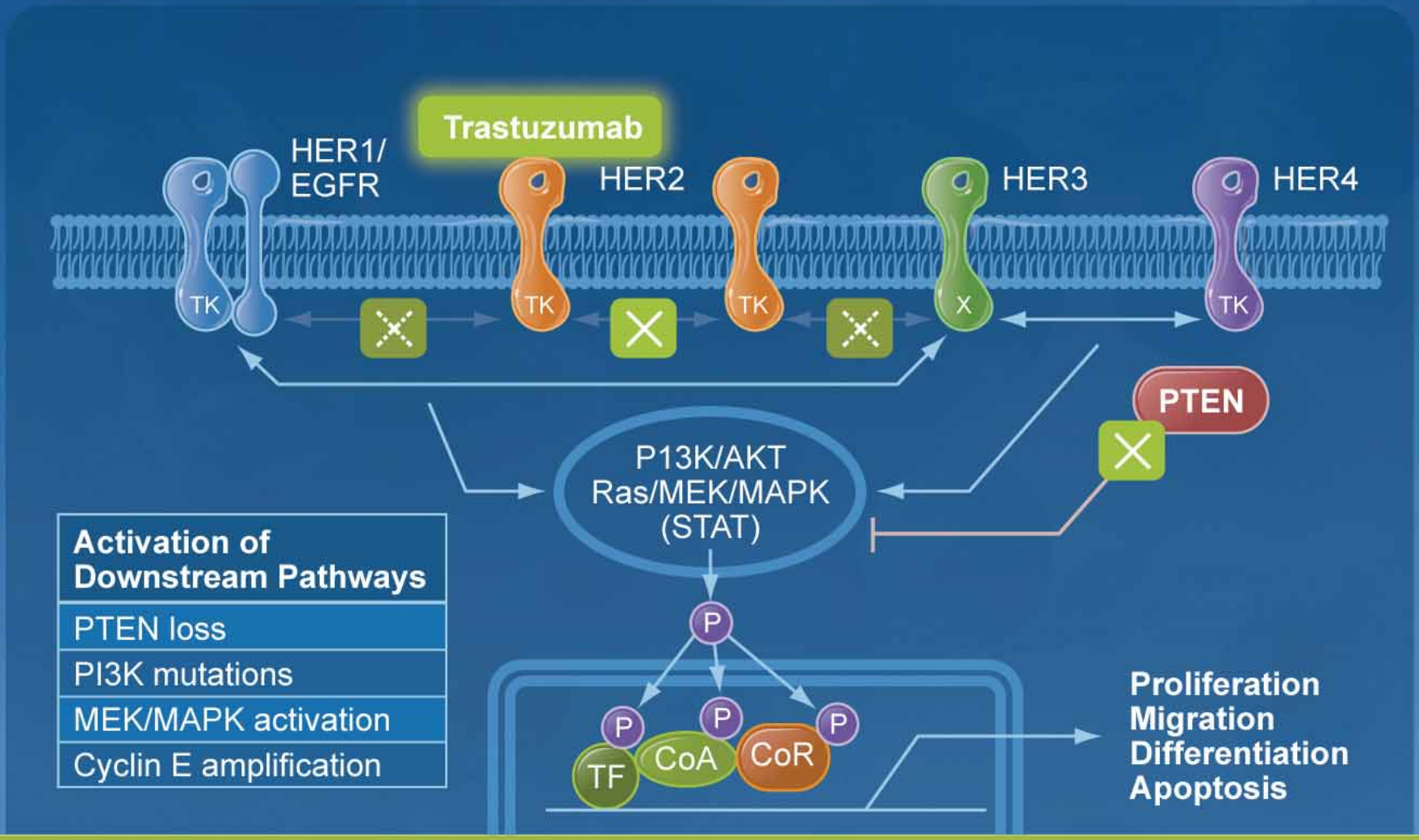
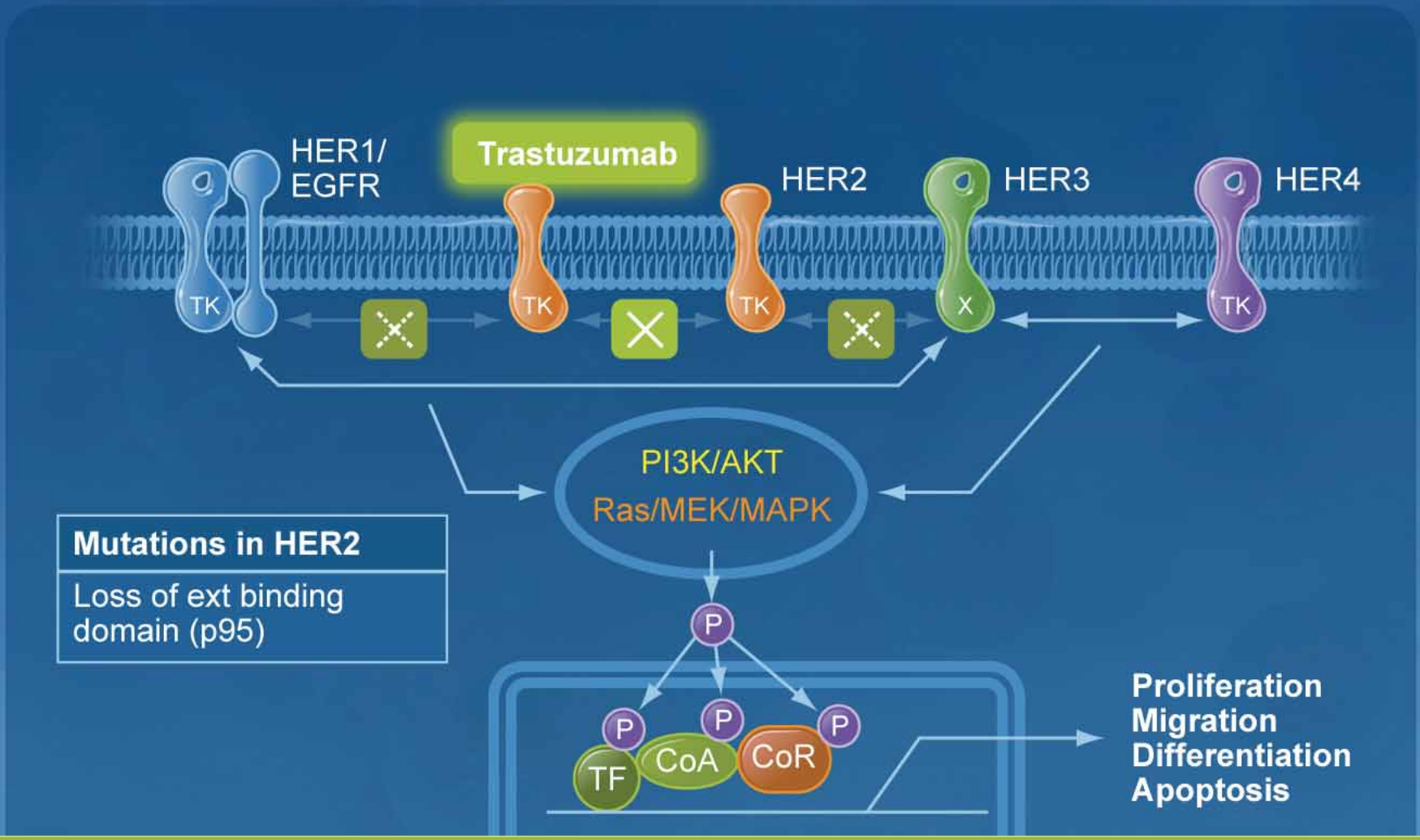
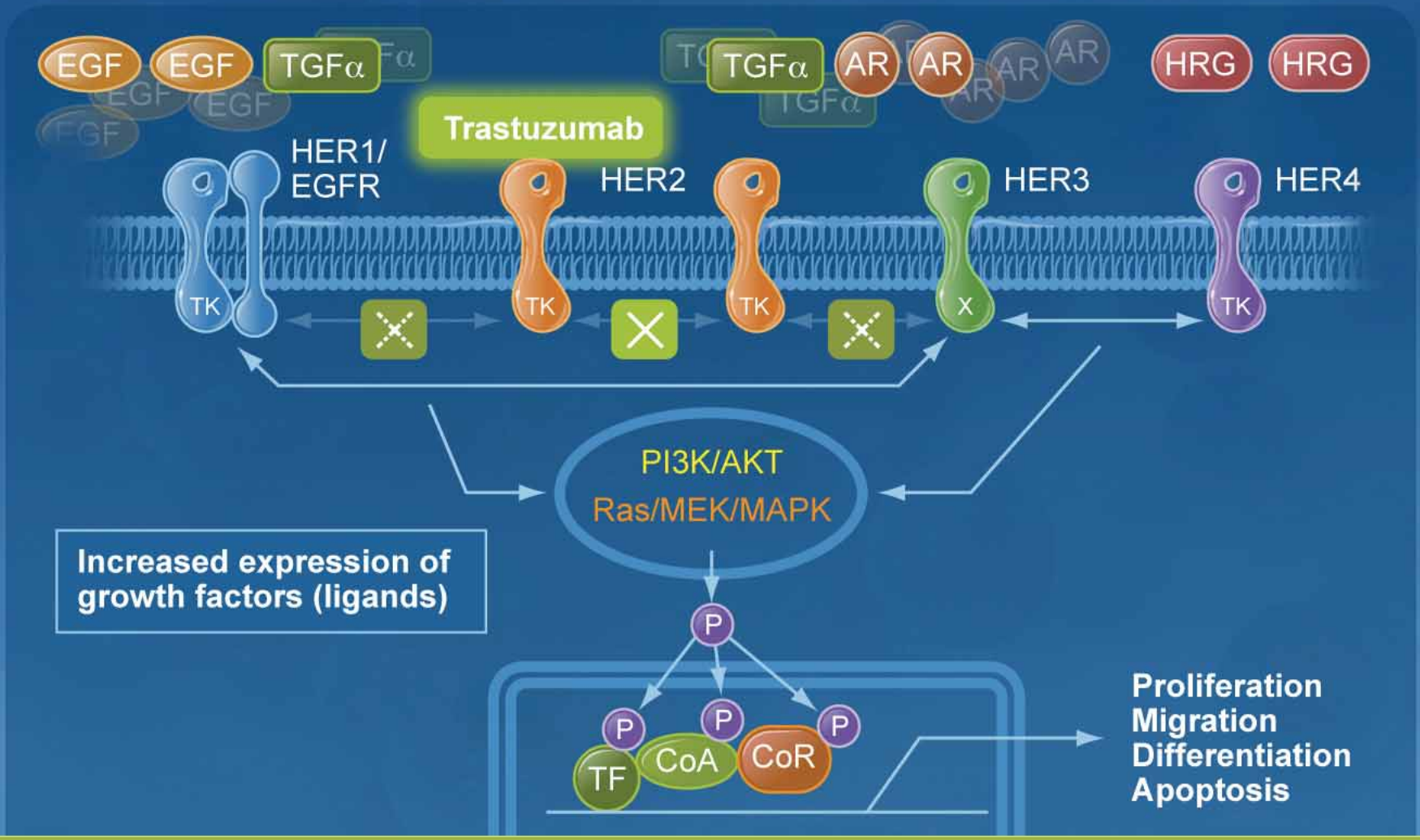


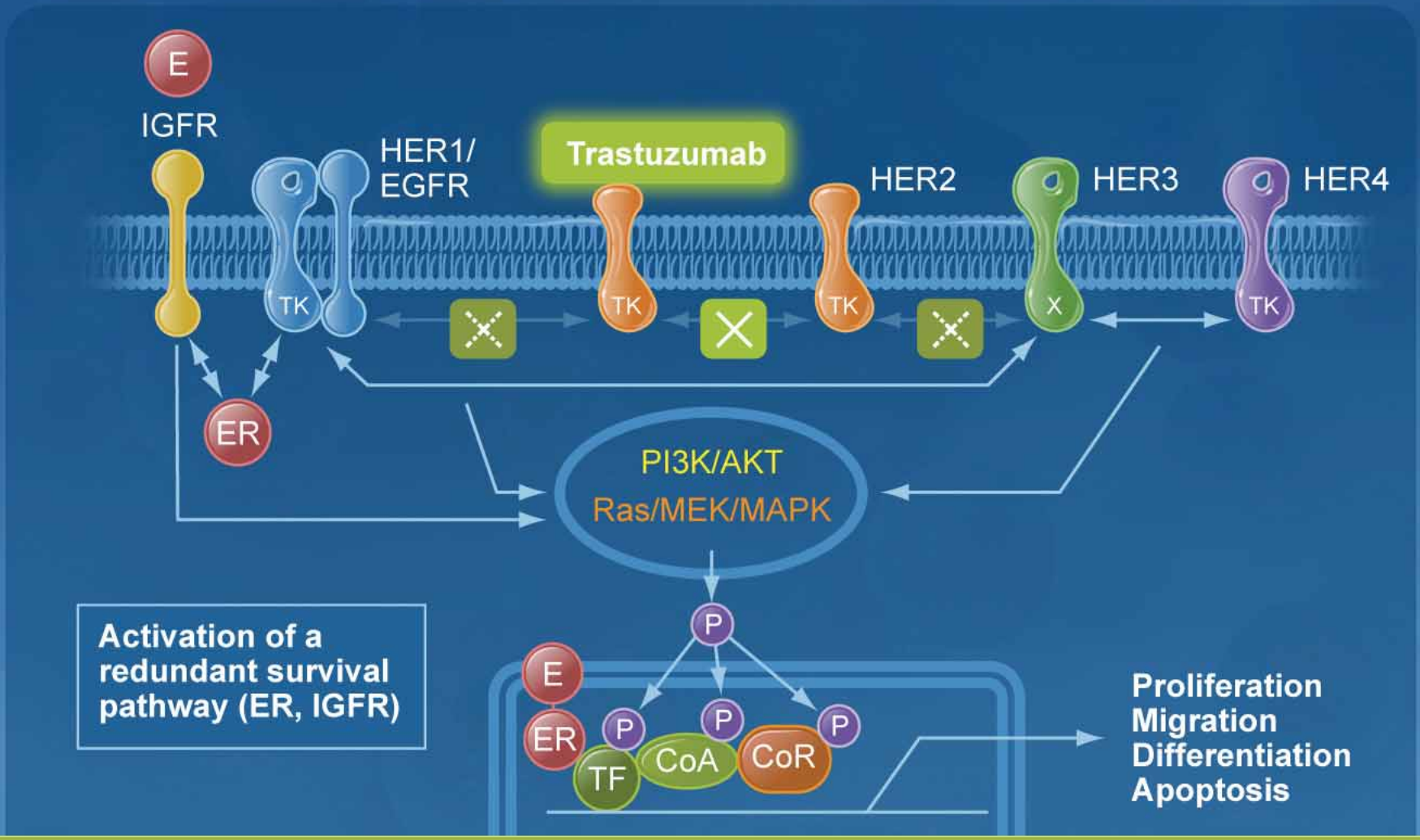
Mechanisms of Resistance to HER Targeted Therapy



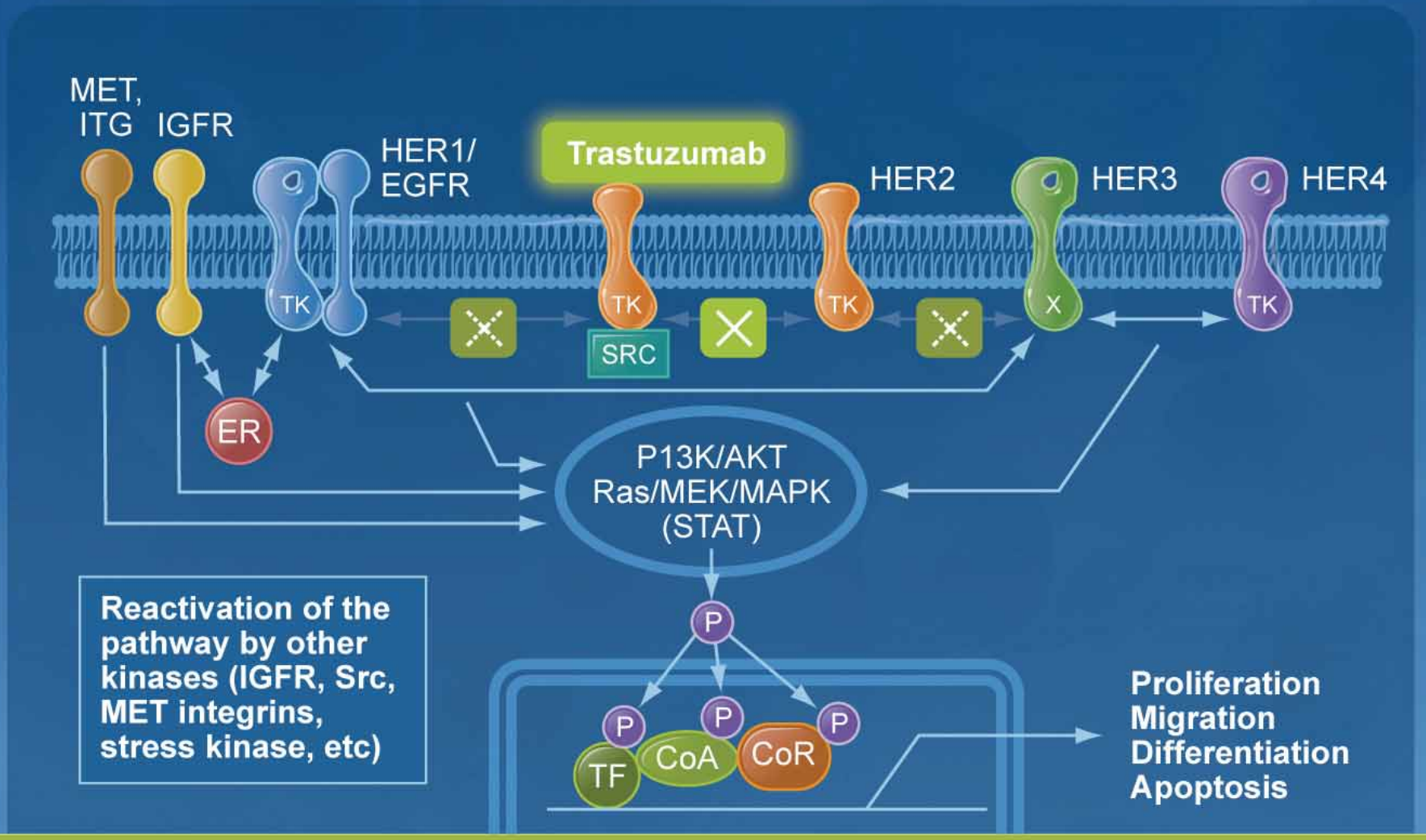
Mechanisms of Resistance to HER Targeted Therapy



Mechanisms of Resistance to HER Targeted Therapy



Mechanisms of Resistance to HER Targeted Therapy



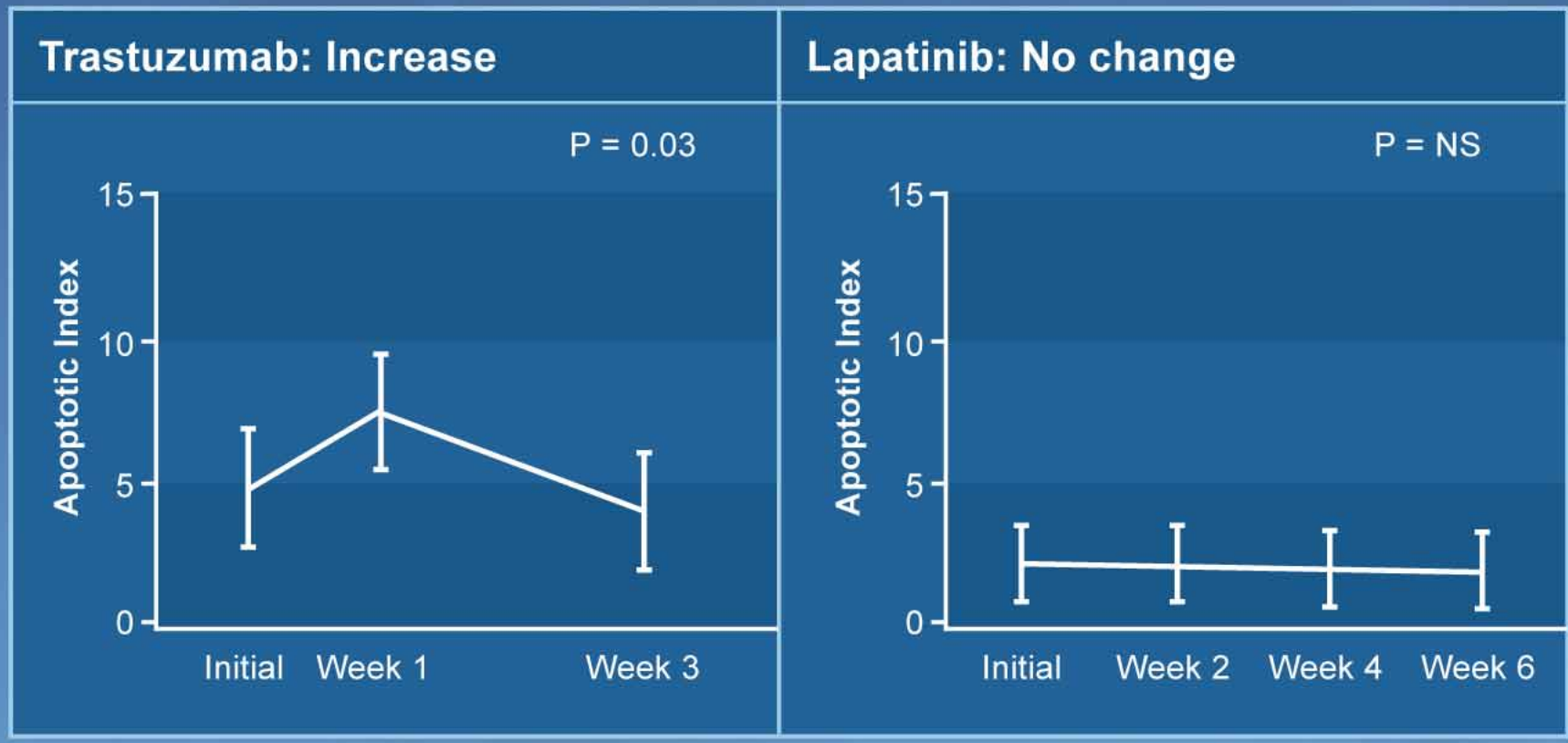
Trials of Trastuzumab Adjuvant Therapy

	Hazard Rate	
Trial	**DFS**	**OS**
B31/N9831	0.67	0.86
HERA	0.76	0.85
BCIRG AC → TH TCH	0.64 0.75	0.63 0.77
FinHer	0.42	0.41

Clinical Trials of Lapatinib

- Activity post trastuzumab in metastatic disease
- Similar activity to trastuzumab in previously untreated HER2+ patients
- Adds to capecitabine
- Rash and diarrhea

Apoptosis



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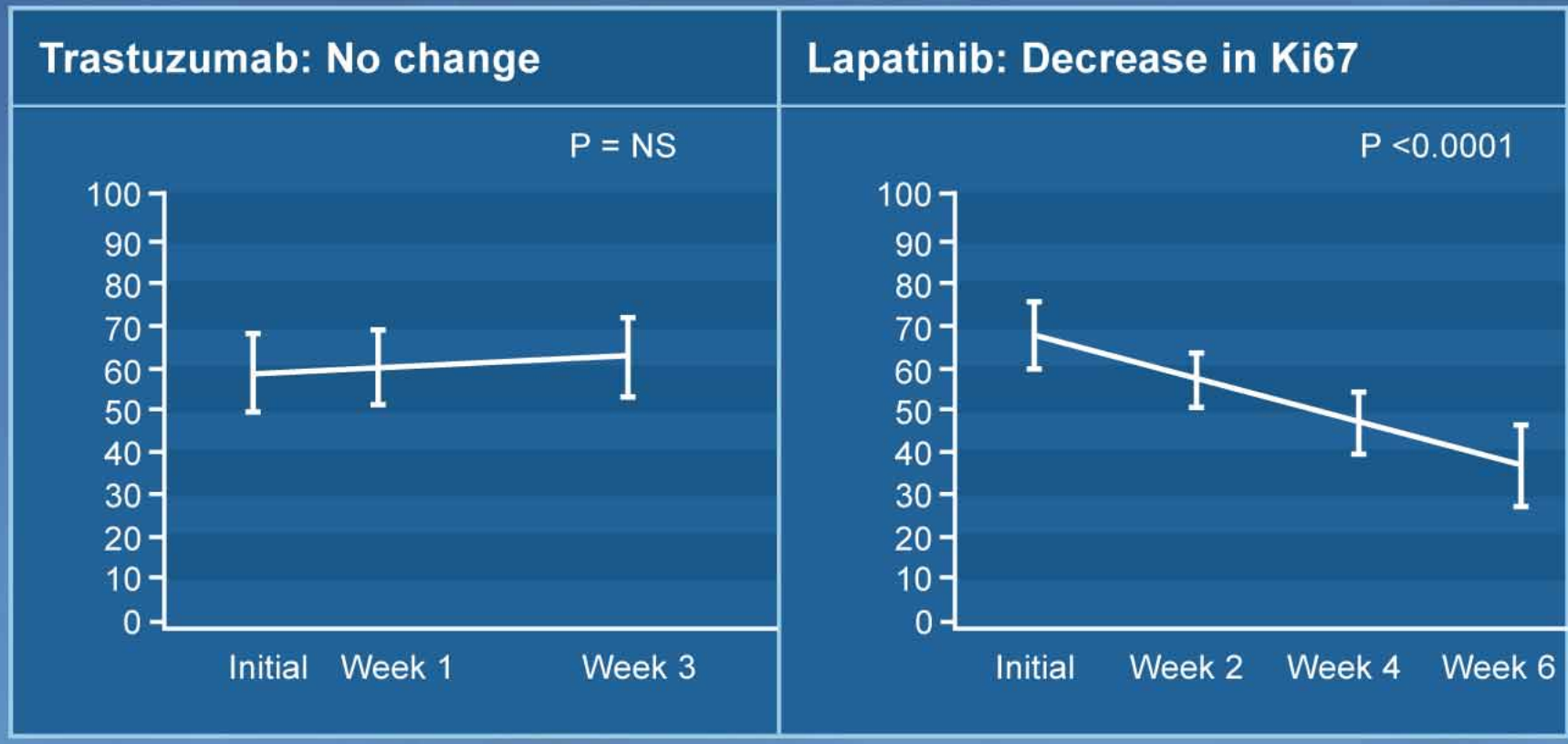
Proliferation: Ki67



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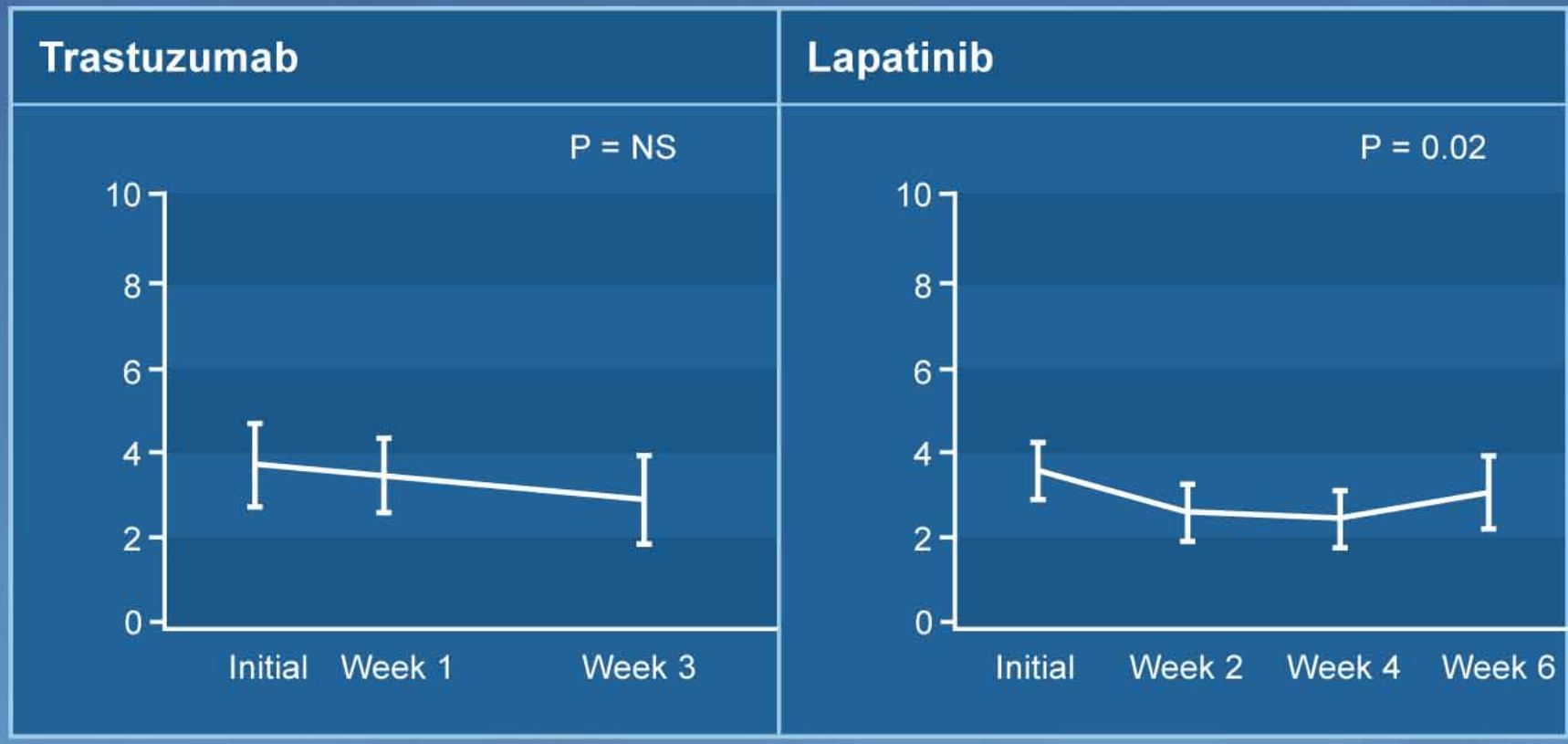
p-MAPK



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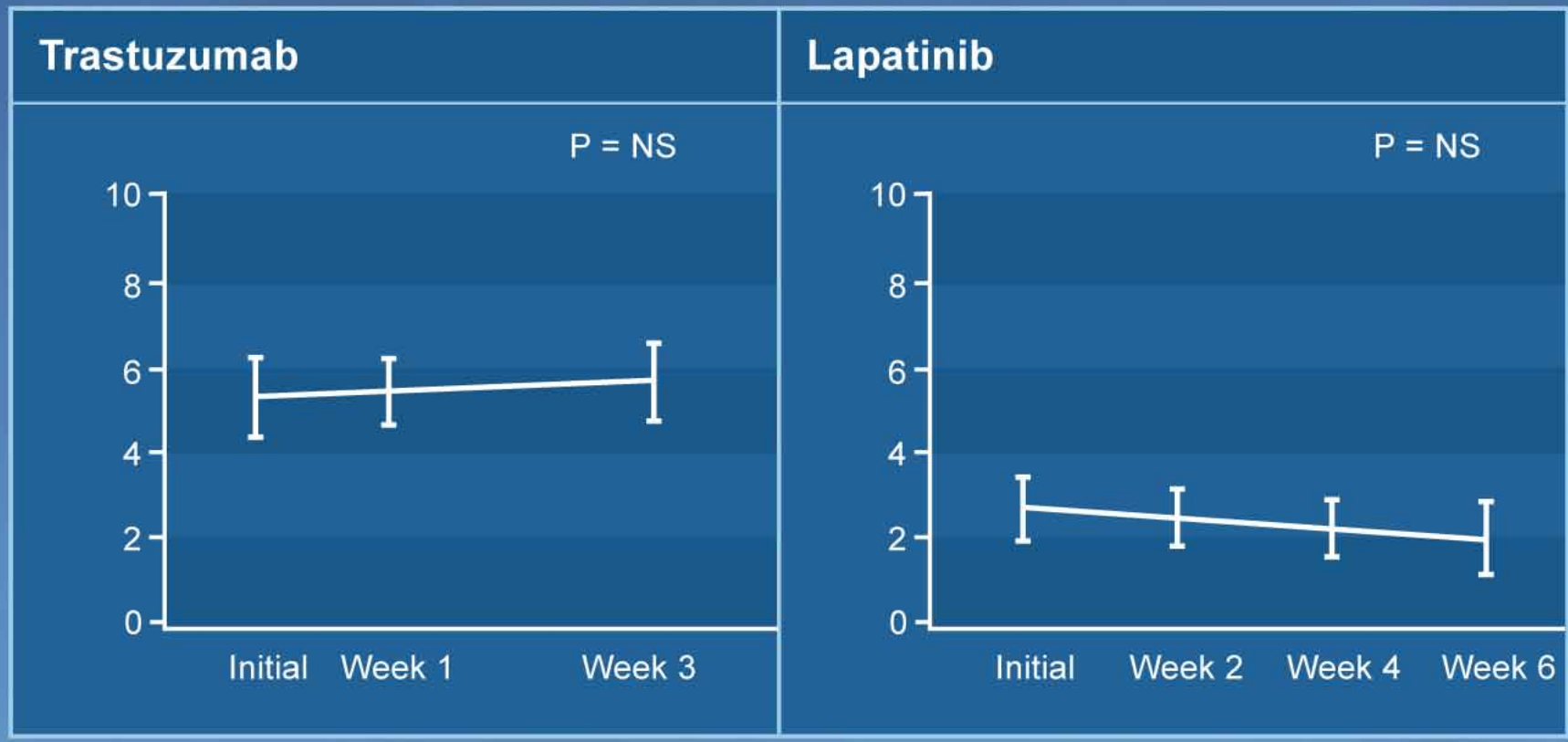
p-AKT



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Low PTEN/PI3KCA-mut

	Trastuzumab (N) %	Lapatanib (N) %
PCR	18% (4/22)	87% (13/15)
Non-pCR	82% (18/22)	13% (2/15)

Logistic regression between low PTEN/PI3KCA-mut and treatment response, p = 0.0016

Summary of Results: Trastuzumab vs Lapatinib

Trastuzumab:

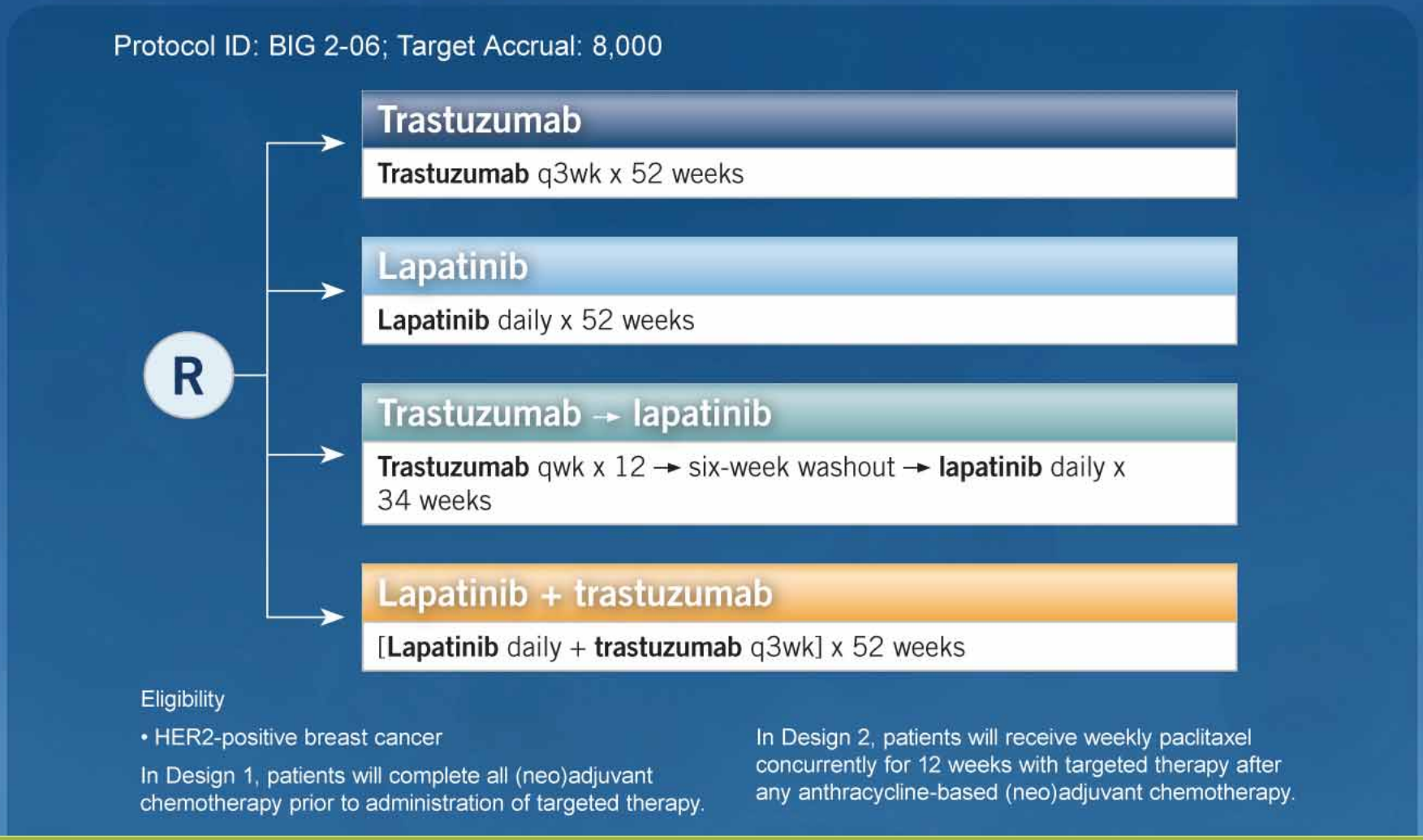
- Induces apoptosis likely through PI3/AKT
- No effect on proliferation (Ki67 or p-MAPK)

Lapatinib:

- Decrease Ki67
- Decreases p-MAPK
- No effect on apoptosis

Migliaccio I et al. SABCS 2008;Abstract 34.

Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) Trial



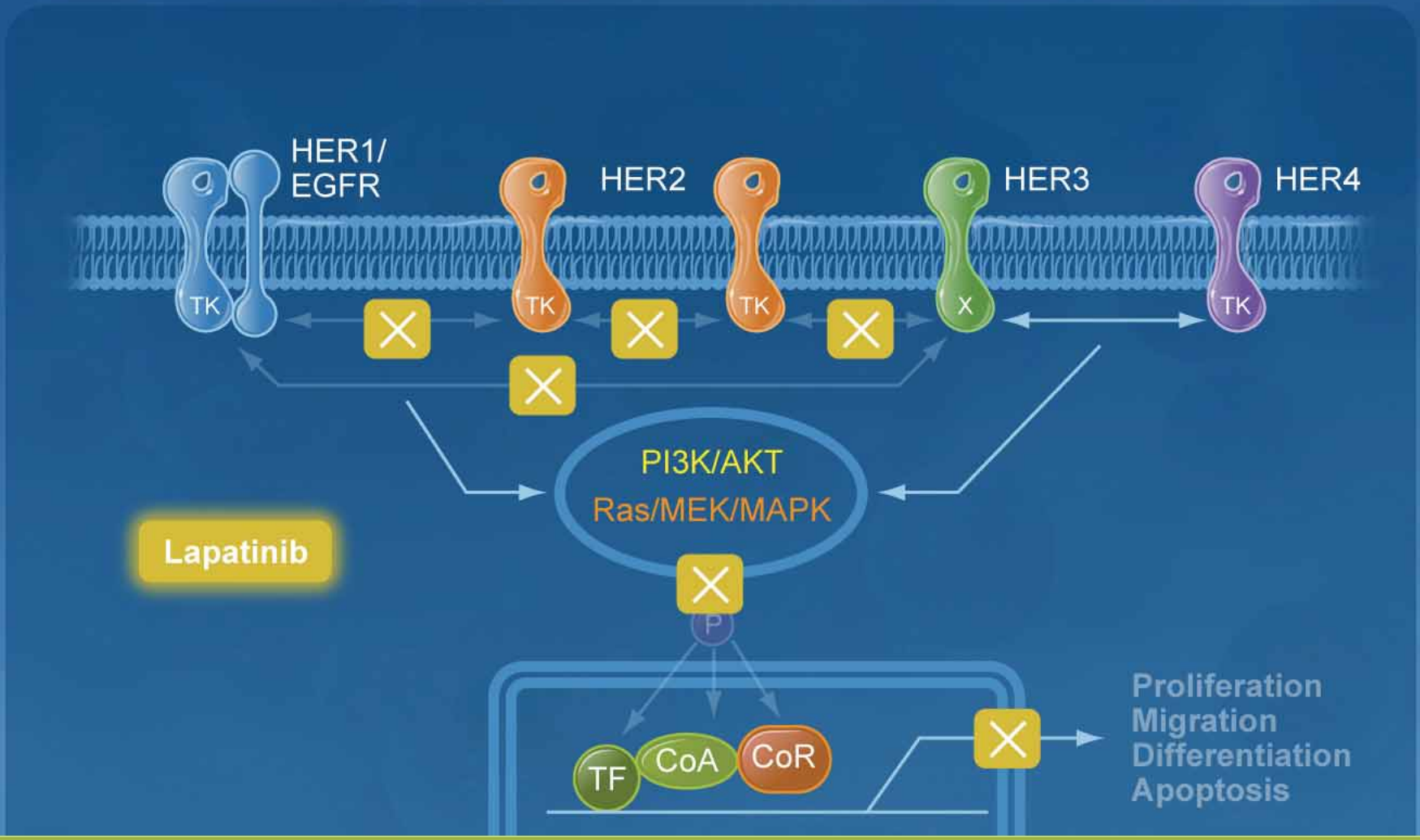
www.breastinternationalgroup.org; www.alttotrials.com

Other HER Targeting Agents

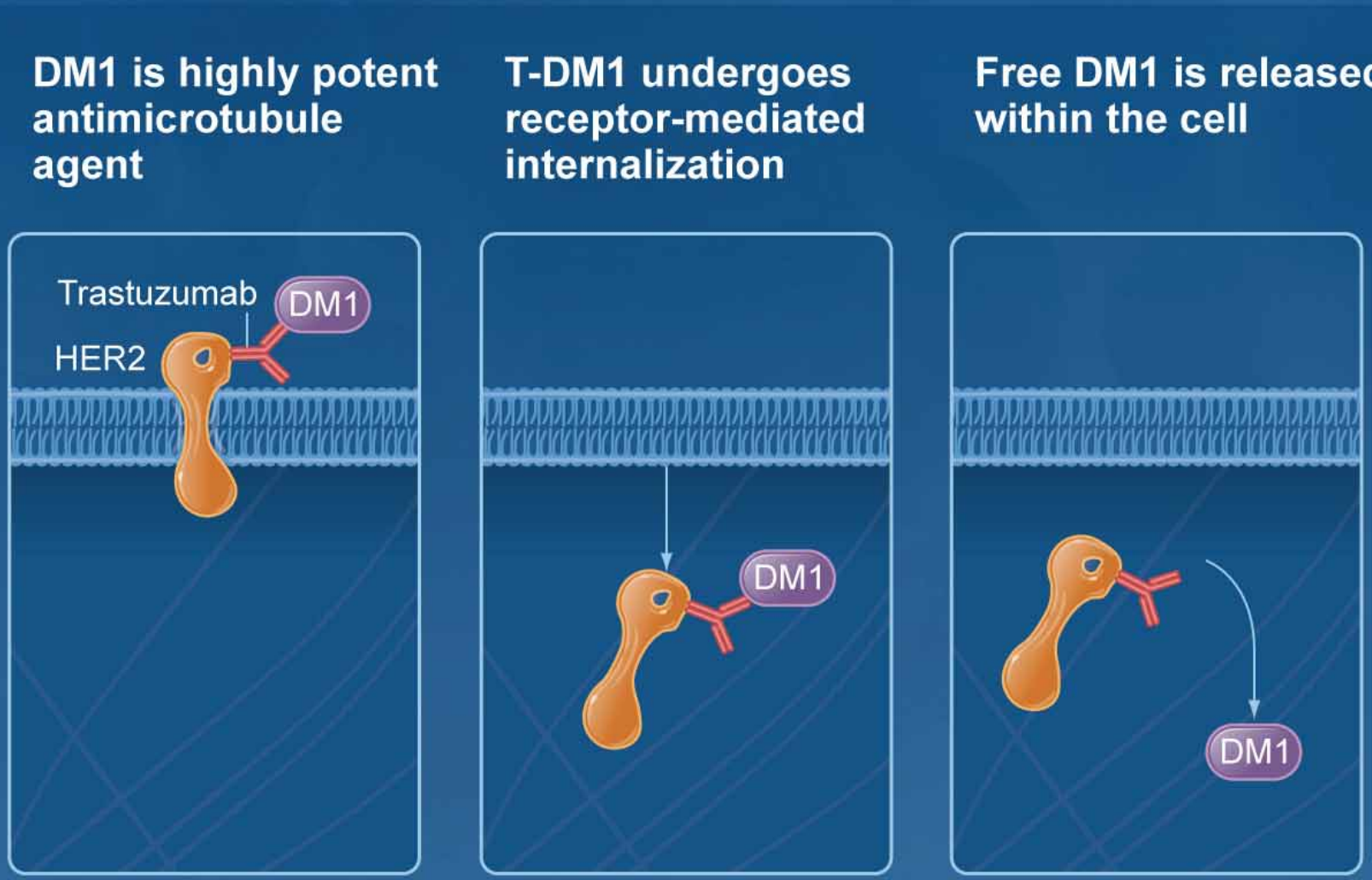
Inhibition of HER Family Signaling

Drug	Block
Gefitinib, Erlotinib, Cetuximab	1-1, 1-2, 1-3
Trastuzumab/T-DM1	2-2, HER2/Src
Pertuzumab	1-2, 2-3
Lapatinib	1-1, 1-2, 1-3, 2-3
Neratinib	1-1, 1-2, 1-4, 2-4

HER Targeted Therapies



Trastuzumab DM1



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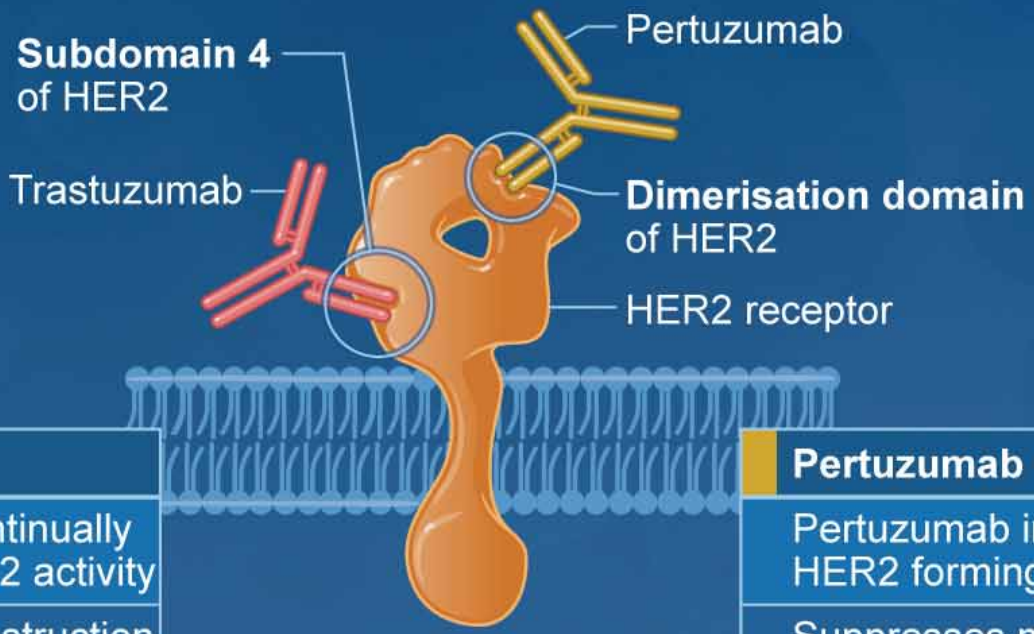
Trastuzumab and Pertuzumab Bind to Different Regions on HER2



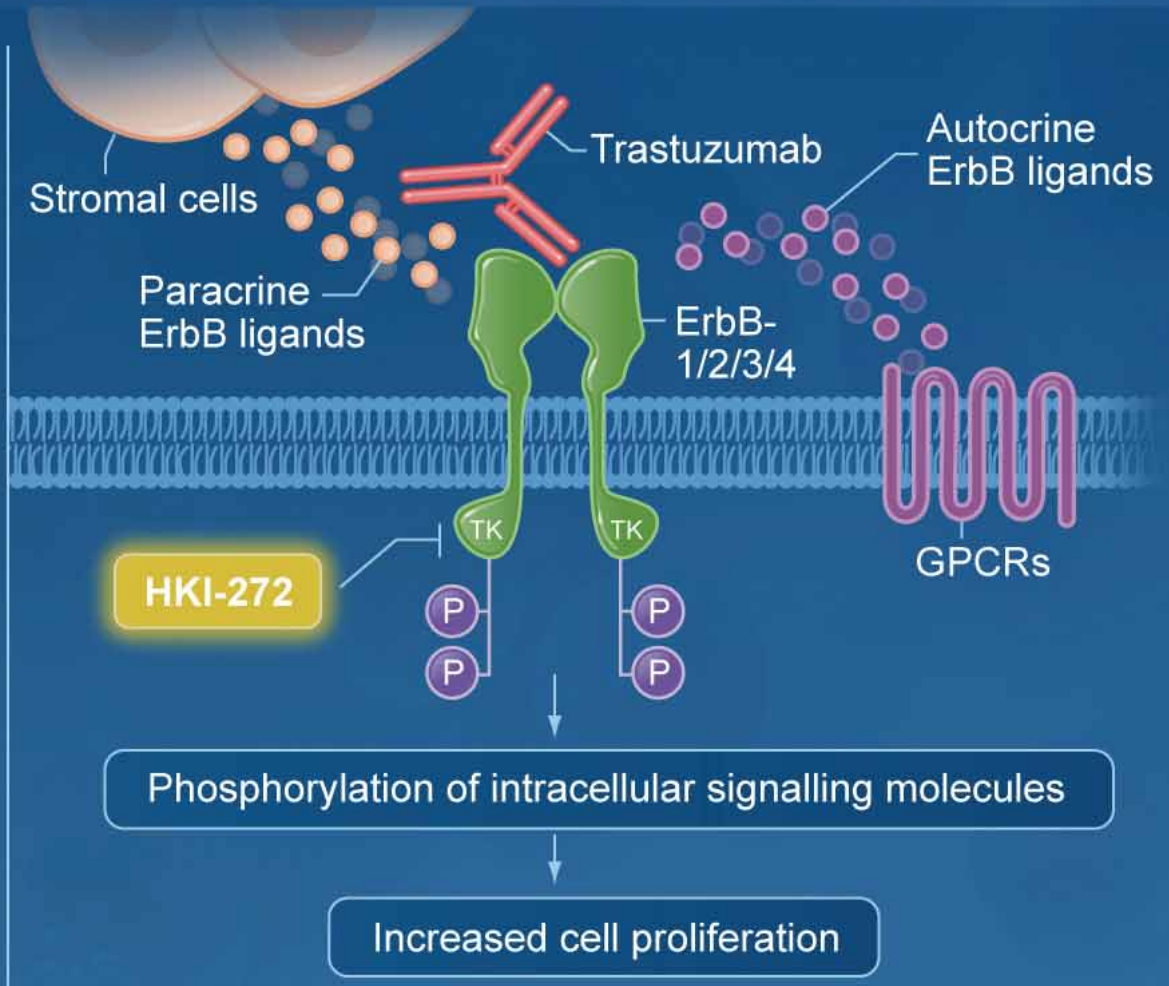
Trastuzumab
Trastuzumab continually suppresses HER2 activity
Flags cells for destruction by the immune system
Does not inhibit HER2 dimerization

Pertuzumab
Pertuzumab inhibits HER2 forming dimer pairs
Suppresses multiple HER signalling pathways
Flags cells for destruction by the immune system

With permission from Cortés J. ASCO 2009;Abstract 1022.

Neratinib (HKI-272) Mechanism of Action

- Potent, low molecular weight, orally administered irreversible pan-ErbB receptor tyrosine kinase inhibitor (ErbB-1/2/4)
- Binds covalently to the intracellular TK domain to inhibit auto-phosphorylation and subsequent downstream signaling



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Summary

- The HER signaling pathway is a complex, redundant, robust and adaptable network.
- Inhibiting the network is very effective in patients with HER2 over-expressing tumors.
- *De novo* and acquired resistance occur and there are many potential mechanisms.
- Incomplete blockade of the receptor layer is one such mechanism that explains resistance in some xenograft models.

Summary (continued)

- Combined receptor inhibitors or receptor inhibitors combined with downstream/alternative signaling inhibitors deserve clinical evaluation.
- Predicting the mechanism of resistance in the primary tumor will be critical.

Acknowledgements

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