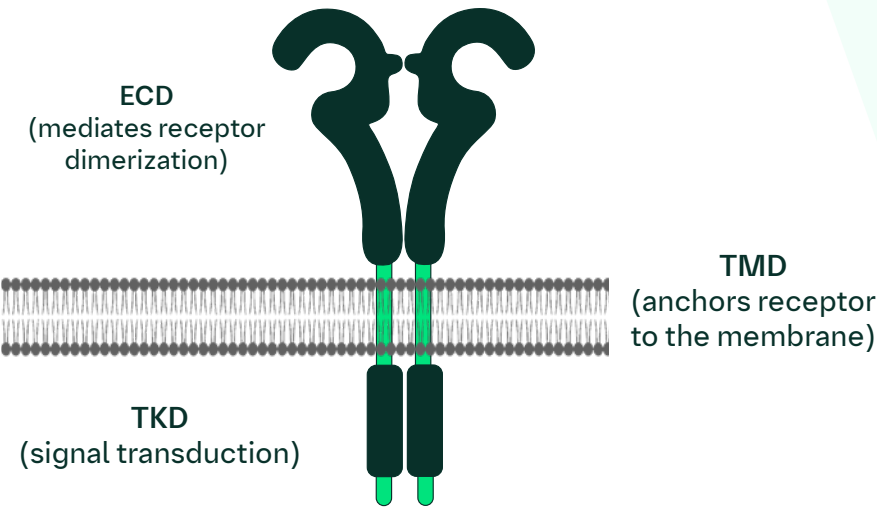


The HER2 (ERBB2) Blueprint: What ‘Activating’ Really Means

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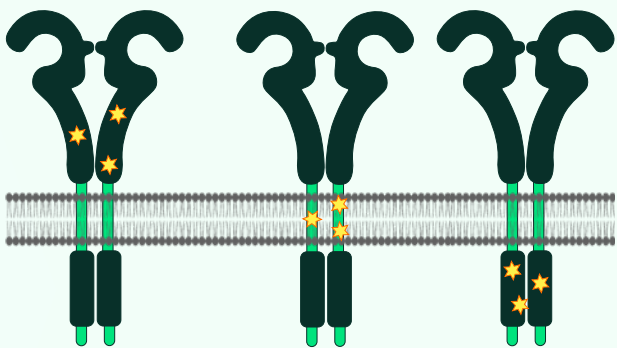
Oncol AMJ. 2026; <https://doi.org/10.33590/oncolamj/C5244JH8>

THE HER2 BLUEPRINT



- The HER2 receptor comprises three key domains: ECD, TMD, and TKD.^{1,2}
- Each domain plays a distinct role in receptor function.^{1,2}
- The active form of the HER2 receptor is a dimer (homo- or heterodimer).^{1,2}

ACTIVATING MUTATIONS CAN OCCUR ANYWHERE IN THE HER2 RECEPTOR



★ Activating mutation

- HER2 activating mutations are not restricted to the TKD.²
- They can be found throughout the receptor: in the ECD, TMD, and TKD.²
- Regardless of the location, activating mutations can dysregulate receptor signaling and drive oncogenesis.^{3,4}

DIFFERENT LOCATIONS, SAME CONSEQUENCES

ECD mutations often lead to stabilization of active, homodimeric HER2 receptors.⁵

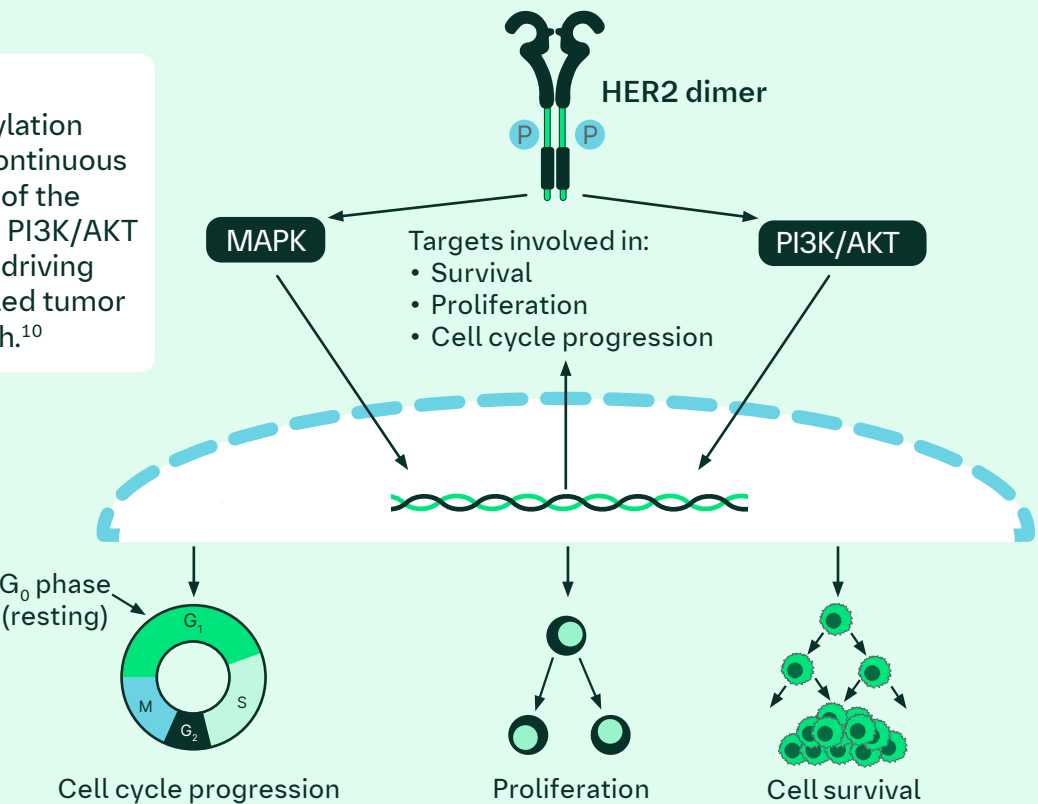
TMD mutations can stabilize the receptor in an active, open dimeric conformation.⁶

TKD mutations can shift the kinase domain from an inactive, closed state to an active, open conformation.⁷

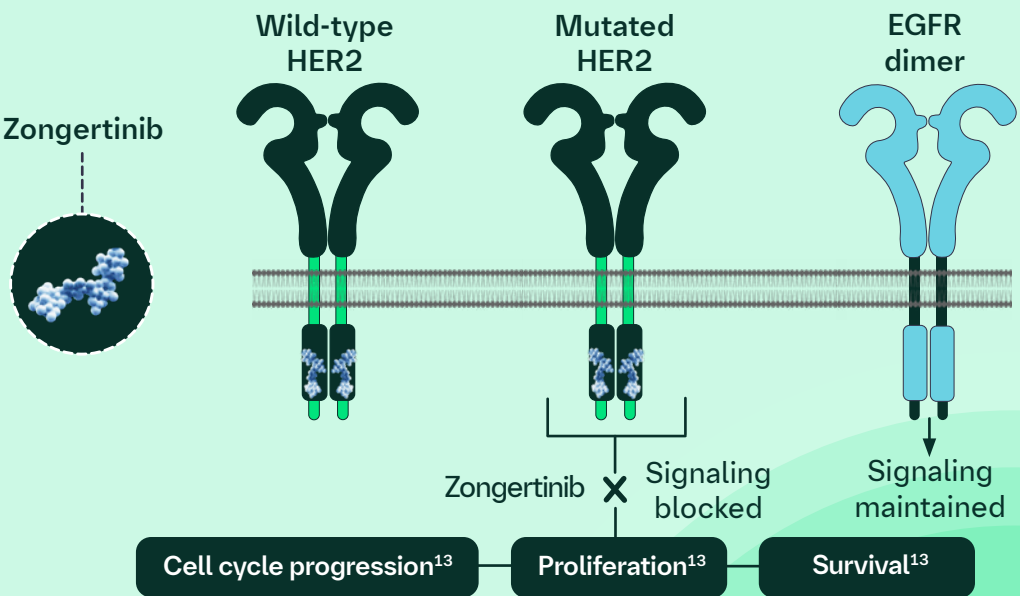
HER2 activating mutations induce constitutive, ligand-independent TKD activation.^{4,5,8,9}

ACTIVATING MUTATIONS ARE CONSIDERED ONCOGENIC OR LIKELY ONCOGENIC

- Persistent phosphorylation triggers continuous activation of the MAPK and PI3K/AKT pathways, driving uncontrolled tumor cell growth.¹⁰



INHIBITING TKD ACTIVITY SUPPRESSES ONCOGENIC SIGNALING INDUCED BY HER2 ACTIVATING MUTATIONS



- Zongertinib is an irreversible TKI that selectively inhibits HER2 while sparing wild-type EGFR.¹¹⁻¹³
- It covalently binds the ATP-binding pocket within the TKD and can inhibit the kinase activity regardless of whether the activating mutation resides in the ECD, TMD, or TKD.^{12,14}

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Abbreviations:

AKT: protein kinase B; ECD: extracellular domain; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; TKD: tyrosine kinase domain; TKI: tyrosine kinase inhibitor; TMD: transmembrane domain.