Approximately 70% of patients with HER2-positive breast cancer are also hormone receptor (HR) positive, representing a distinct molecular subtype characterized by bidirectional crosstalk between the HER2 and estrogen receptor (ER) pathways. Despite this, treatment strategies often mirror those for HER2+/HR– disease, leading to suboptimal outcomes.

Clinical and translational data demonstrate that dual blockade of HER2 and ER signaling improves therapeutic efficacy and delays resistance. Combining HER2-targeted agents (trastuzumab, pertuzumab) with endocrine therapy (ET) such as aromatase inhibitors, fulvestrant, or next-generation selective estrogen receptor degraders (SERDs, e.g., giredestrant) has shown encouraging efficacy and tolerability. Recent studies—including monarcHER, SYSUCC-002, and PHERGAIN—support chemotherapy de-escalation in selected HER2+/HR+ populations through tailored use of HER2 blockade and ET.

Emerging targeted combinations further refine treatment personalization. CDK4/6 inhibitors (palbociclib, abemaciclib, ribociclib) and PI3K/AKT pathway inhibitors (inavolisib, ipatasertib) are being investigated with HER2-targeted therapy to overcome resistance, particularly in tumors harboring PIK3CA mutations. Ongoing phase II–III trials—PATINA, heredERA, INAVO122, and GeparPiPPa—aim to define optimal biological combinations for HER2+/HR+ early and metastatic disease.

HER2+/HR+ breast cancer requires integrated targeting of both HER2 and ER pathways. Dual HER2 blockade combined with endocrine therapy forms the foundation of current management, while next-generation SERDs, CDK4/6 inhibitors, and PI3K inhibitors offer promise for personalized, chemotherapy-sparing strategies that enhance efficacy, reduce toxicity, and improve quality of life.