The management of HER2-positive metastatic breast cancer (mBC) has undergone a paradigm shift over the past decade, driven by the introduction of potent, mechanism-based therapies that have dramatically extended survival. Among the most transformative agents are the antibody–drug conjugate trastuzumab deruxtecan (T-DXd) and the HER2-selective tyrosine kinase inhibitor tucatinib, both of which have redefined clinical expectations and reshaped treatment algorithms.
T-DXd has shown unprecedented efficacy across multiple lines of therapy, producing deep and durable responses even in heavily pretreated populations. Importantly, it has demonstrated robust activity in patients with CNS metastases, addressing a major area of unmet need.
Tucatinib, in combination with trastuzumab and capecitabine, likewise provides meaningful intracranial disease control and overall survival benefit, establishing a new standard for patients with brain involvement.
These advances have made it clear that a fixed, line-based approach to HER2-positive mBC is no longer adequate. The DESTINY-Breast09 trial, exploring T-DXd in earlier disease settings, exemplifies this evolution and supports a transition toward personalized sequencing strategies that consider prior exposure, mechanisms of resistance, biomarker profiles, and CNS status. The therapeutic goal is shifting from a “one-size-fits-all” paradigm to an adaptive, biology-driven continuum of care.
The PATINA trial has further expanded this perspective, demonstrating improved outcomes with the addition of palbociclib plus endocrine therapy to pertuzumab-trastuzumab in HR-positive/HER2-positive mBC. These data highlight the relevance of dual-pathway inhibition and the need to tailor therapy according to tumor biology, reinforcing the concept of intradisease heterogeneity within the HER2-positive population.
Beyond approved agents, a rich development pipeline

promises to extend the therapeutic armamentarium. Zanidetamab, a bispecific antibody targeting two distinct HER2 epitopes, has shown encouraging activity in early trials. Meanwhile, next-generation ADCs, third-generation TKIs, and PIK3CA inhibitors are under active investigation to overcome resistance and further refine patient selection. Taken together, these advances are redefining HER2-positive mBC as a biologically diverse and increasingly manageable disease, where treatment decisions must integrate molecular profiling, CNS disease status, and prior therapeutic history.

This presentation will provide a critical overview of current standards and emerging strategies, emphasizing how the integration of T-DXd, tucatinib, and novel agents such as zanidetamab and next-generation ADCs is transforming clinical practice. The discussion will also explore the implications of pivotal trials—including DESTINY-Breast09 and PATINA—for future treatment algorithms and for the design of more individualized, mechanism-based therapeutic pathways in HER2-positive metastatic breast cancer.