Advances in therapeutic options for patients with HER2-positive metastatic breast cancer have dramatically changed the treatment landscape and long-term clinical outcomes over the past two decades. Furthermore, sequencing of lines of therapy in the metastatic setting has undergone significant evolution, with the introduction of HER2-targeted monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody drug conjugates. Trials such as HER2CLIMB, HER2CLIMB-02, DESTINY-Breast03, DESTINY-Breast09, and DESTINY-Breast12 demonstrate the value of tucatinib-based combinations and of TDXd, alone, or in combination with pertuzumab (in the case of DESTINY-Breast09) in patients with metastatic breast cancer. In addition, recent data from the PATINA trial demonstrate the value of the CDK4/6 inhibitor, palbociclib, in the front-line maintenance setting in patients with ER+/HER2+ disease. With respect to the central nervous system (CNS), both tucatinib and T-DXd have substantial intracranial activity, with data available for patients with parenchymal brain metastases, and those with leptomeningeal disease (LMD). Neratinib-based combinations, either with capecitabine or with T-DM1 also exert clinically relevant effects on brain metastases. CNS activity of HER2-based systemic therapies is sufficient in some cases to displace radiotherapy as a preferred option, which introduces additional complexity into treatment decision-making. In the refractory setting, TDM1 as well as combinations of trastuzumab with cytotoxic chemotherapy remain important options. Looking towards the future, multiple novel HER2-targeted TKIs including ZN1041, IAM1363, and others, will test whether increasing penetration across an intact blood brain barrier might drive further CNS efficacy and/or prevent CNS spread altogether. In addition, CNS activity has been observed with other ADCs, including novel HER2-directed ADCs with distinct payloads compared to T-DXd, and this opens the door to more inclusive eligibility criteria to fully understand the safety and efficacy profile of ADCs in patients with brain metastases and LMD.