CLINICAL IMPLICATIONS OF BASIC RESEARCH

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HER2 and Breast Cancer — A Phenomenal Success Story

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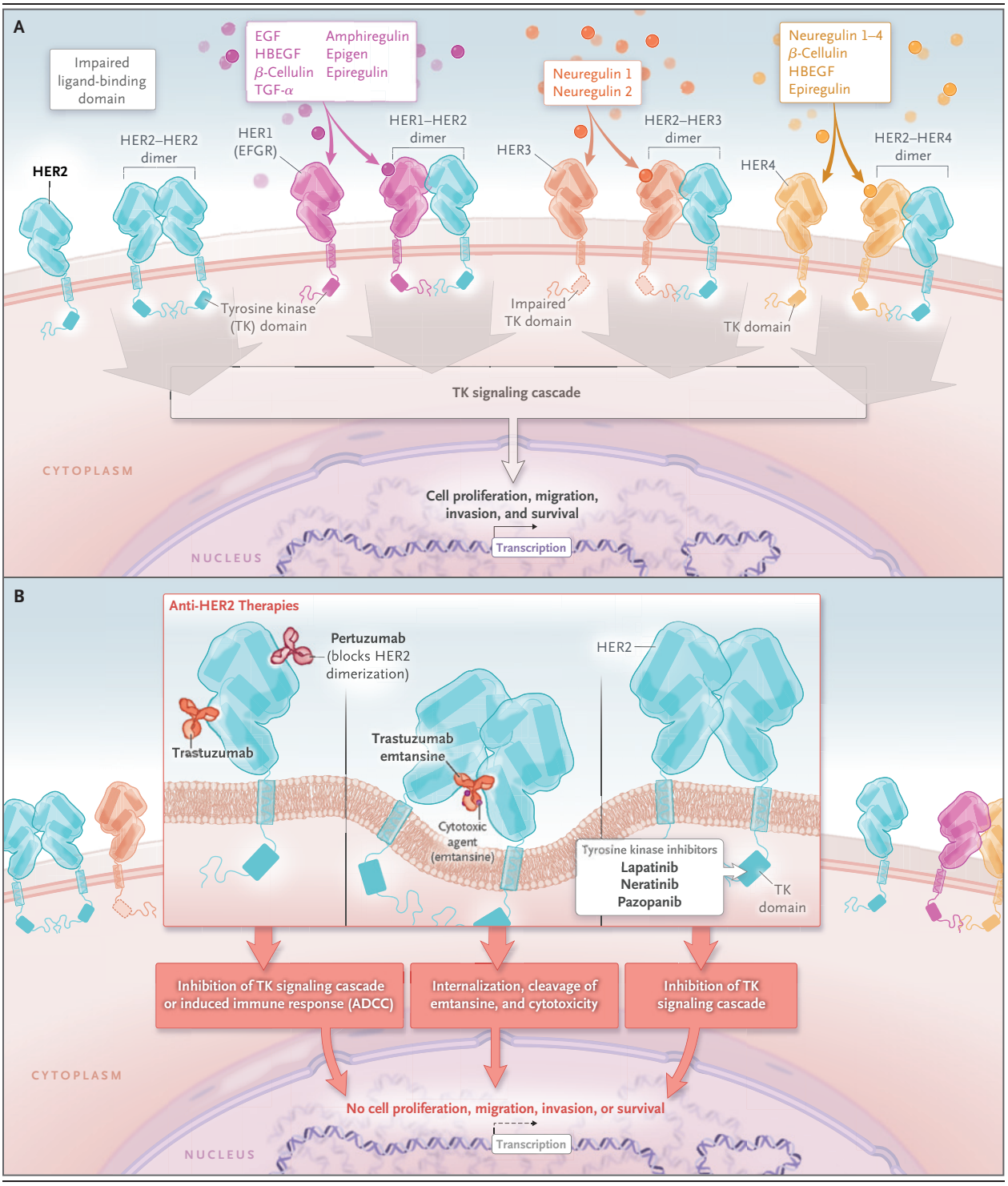
During the past three decades, the risk of dying from breast cancer in the United States has declined by nearly half, thanks to a combination of screening and early therapy as well as more treatments that are effective with fewer side effects, especially in the adjuvant setting.[1] Therefore, it should come as no surprise, but rather with a great deal of satisfaction and happiness, that the 2019 Lasker–DeBakey Clinical Medical Research Award goes to three scientists — Axel Ullrich, Dennis Slamon, and Michael Shepard — whose work on the human epidermal growth factor receptor 2 (HER2) in breast cancer launched a new era in clinical research and the practice of oncology.

In 1980, there were two classes of systemic therapies available for breast cancer: chemotherapy and, for patients with cancers rich in estrogen receptor, antiestrogen therapy (more properly termed "endocrine" therapy). In the late 1970s and 1980s, the explosion of new technologies in molecular biology led to genetic cloning and biologic understanding of a variety of steroid and peptide hormone growth factors and their receptors, stoking hopes of their therapeutic exploitation. Among these discoveries was the identification of the epidermal growth factor (EGF) and its receptor (EGFR),[2] which we now know belongs to a family containing three other receptors, known as the human epidermal receptors, or HERs. Three members of this family, EGFR (also known as HER1), HER3, and HER4, bind to at least 11 known peptide ligands, which results in homodimerization and heterodimerization among these receptors and subsequent downstream tyrosine kinase signaling cascades. These signaling cascades stimulate subsequent cell proliferation, migration, invasion, and survival, all hallmarks of cancer (Fig. 1A).[3] HER2 has no known ligand but is a preferred dimerization partner of the other three receptors (Fig. 1A). The gene that encodes HER2 (*ERBB2*, formerly known as *neu*) is amplified and overexpressed in approximately 20% of newly diagnosed breast cancers.[4] This observation, followed by inspired and dogged research in both academia and pharma, has changed the face of breast cancer. These investigations have been led in particular by the three Lasker–DeBakey awardees.

Soon after the observation that *ERBB2* overexpression occurs frequently in breast cancers, preclinical studies from several investigators showed that tumors that have this aberration are more aggressive than those that do not have it. Working with the late William McGuire and others, Drs. Ullrich and Slamon were the first to report that amplification and overexpression of *ERBB2* is associated with a worse prognosis for women with breast cancer.[5] At the same time, investigators at Genentech had generated a set of mouse monoclonal antibodies against the protein. One of these, designated "MoAb 4D5," was shown in preclinical studies by Drs. Ullrich and Shepard and their colleagues to be particularly potent in reducing the proliferation and survival of HER2-positive breast-cancer cell lines.[6] However, a major obstacle remained to be overcome — the development of a "humanized" murine monoclonal antibody that could be safely and repeatedly administered to patients with HER2-positive breast cancer. Dr. Shephard led a team of colleagues that successfully grafted the murine antigen-binding domain into a human immunoglobulin backbone, opening the door for subsequent clinical trials.[7]

In 1994, I received a telephone call from Dr. Slamon, in which he described phenomenal responses in a phase 1, single-agent trial testing the toxicities of the humanized monoclonal antibody 4D5, now designated trastuzumab. He invited me to participate in a planned phase 2 trial of the antibody plus chemotherapy. I will not forget my first patient involved in this trial — a middle-aged woman with metastatic HER2-positive breast cancer in bone, liver, and lung that had progressed on every chemotherapy then known to have activity in the disease. She had a nearly miraculous response, with complete resolution of



her pulmonary and hepatic metastases and dramatic improvement in her quality of life. I recall telling a colleague, "This is a drug!"

Since then, several clinical trials have shown that trastuzumab improves overall survival in patients with HER2-positive metastatic breast cancer and, even more dramatically, that it reduces mortality when delivered in the adjuvant setting.[8] Subsequently developed anti-HER2 agents have even further improved survival in patients with HER2-positive breast cancer, including another monoclonal antibody (pertuzumab), several HER2

Figure 1 (facing page). The Human Epidermal Receptor (HER) System and Ways to Target It.

As shown in Panel A, the HER system consists of four family members, designated HER1 (also known as epidermal growth factor receptor [EGFR]), HER2 (encoded by *ERBB2*, formerly known as *neu*), HER3, and HER4. At least 11 known peptide growth factors bind to HER1 (epidermal growth factor [EGF], heparin-binding EGF-like growth factor [HBEGF], β-cellulin, transforming growth factor α [TGF-α], amphiregulin, epigen, and epiregulin), HER3 (neuregulins 1 and 2), and HER4 (neuregulins 1, 2, 3, and 4; β-cellulin; HBEGF; and epiregulin). HER2 has no ligand-binding domain but appears to act as a gatekeeper for the mechanism of action of the family. Binding of HER1, HER3, or HER4 induces dimerization with itself or one of the other three receptors. EGFR, HER2, and HER3 each has a tyrosine kinase domain that is activated on dimerization and transmits a signal cascade to a receptive gene, which induces cell proliferation, invasion, migration, or survival, the hallmarks of cancer.[3] HER3 has an impaired tyrosine kinase domain. Panel B shows the cellular binding regions of anti-HER2 therapies. Trastuzumab, pertuzumab, and the antibody–drug conjugate trastuzumab emtansine bind to the extracellular domain of HER2. Trastuzumab and pertuzumab either alter normal tyrosine kinase signaling or induce antibody-dependent complement-mediated cytotoxicity (ADCC). Trastuzumab emtansine is internalized, and the chemotherapeutic agent is enzymatically cleaved, which leads to cytotoxic cell death. The tyrosine kinase inhibitors lapatinib, neratinib, and pazopanib cross the cell membrane and inhibit the intracellular tyrosine kinase domain activities.

tyrosine kinase inhibitors (lapatinib, neratinib, and pazopanib), and an antibody–drug conjugate, trastuzumab emtansine (Fig. 1B).

Oncologic dogma maintains that women who have metastatic breast cancer will not be cured. However, my colleagues and I who specialize in the treatment of this disease all have a few such patients who have been rendered disease-free for prolonged periods of time — challenging that dogma. Regardless, even for the many patients who have HER2-positive metastatic breast cancer who are not cured, anti-HER2 therapy results in considerable and long-lasting improvement in quality of life and overall survival. In this regard, even newer advances in the field of anti-HER2 therapy are being tested. Novel antibody–drug conjugates and tyrosine kinase inhibitors are in clinical trials, as are innovative combinations of anti-HER2 therapies with other strategic approaches, such as immune checkpoint inhibitors. Moreover, trastuzumab has now been shown to be active in other, nonbreast HER2-positive cancers, particularly gastric cancers.

However, to sing a familiar tune in oncology, these treatments are expensive and require some expertise in delivery, factors that limit their availability for patients without adequate health insurance and those in lower-income countries. Ongoing investigations are leading to more widespread availability of anti-HER2 therapies, including use of generic biosimilar anti-HER2 antibodies and subcutaneous, rather than intravenous, delivery of trastuzumab.

The oncologic medical community and, more importantly, our patients owe Drs. Ullrich, Shepard, and Slamon and the numerous other laboratory, translational, and clinical investigators who have played a role in this remarkable story a great debt of appreciation. We must also acknowledge the courageous women who have participated, and continue to do so, in the clinical trials that have gotten us where we are in the treatment of HER2-positive cancers. The ongoing and planned areas of research in this field will continue to lead us into the future in which even more women with HER2-positive breast cancer will live longer or even be cured. The terms “game changer” and “blockbuster” are worn, but in this case the ingenuity, vision, and persistence of these collaborators justify these superlatives.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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