HER2-Targeted Therapy

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Phuong Dinh and Martine J. Piccart

21.1 Introduction

In 1987, the initial description of the HER2 proto-oncogene was described as a poor prognostic factor in breast cancer. In 2001, the first randomized trial of a monoclonal antibody directed against HER2 in combination with chemotherapy for the treatment of metastatic HER2-positive (HER2+) breast cancer was published. In 2005, the dramatic benefit of trastuzumab in the adjuvant setting was presented in multiple presentations at the American Society of Clinical Oncology (ASCO)—which significantly impacted clinical practice worldwide. The HER2+ landscape, since, has not stopped to evolve with research continuing in neoadjuvant strategies and the development of new molecules for dual inhibition of HER family of receptors.

The HER2+ subtype of breast cancer represents less than 25 % of incident breast cancers, and traditionally has been regarded as having the more aggressive phenotype, higher recurrence rates and reduced survival [1, 2]. The remarkable progress in anti-HER2 therapeutics, over the last decades, has undoubtedly improved long-term outcomes for HER2+ patients. Nonetheless, a proportion of these patients still do poorly, and treatment resistance remains a problem. Deciphering the resistance mechanisms will facilitate better tailoring of therapy to individual patient tumors and further improve patient outcomes.

This chapter will discuss the evolution of HER2-targeted therapy, beginning with the initial success of trastuzumab to the controversies that remain, and from there, to the discussion of newer anti-HER2 approaches currently under investigation.

P. Dinh
Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Australia

M.J. Piccart (✉)
Medicine Department, Institut Jules Bordet, 1, rue Heger-Bordet, 1000 Bruxelles, Belgium
e-mail: martine.piccart@bordet.be

21.2 Targeting the HER2 Receptor

HER2 belongs to the human epidermal growth factor receptor family of tyrosine kinases consisting of EGFR (HER1; erbB1), HER2 (erbB2, HER2/*neu*), HER3 (erbB3), and HER4 (erbB4). All these receptors have an extracellular ligand-binding region, a single membrane-spanning region, and a cytoplasmic tyrosine-kinase-containing domain, the last being absent in HER3. Ligand binding to the extracellular region results in homo- and heterodimer activation of the cytoplasmic kinase domain and phosphorylation of a specific tyrosine [3], leading to the activation of various intracellular signaling pathways involved in cell proliferation and survival.

HER2 was first identified as an oncogene activated by a point mutation in chemically induced rat neuroblastomas [4], and soon after, found to be amplified in breast cancer cell lines [5]. In the clinic, patients with HER2 gene amplified tumors were shown to represent less than 25 % of the human breast population, having poorer disease-free survival [1, 6–8], and also displaying resistance to certain chemotherapeutic agents [9–11].

With the accumulating body of evidence supporting the HER2 oncogene hypothesis, the HER2 receptor represented an ideal target for anticancer therapy. By targeting HER2 receptors, either intracellularly or extracellularly, downstream pathways could be indirectly inhibited to induce cell cycle arrest, apoptosis, as well as inhibition of tumor cell invasion and metastases [12].

Up until recently, trastuzumab and lapatinib had been the mainstays of anti-HER2 treatment in combination with chemotherapy. Trastuzumab (Herceptin; Genentech, South San Francisco) is a recombinant, humanized anti-HER2 monoclonal antibody that exerts its action through several mechanisms including (1) induction of receptor downregulation/degradation, (2) prevention of HER2 ectodomain cleavage, (3) inhibition of HER2 kinase signal transduction via ADCC, and (4) inhibition of angiogenesis. Lapatinib is a small molecule tyrosine kinase inhibitor which

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is capable of dual receptor inhibition of both EGFR and HER2. It is an ATP mimetic that competitively binds to the ATP-binding cleft at the activation loop of target kinases, thereby inhibiting both kinase activities.

More recently, two additional HER2-directed therapies have been approved for HER2+ breast cancer. Pertuzumab is a recombinant, humanized, monoclonal antibody directed against the extracellular dimerization domain (subdomain II) of HER2, preventing dimerization of HER2 with other members of the HER family, such as HER3, HER1, and HER4. This results in inhibited downstream signaling of two key pathways that regulate cell survival and growth (the mitogen-activated protein kinase [MAPK] pathway, and the phosphoinositide 3-kinase [PI3 K] pathway), in addition to mediating antibody-dependent cell-mediated cytotoxicity [13]. Ado-trastuzumab emtansine (T-DM1) is a human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate composed of trastuzumab, a stable linker (MCC), and the cytotoxic agent DM1 (derivative of maytansine; mertansine). T-DM1 retains the mechanisms of action of trastuzumab, but also acts as a, selectively delivered, tubulin inhibitor. Following antigen-mediated binding to the tumor cell, T-DM1 is endocytosed and intracellularly catabolized resulting in the release of its cytotoxic moiety [14].

21.2.1 ASCO/CAP Updated Recommendations for HER2 Testing

A HER2 positive status is not only an adverse prognostic marker in breast cancer but also a positive predictive marker of response to anti-HER2 therapies. Tailored treatment requires proper identification of these patients who are most likely to derive benefit, and least likely to experience unnecessary toxicity. Recently, the American Society of Clinical Oncology and the College of American Pathologists have updated their 2007 clinical practice guidelines for HER2 testing in breast cancer with the 2013 version [15]. The update not only provides guidelines for the test performance parameters, with the aim of improving test accuracy, reproducibility, and precision, but also provides comprehensive recommendations on the post-analytical interpretation of the results, and requires improved communication among healthcare providers. Notably, for in situ hybridization interpretation, the 2013 guidelines returned to the prior threshold of a HER2/CEP17 ratio of 2.0 or greater for positive and eliminated 1.8–2.2 as the equivocal range. Also, the HER2 signal/nucleus ratio was accounted for, with 6.0 or greater for positive and 4.0 to less than 6.0 for equivocal, even in cases with a HER2/CEP17 ratio less than 2.0.

HER2 status is thus reported as an algorithm of positive, equivocal, negative, or indeterminate. The HER2 test is reported as positive if: (a) IHC 3+ positive or (b) ISH positive using either a single probe ISH or dual-probe ISH. The HER2 test is reported equivocal if: (a) IHC 2+ equivocal or (b) ISH equivocal using single probe ISH or dual probe ISH. For equivocal cases, a reflex test should be ordered on the same specimen using the alternative test. The HER2 test is reported as negative if a single test (or all tests) performed in a tumor specimen show: (a) IHC 1+ negative or IHC 0 negative or (b) ISH negative using single probe ISH or dual probe ISH. The HER2 test is reported as indeterminate if technical issues prevent one or both tests (IHC and ISH) performed in a tumor specimen from being reported as positive, negative, or equivocal. This may occur if specimen handling was inadequate, if artifacts (crush or edge artifacts) make interpretation difficult, or if the analytic testing failed.

21.3 Trastuzumab in the Metastatic Setting

Since the first reports of trastuzumab's activity in HER2+ MBC, many studies have been conducted to investigate the optimum schedule in this patient group, both as single-agent therapy and in combination.

21.3.1 Single-Agent Therapy in Heavily Pretreated Patients

In an early trial evaluating weekly trastuzumab efficacy in 222 women with HER2+ MBC that had progressed after one or two chemotherapy regimens [16], the response rate (RR) was 15 % in the intent-to-treat population and was significantly higher in strong HER2+ overexpressers (18 % vs. 6 % for those with 3+ and 2+ IHC, respectively). The median response duration was 9.1 months. Cardiac dysfunction was the most common adverse event, occurring in 5 % of treated patients, many of whom had received prior doxorubicin. The alternative 3-weekly schedule of trastuzumab was investigated in a phase II study [17] of 105 patients where comparable results were achieved (overall RR of 19 % and clinical benefit rate of 33 %). Median time to progression (TTP) was 3.4 months (range 0.6–23.6 months).

21.3.2 First-Line Single-Agent Therapy

The benefit of first-line trastuzumab monotherapy was studied in 114 women with HER2+ MBC [18] randomized to receive first-line treatment with trastuzumab 4 mg/kg loading dose, followed by 2 mg/kg weekly, or a higher 8 mg/kg loading dose, followed by 4 mg/kg weekly. RRs in 111 assessable patients with 3+ and 2+ HER2 overexpression by IHC were 35 % (95 % CI 24.4–44.7 %) and none

(95 % CI, 0–15.5 %), respectively. The RRs in 108 assessable patients with and without HER2 gene amplification by FISH analysis were 34 % (95 % CI 23.9–45.7 %) and 7 % (95 % CI 0.8–22.8 %), respectively. Interestingly, overall RR was nearly double that reported for previously treated patients [19]. There was no clear evidence of a dose–response relationship for response, survival, or adverse events.

21.3.3 Trastuzumab in Combination with Chemotherapy

21.3.3.1 Trastuzumab and Taxanes

Preclinical studies have shown additive or synergistic interactions between trastuzumab and multiple cytotoxic agents, including platinum analogs, taxanes, anthracyclines, vinorelbine, gemcitabine, capecitabine, and cyclophosphamide [19]. The pivotal randomized combination trials of trastuzumab [20] demonstrated that trastuzumab plus a taxane is associated with a clinical benefit that is superior to that of a taxane alone.

The first trial enrolled 469 HER2+ MBC patients who had not received prior treatment for advanced disease. For those patients who had previously received anthracyclines in the adjuvant setting or who were not suitable to receive anthracyclines (n = 188), randomization took place between paclitaxel with or without trastuzumab. All other patients (n = 281) were randomized to receive an anthracycline plus cyclophosphamide with or without trastuzumab. The addition of trastuzumab to chemotherapy was associated with a longer TTP (median 7.4 vs. 4.6 months; $P < 0.001$), a higher rate of objective RR (50 % vs. 32 %, $P < 0.001$), a longer duration of response (median 9.1 vs. 6.1 months; $P < 0.001$), a lower rate of death at 1 year (22 % vs. 33 %, $P = 0.008$), and longer survival (median survival 25.1 vs. 20.3 months; $P = 0.01$ and 20 % relative reduction in the risk of death overall) [21]. However, cardiotoxicity was more common with combined treatment, especially with AC plus trastuzumab (27 %), leading to the recommendation that anthracyclines and trastuzumab should not be combined.

In a phase II study of 95 HER2-normal and HER2+ MBC patients evaluating weekly trastuzumab and paclitaxel therapy [21], the overall RR was 56.8 % (95 % CI 47–67 %). In those with HER2+ tumors, the overall RR was higher than those with HER2-normal tumors (range of 67–81 % compared with range of 41–46 %). Treatment was associated with grade 3/4 neutropenia in 6 %, and 3 patients had severe cardiac complications.

In the M77001 trial which investigated the combination of weekly trastuzumab plus weekly or 3-weekly docetaxel in 188 MBC patients, the median overall survival (OS) was 22.7 months with docetaxel alone and 31.2 months with trastuzumab plus docetaxel. Median TTP (10.6 vs. 5.7 months) was superior for trastuzumab plus docetaxel versus docetaxel alone [22].

In a multicenter phase II trial with 101 HER2+ MBC patients randomized between combination therapy trastuzumab plus docetaxel and sequential therapy of single-agent trastuzumab followed at disease progression by docetaxel alone as first-line chemotherapy [23], the median PFS was 9.4 versus 9.9 months and the 1-year PFS rates were 44 % versus 35 %, respectively. The overall response rates (RRs) were 79 % versus 53 %, ($P = 0.016$), and overall survival was 30.5 versus 19.7 months, ($P = 0.11$). In the sequential group, RRs to monotherapy trastuzumab and subsequent docetaxel were 34 and 39 %, respectively, with a median PFS during single-agent trastuzumab of 3.9 months. The incidence and severity of neuropathy were significantly higher in the combination group. Retrospective analysis of trastuzumab treatment beyond progression (applied in 46 % of patients in the combination group and 37 % in the sequential group) showed a correlation with longer overall survival in both treatment arms (36.0 vs. 18.0 months and 30.3 vs. 18.6 months, respectively). Thus, first-line treatment with sequential trastuzumab, then docetaxel resulted in a similar PFS compared with combination trastuzumab and docetaxel, but the RR was lower and the overall survival nonsignificantly shorter.

21.3.3.2 Trastuzumab and Platinum Salts

In addition to a possible synergistic interaction [24], in vitro data suggests that trastuzumab may also reverse primary platinum resistance by modulating HER2 activity [25]. The benefit of adding platinum salts to trastuzumab-based combination therapy was shown in a phase III trial comparing trastuzumab and paclitaxel with and without carboplatin in 194 women with HER2+ MBC [26]. The addition of carboplatin to paclitaxel and trastuzumab significantly improved RR (52 % vs. 36 %) and median PFS (10.7 vs. 7.1 months). Although the triple therapy was associated with higher rates of grade 3/4 hematologic toxicity, there was no difference in the rates of neurologic, cardiopulmonary, or febrile complications.

In contrast, a lack of benefit for adding carboplatin to trastuzumab plus a taxane was shown in the BCIRG 007 trial [27], in which 263 previously untreated patients with HER2 FISH+ MBC were randomly assigned to trastuzumab plus 8 courses of either docetaxel alone (TH) (100 mg/m^2 every 3 weeks) or docetaxel (75 mg/m^2 every 3 weeks) plus carboplatin (TCH) (AUC of 6). There was no significant difference in terms of the primary endpoint, time to progression (medians of 11.1 and 10.4 months, respectively; hazard ratio, 0.914; 95 % CI, 0.694–1.203; $P = 0.57$), RR (72 % for both groups), or overall survival (medians of 37.1 and 37.4 months, respectively; $P = 0.99$). Rates of grades 3 or 4

adverse effects for doublet versus triplet therapy respectively, were neutropenic-related complications, 29 and 23 %; thrombocytopenia, 2 and 15 %; anemia, 5 and 11 %; sensory neuropathy, 3 and 0.8 %; fatigue, 5 and 12 %; peripheral edema, 3.8 and 1.5 %; and diarrhea, 2 and 10 %. Adding carboplatin, therefore, did not enhance docetaxel–trastuzumab antitumor activity.

21.3.3.3 Trastuzumab Plus Vinorelbine

Trastuzumab and vinorelbine constitute effective and well-tolerated first-line treatment for HER2+ MBC. In a multicentre phase II study evaluating this combination in 54 women [28], the RR was 68 % (95 % CI 54–80 %). Two patients experienced cardiotoxicity in excess of grade 1; one patient experienced symptomatic heart failure. This combination was also shown to be effective in patients who had progressed while receiving anthracyclines and taxanes [29–31]. The combination of trastuzumab with vinorelbine was well tolerated in all of these trials. There was no evidence that this combination resulted in more cardiac events compared with trastuzumab alone.

21.3.3.4 Trastuzumab with Capecitabine

Several studies have demonstrated that trastuzumab and the 5-fluorouracil prodrug, capecitabine, have at least additive antitumor activity in human breast cancer models [32], and this has been supported by several clinical studies. In a phase II trial of 27 MBC patients refractory to anthracyclines and taxanes who received capecitabine (1250 mg/m^2 twice daily for 14 of every 21 days) plus weekly trastuzumab, there were 12 objective responses (45 %) with 4 complete responses [33]. Nine additional patients (33 %) had disease stabilization for at least 9 weeks, and the median PFS was 6.7 months. There was a low incidence of grade 3 or 4 adverse events. This high RR was mirrored in a phase II study of first line trastuzumab–capecitabine therapy, in which an objective RR of 76 % (5 CR, 14 PR) was recorded [34]. In both phase II studies, the combination of trastuzumab plus capecitabine was generally well tolerated. There was no evidence of greater cardiotoxicity with this combination.

21.3.3.5 Trastuzumab Plus Gemcitabine

Trastuzumab plus gemcitabine was evaluated in a phase II study [35] with 64 patients where the majority (95 %) had been treated with prior anthracyclines and taxanes. Gemcitabine (1200 mg/m^2 weekly Day 1, 8 in a 21-day cycle) plus weekly doses of trastuzumab was administered until disease progression. The objective RR was 38 % in the intent-to-treat population (23 of 61) and 44 % among the 39 patients with HER2 3+ expression. The median response duration was 5.8 months, median OS was 14.7 months, and median TTP was 5.8 months. Trastuzumab plus gemcitabine was well tolerated with no cases of clinical congestive heart failure.

21.3.3.6 Trastuzumab and Eribulin

Eribulin mesylate [36] is a non-taxane inhibitor of microtubule dynamics in the halichondrin class of antineoplastic drugs. Eribulin has a novel mode of action that is distinct from those of other tubulin-targeting agents; it only binds to the growing positive ends, inhibiting the microtubule growth phase without affecting the shortening phase and causing tubulin sequestration into nonproductive aggregates.

In a multicenter, phase II, single arm study of 52 patients [37] with recurrent or metastatic HER2+ breast cancer, eribulin mesylate at 1.4 mg/m^2 was administered intravenously (I.V.) on days 1 and 8 of each 21-day cycle with an initial trastuzumab dose of 8 mg/kg I.V. on day 1, followed by 6 mg/kg of trastuzumab on day 1 of each subsequent cycle. The overall RR was 71.2 % (n = 37) with median TTR of 1.3 months, DOR of 11.1 months, and PFS of 11.6 months. The most common grade 3/4 treatment-emergent adverse events were neutropenia in 20 (38.5 %) patients, peripheral neuropathy in 14 (26.9 %; all Grade 3) patients, fatigue in 4 (7.7 %) patients, and febrile neutropenia in 4 (7.7 %) patients. Because of the high overall RR, prolonged median PFS, and acceptable safety profile, combination eribulin/trastuzumab is an acceptable treatment option for locally recurrent or metastatic HER2+ breast cancer.

A Phase II study is currently being conducted to look at the combination of eribulin, trastuzumab, and pertuzumab in metastatic, unresectable locally advanced, or locally recurrent HER2+ breast cancer [38].

21.3.3.7 Trastuzumab with Polychemotherapy

Trastuzumab has also been added to combination chemotherapy for MBC. Several studies have shown that triple combinations are effective and produce high RRs [27, 39–44], although overlapping toxicities must be carefully considered.

21.3.4 Trastuzumab in Combination with Hormonal Therapy

In the estrogen receptor (ER) positive patient populations, the rate of HER2 positivity is between 11 and 35 % [45–47]. Resistance to hormonal therapy, particularly tamoxifen, appears to be a characteristic of ER+, HER2+ tumors [48], and it has been hypothesized that the addition of trastuzumab to hormonal therapy may overcome this relative resistance. In preclinical studies, the combination of tamoxifen with anti-HER2 antibodies can produce a greater inhibitory effect on cell growth than either agent alone [49, 50]. There is also some evidence that compared with tamoxifen, aromatase

inhibitors may elicit a greater response in HER2+ tumors [51]. Taken together, these findings provide a clear rationale for combining trastuzumab with hormonal agents in patients with HER2+/ER+ MBC.

In a multicenter, open-label, phase II trial assessing the combination of letrozole and trastuzumab in 31 evaluable patients with HER2+/ER+ MBC [52], a RR of 26 %, including 1 CR, was reported. An additional 8 patients had stable disease. Two patients withdrew from the study due to toxicity (1 patient had grade 3 arthralgia and 1 patient developed congestive heart failure).

The international, multicenter, randomized, phase III TAnDEM trial evaluated anastrozole with or without trastuzumab in the first- and second-line treatment of postmenopausal women with HER2+/ER+ MBC [53], and allowed for crossover at the time of progression. A total of 208 patients were randomized (103 patients received trastuzumab plus anastrozole; 104 received anastrozole alone). Patients in the trastuzumab plus anastrozole arm experienced significant improvements in PFS compared with patients receiving anastrozole alone (hazard ratio = 0.63; 95 % CI, 0.47–0.84; median PFS, 4.8 vs. 2.4 months; log-rank $P = 0.0016$). In patients with centrally confirmed hormone receptor positivity ($n = 150$), median PFS was 5.6 and 3.8 months in the trastuzumab plus anastrozole and anastrozole alone arms, respectively (log-rank $P = 0.006$). Overall survival in the overall and centrally confirmed hormone receptor-positive populations showed no statistically significant treatment difference; however, 70 % of patients in the anastrozole alone arm crossed over to receive trastuzumab after progression on anastrozole alone. Incidence of grade 3 and 4 adverse events was 23 and 5 %, respectively, in the trastuzumab plus anastrozole arm, and 15 and 1 %, respectively, in the anastrozole alone arm; one patient in the combination arm experienced New York Heart Association class II congestive heart failure.

21.3.5 Trastuzumab After Disease Progression

An important clinical question is whether trastuzumab should be continued after progression on a first-line trastuzumab-containing regimen. Preclinical data and retrospective analysis of clinical trials support the hypothesis that continuing treatment with trastuzumab after disease progression may provide patient benefit [54–56].

An extension study of the pivotal phase III trial of trastuzumab combined with chemotherapy as first-line treatment evaluated the safety of continuing the biological agent monotherapy beyond disease progression [53]. Although not designed to evaluate efficacy, the RR to second-line trastuzumab was similar for patients who initially received chemotherapy alone and for those who initially received chemotherapy plus trastuzumab (14 and 11 % respectively), as was median response duration (about 7 months). In another retrospective analysis, trastuzumab alone or combined with a different chemotherapy was continued beyond disease progression in 80 patients with HER2+ MBC [54]. Continued trastuzumab appeared safe, and 32 responses were noted (4 complete responses).

In a study of 105 patients with HER2+ MBC who had received two or more trastuzumab-containing regimens [55], RRs were, in fact, similar for second line as compared to first-line therapy, with some first-line nonresponders eventually achieving a response in second-line treatment. Nonfatal cardiac events were reported in 22 patients and most patients were able to continue trastuzumab.

Two prospective trials looking at this issue prematurely closed. The first was the US Intergroup study randomizing patients who had progressed on taxanes plus trastuzumab to vinorelbine versus vinorelbine plus trastuzumab. This trial closed early due to low accrual. The other was the BIG 3-05 study [57] which randomized 152 patients who had progressed on trastuzumab to either capecitabine or capecitabine plus trastuzumab. This trial also closed early due to slow accrual but the preplanned interim analysis of 119 patients showed a longer TTP favoring the combination arm (33 vs. 24 weeks, $P = 0.178$), and no difference in serious adverse events.

In a pooled analyses [58] of 2618 patients treated with trastuzumab beyond progression in 29 studies (4 randomized controlled phase III trials, 2 observational studies, 8 prospective nonrandomized trials, and 15 retrospective case series), the median RR, TTP, and OS obtained from the selected articles were 28.7 %, 7, and 24 months. This pooled analysis confirms that continuing trastuzumab beyond the first progression continues to be 1 of the effective and preferred choices in HER2+ MBC, failing a trastuzumab-based first-line regimen.

In a large German observational study of 1843 trastuzumab-treated patients [59], a sub-cohort of 418 fulfilled the selection criteria for the trastuzumab beyond progression analysis with 261 continuing trastuzumab and 157 discontinuing. Survival from progression was significantly longer in those patients continuing trastuzumab treatment beyond disease progression (median 22.1 months vs. 14.9 months; HR = 0.64; $P = 0.00021$).

21.3.6 Trastuzumab and New Drugs

21.3.6.1 Lapatinib

Lapatinib is a small molecule tyrosine kinase inhibitor which is capable of dual receptor inhibition of both EGFR and HER2. It is an ATP mimetic that competitively binds to the

ATP-binding cleft at the activation loop of target kinases, thereby inhibiting both kinase activities. Lapatinib also has the advantage of being able to bind and inhibit p95HER2, which is the truncated form of HER2 lacking an extracellular domain but possessing greater kinase activity than wild-type HER2. Because trastuzumab is unable to neither bind nor inhibit p95HER2, its resistance may be mediated at least, in part, through the expression of p95HER2 in disease progression.

In single-agent phase I/II studies, lapatinib has resulted in objective responses between 4.3 and 7.8 % in HER2+ patients who had progressed on multiple trastuzumab-containing regimens [60], with a substantial number having stable disease at 4 months (34–41 %) and 6 months (18–21 %).

A randomized study of lapatinib alone or in combination with trastuzumab in 296 women [61] with HER2+ trastuzumab-refractory metastatic breast cancer was conducted to investigate a chemotherapy-free option. The combination of lapatinib with trastuzumab was superior to lapatinib alone for PFS (hazard ratio [HR] = 0.73; 95 % CI, 0.57–0.93; $P = 0.008$) and CBR (24.7 % in the combination arm vs. 12.4 % in the monotherapy arm; $P = 0.01$). A trend for improved OS in the combination arm was observed (HR = 0.75; 95 % CI, 0.53–1.07; $P = 0.106$). There was no difference in overall RR (10.3 % in the combination arm vs. 6.9 % in the monotherapy arm; $P = 0.46$). The most frequent adverse events were diarrhea, rash, nausea, and fatigue; diarrhea was higher in the combination arm ($P = 0.03$). The incidence of symptomatic and asymptomatic cardiac events was low (combination therapy = 2 and 3.4 %; monotherapy = 0.7 and 1.4 %, respectively).

In the updated analyses of the combination study EGF10151, which was a phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in 399 women with advanced HER2+ breast cancer that had progressed on trastuzumab, the addition of lapatinib prolonged TTP with a hazard ratio (HR) of 0.57 (95 % CI, 0.43–0.77; $P < 0.001$) and provided a trend toward improved overall survival (HR: 0.78, 95 % CI: 0.55–1.12, $P = 0.177$), and fewer cases with CNS involvement at first progression (4 vs. 13, $P = 0.045$) [62].

A multicenter phase II study of lapatinib in 242 patients with brain metastases from HER2+ breast cancer [63] demonstrated objective responses to lapatinib in 6 % of patients. In an exploratory analysis, 21 % of patients experienced a ≥20 % volumetric reduction in their CNS lesions. An association was observed between volumetric reduction and improvement in progression-free survival and neurologic signs and symptoms. Of the 50 evaluable patients who entered the lapatinib plus capecitabine extension, 20 % experienced a CNS objective response and 40 % experienced a ≥20 % volumetric reduction in their CNS lesions. This study confirmed the modest CNS antitumor activity of lapatinib, with additional responses observed with the combination of lapatinib and capecitabine.

21.3.6.2 Pertuzumab

In preclinical models, pertuzumab inhibits the growth of HER2-overexpressing cell lines in vitro and potent synergy is observed with the combination of trastuzumab and pertuzumab. Tumor regression also occurs when pertuzumab is added after progression on trastuzumab alone [64, 65].

In a phase II single arm clinical trial, 66 patients with HER2+ MBC who had progressed on trastuzumab were treated with trastuzumab and pertuzumab. Trastuzumab was given either as an 8 mg/kg IV loading dose followed by 6 mg/kg q3 weeks or as a 4 mg/kg loading dose followed by 2 mg/kg IV weekly, and pertuzumab was given as an 840 mg IV loading dose followed by 420 mg IV q3 weeks. An objective RR of 24.2 % with a clinical benefit rate (CBR) of 50 % was seen including 5 (7.6 %) complete responses (CR), 11 (16.7 %) PR, and 17 (25.8 %) SD lasting 6 months or greater [66].

These results led to the phase III randomized, double-blind trial called CLEOPATRA [67], which was a study of 808 patients with HER2+ MBC who had not received prior trastuzumab therapy in the metastatic setting. These patients were randomized to receive docetaxel and trastuzumab with either pertuzumab (THP) or placebo (TH). Only 11 % of patients had received trastuzumab in the adjuvant or neoadjuvant setting, thus this study primarily tested the activity of dual HER2 monoclonal antibody therapy in a trastuzumab-naïve population. Median PFS was 12.4 months with placebo and 18.5 months with pertuzumab [hazard ratio (HR) 0.62 (95 % CI: 0.51–0.75), $P < 0.0001$]. At the time of the independent assessment of PFS, the interim analysis of OS showed a trend in favor of the pertuzumab group, but this was not significant. After a follow-up of 30 months, the results showed a statistically significant improvement in OS favoring the pertuzumab-containing arm, with a 34 % reduction in the risk of death (HR: 0.66; 95 % CI: 0.52–0.84; $P = 0.0008$). At median follow-up of 50 months, the statistically significant improvement in OS in favor of the pertuzumab group was maintained (HR: 0.68; 95 % CI: 0.56–0.84; $P = 0.0002$). The median OS was 40.8 months in the control group and 56.5 months in the pertuzumab group, with difference of 15.7 months. The objective RR in the CLEOPATRA trial was 69.3 % in the control group and 80.2 % in the pertuzumab group. The difference in RR was 10.8 percentage points (95 % CI: 4.2–17.5; $P = 0.001$). As OS at the interim analysis did not cross the stopping boundary for significance, the statistical test result for objective RR was considered to be exploratory. An analysis of the incidence and time to development of CNS metastases

[68] in patients from the CLEOPATRA trial showed that the proportion of patients developing CNS as first site of disease progression was similar between the control group (51 of 406, 12.6 %) and the pertuzumab group (55 of 402, 13.7 %). The median time to progression in the CNS was 11.9 months in the control group and 15.0 months in the pertuzumab group (HR: 0.58; 95 % CI: 0.39–0.85; $P = 0.0049$). Median OS in patients who developed CNS metastases showed a trend in favor of the pertuzumab group, being 26.3 months versus 34.4 months in the control and pertuzumab groups, respectively (HR: 0.66; 95 % CI: 0.39–1.11). The difference observed was not statistically significant for the log-rank test ($P = 0.1139$) but was significant for the Wilcoxon test ($P = 0.0449$). In June 2012, the FDA approved pertuzumab in combination with trastuzumab and docetaxel for HER2+ MBC in patients who had not received prior HER2-directed therapy or chemotherapy for metastatic disease. The European Medicines Agency (EMA) gave its approval in March 2013.

Several studies with pertuzumab are ongoing. In the frontline metastatic setting, PHEREXA (NCT01026142) will evaluate pertuzumab, trastuzumab with capecitabine in improving PFS in 452 patients. PERUSE (NCT01572038) will evaluate the combination of pertuzumab, trastuzumab and taxane in the first-line treatment of 1438 HER2+ patients. PERTAIN (NCT01491737) is a phase II study randomizing 250 patients, studying the combination of pertuzumab, trastuzumab and an aromatase Inhibitor in ER+ and HER2+ MBC. VELVET (NCT01565083) is evaluating pertuzumab, trastuzumab and vinorelbine in a single arm phase II study of first line metastatic or locally advanced HER2+ breast cancer.

21.3.6.3 Ado-Trastuzumab Emtansine (T-DM1)

T-DM1 is an ADC consisting of DM1, a maytansinoid antimicrotubule agent, bound to trastuzumab through nonreducible thioether bonds. T-DM1 delivers this highly potent cytotoxic agent specifically to HER2-expressing cells. Once T-DM1 binds to HER2 on the cell surface, the T-DM1-HER2 complex is internalized and the antibody component is proteolytically degraded, releasing the DM1 into the cytoplasm [69]. Importantly, T-DM1 retains the biologic activity of trastuzumab (i.e., HER2 signaling blockade and induction of ADCC) [70].

Given the promising activity seen in phase I studies, several phase II studies have been completed with the 3.6 mg/kg q3-week dosing schedule. In the single arm proof-of-concept study that enrolled 112 patients with HER2 + MBC who progressed on HER2-directed therapy [71] (median of 8 prior therapies, with prior trastuzumab and almost two-thirds (66/112) had received prior lapatinib), the objective RR was 25.9 % (95 % CI: 18.4–34.4 %). Of 75 patients who had previously discontinued trastuzumab due to progression, 21 achieved objective responses (ORR 28.0 %, 95 % CI: 18.2–38.9 %). Of the 66 patients who previously had received lapatinib, the objective RR was 24.2 % (95 % CI: 14.5–36.0 %). The median PFS was 4.6 months (95 % CI: 3.9–8.6 months).

In a confirmatory phase II study of T-DM1 in 110 patients who previously received chemotherapy and two HER2-directed therapies including lapatinib and trastuzumab [72], the objective RR was 32.7 % (95 % CI: 24.1–42.1 %) and median PFS 7.2 months.

In the frontline setting, T-DM1 was compared head-to-head with trastuzumab plus docetaxel (HT) in a randomized phase II trial for the treatment of HER2+ locally advanced or MBC [73] with 137 patients who had not received chemotherapy for metastatic disease and if they were ≥6 months from prior chemotherapy in the adjuvant setting. Sixty-seven patients were treated with T-DM1, compared to 70 patients treated with HT. The median PFS was 14.2 months for T-DM1 versus 9.2 months for HT (HR 0.59; 95 % CI: 0.36–0.97; $P = 0.035$). There were three CRs in the HT arm and seven CRs in the T-DM1 arm ($P = 0.453$). For patients who received T-DM1, the ORR was 64.2 % (95 % CI: 51.8–74.8 %) compared to 58.0 % (95 % CI: 45.5–69.2 %) for HT. OS was similar between the two arms, although at the time of reporting, only 13 deaths had occurred. Compared to HT, fewer grade 3/4 AEs were seen in the T-DM1 arm (46.4 % vs. 90.9 % for TDM-1 and HT, respectively). Overall, T-DM1 treatment resulted in fewer treatment discontinuations (7.2 %) compared to for HT (34.8 %) and fewer serious AEs (20.3 % vs. 25.8 %).

The phase III randomized EMILIA trial unequivocally demonstrated the efficacy of T-DM1 in patients with HER2 +, trastuzumab-pretreated MBC [74]. A total of 991 subjects with HER2+ advanced breast cancer, previously treated with taxane and trastuzumab were randomized to receive TDM-1 or lapatinib plus capecitabine. A statistically significant improvement in ORR was seen with T-DM1 compared with lapatinib and capecitabine (43.6 % vs. 30.8 %, $P < 0.001$). Median PFS was 9.6 months for T-DM1 vs. 6.4 months with lapatinib and capecitabine (HR 0.65; 95 % CI: 0.55–0.77; $P < 0.001$), and median OS at the second interim analysis was 30.9 versus 25.1 months (HR 0.68; 95 % CI: 0.55–0.85; $P < 0.001$). Fewer grade 3 or greater toxicities were seen with T-DM1 compared to lapatinib and capecitabine, with rates of 41 and 57 %, respectively. Thrombocytopenia and elevated transaminases were more common with T-DM1, while diarrhea, nausea, vomiting, palmar-plantar dysesthesia were more common in the lapatinib and capecitabine arm. Based on this seminal result, both the FDA and EMA have licensed T-DM1 as monotherapy for HER2+ MBC in patients who had previously received taxane and trastuzumab-based therapy [75].

TH3RESA [76] was a randomized, open-label trial evaluating T-DM1 versus treatment of physician's choice in

patients who had previously received two or more HER2-directed therapies, including trastuzumab and lapatinib as well as taxane chemotherapy. A total of 602 patients were enrolled: 404 received T-DM1 and 198 patients received therapy per physician's choice. For the T-DM1 arm, median PFS was 6.2 months, compared to 3.3 months for TPC (stratified HR 0.528, 0.422–0.661, $P < 0.001$). Interim OS data also demonstrated a trend toward improvement in the T-DM1 arm (HR 0.552, 95 % CI: 0.369–0.826, $P = 0.0034$). T-DM1 treatment resulted in fewer grade 3 or greater AE compared to TPC: 32 % versus 43 %, respectively. Grade 3 thrombocytopenia was the only AE more frequently seen with T-DM1 and was seen in 5 % of patients treated with T-DM1, compared with 2 % in the control arm. Grade 3 neutropenia, diarrhea and febrile neutropenia were all more common for TPC than for T-DM1 arm.

There are several ongoing phase II and III studies with T-DM1. MARIANNE (NCT01120184) is a three-arm phase III study randomly assigning 1095 patients with progressed or recurrent locally advanced or previously untreated metastatic HER2+ breast cancer to receive T-DM1 plus pertuzumab (363 patients), T-DM1 plus placebo (367 patients), or HT (docetaxel or paclitaxel; 365 patients). At the time the trial was initiated, the control arm represented the standard of care for this patient population. After a median follow-up of 35 months [77], both T-DM1—containing regimens showed non-inferior PFS, but not superiority, over HT. The median PFS was 15.2 months in the T-DM1 plus pertuzumab arm (hazard ratio [HR] 0.87, 95 % CI [0.69, 1.08]; $P = 0.14$), 14.1 months with T-DM1 alone (HR 0.91, 95 % CI [0.73, 1.13]; $P = 0.31$) compared with 13.7 months with HT. The overall survival data were not yet reached. The objective response rate was 64.2, 59.7, and 67.9 % among the T-DM1 plus pertuzumab, T-DM1 alone, and HT arms, respectively. However, the median duration of response was 21.2 months (95 % CI [15.8, 29.3]) in the T-DM1 plus pertuzumab arm, 20.7 months (95 % CI [14.8, 25.0]) in the T-DM1 alone arm, and 12.5 months (95 % CI [10.5, 16.6]) in the HT arm. Rates of grade 3/4 neutropenia, febrile neutropenia, and diarrhea were lower in the T-DM1—containing arms. Rates of alopecia were also substantially lower with T-DM1, as were health-related quality of life outcomes as assessed by patient-reported physical and functional well-being. The median time to a five-point or more decrease from baseline in the Health-Related Quality of Life score ranged from 7.7 months with T-DM1 and 9.0 months with T-DM1 plus pertuzumab to 3.6 months with HT.

21.3.7 The Algorithm for Treating Metastatic HER2+ Breast Cancers (ASCO 2014 Guidelines)

21.3.7.1 First-Line Therapy

HER2-targeted therapy in combination with chemotherapy in the first-line setting is associated with improvements in RR, PFS, TTP and OS, when compared with chemotherapy alone. The recommended regimen is a combination of trastuzumab, pertuzumab, and a taxane-based primarily on the results of CLEOPATRA [64].

For patients who had disease recurrence greater than 12 months of trastuzumab-based adjuvant treatment, clinicians should follow the first-line therapy recommendation—i.e., offer pertuzumab/trastuzumab/taxane.

For patients who had disease recurrence within 12 months of trastuzumab-based adjuvant treatment, clinicians should follow the second-line therapy recommendation—i.e., offer T-DM1.

21.3.7.2 Second-Line Therapy

If a patient's HER2+ advanced breast cancer has progressed during or after first-line HER-2 targeted therapy, clinicians should recommend T-DMI as a second line treatment-based primarily on the results of EMILIA [74].

21.3.7.3 Third-Line Therapy and Beyond

If a patient's HER2+ advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, clinicians should recommend further HER-2 targeted therapy. If the patient has not received TDM-1 or pertuzumab, then clinicians should offer TDM-1 (EMILIA [74]) or pertuzumab (informal consensus) respectively. If the patient has received both TDM-1 and pertuzumab, options include: lapatinib and capecitabine, as well as other combinations of chemotherapy and trastuzumab, lapatinib and trastuzumab, or hormonal therapy (in ER+ and HER2+ patients only).

21.4 Trastuzumab in the Adjuvant Setting

21.4.1 Adjuvant Trastuzumab Trials—Efficacy Results

Current clinical guidelines clearly state that standard of care in 2015 recommends the use of the monoclonal anti-HER2 antibody, trastuzumab, in combination with or after adjuvant chemotherapy in medically fit patients diagnosed with

Stage I to III HER2+ breast cancer. The four landmark randomized trials investigating the benefit of adjuvant trastuzumab National Surgical Adjuvant Breast and Bowel Project [NSABP] B-31 and North Central Cancer Treatment Group [NCCTG] N9831 [78], HERA [79] and Breast Cancer International Research Group [BCIRG] 006 [80] in their initial analyses reported outcomes with median follow-ups of 24–36 months. With enrollment of over 13,000 women, the range in benefit in disease-free survival (DFS) in favor of trastuzumab was with hazard ratios (HRs) between 0.48 and 0.67 ($P < 0.0001$), and the range in benefit in overall survival (OS) was between 0.59 and 0.67 (P = NS to $P = 0.015$). Absolute improvements in DFS ranged from 6 to 11 %, with corresponding absolute differences in OS of 1–2.5 %.

With longer follow-up from these trials (8-year median follow-up from HERA [79] and from the combined analyses of NSABP B-31 and NCCTG N9831 [78]), there continues to be statistically and clinically significant improvements in DFS and OS. Though the magnitude of benefit, as measured by HRs, appears to have lessened slightly over time as more events (both relapses and deaths) occur, absolute gains in overall survival are larger now than in earlier analyses. Relapses unfortunately continue to occur at a relatively constant rate over time in the trastuzumab-treated arm(s)—with an estimated 10-year DFS of 73.7 % from the combined analyses of NSABP B-31 and NCCTG N9831 [78] (Tables 21.1 and 21.2).

21.4.2 Adjuvant Trastuzumab Trials: Safety Results

Hypersensitivity was the most common adverse effect of trastuzumab, and occurred mainly with the first infusion. Unexpected short-term side effects did not emerge in any of the trials, with the exception of 9 cases of interstitial pneumonitis in B-31 and N9831 [78], though the relationship to trastuzumab is still not clearly defined. Cardiotoxicity remains the most important adverse effect of trastuzumab. Across the adjuvant trials, the definitions for cardiac events, the schedules for cardiac monitoring, analyses of cardiac endpoints and follow-up times all differed.

Nonetheless, it appeared that the incidence of cardiac events with trastuzumab was not high, with initial reports ranging from 0.4 % in the BCIRG 006 trial [80] and 4.1 % in the B-31 [78] trial. Within the control arms of all studies, the incidence of cardiac events ranged from 0 to 0.8 %. With longer follow-up, the cumulative incidence of cardiac adverse events plateaus, with cardiac events rarely occurring following completion of trastuzumab treatment. In the HERA [79] study, at 8-year follow-up, only 4.1 % of patients experienced NYHA Class I/II cardiac dysfunction with a left ventricular ejection fraction (LVEF) drop of 10 % or more below baseline and to an absolute LVEF of 50 % or less. The majority of cardiac events secondary to trastuzumab were reversible in nature.

Table 21.1 Initial reports from the large adjuvant trastuzumab trials

Trial	Herceptin duration	Median F/U	Treatment arms	No. patients	HR for DFS (95 % CI)	2–3 year DFS (%)	HR for OS (95 % CI)	2 year OS (%)
HERA [79]	1 year	24 months	Chemo	1698		77.4		95.1
			Chemo → H	1703	0.64 (0.64 − 0.76)	85.8	0.66 (0.47 − 0.91)	96.0
NSABP B-31 [78]	1 year	24 months	AC → P	1679		75.4		91.7
NCCTG N9831			AC → P→H	1672	0.48 (0.39 − 0.59)	87.1	0.67 (0.48 − 0.93)	94.3
BCIRG 006 [80]	1 year	36 months	AC → T	1073		81		N/A
			AC → TH	1074	0.61 (0.46 − 0.76)	88	0.59 (0.42 − 0.85)	N/A
			TcarboH	1075	0.67 (0.54 − 0.83)	87	0.66 (0.47 − 0.93)	N/A

Abbreviations: *HR* hazard ratio; *DFS* disease-free survival; *OS* overall survival; *H* trastuzumab; *NSABP* National Surgical Adjuvant Breast and Bowel Project; *A* doxorubicin; *C* cyclophosphamide; *P* paclitaxel; *NCCTG* National Central Cancer Treatment Group; *BCIRG* Breast Cancer International Research Group; *T* docetaxel; *carbo* carboplatin

Table 21.2 Longer term follow-up from the large adjuvant trastuzumab trials

Trial	Median F/U	Treatment arms	HR for DFS (95 % CI)	DFS (%)	HR for OS (95 % CI)	OS (%)
HERA [79]	8 year	Chemo		76.0		N/A
		Chemo → H	0.76 (0.67 − 0.86)		0.76 (0.65 − 0.88)	N/A
NSABP B-31 [78]	8.4 year	AC → P		62.2		75.2
NCCTG N9831		AC → P→H	0.60 (0.53 − 0.68)	73.7	0.63 (0.54 − 0.73)	84.0
BCIRG 006 [80]	5.5 year	AC → T		75		87
		AC → TH	0.64 (0.53 − 0.78)	84	0.63 (0.48 − 0.81)	92
		TcarboH	0.67 (0.54 − 0.83)	81	0.77 (0.60 − 0.99)	91

Abbreviations: *HR* hazard ratio; *DFS*, disease-free survival; *OS* overall survival; *H* trastuzumab; *NSABP* National Surgical Adjuvant Breast and Bowel Project; *A* doxorubicin; *C* cyclophosphamide; *P* paclitaxel; *NCCTG* National Central Cancer Treatment Group; *BCIRG* Breast Cancer International Research Group; *T* docetaxel; *carbo* carboplatin

21.4.3 The Sequencing and Timing of Adjuvant Trastuzumab Treatment

In the 4 adjuvant trials, the timing of trastuzumab initiation varied considerably. In HERA [79], trastuzumab was delayed for a median time of 8 months after surgery; for 4 months in the combined B-31 and N9831 [78] group, and for 1 month in the platinum-taxane arm of BCIRG 006 [80]. In the NCCTG N9831 study, an unplanned, premature analysis directly comparing arms C (concurrent) and B (sequential) showed a numerical increase in DFS (84.4 % vs. 80.1 %), favoring the concurrent arm, although it did not meet statistical significance. There was no difference in toxicity between the two arms either. Despite these results, for convenience and earlier completion of therapy, it may be overall advantageous to deliver the trastuzumab concurrent with the taxane [81].

21.4.4 The Duration of Adjuvant Trastuzumab Treatment

At present, the standard of care is for 1 year of adjuvant trastuzumab therapy. The FinHer [82] was a phase III randomized adjuvant trial of 1010 breast cancer patients, of which 232 had HER2+ tumors. In the HER2+ cohort, patients were randomly assigned to 9 weeks of trastuzumab versus 12 months of trastuzumab, with chemotherapy. The shorter trastuzumab treatment in FinHer produced comparable hazard ratios for 3-year RFS (0.42) and OS (0.41), although, the confidence intervals were wide for both (95 % CI 0.21–0.83, $P = 0.001$ and 95 % CI 0.16–1.08, $P = 0.07$ respectively). This may, in part, be explained by the upfront use of trastuzumab within a synergistic chemotherapy combination with vinorelbine or docetaxel, or the efficacious administration of FEC itself. Furthermore, synergism between FEC and trastuzumab may have occurred, due to the long half-life of trastuzumab exerting its action several weeks after the last administration [83]. This group of investigators has successfully completed recruitment of 2168 patients in November 2014 into a trial directly comparing the 9-weeks of trastuzumab therapy to 52-weeks—the SOLD trial (NCT00593697)—and results are awaited.

Other studies including PHARE [84] (Protocol of Herceptin Adjuvant with Reduced Exposure) and PERSEPHONE (no longer recruiting; results awaited), also compared shorter duration trastuzumab (6 months) versus 1 year of standard treatment. PHARE is an open-label, randomized, phase III trial with 1691 patients randomly assigned to receive 12 months of trastuzumab and 1693 to receive 6 months of trastuzumab. After a median follow-up of 42.5 months, 175 disease-free survival events were noted in the 12-month group and 219 in the 6-month group. A 2-year disease-free survival was 93.8 % (95 % CI 92.6–94.9) in the 12-month group and 91.1 % (89.7–92.4) in the 6-month group (hazard ratio 1.28, 95 % CI 1.05–1.56; $P = 0.29$). 119 (93 %) of the 128 cardiac events (clinical or based on assessment of left ventricular ejection fraction) occurred while patients were receiving trastuzumab. Significantly more patients in the 12-month group experienced a cardiac event than did those in the 6-month group (96 [5.7 %] of 1690 patients vs. 32 [1.9 %] of 1690 patients, $P < 0.0001$). The study failed to meet its no-inferiority endpoint to show that 6 months of treatment with trastuzumab was non-inferior to 12 months of trastuzumab.

In the HERA study [79], the comparison of 2 years versus 1 year of trastuzumab treatment involved a landmark analysis of 3105 patients who were disease-free 12 months after randomisation to one of the trastuzumab groups, and was planned after observing at least 725 disease-free survival events. 367 events of disease-free survival in 1552 patients in the 1 year group and 367 events in 1553 patients

in the 2-year group (hazard ratio [HR] 0.99, 95 % CI 0.85–1.14, $P = 0.86$). HRs for a comparison of 1 year of trastuzumab treatment versus observation were 0.76 (95 % CI 0.67–0.86, $P < 0.0001$) for disease-free survival and 0.76 (0.65–0.88, $P = 0.0005$) for overall survival, despite crossover of 884 (52 %) patients from the observation group to trastuzumab therapy. Thus, the updated HERA results confirmed that 1 year of treatment provides a significant disease-free and overall survival benefit compared with observation, and that 2 years of trastuzumab did not produce any additional benefit compared with 1 year of trastuzumab [85].

21.4.5 Avoiding Anthracyclines

BCIRG 006 [80] was interesting in its suggestion that a non-anthracycline regimen, combined with trastuzumab may be adequate to treat HER2+ early breast cancer patients. The study randomly assigned 3222 women with HER2+ early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). At a median follow-up of 65 months [86], with 656 events, the estimated disease-free survival rates at 5 years were 75 % among patients receiving AC-T, 84 % among those receiving AC-T plus trastuzumab, and 81 % among those receiving TCH. Estimated rates of overall survival were 87, 92, and 91 %, respectively. No significant differences in efficacy (disease-free or overall survival) were found between the two trastuzumab regimens, whereas both were superior to AC-T. The rates of congestive heart failure and cardiac dysfunction were significantly higher in the group receiving AC-T plus trastuzumab than in the TCH group ($P < 0.001$). Eight cases of acute leukemia were reported: seven in the groups receiving the anthracycline-based regimens and one in the TCH group subsequent to receiving an anthracycline outside the study. The addition of 1 year of adjuvant trastuzumab significantly improved disease-free and overall survival among women with HER2-positive breast cancer. The authors argued that the risk—benefit ratio favored the non-anthracycline TCH regimen over AC-T plus trastuzumab, given its similar efficacy, fewer acute toxic effects, and lower risks of cardiotoxicity and leukemia.

21.4.6 Small HER2+ Tumors

In the four phase 3 randomized trials involving more than 8000 patients [78–80], trastuzumab when administered in combination with or after chemotherapy, resulted in recurrence risk reduction by approximately 50 %, with improvement in overall survival. However, all of these trials focused largely on patients with stage II or stage III HER2+ breast cancers, with limited information to guide optimal treatment of T1a–bN0 HER2+ breast cancers. Currently, no single standard treatment regimen is recommended for patients with stage I HER2+ breast cancer.

Several studies have examined the risk of disease recurrence in small HER2+ breast cancer patients who have not received trastuzumab or, in most cases, chemotherapy. The largest of the studies focused on 520 patients in the NCCN [87] database who had small HER2+ breast cancers (≤1 cm). The 5-year rate of DFS was 94 % for patients with T1bN0 ER− tumors, 93 % for T1aN0 ER− tumors, and 94–96 % for patients with T1a–bN0 ER+ disease. A study from the M.D. Anderson Cancer Center [88] suggested that among 98 patients with T1a–bN0 HER2-positive tumors, the 5-year rate of recurrence-free survival was 77.1 %, and the 5-year rate of survival free from distant recurrence was 86.4 %. In a study of 117 node-negative, HER2-positive tumors measuring up to 2 cm in a tumor registry in British Columbia, Canada [89], the 10-year rate of relapse-free survival was 68.3 % among patients with hormone-receptor-negative tumors and 77.5 % among patients with hormone-receptor-positive tumors. Although recurrence rates vary across these studies, the rates range from approximately 5 to 30 %, with distant recurrences occurring in as many as 20 % of patients with tumors measuring up to 1 cm. The studies consistently suggest that the risk of recurrence, at least in the first 5 years, is higher in the ER- group than in the ER+ group.

Although patients with stage I HER2+ tumors are expected to derive a smaller absolute benefit from adjuvant therapy than those with larger or node-positive tumors, the data suggest that they remain at more than minimal risk for a recurrence of breast cancer, and therefore, adjuvant trastuzumab should be actively considered for these smaller tumors.

In an uncontrolled, single group, multicenter, investigator-initiated study of adjuvant paclitaxel and trastuzumab [90] in 406 early HER2+ breast cancer patients (tumors ≤3 cm), patients received weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by 9 months of trastuzumab monotherapy. With a median follow-up period of 4.0 years, the 3-year rate of DFS was 98.7 % (95 % CI 97.6–99.8). A total of 13 patients (3.2 %; 95 % CI, 1.7–5.4) reported at least one episode of grade 3 neuropathy, and 2 had symptomatic congestive heart failure (0.5 %; 95 % CI, 0.1–1.8), both of whom had normalization of the left ventricular ejection fraction after discontinuation of trastuzumab. A total of 13 patients had significant asymptomatic declines in ejection fraction (3.2 %; 95 % CI, 1.7–5.4), as defined by the study, but 11 of these patients were able to resume trastuzumab therapy after a brief interruption.

21.4.7 Trastuzumab and/or Other Targeted Therapies

21.4.7.1 Lapatinib

The ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial [91] was a four-arm randomized adjuvant study comparing trastuzumab for 12 months (T), lapatinib for 12 months (L), trastuzumab for 12 weeks followed sequentially by lapatinib for 34 weeks (T → L), and the combination of trastuzumab and lapatinib for 12 months (TL). It randomly assigned 8381 patients, of whom 40 % had node-negative disease and 57 % had hormone receptor-positive disease. Although the study was powered for 850 DFS events, the study was analyzed at 4.5 years (median) of follow-up as per protocol stipulation but with only 555 DFS events. At the first efficacy interim analysis, the comparison of L to T crossed the futility boundary, and as such, the L arm was crossed over to a recommended course of trastuzumab for 12 months. At the time of reporting of the efficacy of the primary endpoint at the 2014 ASCO Annual Meeting, the 4-year DFS for the T, T → L, and TL arms were 86, 87 and 88 %, respectively. The HR comparing TL and T was 0.84 (0.70–1.02; $P \leq 0.048$), which was not significant, for a $P \leq 0.025$ was required for statistical significance. The interaction test for hormone receptor status and for schedule of anti-HER2 therapy was not significant. However, numerically, the sequential administration of anti-HER2 therapy arms had some difference (T vs. T → L 4-year DFS of 83 % vs. 86 %, respectively), whereas the combination arms did not (T vs. TL 4-year DFS of 90 % vs. 90 %, respectively). Lapatinib was also associated with a greater rate of adverse events, which subsequently led to only 60–78 % of patients in the lapatinib treatment arms receiving at least 85 % of the intended dose intensity of L.

TEACH (Tykerb® Evaluation After Chemotherapy) was a placebo-controlled, multicentre, randomized phase 3 trial which evaluated the effectiveness of 12 months of lapatinib versus placebo, given as either immediate or delayed therapy, in HER2+ early breast cancer [92]. 3161 women were enrolled and 3147 were assigned to lapatinib ($n = 1571$) or placebo ($n = 1576$). After a median follow-up of 47.4 months (range 0.4–60.0) in the lapatinib group and 48.3 (0.7–61.3) in the placebo group, 210 (13 %) disease-free survival events had occurred in the lapatinib group versus 264 (17 %) in the placebo group (hazard ratio [HR] 0.83, 95 % CI 0.70–1.00; $P = 0.053$). Central review of HER2 status showed that only 2490 (79 %) of the randomized women were HER2+. 157 (13 %) of 1230 confirmed HER2+ patients in the lapatinib group and in 208 (17 %) of 1260 in the placebo group had a disease-free survival event (HR 0.82, 95 % 0.67–1.00; $P = 0.04$). Serious adverse events occurred in 99 (6 %) of 1573 patients taking lapatinib and 77 (5 %) of 1574 patients taking placebo, with higher incidences of grade 3-4 diarrhea (97 [6 %] vs. nine [<1 %]), rash (72 [5 %] vs. three [<1 %]), and hepatobiliary disorders (36 [2 %] vs. one [<1 %]). This study did not show any significant difference in disease-free survival between groups when analyzed in the intention-to-treat population.

21.4.7.2 Pertuzumab

APHINITY (NCT0135887—Adjuvant Pertuzumab and Herceptin IN IniTial therapY of breast cancer) is a large adjuvant study that randomized 4800 patients with stage I-III HER2+ breast cancer to standard chemotherapy (non-anthracycline- or anthracycline-based) concurrent with pertuzumab/trastuzumab, or to standard chemotherapy concurrent with trastuzumab. In both arms, the same HER2-targeted therapy is administered postchemotherapy to complete 1 year of therapy. Recruitment has completed and the results are awaited. Indeed, if these results were to be positive, the addition of pertuzumab to chemotherapy/trastuzumab in the adjuvant setting will likely become standard of care.

21.4.7.3 Neratinib

Neratinib is an orally available, 6,7-disubstituted-4-anilinoquinoline-3-carbonitrile irreversible inhibitor of the HER-2 receptor tyrosine kinase with potential antineoplastic activity. Neratinib binds to the HER-2 receptor irreversibly, thereby reducing autophosphorylation in cells, apparently by targeting a cysteine residue in the ATP-binding pocket of the receptor. Treatment of cells with this agent results in inhibition of downstream signal transduction events and cell cycle regulatory pathways; arrest at the G1-S (Gap 1/DNA synthesis)-phase transition of the cell division cycle; and ultimately decreased cellular proliferation. Neratinib also inhibits the epidermal growth factor receptor (EGFR) kinase and the proliferation of EGFR-dependent cells [93].

ExteNET is a double-blind phase III trial of neratinib (240 mg orally once daily) versus placebo in 2821 women with early-stage HER2+ (local confirmation) breast cancer after adjuvant treatment with trastuzumab, the primary endpoint being iDFS. At 24 months [94], patients who received neratinib had an iDFS rate of 93.9 % compared to 91.6 % in the placebo group (hazard ratio [HR] 0.67, 95 % CI [0.50, 0.91]; $P = 0.009$). There were 73 distant recurrences (5.1 %) in the placebo group, and 52 (3.7 %) in the neratinib group. Patients with hormone receptor-positive disease were observed to derive an even greater benefit with neratinib therapy, and the iDFS rates were 95.4 % for neratinib and 91.2 % for placebo ($P = 0.001$). There was no

significant difference in the patients with hormone receptor-negative disease (92.0 % vs. 92.2 %). Diarrhea was the most common adverse event with neratinib; grade 3/4 diarrhea occurred in 39.9 % of patients compared with 1.6 % of patients who received placebo. Overall survival data are still needed before neratinib could be considered a new standard, and questions remain about which populations will benefit from this therapy.

21.4.7.4 Bevacizumab

In HER2+ breast cancer, preclinical models have demonstrated that HER2 amplification is associated with an increase in VEGF gene expression [95]. The vascular endothelial growth factor (VEGF) receptor family plays an essential role in angiogenesis, and therefore, in cancer metastases dissemination [96]. The principal agent targeting VEGF is bevacizumab, a humanized monoclonal antibody directed against VEGF which can reduce tumor angiogenesis [97] and the tumor interstitial fluid pressure, leading to a better delivery of large therapeutic molecules into solid tumors.

The addition of bevacizumab (Avastin) to adjuvant chemotherapy did not improve invasive disease-free survival or overall survival in patients with high-risk HER2-positive breast cancer in the large randomized phase III BETH trial [98]. BETH enrolled 3509 women with HER2+ node-positive or high-risk node-negative breast cancer in two cohorts. Cohort 1 included 3231 patients randomly assigned to receive the non-anthracycline regimen TCH (docetaxel, carboplatin, and trastuzumab) or TCH plus bevacizumab. In cohort 2, 278 patients were randomly assigned to anthracycline-based therapy with T-FEC-H (docetaxel, fluorouracil, epirubicin, cyclophosphamide, plus trastuzumab) with or without bevacizumab.

At a median follow-up of 38 months, the rate of invasive disease-free survival in cohort 1 was 92 % in both TCH arms (with and without bevacizumab), and in cohort 2, 89 % in the anthracycline-containing arms without bevacizumab versus 91 % with bevacizumab. This difference between the anthracycline and non-anthracycline-containing arms was not statistically significant.

21.5 Neoadjuvant HER2+ Approaches

21.5.1 Neoadjuvant Trastuzumab

The standard clinical use of neoadjuvant chemotherapy today can be categorized into two populations of patients: the locally advanced breast cancers (LABC) and the primary operable breast cancers (POBC). The defined purpose for the use of neoadjuvant chemotherapy for LABC is to convert a baseline inoperable condition to an operable state. In POBC, neoadjuvant chemotherapy has the potential to downstage a tumor and thus convert a baseline mastectomy candidate into a breast conservation candidate. Other advantages of delivery in the neoadjuvant setting include the ability to study new agents with the utility of a surrogate endpoint for outcome; the ability to obtain tumor tissue for pharmacodynamic assessment, understanding of biology and discovery of predictive biomarkers; earlier initiation of systemic therapies; and the ability to monitor response. There remains an ongoing debate regarding the correlation of pCR status and long-term clinical outcomes such as DFS, EFS, and OS. Multiple studies have repeatedly demonstrated a prognostic effect for the cohort of patients achieving a pCR—particularly those achieving a pCR in breast and lymph nodes (tpCR). Recently, a pooled analysis of 12 large trials of 11,955 patients treated with preoperative chemotherapy with available data on pCR and at least 3-year follow-up data on EFS and OS was performed by the FDA (CTNeoBC pooled analysis) [99]. The analysis demonstrated that the association between pCR and long-term outcomes was strongest in triple negative breast cancer and HER2+/ER− breast cancers treated with trastuzumab. The German Breast Group also performed a similar analysis with seven of their trials involving 6366 patients [100]. They found similar results to the CTNeoBC pooled analyses (Table 21.3).

The first landmark trial investigating the benefit of neoadjuvant trastuzumab in the LABC setting was the NOAH trial [101]. NOAH randomly selected 228 patients with HER2+ disease to receive a neoadjuvant regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) with or without concurrent trastuzumab (throughout the entire chemotherapeutic regimen). This is the largest randomized trial of a true locally advanced and inflammatory population to date. The trastuzumab-treated cohort demonstrated a significantly superior rate of pCR in breast and nodes (total pCR [tpCR]; 38 % vs. 19 %; $P \leq 0.001$), which ultimately translated to an improved 3-year event-free survival (EFS; 71 % vs. 56 %, HR 0.59; 95 % CI, 0.38–0.90). Although the use of the specific chemotherapy regimen from NOAH is not likely to be common, the concept of neoadjuvant trastuzumab concurrent with chemotherapy now is.

21.5.2 Lapatinib-Based Neoadjuvant Regimens

The GeparQuinto study [102] compared trastuzumab (8 mg/kg loading dose followed by 6 mg/kg every 3 weeks given concurrently with chemotherapy during the preoperative period) with lapatinib (1250 mg/day continuously for 12 weeks) added to a backbone of four cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) followed

Table 21.3 Neoadjuvant trials of dual HER2 targeted therapies

Trial	No. of patients	Treatment arms	Pcr (breast and nodes) (%)	*p*	3-year EFS (%)
GeparQuinto	309	ECH → TH	31.3	$P < 0.05$	N/A
	311	ECL→	21.7		N/A
NeoALTTO	149	H → HP	27.6		76
	154	L → LP	20.0	$P = 0.13$	78
	152	HL → HLP	46.9	$P = 0.001$	84
CHER-LOB	36	HP → FECH	25		N/A
	39	LP → FECL	26.3		N/A
	46	HLP → FECHL	46.7		N/A
NSABP B-41	177	AC → HP	52.5 (breast)		N/A
	171	AC → LP	53.2 (breast)	$P = 0.9852$	N/A
	171	AC → HLP	62.0 (breast)	$P = 0.095$	N/A
CALGB 40601	120	HP	40 (breast)		N/A
	67	LP	32 (breast)		N/A
	118	HLP	51 (breast)	$P = 0.11$	N/A
NeoSphere	107	TH	29.0 (breast)		N/A
	107	PerHT	45.8 (breast)	$P = 0.0141$	N/A
	107	PerH	24.0 (breast)		N/A
	96	PerT	16.8 (breast)		N/A
Tryphena	73	PerHFEC → PerTH	61.6 (breast)		N/A
	75	FEC → PerTH	57.3 (breast)		N/A
	77	TcarboHPer	66.2 (breast)		N/A

Abbreviations: *pCR* pathologic complete response; *EFS* event-free survival; *E* epirubicin; *C* cyclophosphamide; *H* trastuzumab; *T* docetaxel; *L* lapatinib; *P* paclitaxel; *F* 5-fluorouracil; *NSABP* National Surgical Adjuvant Breast and Bowel Project; *A* doxorubicin; *CALGB* Cancer and Leukemia Group B; *Per* pertuzumab; *carbo* carboplatin

by four of docetaxel (100 mg/m^2) in 615 patients with HER2 + disease. A significantly higher tpCR rate (breasts and nodes) was seen in the trastuzumab arm (30.3 % vs. 22.7 %; odds ratio 0.68; 95 % CI, 0.47–0.97; $P \leq 0.04$). Furthermore, in this study, dose reductions were required in nearly one-third of patients receiving lapatinib, prompting a protocol amendment reducing the lapatinib dose to 1000 mg/m^2. The smaller CHER-LOB study [103] was conducted using a chemotherapy backbone of weekly paclitaxel (80 mg/m^2) for 12 weeks followed by three-weekly 5-fluorouracil, epirubicin, cyclophosphamide (FEC; 500/75/500 mg/m^2, respectively) with either weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly) or lapatinib (1250 mg daily) given concurrently with chemotherapy. This study also examined the efficacy of a trastuzumab-lapatinib doublet with dose-adjusted lapatinib (750 mg/day). Dual HER2 targeting substantially improved pCR (breast and nodes) over either trastuzumab or lapatinib alone. pCR rates were 46 % (90 % CI, 34.4–58.9 %), 25 % (90 % CI, 13.1–36.9 %), and 26.3 % (90 % CI, 14.5–38.1 %), respectively. As was seen in the GeparQuinto trial, gastrointestinal toxicity with lapatinib was a significant adverse event. More than 50 % of those receiving lapatinib experienced diarrhea of grade 1 or higher, even after a protocol amendment directing a dose reduction from 1500 to 1250 mg/day in the single-agent arm, and from 1000 to 750 mg/day in the doublet arm. The NeoAdjuvant Lapatinib and/or Trastuzumab Optimization (NeoALTTO) trial [104] was a three-armed study addressing the comparative efficacy of single compared with dual HER2 blockade using trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly), lapatinib (1500 mg daily), or a combination (trastuzumab standard dose and lapatinib 1000 mg daily), alongside weekly paclitaxel (80 mg/m^2) chemotherapy. This trial scheduled a 6-week lead in period of targeted therapy alone before introduction of paclitaxel for a further 12 weeks of therapy. Dual HER2 targeting induced tpCR (breast and nodes) rates in 46.8 % of patients compared with 27.6 % in the trastuzumab alone arm ($P \leq 0.0007$). There was no statistically significant difference in pCR rates between the trastuzumab alone and lapatinib alone arms (27.6 and 20 %; $P \leq 0.13$). The NSABP B-41 study [105] randomly selected 529 patients with HER2+ disease to receive doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for four cycles, followed by weekly paclitaxel (80 mg/m^2) for a further 12 weeks with either concurrent

weekly trastuzumab (4 mg/kg loading dose followed by 2 mg/kg weekly), 1250 mg of lapatinib daily, or weekly trastuzumab plus lapatinib (750 mg/day). pCR was achieved for 62 % of patients receiving combination HER2 targeting compared with 52.5 % in the trastuzumab arm ($P \leq 0.095$). There was no significant difference between the trastuzumab and lapatinib alone arms (52.5 % vs. 53.2 %; $P \leq 0.990$). The Cancer and Leukemia Group B 40601, a neoadjuvant phase III trial of weekly paclitaxel (T) and trastuzumab (H) with and without lapatinib (L) in HER2-positive breast cancer, was presented at the 2013 ASCO Annual Meeting [106]. This trial randomly selected 305 patients, of which two-thirds had clinical stage II disease. The pCR rates in the breast alone were 51 % (42–60 %) THL, 40 % (32–49 %) TH, 32 % (22–44 %) TL. The combination arm of THL was not significantly different from the standard arm of trastuzumab and paclitaxel ($P \leq 0.11$).

21.5.3 Pertuzumab-Based Neoadjuvant Regimens

In the NeoSphere trial [107], 417 women with HER2+ POBC/LABC disease were randomly selected to receive either four cycles of neoadjuvant trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks), docetaxel (75 mg/m^2 escalating to 100 mg/m^2 as tolerated) and pertuzumab (loading dose 840 mg, followed by 420 mg every 3 weeks), or trastuzumab plus docetaxel, or pertuzumab and trastuzumab without chemotherapy, or pertuzumab plus docetaxel. The combination of dual-HER2 targeting and docetaxel induced a pCR (breast) for 45.8 % (95 % CI, 36.1–55.7) compared with 29 % of those randomly assigned to trastuzumab and docetaxel (95 % CI, 20.6–38.5; $P \leq 0.0141$). After surgery, all patients received three cycles of FEC and the remainder of 1 year of trastuzumab. pCR was achieved for 24.0 % of those receiving pertuzumab and docetaxel and 16.8 % of women who were treated with dual HER2 targeted therapy in the absence of chemotherapy. Neither short nor long-term clinical outcomes (EFS and OS) have been reported yet from NeoSphere.

TRYPHENA [108] was a phase II trial with cardiac safety as the primary endpoint. All 225 participants received dual HER2 targeting with trastuzumab and pertuzumab. The three study arms were randomly assigned to 500 mg 5-fluorouracil, 100 mg epirubicin, and 500 mg/m^2 cyclophosphamide (FEC100) for three cycles, followed by docetaxel (75 mg/m^2) with concurrent with trastuzumab and pertuzumab; FEC for three cycles followed by docetaxel with trastuzumab and pertuzumab given only alongside docetaxel; or six cycles of docetaxel, carboplatin, trastuzumab, and pertuzumab. In this trial, pCR (breast) was a secondary endpoint, with rates ranging between 57.3 and 66.2 %, in keeping with results published in other studies. The lack of an arm without pertuzumab limits the extrapolation of these results to other studies and to standard clinical practice. In September 2013, the U.S. Food and Drug Administration (FDA) granted accelerated approval to pertuzumab in combination with trastuzumab and chemotherapy as a neoadjuvant treatment regimen in patients with HER2+ locally advanced, inflammatory, or early-stage disease (tumor size <2 cm or with positive lymph nodes).

21.5.4 Neratinib-Based Neoadjuvant Regimens

Neratinib has been studied in a neoadjuvant manner as part of the I-SPY 2 program, as well as in an extended manner in a placebo-controlled trial in a population of patients following 1 year of standard adjuvant trastuzumab-based therapy. In the I-SPY 2 trial, neratinib was given in combination with weekly paclitaxel (80 mg/m^2 for 12 weeks) in both the HER2+ and HER2− cohorts [109]. All patients subsequently received sequential doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) for four cycles without neratinib or trastuzumab before proceeding to definitive surgery. In the HER2+ signature cohort, the pCR rate was 39 % in the neratinib plus paclitaxel arm, compared to 23 % in the trastuzumab plus paclitaxel arm. The magnitude of improvement in pCR was similar regardless of the hormone receptor status in the HER2+ cohort. No significant difference in pCR rates was seen in the HER2− signature cohort. A significant rate of grade 2–3 diarrhea was seen, however, in the neratinib arms resulting in dose reductions/holds in 65 % of cases for neratinib (vs. 15 % in the control arm).

21.6 Other Exploratory Anti-HER2 Blockade Strategies

The main mechanisms for resistance to anti-HER2 therapy with trastuzumab include redundancy, reactivation and escape. Redundancy within the HER receptor layer refers to the ability of the pathway to continue to signal despite being partially inhibited because of redundant ligands and receptors that enable alternative dimerization patterns. Reactivation, on the other hand refers to the ability to reactivate pathway signaling at or downstream of the receptor layer such as with activating HER or downstream mutations, or loss of downstream pathway negative-regulating mechanisms. Escape refers to the use of other pathways, which may preexist or be acquired at the time of resistance, but are not usually driving the cancer cell when HER2 is uninhibited [110, 111].

Multiple other pathways and mechanisms involved in intrinsic and acquired resistance to HER-targeted therapy have been suggested, including various receptor and cellular tyrosine kinases (e.g., MET, IGFR-1, c-SRC, and EphA2) [112–114], mucins [115], regulators of cell cycle and apoptosis [116–118] and various elements of the tumor microenvironment and the host immune system [119–121].

21.7 Conclusion

HER2 is a redundant, robust and powerful signaling pathway and understanding the mechanisms mediating resistance to HER2 blockade has opened new therapeutic avenues which have resulted in significant improvements in patient outcomes. Different combinations of anti-HER2 therapies have been explored and the next challenge is to find predictive biomarkers to identify cohorts of patients that may need differential combinations and/or durations of anti-HER2 therapies. HER2+ breast cancer has, indeed, come a long way, and trastuzumab has revolutionized the HER2+ subtype from being one with the worst prognosis to one arguably with the best long-term outcomes. The evolution continues as the mechanisms of HER2 resistance get further unraveled.

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