Towards personalized treatment for early stage HER2-positive breast cancer

Kristina Goutsouliak[1,2,3,7], *Jamunarani Veeraraghavan*[1,2,3,7], *Vidyalakshmi Sethunath*[1,2,4], *Carmine De Angelis*[1,2,5], *C. Kent Osborne*[1,2,3,6], *Mothaffar F. Rimawi*[1,2,3]* *and Rachel Schiff*[1,2,3,6]*

Abstract | Advances in HER2-targeted therapies have improved the survival of patients with HER2-positive breast cancer. The standard-of-care treatment for localized disease has been chemotherapy and 1 year of adjuvant HER2-targeted therapy, typically with the anti-HER2 antibody trastuzumab. Despite the effectiveness of this treatment, disease relapse occurs in a subset of patients; thus, focus has been placed on escalating treatment by either combining different HER2-targeted agents or extending the duration of HER2-targeted therapy. Indeed, dual HER2-targeted therapies and extended-duration anti-HER2 therapy, as well as adjuvant therapy with the anti-HER2 antibody–drug conjugate T-DM1, have all been approved for clinical use. Emerging evidence suggests, however, that some patients do not derive sufficient benefit from these additional therapies to offset the associated toxicities and/or costs. Similarly, the universal use of chemotherapy might not benefit all patients, and treatment de-escalation through omission of chemotherapy has shown promise in clinical trials and is currently being explored further. The future of precision medicine should therefore involve tailoring of therapy based on the genetics and biology of each tumour and the clinical characteristics of each patient. Predictive biomarkers that enable the identification of patients who will benefit from either escalated or de-escalated treatment will be crucial to this approach. In this Review, we summarize the available HER2-targeted agents and associated mechanisms of resistance, and describe the current therapeutic landscape of early stage HER2-positive breast cancer, focusing on strategies for treatment escalation or de-escalation.

HER2-positive (HER2$^+$) breast cancer accounts for ~15–20% of all breast cancers[1,2]. This aggressive disease subtype is characterized by overexpression of the human epidermal growth factor receptor 2 (HER2, also known as erbB2), typically through *ERBB2* amplification. HER2 belongs to a family of receptor tyrosine kinases with four members: HER1 (also known as EGFR), HER2, HER3 and HER4. When activated, the HER proteins homodimerize or heterodimerize and subsequently activate intricate cellular signalling cascades, including the PI3K–AKT and RAS–MAPK (ERK) pathways, which regulate cell proliferation and survival, as well as the metastasis of tumour cells[3,4] (FIG. 1a). Accordingly, HER2 is a major oncogenic driver of breast tumours that overexpress this protein[5] and thus offers a therapeutic vulnerability that can be effectively targeted in patients with HER2$^+$ tumours.

The past two decades — since the humanized anti-HER2 monoclonal antibody trastuzumab became the first molecularly targeted agent to be approved by the FDA for the treatment of patients with HER2$^+$ breast cancer — have witnessed a surge in the number of anti-cancer agents targeting HER2 and other HER family members[6,7]. The use of biologic anti-HER2 agents in combination with chemotherapy has yielded pronounced clinical success and has dramatically improved the outcomes in patients with HER2$^+$ breast cancer[3,4]. Despite these improvements, the emergence of treatment resistance remains a common and challenging event, especially in the advanced-stage disease setting, and is a grave reminder that more effective therapies are needed. Deciphering the mechanisms of resistance will lay the foundations for developing effective methods of circumventing disease relapse.

Herein, we provide an overview of the currently approved and emerging HER2-targeted therapies for patients with breast cancer, as well as mechanisms of resistance to such therapies. We then focus on the past and ongoing clinical efforts to optimize treatments for early stage HER2$^+$ disease, through either escalation

*e-mail: rimawi@bcm.edu; rschiff@bcm.edu

https://doi.org/10.1038/s41571-019-0299-9

Key points

- Advances in HER2-targeted therapy have improved the outcomes of patients with HER2-positive breast cancer; however, intrinsic and acquired resistance to such treatment remain a major clinical challenge.
- Emerging preclinical and clinical evidence suggests that simultaneous therapeutic blockade of the HER2 and oestrogen receptor signalling pathways in tumours co-expressing both of these receptors should be considered in order to improve patient outcomes.
- In the era of precision medicine, treatment based on the biological and molecular characteristics of the tumour and the clinical characteristics of the patient is a logical approach.
- The development of a molecular approach to differentiate patients who are likely to benefit from HER2-targeted therapy with less or no chemotherapy (treatment de-escalation) from those who require chemotherapy or need additional treatment (escalation) remains an overarching challenge.
- Prospective testing and validation of risk-stratified biomarker-driven treatment approaches will pave the way towards personalized therapy for patients with HER2-positive breast cancer.

or de-escalation of therapy. Finally, we summarize the molecular determinants of response and the clinical correlative studies aimed at developing biomarkers for tailored HER2-targeted therapy.

HER2-targeted agents

Several classes of anti-HER2 agents have been developed (TABLE 1), including: (1) monoclonal antibodies that bind to the extracellular domain of HER2, such as trastuzumab and pertuzumab, which have direct antitumour effects by inhibiting HER2 signalling and indirect activity via engagement of the host immune system to elicit antibody-dependent cellular cytotoxicity (ADCC)[3,8–10]; (2) small-molecule tyrosine kinase inhibitors (TKIs), including lapatinib, neratinib and afatinib, that bind to the intracellular tyrosine kinase domains of HER2 and other HER family members; and (3) antibody–drug conjugates (ADCs), for example, trastuzumab emtansine (T-DM1), composed of a monoclonal antibody directed at the extracellular domain of HER2 linked to a cytotoxic agent (FIG. 1b). While trastuzumab, pertuzumab, lapatinib, neratinib and T-DM1 are currently approved by both the FDA and the European Medicines Agency (EMA) for clinical use in patients with HER2$^+$ breast cancer, several novel HER2-targeted agents are being investigated in clinical trials involving patients with breast cancer, including the Fc-optimized monoclonal antibody margetuximab, the TKIs tucatinib and pyrotinib, and the ADC trastuzumab deruxtecan (TABLE 1). Moreover, various trastuzumab biosimilars[11–18] and subcutaneous administration[19] of trastuzumab have also been approved by the FDA. These treatment options have further enriched the armamentarium of HER2-targeted therapies and, in the near future, are likely to be used more widely in the clinical management of HER2$^+$ disease[20,21], and might improve patient access to biologic therapy and quality of life owing to time and/or cost savings (relating to ease of administration, without the need for infusion infrastructure, for the subcutaneous formulation of trastuzumab). With a wealth of agents available in the busy space of HER2-targeted therapy, the efficacy and safety profiles of these and other newly emerging HER2-targeted drugs, as well as ways to effectively integrate them into the current treatment regimens, continue to be explored.

Given the redundancy in HER family signalling[22] (FIG. 1a), the effectiveness of HER2-targeted therapy relies on complete functional inhibition of the entire HER network, especially at the level of the HER proteins themselves[23–25]. In experimental models, combinatorial HER2 blockade, with simultaneous use of two or three HER2-targeted agents, yields superior antitumour activity to that of single-agent anti-HER2 therapy[23–25]. The superiority of dual HER2-targeted therapy in patients with breast cancer has also been demonstrated in clinical trials conducted in the neoadjuvant, adjuvant and metastatic settings[26–28]. Furthermore, new-generation irreversible dual or pan-HER TKIs, including the approved agent neratinib and also pyrotinib (TABLE 1), hold the potential to comprehensively suppress HER signalling[29]. In addition, some of these TKIs might be a plausible treatment option for patients with tumours harbouring resistance mutations affecting HER2 or other HER family members, which are most commonly detected in metastases, especially those that arise or progress following prior treatment with anti-HER2 agents[30–32]. Agents targeting other members of the HER family have also been developed and, if used in combination with HER2-targeted agents, could potentially result in more potent and comprehensive inhibition of HER signalling[23,25,33–36]. Of note, the use of agents that effectively suppress EGFR increases the incidence of adverse events, particularly diarrhoea and rash attributable to inhibition of EGFR expressed in the gastrointestinal mucosa and skin, respectively[37–41].

With the development of effective dual HER2-targeted therapies, a disproportionate increase in the incidence of brain-only recurrence has been observed in patients with early stage HER2$^+$ breast cancer[42]. This phenomenon necessitates the development of agents that can efficiently cross the blood–brain barrier, such as tucatinib, which has been associated with activity against central nervous system (CNS) disease in the metastatic setting[43]. Results from the phase II HER2CLIMB trial (NCT02614794) evaluating the benefit of adding tucatinib to trastuzumab and capecitabine in patients with previously treated metastatic breast cancer, including those with brain metastases, are awaited; however, the manufacturer of tucatinib has reported that the primary end point of this trial has been met, with a 46% reduction in the risk of disease progression, and a 52% reduction in patients with brain metastases specifically, as well as a 34% reduction in the risk of death[44].

Author addresses

[1]Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, TX, USA.
[2]Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX, USA.
[3]Department of Medicine, Baylor College of Medicine, Houston, TX, USA.
[4]Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX, USA.
[5]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy.
[6]Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA.
[7]These authors contributed equally: Kristina Goutsouliak, Jamunarani Veeraraghavan.

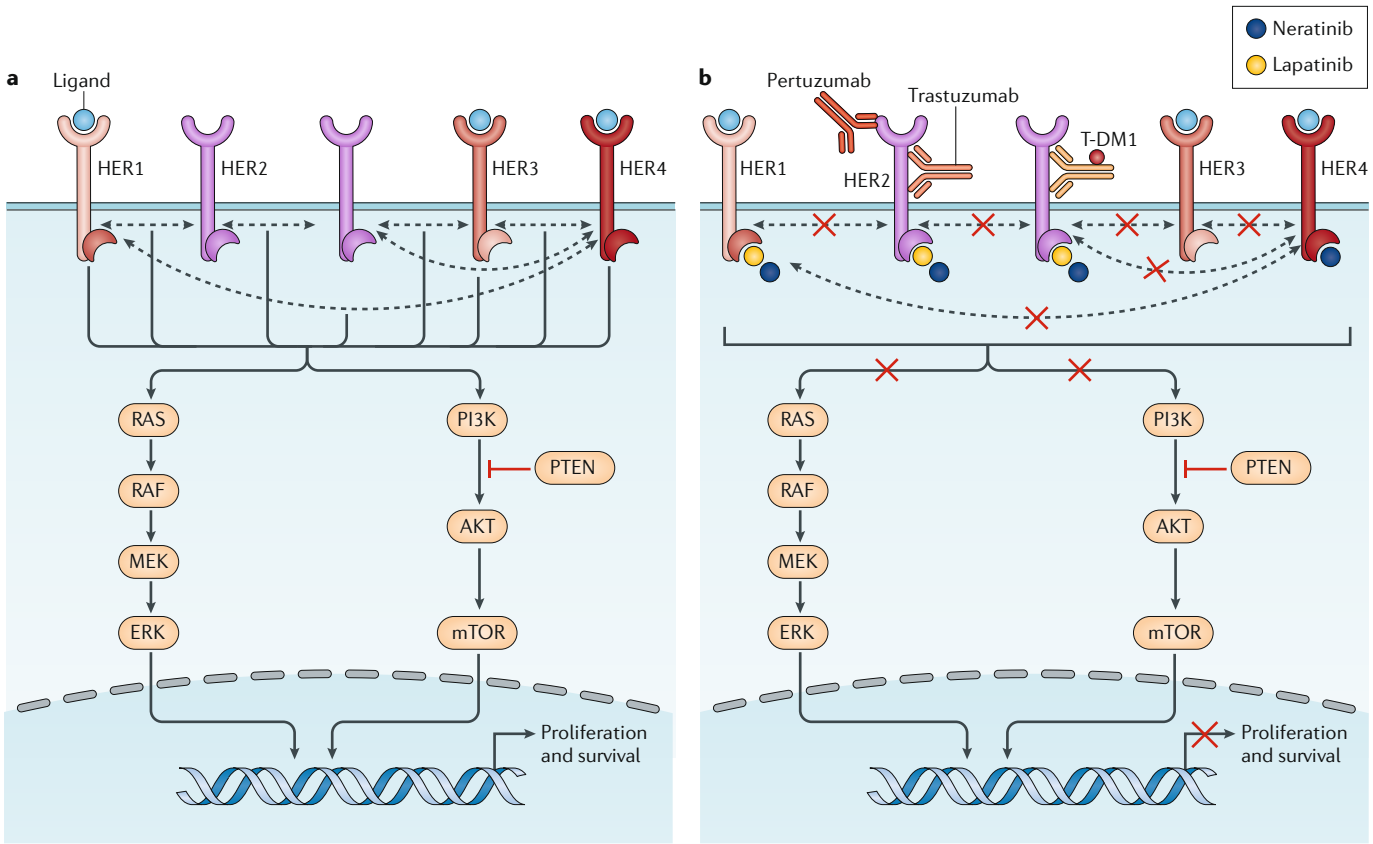

Fig. 1 | **Signalling by HER2 and other HER family members and the clinically approved HER2-targeted agents.** **a** | The HER family of receptor tyrosine kinases consists of four receptors: HER1 (also known as EGFR), HER2, HER3 and HER4. Activation of signalling through all of the HER proteins, except HER2, is induced by ligand binding. Upon ligand binding, these receptors undergo conformational changes leading to the formation of homodimers or heterodimers. HER2 lacks any known ligands but has a conformation that is conducive to dimerization and can thus be activated through homodimerization, when it is overexpressed, or heterodimerization with other ligand-bound members of the HER family. HER3 has a catalytic domain with very low levels of intrinsic kinase activity[165] but is known to promote potent signalling through heterodimerization with other HER family members. Dimerization of HER proteins results in transphosphorylation of specific tyrosine residues in their intracellular domains, which in turn activates downstream signalling cascades, including the PI3K–AKT and MAPK (ERK) pathways. These signalling pathways mediate diverse cellular activities, including those controlled by transcription factors that regulate the transcription of multiple genes associated with survival and proliferation. **b** | Five HER2-targeted agents are currently approved for the treatment of patients with $HER2^+$ breast cancer, which are categorized as monoclonal antibodies (trastuzumab and pertuzumab), small-molecule tyrosine kinase inhibitors (lapatinib and neratinib) or antibody–drug conjugates (trastuzumab emtansine, also known as T-DM1). Trastuzumab and pertuzumab are monoclonal antibodies that bind to the extracellular domain of the HER2 receptor. These agents are often combined together or administered sequentially to more comprehensively inhibit HER signalling and counter the distinct mechanisms of resistance associated with different classes of agents.

Resistance to anti-HER2 therapy

In general, resistance to HER2-targeted agents can be attributed to disparate mechanisms, although some might be shared between different agents, that are either prevalent at the time of initial treatment (intrinsic resistance) or emerge during treatment owing to the selection and eventual predominance of rare pre-existing or newly acquired resistant subclones (acquired resistance). The myriad mechanisms of resistance to anti-HER2 therapy have been thoroughly reviewed elsewhere[3,45–47] and thus are only briefly summarized here (FIG. 2). Incomplete inhibition of the HER family receptors, enabling sustained signalling through compensatory signals from the uninhibited HER proteins, is a pre-eminent cause of anti-HER2 treatment failure. This deficiency could potentially be overcome through combinatorial use of HER-targeted agents, including the two anti-HER2 antibodies (trastuzumab and pertuzumab) together or in combination with a potent TKI, to achieve comprehensive inhibition of the HER family receptors[23–25,48–50]. Despite the availability of highly potent HER-targeted agents, effective inhibition of HER2 might remain challenging owing to the emergence of genetic, epigenetic and post-translational alterations involving HER2 itself. These aberrations include activating *ERBB2* point mutations (such as L755S), p95HER2 (REF.[51]) (a truncated form of the receptor lacking the extracellular epitopes recognized by anti-HER antibodies, which is generated from alternative translational initiation sites in *ERBB2* transcripts or by proteolytic cleavage of HER2) and Δ16HER2 (REF.[52]) (a splice variant with omission of the extracellular domain encoded by exon 16, which

Table 1 | **Currently approved HER2-targeted therapies for breast cancer and new agents in phase III trials**

Drug	Mechanism of action	Administration route	Phase of development
Monoclonal antibodies			
Trastuzumab	Binds to HER2 juxtamembrane domain IV	Intravenous or subcutaneous	Clinically approved in combination with chemotherapy for the adjuvant treatment of early stage HER2$^+$ breast cancer and alone or in combination with chemotherapy for the treatment of advanced-stage disease
Pertuzumab	Binds to HER2 heterodimerization domain II	Intravenous	Clinically approved in combination with trastuzumab and chemotherapy for the treatment of advanced-stage HER2$^+$ breast cancer and for the neoadjuvant and/or adjuvant treatment of early stage disease
Margetuximab	Fc-optimized HER2 monoclonal antibody with enhanced immune-effector function	Intravenous	Phase III SOPHIA trial: improved PFS with margetuximab and chemotherapy versus trastuzumab and chemotherapy in patients with pretreated metastatic HER2$^+$ breast cancer[166]
Tyrosine kinase inhibitors			
Lapatinib	Reversible inhibitor of HER1 (also known as EGFR) and HER2	Oral	Clinically approved in combination with capecitabine for the treatment of pretreated advanced-stage HER2$^+$ breast cancer and in combination with letrozole for the first-line treatment of advanced-stage HER2$^+$/HR$^+$ disease
Neratinib	Irreversible pan-HER (HER1, 2, and 4) inhibitor	Oral	Clinically approved for extended adjuvant treatment of early stage HER2$^+$ breast cancer after trastuzumab-based therapy
Tucatinib	Selective HER2 inhibitor	Oral	Phase III HER2CLIMB-02 (NCT03975647): T-DM1 ± tucatinib in patients with pretreated metastatic HER2$^+$ breast cancers. Phase I trials revealed promising PFS and CNS response rates[43,167]
Pyrotinib	Irreversible EGFR and HER2 inhibitor	Oral	Phase III PHENIX trial: pyrotinib plus capecitabine significantly improved PFS versus placebo plus capecitabine (11.1 months versus 4.1 months; HR 0.18, 95% CI 0.13–0.26; $P < 0.001$) in patients with metastatic HER2$^+$ breast cancer previously treated with trastuzumab and a taxane[168]
Antibody–drug conjugates			
Trastuzumab emtansine (T-DM1)	Humanized monoclonal antibody trastuzumab covalently linked to the cytotoxic agent DM1	Intravenous	Clinically approved for the treatment of metastatic HER2$^+$ breast cancer and for the adjuvant treatment of residual disease after neoadjuvant treatment with trastuzumab and chemotherapy
Trastuzumab deruxtecan	A humanized anti-HER2 antibody, a cleavable peptide-based linker and potent topoisomerase I inhibitor	Intravenous	Phase III DESTINY trial: trastuzumab deruxtecan versus T-DM1 in patients with advanced-stage HER2$^+$ breast cancer previously treated with trastuzumab and a taxane[169]
Biosimilars			
Trastuzumab-dkst	Similar mechanism of action and efficacy to trastuzumab	Intravenous	Clinically approved[a]
Trastuzumab-pkrb (CT-P6)	Similar mechanism of action and efficacy to trastuzumab	Intravenous	Clinically approved[a]
Trastuzumab-dttb	Similar mechanism of action and efficacy to trastuzumab	Intravenous	Clinically approved[a]
Trastuzumab-qyyp	Similar mechanism of action and efficacy to trastuzumab	Intravenous	Clinically approved[a]
Trastuzumab-anns	Similar mechanism of action and efficacy to trastuzumab	Intravenous	Clinically approved[a]

CNS, central nervous system; PFS, progression-free survival. [a]For the same indications as originator trastuzumab.

results in stabilization of HER2 homodimers and constitutive HER2 signalling), amongst others. The presence or acquisition of these alterations in patients with HER2$^+$ breast cancer has a well-documented role in intrinsic and acquired resistance[3,32,53–55]. Importantly, *ERBB2* mutations, including the most common *ERBB2* L755S mutation, have been detected in patients with metastatic breast cancer who had previously received trastuzumab in the adjuvant setting, emphasizing their clinical importance[30,31,56,57]. Our understanding of the incidence and clinical implications of *ERBB2* mutations arising in the advanced-stage setting following prior anti-HER2 therapy — reminiscent of *ESR1* mutations that can emerge in patients with oestrogen receptor (ER)-positive breast cancers receiving endocrine therapy and subsequently confer resistance to such therapy — continues to evolve.

When HER2 does remain effectively inhibited, resistance to HER2-targeted therapy can arise by three major

mechanisms: (1) dysregulation of components of the downstream signalling cascades, leading to constitutive activation of the HER pathway (for example, activation of the PI3K–AKT pathway via *PIK3CA* mutations or low levels of PTEN)[58–63]; (2) bidirectional crosstalk with the ER[64,65] and other transcription factors[66]; and (3) upregulation of alternative escape pathways that transmit proliferative stimuli (for example, involving signalling adaptors such as insulin receptor substrate[67,68] or the MET[69] or β integrin–SRC–FAK pathways[70,71]) (FIG. 2). Additionally, upregulation of membrane-associated mucin glycoproteins has been implicated

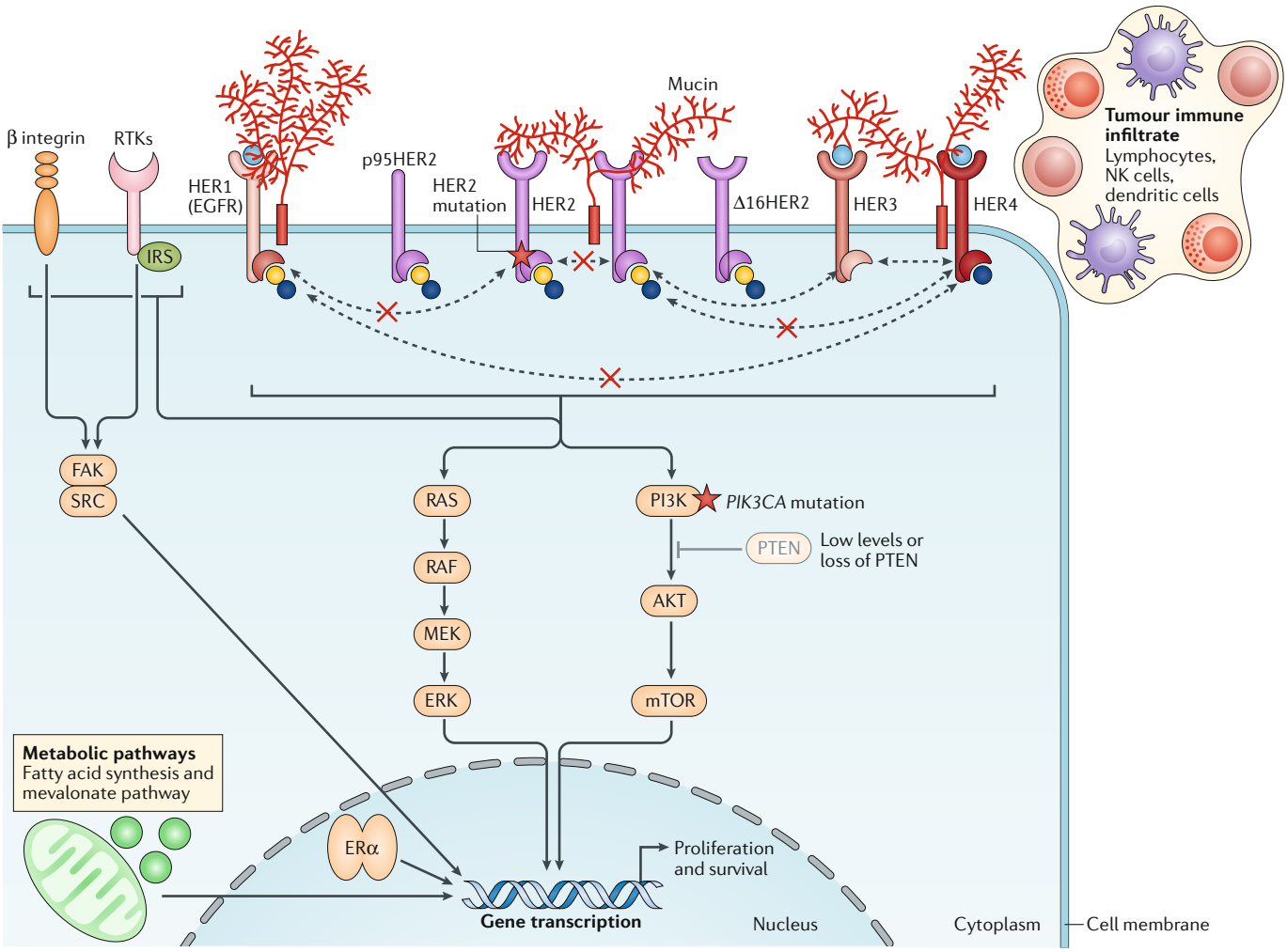

Fig. 2 | **Major mechanisms of resistance to HER2-targeted therapy.** One of the foremost reasons for resistance of breast cancers to HER2-targeted therapy relates to the lack of complete survival dependence of all tumour cells present in the patient on HER2 signalling. This phenomenon could be attributed to intratumour HER2 heterogeneity, whereby both HER2-amplified and non-amplified tumour cell populations coexist within a clinically HER2-positive (HER^+) tumour[142]. While the HER2-amplified and addicted cells of such heterogeneous tumours can be effectively eradicated using biologic anti-HER2 agents, including antibody–drug conjugates that target the HER2 receptor and deliver a cytotoxic drug specifically to the $HER2^+$ cells, the non-HER2-amplified cells will continue to thrive, ultimately manifesting as treatment resistance[133]. For tumours with intratumour HER2 heterogeneity, continued use of chemotherapy together with anti-HER2 therapy is required, until the alternative molecular drivers are elucidated[142]. In tumours with homogeneous HER2 amplification, resistance to HER2-targeted therapy can arise owing to alterations in the HER signalling pathway itself or the activation of alternative bypass signalling pathways supporting cell survival or proliferation. Mutations affecting HER2 itself (such as the activating L755S mutation)[32] or the downstream kinase PI3K (encoded by *PIK3CA*) and/or low levels of the inhibitory protein PTEN[58–63] provide mechanisms by which survival and proliferative signalling through the HER family receptors or their downstream pathways can be reactivated. Aberrations of HER2 that generate alternative forms of the receptor, such as the truncated protein p95HER2 (REF.[51]) and the splice variant Δ16HER2 (REF.[52]), can also mediate resistance to HER2-targeted therapies through loss of the epitopes recognized by therapeutic antibodies or by promoting dimerization and thus constitutive signalling. When the HER receptor network is effectively inhibited, however, resistance can arise owing to the emergence of several genomic and adaptive 'escape' mechanisms. These include crosstalk with transcription factors, such as the oestrogen receptor α (ERα)[64,65], activation of alternative cell-surface receptors (including other receptor tyrosine kinases (RTKs) or β integrin)[69–71], amplification of signalling adapter proteins (for example, those of the insulin receptor substrate (IRS) family)[67,68] or alterations in components of downstream signalling pathways, such as SRC and FAK. Resistance can also be caused by upregulation of membrane-associated mucin glycoproteins, which can interact with HER2–HER3 complexes and/or can mask the extracellular regions of HER2 and thus restrict the accessibility of this protein to drugs, particularly monoclonal antibodies[72,73]. Additionally, proliferative signalling can originate from metabolic pathways, such as the fatty acid synthesis[78,79] and mevalonate pathways[80,81], supporting the survival and the emergence of resistance to therapy in tumour cells. Finally, tumour immune infiltrates, including lymphocytes, natural killer (NK) cells and dendritic cells, have also been reported to modulate responses and resistance to HER2-targeted therapy[74–76].

in resistance to anti-HER2 therapy by interacting with HER2–HER3 complexes and/or masking the antibody-binding epitopes on HER2 (REFS[72,73]). Furthermore, the roles of the tumour microenvironment and stromal factors (including infiltrating immune cells)[74–77], metabolic pathways (such as the fatty acid synthase[78,79] and mevalonate pathways[80,81]), and genomic instability[82] in modulating responses and resistance to anti-HER2 therapy are receiving increased research attention, and further studies are warranted.

Embracing a tailored treatment approach

The incorporation of additional HER2-targeted therapies in combination with chemotherapy has been a commonly adopted approach in the clinical management of HER2$^+$ breast cancer. An often overlooked perspective, however, relates to the mounting medical and financial toxicities from unnecessary escalation of treatment in the subgroups of patients who could otherwise benefit from less-intensive chemotherapy or even be spared from chemotherapy altogether. In the era of precision medicine, the more logical approach would be to embrace tailored treatment regimens, with escalation or de-escalation of HER2-targeted therapy or chemotherapy according to the underlying genomic and biological make-up of the tumour as well as the clinical characteristics of each patient.

Relevance of the oestrogen receptor

Approximately 50% of HER2$^+$ tumours co-express the ER and are thus termed HER2$^+$/ER$^+$ tumours, or hormone receptor-positive (HR$^+$) when expression of the progesterone receptor is also considered[83]. Owing to the aggressive nature of HER2$^+$ disease, the mainstay of treatment for both HER2$^+$/HR$^-$ tumours and HER$^+$/HR$^+$ tumours has been chemotherapy with HER2-targeted therapy, although this approach is gradually being reconsidered[6,84,85]. HER2$^+$/ER$^+$ tumours present a unique therapeutic challenge because they are driven by both HER2 and ER signalling, and convincing data indicate the occurrence of bi-directional crosstalk between these pathways that, as mentioned previously, can result in resistance to therapy[64,65]. In HER2$^+$/ER$^+$ cell line-derived tumour xenograft models, anti-HER2 therapy yields only transient tumour regression when the ER is not also targeted, whereas concurrent anti-HER2 and endocrine therapy results in complete tumour eradication[23–25]. Furthermore, acquired resistance to anti-HER2 therapy in preclinical models of HER2$^+$ breast cancer is associated with increased expression of the ER and its downstream targets[25,86,87], suggesting that the ER, when left uninhibited, can transmit alternative proliferative and survival signals to evade sustained HER2 inhibition. Thus, HER2$^+$/ER$^+$ and HER2$^+$/ER$^-$ breast cancers have a distinct biology and should be considered as two distinct disease subtypes[85,88,89], and the importance of concurrent blockade of both the HER2 and ER pathways in patients with HER2$^+$/ER$^+$ tumours is becoming increasingly evident.

Clinically, HER2$^+$/HR$^+$ breast cancer is also distinct from HER2$^+$/HR$^-$ disease in terms of its clinical course and sensitivity to treatment. In patients with HER2$^+$/HR$^+$ breast cancer, relapses tend to occur later, with more frequent bone involvement, than in patients with HER2$^+$/HR$^-$ disease[85,88,90,91]. For example, Park et al.[90] investigated the patterns of disease relapse in patients with HER2$^+$ breast cancer stratified by HR status and found that those with HER2$^+$/HR$^+$ disease were younger at the time of relapse (median age 48 years versus 53 years) but had longer recurrence-free survival (RFS) that those with HER2$^+$/HR$^-$ disease (RFS <24 months in 29% versus 56% of patients; $P<0.001$). Indeed, treatment outcomes also vary by ER status. Clinical trials of neoadjuvant chemotherapy and dual HER2-therapy have revealed that patients with HER2$^+$/HR$^+$ breast cancer are less likely to have a pathological complete response (pCR) than their HER2$^+$/HR$^-$ counterparts[26,48,92–96] (FIG. 3a). Despite the lower rates of pCR, the association between a pCR and a favourable long-term outcome is weakest in patients with HER2$^+$/HR$^+$ disease, possibly owing to the added benefit of adjuvant endocrine therapy in this subgroup[97,98]. Preclinically, HER2$^+$ tumours also expressing ERs, or that transform from ER$^-$ to ER$^+$, have been demonstrated to have either intrinsic or acquired resistance to HER2-based therapy owing to cell survival signalling mediated by ER[25]. Among patients treated with neoadjuvant chemotherapy and HER2-targeted therapy without endocrine therapy in the CALGB 40601 trial[92], the most frequent post-treatment subtype conversion among the residual tumours was to the luminal A subtype, which is known to be dependent on ER signalling. This finding supports the concept that ER signalling provides an escape pathway for HER2$^+$ disease, thus necessitating concurrent inhibition of ER and HER2. Together these preclinical and clinical findings provide a biological rationale for exploring co-targeted treatment approaches.

The ER and HER2 co-targeting strategy has been tested in several trials involving patients with HER2$^+$/HR$^+$ breast cancer. In the metastatic setting, the benefit of adding trastuzumab or lapatinib to endocrine therapy in patients with HER2$^+$/HR$^+$ breast cancer has been evaluated in two trials, both of which revealed prolonged progression-free survival (PFS) with simultaneous inhibition of both pathways, compared with targeting the ER alone[100,101]. Of note, the PERTAIN[102] and ALTERNATIVE[103] trials, although not designed to directly assess the benefit of combining endocrine therapy and HER2-targeted therapy, revealed that the use of dual HER2-targeted therapy together with an aromatase inhibitor (AI) is an effective treatment strategy for HER2$^+$/HR$^+$ metastatic breast cancer. In the NSABP B-52 trial[104], patients with locally advanced HER2$^+$/HR$^+$ breast cancer were randomly assigned to receive neoadjuvant treatment with docetaxel, carboplatin, trastuzumab and pertuzumab (TCHP) alone or in combination with endocrine therapy (consisting of oestrogen deprivation with an AI, and additional ovarian suppression with goserelin in premenopausal women)[104]. The overall pCR rates were modestly numerically higher with the addition of endocrine therapy to TCHP, although the difference did not reach statistical significance (46% versus 41%; $P=0.36$)[104]. The benefit of endocrine therapy was more pronounced in postmenopausal women (pCR rate 45% versus 38%; $P=0.33$) than in premenopausal women (46% versus 44%; $P=0.80$)[104], perhaps reflecting oestrogen deprivation

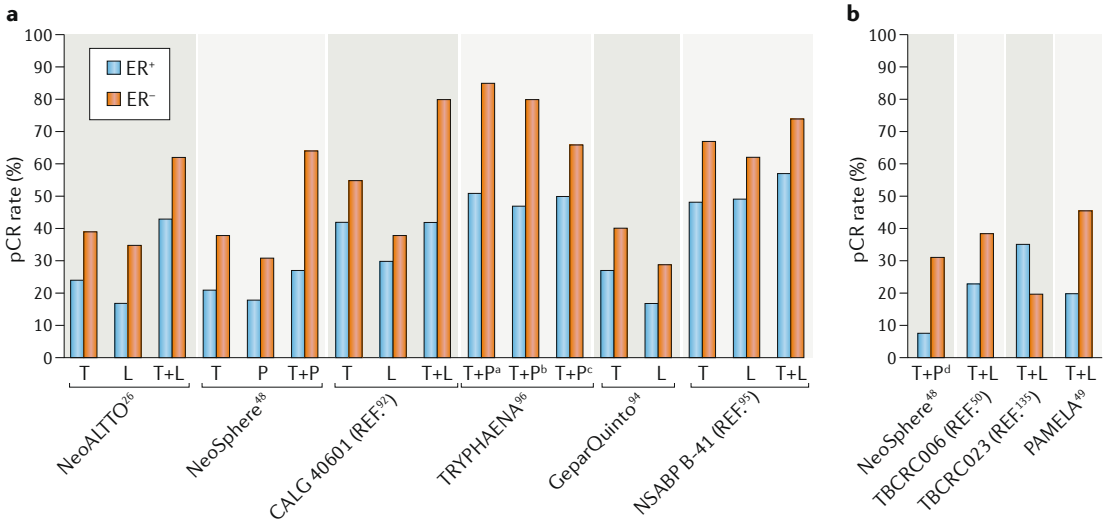

Fig. 3 | **pCR rates stratified by ER status and treatment arm in clinical trials of neoadjuvant HER2-targeted therapy for HER2⁺ breast cancer. a** | Pathological complete response (pCR) rates observed with HER2-targeted therapy in combination with chemotherapy. **b** | pCR rates observed with HER2-targeted therapy, plus endocrine therapy for the oestrogen receptor-positive (ER⁺) patient subgroups, without chemotherapy. For some trials, ER status actually reflects the hormone receptor status (that is, positive or negative for ER and/or progesterone receptor expression). L, lapatinib; P, pertuzumab; T, trastuzumab. [a]Docetaxel and carboplatin plus T+P. [b]5-fluorouracil, epirubicin and cyclophosphamide plus T+P followed by docetaxel plus T+P. [c]5-fluorouracil, epirubicin and cyclophosphamide followed by docetaxel plus T+P. [d]Chemotherapy-free arm.

caused by chemotherapy-induced ovarian suppression in the premenopausal patients who did not receive endocrine therapy. Notably, the addition of oestrogen deprivation did not seem to be antagonistic to the activity of chemotherapy, a finding that is in keeping with evidence from several other studies[104,105]. Interestingly, no statistically significant improvement in the pCR rate was observed with the addition of endocrine therapy to T-DM1 treatment in the WSG-ADAPT trial involving patients with HER2⁺/HR⁺ early stage breast cancer (45.8% versus 40.5% with T-DM1 alone; $P < 0.001$)[106]; however, results of an exploratory analysis suggested benefit from the addition of endocrine therapy to T-DM1 in premenopausal women (pCR 45.5% versus 27.3% with T-DM1 alone), but not in postmenopausal patients (pCR 46.2% versus 60%).

Together, these data suggest that simultaneous inhibition of the HER2 and ER signalling pathways has the potential to be more effective than suppression of either pathway alone; although the optimal treatment strategy for HER2⁺/HR⁺ breast cancer remains unclear, ER blockade seems to be necessary in patients with this disease subtype. Moreover, the optimal timing, sequencing and duration of ER inhibition, and how much chemotherapy is required with this strategy, remain open questions.

The combination of endocrine therapy with dual HER2-targeted therapy (trastuzumab plus lapatinib), without chemotherapy, has been evaluated in several trials in the neoadjuvant setting[49,50,107,108]. Collectively, pCR rates in patients with HER⁺/HR⁺ disease ranged from 20% to 30% in the PAMELA trial[49], the TBCRC006 trial[50] and the TBCRC023 trial[108] (FIG. 3b). In the chemotherapy-free arm of NeoSphere, in which endocrine therapy was not used, the pCR rate in the HER2⁺/HR⁺ subgroup was only 6%[48]. While cross-trial comparisons are often misleading, these data, when considered in the context of other evidence, suggest that endocrine therapy might add to the benefit of dual HER2 inhibition in patients with HER2⁺/ER⁺ tumours. Moreover, these findings indicate that a subset of patients might benefit from chemotherapy-free regimens, which highlights the need to more accurately identify this subset to spare them the unwarranted chemotherapy.

Treatment escalation: is more better?

Neoadjuvant dual HER2-targeted therapy. In the era of trastuzumab, 15–25% of patients with early stage HER2⁺ tumours have disease recurrence despite receiving this agent and chemotherapy[109,110], which might partly be attributable to incomplete inhibition of the HER family receptors. The superior efficacy of dual HER2-targeted therapy was first demonstrated in the CLEOPATRA trial involving patients with metastatic breast cancer, in which the addition of pertuzumab to trastuzumab and docetaxel conferred an unprecedented overall survival (OS) benefit of 15.7 months (median OS 56.5 months versus 40.8 months; HR 0.68, 95% CI 0.56–0.84; $P < 0.001$)[27]. Dual HER2 blockade has subsequently been tested in the neoadjuvant setting, in an effort to improve pCR rates, with the results of several trials indeed demonstrating superior pCR rates with the addition of either pertuzumab or lapatinib to trastuzumab and chemotherapy (TABLE 2). In the NeoSphere study[48], which led to the initial approval of pertuzumab in the neoadjuvant setting, significantly higher pCR rates were achieved by adding pertuzumab to trastuzumab and docetaxel (45.8% versus 29.0%; $P = 0.014$). The combination of lapatinib with neoadjuvant trastuzumab and paclitaxel was evaluated in the NeoALTTO trial[26], and the results showed similar

Table 2 | **pCR rates in trials of neoadjuvant dual HER2-targeted therapy plus chemotherapy**

Clinical trial	Dual HER2 therapy	pCR with single-agent HER2-targeted therapy agent (%)	pCR with dual HER2 therapy (%)
NeoALTTO[26]	L+T	30 (95% CI 22.4–37.5) with T; 25 (95% CI 18.1–32.3) with L	51 (95% CI 43.1–59.5; $P=0.0001$)
NeoSphere[48]	T+P	29 (95% CI 20.6–38.5) with T; 24 (95% CI 15.8–33.7) with P	46 (95% CI 36.1–55.7; $P=0.0141$)
CALGB 40601 (REF.[92])	L+T	40 (95% CI 32–49) with T; 32 (95% CI 22–44) with L	51 (95% CI 42–60; $P=0.11$)
NSABP B-41 (REF.[95])	L+T	53 (95% CI 44.9–59.5) with T; 53 (95% CI 45.4–60.3) with L	62 (95% CI 54.3–68.8; $P=0.095$)
TRYPHAENA[96]	T+P	NA	57–66[a]

CI, confidence interval; L, lapatinib; NA, not applicable; P, pertuzumab; pCR, pathological complete response; T, trastuzumab.
[a]95% CI presented graphically in REF.[96].

superior pCR rates with dual HER2-targeted therapy (51.3% versus 29.5%; $P=0.0001$). Updated survival data demonstrated a numerically higher event-free survival (EFS) and OS at 6 years in the dual HER2-targeted therapy arm compared with the trastuzumab-alone arm (74% versus 67% (HR 0.81, 95% CI 0.52–1.26; $P=0.35$) and 85% versus 79% (HR 0.72, 95% CI 0.41–1.27; $P=0.26$), respectively), especially in patients with HR$^-$ disease (EFS 74% versus 63%; HR 0.81, 95% CI 0.44–1.51; $P=0.52$), although these differences were not statistically significant[111]. Patients who achieved a pCR did, however, have a significantly higher 6-year EFS (77% versus 65% in those without a pCR; HR 0.54, 95% CI 0.34–0.82; $P=0.005$) and OS (89% versus 77%; HR 0.43, 95% CI 0.23–0.75; $P=0.005$)[111]. The long-term benefits of neoadjuvant dual HER2-targeted therapy require confirmation in randomized clinical trials sufficiently powered for survival end points, unlike NeoALTTO and NeoSphere.

Despite remaining uncertainties, pCR seems to be a reasonable surrogate marker of long-term outcomes of patients with breast cancer, especially those with HER2$^+$ disease subtypes[112]. In a meta-analysis by Cortazar et al.[97], a patient-level analysis demonstrated that achievement of a pCR was significantly correlated with longer EFS and OS (for example, HR 0.15, 95% CI 0.09–0.27, and HR 0.08, 85% CI 0.03–0.22, respectively, for patients with HER2$^+$/ER$^-$ tumours who received trastuzumab); however, this correlation was lost in a trial-level analysis that included studies with more heterogeneous cohorts. The small absolute improvements in pCR rates of some of the included trials might have contributed to the lack of an association with improvement in survival outcomes. Perhaps greater improvements in pCR rates with neoadjuvant therapy in certain patient subgroups, if considered separately, would unmask significant associated improvements in long-term survival (for example, in those with HER2$^+$/HR$^-$ or triple-negative breast cancer). A meta-analysis of data from 27,895 patients with breast cancer enrolled in a total of 52 studies, reported in abstract form in 2019 (REF.[112]), revealed that a pCR to neoadjuvant therapy is associated with a lower risk of disease recurrence (HR 0.31, 95% CI 0.24–0.39) and death (HR 0.22, 95% CI 0.15–0.30). The correlations between pCR and long-term outcomes were strongest in the HER2$^+$/ER$^-$ and triple-negative disease subgroups[112]. Notably, EFS and OS were similar regardless of whether patients received additional adjuvant chemotherapy after achieving pCR[112].

Escalating adjuvant HER2-targeted therapy. In the era of personalized medicine, a key challenge lies in differentiating patients who will derive substantial benefit from treatment escalation from those who will do equally well with standard therapy or even de-escalation of treatment. With the encouraging results of dual HER2 inhibition in the neoadjuvant setting, exploration of this concept in the adjuvant setting has been approached with great enthusiasm. This strategy was first tested in the ALTTO trial, with disappointing results; the significant increases in pCR rates observed in the neoadjuvant setting were not mirrored by improved outcomes in the adjuvant setting[113]. A 6-year follow-up analysis of the ALTTO cohort failed to demonstrate the superiority of lapatinib and trastuzumab plus chemotherapy over trastuzumab plus chemotherapy in terms of disease-free survival (DFS; 85% versus 82%; HR 0.86, 95% CI 0.74–1.00) or OS (93% versus 91%; HR 0.86, 95% CI 0.70–1.06)[114]. The APHINITY trial was designed to evaluate the addition of pertuzumab to trastuzumab and chemotherapy in the adjuvant setting[28]. The highly anticipated results were positive, although pertuzumab conferred only a modest absolute 3-year invasive-DFS (iDFS) benefit of 0.9% (94.1% versus 93.2%; HR 0.81, 95% CI 0.66–1.00; $P=0.045$)[28]. Patients with high-risk, node-positive disease derived the most benefit (3-year iDFS 92.0% versus 90.2%; HR 0.77, 95% CI 0.62–0.96; $P=0.02$); no benefit was observed in the node-negative subgroup (3-year iDFS 97.5% versus 98.4%; HR 1.13, 95% CI 0.68–1.86; $P=0.64$)[28]. The incidence of heart failure was similar in both groups (0.6% with pertuzumab versus 0.2% with trastuzumab alone); however, grade ≥3 diarrhoea was more common in the pertuzumab group (occurring in 9.8% versus 3.7% of patients)[28]. These results indicate only limited benefit from pertuzumab and argue that adjuvant dual HER2-targeted therapy incorporating this agent should be reserved for high-risk subgroups (with node-positive disease and possibly with ER$^-$ tumours). We should emphasize, however, that neither the ALTTO trial nor the APHINITY trial were designed to validate the findings of the NeoALTTO and NeoSphere trials. Notably, single-agent chemotherapy was used in the neoadjuvant trials[26,48], whereas more aggressive combination

chemotherapy was used in the two adjuvant trials and this might have diluted any effect of adding lapatinib or pertuzumab to trastuzumab[28,113]. Indeed, chemotherapy can be effective against cells harbouring additional drivers beyond HER2 in both HER2$^+$ cells and HER2$^-$ cells (for example, those with *PIK3CA* mutations) and, therefore, the benefits of adding lapatinib or pertuzumab to trastuzumab will probably be greatest in the context of de-escalation or omission of chemotherapy.

Attempts to further improve the outcomes of patients with early stage HER2$^+$ breast cancer by extending the duration of adjuvant trastuzumab beyond the current standard duration of 1 year have failed, as demonstrated by results of the HERA trial, in which 1 or 2 years of trastuzumab after completion of all primary therapy was compared with observation only[109]. After a median follow-up duration of 11 years, no additional DFS benefit was gained from 2 years versus 1 year of adjuvant trastuzumab (HR 1.02, 95% CI 0.89–1.17) in either the HR$^+$ or the HR$^-$ subgroups[109].

One can envisage that outcomes could be improved with extended therapy by switching to a different HER2-targeted therapy with a mechanism of action different from that of trastuzumab. The ExteNET trial was designed to explore this concept using the irreversible pan-HER inhibitor neratinib. Patients were randomly assigned to 1 year of neratinib or placebo following standard chemotherapy and 1 year of trastuzumab[29]. Extended treatment with neratinib conferred a modest but statistically significant 2.5% absolute benefit in 5-year iDFS (90.2% versus 87.7% with placebo; HR 0.73, 95% CI 0.57–0.92; $P = 0.0083$)[115]. Notably, this benefit of neratinib was driven by the HR$^+$ subgroup: 5-year iDFS 91.2% versus 86.8% with placebo (HR 0.60, 95% CI 0.43–0.83), as compared with 88.8% versus 88.9% in the HR$^-$ subgroup (HR 0.95, 95% CI 0.66–1.35)[115]. These results contrast with those of the HERA trial[109]. In subgroup analyses of ExteNET trial data, patients with four or more tumour-positive lymph nodes and those who received sequential neratinib within 1 year of completing trastuzumab therapy derived the greatest benefit from extended HER2-targeted therapy (HR 0.67, 95% CI 0.46–0.96, and HR 0.70, 95% CI 0.54–0.90, respectively)[115]. No significant differences in 5-year distant DFS (91.6% versus 89.9%; $P = 0.065$) or the rates of CNS recurrences (1.3% versus 1.8%; $P = 0.333$) were observed between the treatment groups[115]. Grade 3 and 4 diarrhoea occurred in 40% and <1%, respectively, of patients receiving neratinib (compared with 2% of patients in the placebo group in total); however, prophylaxis with loperamide was not mandated[115]. Neratinib gained FDA approval for extended adjuvant treatment of any patients with early stage HER2$^+$ breast cancer, although the EMA limited its approval of neratinib to the HER2$^+$/HR$^+$ subgroup; perhaps this agent should be considered only for patients with high-risk, node-positive HER2$^+$/HR$^+$ disease[116].

Approximately 30–60% of patients have a pCR to neoadjuvant chemotherapy and HER2-targeted therapy (TABLE 2), and those with residual disease at surgery have a higher risk of disease recurrence and death[97]. The phase III KATHERINE trial[117] was designed to compare the efficacy of adjuvant treatment with 14 cycles of T-DM1 versus 1 year of trastuzumab in patients with early stage HER2$^+$ breast cancer and residual disease following neoadjuvant therapy. At a median follow-up duration of 41 months, the substitution of T-DM1 for trastuzumab led to a 50% reduction in risk of invasive disease recurrence (3-year iDFS 88.3% versus 77%; HR 0.50, 95% CI 0.39–0.64; $P < 0.001$) and reduced the rate of distant recurrence as the first iDFS event by 5.4% (10.5% versus 15.9%)[117]. Notably, the benefit of T-DM1 was observed irrespective of clinicopathological characteristics, including disease stage and HR status; even patients with minimal residual disease (≤1 cm) and those treated with neoadjuvant dual HER2-targeted therapy (~19% of the cohort) derived benefit[117]. Greater absolute and relative improvements in iDFS with T-DM1 were, however, observed in those with a higher pathological disease stage at the time of surgery and with tumour-positive lymph nodes after preoperative therapy, as well as those with HR$^-$ disease[117]. The one area in which T-DM1 did not out-perform trastuzumab was the rate of CNS recurrence, which was around 5% in both treatment groups[117]; this finding highlights an unmet need in patients with HER2$^+$ breast cancer, specifically, the lack of approved, effective therapies with adequate CNS penetration and activity. Grade ≥3 toxicities, including thrombocytopenia and sensory neuropathy, were more frequently observed with T-DM1 than with trastuzumab (25.7% versus 15.4%)[117]. The results of the KATHERINE trial establish adjuvant therapy with T-DM1 as the new standard of care for patients with residual disease after neoadjuvant therapy.

In summary, the APHINITY, ExteNET and KATHERINE trials all demonstrated improved outcomes, at least in selected patient subgroups, with escalated adjuvant HER2-targeted therapy. The varying patient populations and treatment regimens of these studies complicate cross-trial comparisons and clinical application of the treatment approaches, although the clinical scenarios in which optimal benefit might be gained from these escalated treatment approaches can be postulated based on available data (TABLE 3). Many questions remain unanswered, however, including how effective neratinib will be after 1 year of T-DM1 and whether patients currently receiving adjuvant trastuzumab or adjuvant trastuzumab and pertuzumab should be transitioned to T-DM1 if they did not have a pCR to neoadjuvant therapy. Clinical judgement and patient involvement in decision-making are paramount in this setting. Finally, consideration of therapy-induced toxicity is imperative in clinical decision-making. Chemotherapy-free or de-escalated regimens spare patients from chemotherapy-associated toxicities, and HER2-targeted therapies are generally associated with more favourable but different toxicity profiles, although the adverse effects of more potent individual or combination HER2-targeted therapies, especially diarrhoea, can be debilitating.

Treatment de-escalation strategies

Duration of adjuvant trastuzumab. Many potential approaches to treatment de-escalation are possible; one approach is to shorten the duration of therapy. The 5-year follow-up data from the FinHer trial involving

Table 3 | **Comparison of key parameters in trials involving escalation of adjuvant HER2-targeted treatment**

Parameter	APHINITY[28]	ExteNET[115]	KATHERINE[117]
Treatment regimen	Adjuvant trastuzumab plus pertuzumab for 1 year	Neratinib following 1 year of adjuvant trastuzumab	Adjuvant T-DM1 for 14 cycles versus 1 year of trastuzumab for residual disease after neoadjuvant therapy
iDFS	3-year iDFS: 94.1% versus 93.2% (HR 0.81, 95% CI 0.66–1.00; $P = 0.045$); node-positive subgroup: 92% versus 90.2% (HR 0.77, 95% CI 0.62–0.96; $P = 0.02$); node-negative subgroup: 97.5% versus 98.4% (HR 1.13, 95% CI 0.68–1.86; $P = 0.64$); ER^+ subgroup: 94.8% versus 94.4% (HR 0.86, 95% CI 0.66–1.13; $P = 0.28$); ER^- subgroup: 92.8% versus 91.2% (HR 0.76, 95% CI 0.56–1.04; $P = 0.08$)	5-year iDFS: 90.2% versus 87.7% (HR 0.73, 95% CI 0.57–0.92; $P = 0.0083$); ER^+ subgroup: 91.2 versus 86.8% (HR 0.60, 95% CI 0.43–0.83); ER^- subgroup: 88.8% versus 88.9% (HR 0.95, 95% CI 0.66–1.35)	3-year iDFS: 88.3% versus 77% (HR 0.50, 95% CI 0.39–0.64; $P < 0.001$)
Key grade 3 toxicities	Diarrhoea (9.8%)	Diarrhoea (40%), rash (<1%) and transaminitis (1.7%)	Thrombocytopenia (3.6%), peripheral neuropathy (1.4%) and transaminitis (0.5%)
Ideal patient population on the basis of the trial results	Patients with high-risk, node-positive $HER2^+/ER^-$ breast cancer and a pCR after neoadjuvant therapy	Patients with high-risk, node-positive (especially four or more involved nodes), $HER2^+/ER^+$ breast cancer, within 1 year of completion of adjuvant trastuzumab therapy	Any patients with residual disease after neoadjuvant treatment
Remaining uncertainties	NA	Benefit of neratinib after 1 year of adjuvant treatment with trastuzumab and pertuzumab	Benefit of neratinib after 14 cycles of adjuvant therapy with T-DM1

For all trials, ER status actually reflects the hormone receptor status (that is, positive or negative for ER and/or progesterone receptor expression). CI, confidence interval; ER, oestrogen receptor; HR, hazard ratio; iDFS, invasive disease-free survival; NA, not applicable; pCR, pathological complete response; T-DM1, trastuzumab emtansine.

patients with axillary node-positive or high-risk node-negative $HER2^+$ breast cancer demonstrated a numerical improvement in distant DFS — although not statistically significant — with the addition of just 9 weeks of trastuzumab to chemotherapy (83.3% versus 73.0% with chemotherapy alone; HR 0.65, 95% CI 0.38–1.12; $P = 0.12$)[118]. However, non-inferiority of 9 weeks versus 1 year of adjuvant trastuzumab therapy, in terms of DFS, was not demonstrated in the SOLD trial (HR 1.39, two-sided 90% CI 1.12–1.72)[119].

In other trials[119–123], investigators have evaluated shorter durations of adjuvant trastuzumab treatment in the hope of curtailing cardiotoxicities and costs, but until the reporting of the PERSEPHONE trial in 2019 (REF.[124]), none of these trials demonstrated the non-inferiority of this approach compared with the standard duration. For example, the updated 7.5-year follow-up results of the PHARE trial[123] did not prove the non-inferiority of 6 months versus 12 months of trastuzumab, with the hazard ratio of 1.08 (95% CI 0.93–1.25) crossing the pre-specified non-inferiority margin of 1.15 (corresponding to a 2% absolute decrease in DFS at 2 years). By contrast, the results of the PERSEPHONE trial[124], at a median follow-up duration of 5.4 years, demonstrated non-inferiority between 6 months and 12 months of trastuzumab therapy for the first time (HR 1.07, 90% CI 0.93–1.24; $P = 0.011$); however, the non-inferiority margin was set at 1.32, corresponding to a 3% absolute decrease in 4-year DFS. Although intriguing, caution is needed in accepting 6 months of adjuvant trastuzumab as the new standard of care. Concurrent trastuzumab with chemotherapy is known to yield better outcomes[125], but 53% of patients in the PERSEPHONE trial received sequential trastuzumab and those who did receive concurrent trastuzumab and chemotherapy derived greater benefit from 12 months of trastuzumab (HR 1.53, 95% CI 1.16–2.01; $P = 0.001$)[126]. Furthermore, more patients in this trial had low-risk disease (59% node-negative and 69% HR^+)[124] compared with those included in similar non-inferiority trials[127]. Importantly, those deemed at high risk of recurrence did not receive dual HER2-targeted therapy, which goes against current standard treatment guidelines, and thus the optimal duration of combined HER-targeted therapy remains unknown. Some might also argue that the more generous non-inferiority confidence interval used in the PERSEPHONE trial compared with that of the PHARE trial might explain the disparate results.

Of note, a meta-analysis by Chen et al.[128], which included updated data from adjuvant trials including the PHARE and PERSEPHONE trials, indicated that both DFS (HR 1.13, 95% CI 1.03–1.25; $P = 0.01$) and OS (HR 1.16, 95% CI 1.01–1.32; $P = 0.03$) are significantly better with 1 year of trastuzumab than with shorter treatment durations[128]. The benefit was more pronounced with concurrent administration of trastuzumab and chemotherapy (HR 1.22, 95% CI 1.09–1.38; $P = 0.0008$; $P_{interaction} = 0.02$), which is currently the most commonly used adjuvant treatment strategy[128]. This effect was less pronounced in patients with ER^+ and node-negative tumours[128]. Thus, the follow-up data spanning beyond 5 years that are available from the four other large randomized controlled trials[119,121–123] included in this meta-analysis[128] suggest that 1 year of adjuvant trastuzumab should remain the standard of care for most patients with early stage $HER2^+$ breast cancer. In selected patients, in whom the administration of trastuzumab is likely to be limited by toxicities or comorbidities, and in

areas of the world where access is often limited by financial costs, a shorter duration of trastuzumab therapy can be considered carefully.

De-escalating chemotherapy. The results of the Adjuvant Paclitaxel and Trastuzumab (APT) trial illustrate that excellent outcomes can be achieved in patients with low-risk HER2$^+$ tumours with the use of anthracycline-free regimens, thereby reducing the incidence of serious toxicities, including cardiotoxicity[129]. In this single-arm phase II study[129], patients with node-negative disease and mostly small primary tumours (<3 cm in diameter in 91%) received 12 weekly doses of paclitaxel concurrently with the start of 1 year of adjuvant trastuzumab. The 7-year follow-up data demonstrated a DFS of 93.3% (94.6% for the HR$^+$ subgroup and 90.7% for the HR$^-$ subgroup)[129]. The rate of distant disease recurrence was only 1%[129]. These results have defined the current standard-of-care regimen for patients with small, node-negative HER2$^+$ breast cancers, irrespective of HR status, although some trepidation remains with this approach in patients with HR$^-$ tumours of 2–3 cm diameter, in view of the fact that only 8.9% of patients enrolled in the APT trial had tumours of this size[129]. Avoidance of anthracyclines has been further supported by results of the phase III TRAIN-2 trial in the neoadjuvant setting[130]. In this study, involving patients with stage II–III HER2$^+$ disease receiving dual HER2-targeted therapy with trastuzumab and pertuzumab plus chemotherapy[130], omission of anthracyclines from the treatment regimen was associated with a pCR rate of 68% compared with 67% in the anthracycline group.

The ongoing ATEMPT trial (NCT02246621) was designed to build on what had been demonstrated in the APT trial. In this study, patients with stage I HER2$^+$ disease were randomly assigned to 1 year of adjuvant treatment with either T-DM1 or paclitaxel and trastuzumab. If the results are positive, T-DM1 will become another well-tolerated treatment option for this subset of patients. This study has completed accrual and results are expected soon.

T-DM1 has also been investigated in the neoadjuvant setting, with results of several trials having been reported in the past few years[131–133]. In the KRISTINE trial[132], neoadjuvant T-DM1 plus pertuzumab was compared with the TCHP regimen, revealing a substantial, although inferior, pCR rate of 44% in the T-DM1 plus pertuzumab arm versus 56% in the TCHP arm ($P = 0.016$). Similarly, the pCR rates observed in the PREDIX HER2 trial of T-DM1 versus docetaxel, trastuzumab and pertuzumab (THP) were 44.1% and 46.4%, respectively[131]. Notably, more locoregional progression and lower EFS rates were observed in the T-DM1 plus pertuzumab arm (85.3% compared with 94.2% in the TCHP arm) of the KRISTINE trial[132], possibly owing to intratumour heterogeneity in HER2 expression. Theoretically, T-DM1 would be less effective in patients with HER2$^+$ tumours harbouring a subpopulation of HER2$^-$ cells. Indeed, in a phase II study, no pCR to T-DM1 plus pertuzumab was observed among patients harbouring tumours with a heterogeneous HER2 status[133]. Overall, these results suggest that, although T-DM1 might have a role in the neoadjuvant setting as a less toxic alternative to conventional chemotherapy, appropriate patient selection is essential. Further validation of these findings in trials with larger cohorts is needed.

Importantly, patient age must always be considered in treatment decisions, as demonstrated by the results of the RESPECT trial in which elderly patients (>70 years of age) with HER2$^+$ breast cancer were randomly assigned to receive adjuvant trastuzumab with or without chemotherapy[134]. The trial failed to meet its primary end point, but few recurrence events occurred in either arm and the 3-year iDFS was 89% with trastuzumab alone (compared with 94.8% in the combination group; HR 1.42, 95% CI 0.68–2.95; $P = 0.35$), suggesting that foregoing chemotherapy in certain elderly patients will not significantly compromise outcomes[134].

Are we ready to omit chemotherapy?

Testing the approach. Enthusiasm for a chemotherapy-free approach first stemmed from preclinical studies demonstrating complete tumour eradication with dual HER2-targeted therapy combined with endocrine therapy[23,24]. Subsequently, the pertuzumab plus trastuzumab-only arm of the NeoSphere trial revealed an intriguing pCR rate of 17%[48], and thus this study was one of the first to demonstrate the efficacy of a chemotherapy-free regimen in the neoadjuvant setting. Notably, patients with HR$^+$ tumours in the NeoSphere trial did not receive additional endocrine therapy and the pCR rate with trastuzumab and pertuzumab alone in this group was only 6%[48].

In the HER2$^+$/ER$^-$ group of the WSG-ADAPT trial[135], pCR rates were substantially higher with the use of neoadjuvant chemotherapy (taxane-based) in addition to trastuzumab and pertuzumab (90.5% versus 36% without chemotherapy). In the PAMELA trial[49], the TBCRC006 trial[50] and the TBCRC023 trial[108], the efficacy of neoadjuvant trastuzumab and lapatinib, without chemotherapy, was evaluated, yielding pCR rates ranging from 20% to 30%, suggesting that a sizeable proportion of patients derive benefit from such an approach (TABLE 4). In contrast to the NeoSphere trial, these trials included endocrine therapy for the ER$^+$ patient subgroups. In the single-arm phase II TBCRC006 study[50], patients with locally advanced HER2$^+$ breast cancer and a median tumour diameter of 6 cm received 12 weeks of trastuzumab and lapatinib, plus endocrine therapy if ER$^+$, prior to surgery. At the end of neoadjuvant treatment, 49% of patients had a pCR or near-pCR (residual disease ≤1 cm). Of these patients, 27% had a pCR, which was more commonly observed in the ER$^-$ subgroup (36% versus 21% in the ER$^+$ subgroup)[50]. Thus, a meaningful proportion of patients had a pCR without chemotherapy. The higher rate of near-pCR in patients with ER$^+$ tumours than in those with ER$^-$ disease (33% versus 4%) might reflect the generally slower regression of ER$^+$ tumours during therapy[50]. A follow-up study, TBCRC023 (REF.[108]), was designed to determine whether a longer duration of neoadjuvant treatment would result in conversion of some of the near-pCRs to pCRs, especially in the ER$^+$ subgroup. Patients were randomly assigned to receive 12 weeks versus 24 weeks

Table 4 | **Comparison of pCR rates in trials of neoadjuvant chemotherapy-free dual HER2-targeted treatment**

Clinical trial	Dual HER2-targeted therapy	Concurrent endocrine therapy for HR$^+$ disease	Treatment duration (weeks)	Overall pCR (%)
NeoSphere[48] (targeted therapy-only arm)	T+P	None	16	17 (95% CI 10.3–33.7)
TBCRC006 (REF.[50])	T+L	Letrozole, plus ovarian suppression in premenopausal women	12	27
TBCRC023 (REF.[108])	T+L	Letrozole, plus ovarian suppression in premenopausal women	12	12
			24	28
PAMELA[49]	T+L	Letrozole, or tamoxifen in premenopausal women	18	31 (95% CI 23–39)
PerELISA[136]	T+P	Letrozole	13	21 (95% CI 11.1–34.5)

CI, confidence interval; HR, hormone receptor; L, lapatinib; P, pertuzumab; pCR, pathological complete response; T, trastuzumab.

of trastuzumab plus lapatinib (with endocrine therapy for patients with ER$^+$ disease)[108]. After 24 weeks of treatment, 28% of patients had a pCR and the pCR rate in the ER$^+$ subgroup was increased to 33%, from 9% with only 12 weeks of treatment[108]. In the ER$^-$ subgroup, no difference in the pCR rate was seen between patients who received 12 weeks and those who received 24 weeks of neoadjuvant therapy (20% versus 18%)[108]. Despite the lower than expected overall pCR rates, the results of the TBCRC023 trial suggest that ER status and treatment duration both influence response rates.

One might argue that ER$^+$ tumours warrant different end point definitions regarding a pCR, such as near-pCR and Ki67-based criteria, in order to enable more accurate prediction of patient outcomes. The PAMELA trial was designed to evaluate the same neoadjuvant regimen[49], but given for 18 weeks, and demonstrated an overall pCR rate of 30%. Consistent with the results of prior studies, the pCR rate was significantly higher in the HR$^-$ subgroup than in the HR$^+$ subgroup (43% versus 18%; OR 3.42, 95% CI 1.647.2; $P = 0.0011$)[49]. The investigators of the PerELISA study evaluated a different chemotherapy-free approach in patients with HER2$^+$/ER$^+$ tumours[136]. In this trial, tumour Ki67 index was evaluated at baseline and after 2 weeks of letrozole in order to select patients most likely to benefit from endocrine therapy; molecularly responding patients, defined by a decrease in Ki67 index of >20%, continued treatment with letrozole with additional trastuzumab and pertuzumab and had a pCR rate of 20% in the breast and axilla[136].

The pCR rates observed in the aforementioned trials are lower than those observed with chemotherapy, although these data indicate that 20–30% of early stage HER2$^+$ breast cancers can be eradicated without chemotherapy. Successful de-escalation of treatment is contingent upon the identification of predictive biomarkers that can be used to reliably distinguish patients who will benefit from targeted therapy alone from those who need additional chemotherapy. Additionally, supported by evidence from preclinical studies[137], several ongoing clinical trials are testing novel treatment approaches including anti-HER2 treatment with concurrent CDK4/6 inhibition, especially for ER$^+$ disease, or with immunomodulatory agents (TABLE 5). Whether data from these ongoing studies will prove promising and result in refinement of the current treatment strategies for HER2$^+$ disease remains to be seen.

Molecular determinants of response

Increased understanding of the complex biology, heterogeneity and genomic underpinnings of HER2-driven tumours has led to the discovery of potential predictive biomarkers of a response to HER2-targeted therapy[3,75,92,99,133,136,138–146]; however, none of these biomarkers has been validated to predict a response and DFS benefit with chemotherapy-free regimens. Currently, only disease stage, HR status and amplification and/or overexpression of HER2 guide therapeutic decisions and, given the underlying molecular complexity and interplay of HER2$^+$ breast cancers, additional biomarkers are necessary. Overall, the differential pCR rates observed between HER2$^+$/ER$^+$ and HER2$^+$/ER$^-$ tumours highlight the relevance of simultaneous blockade of both the HER2 and ER signalling pathways in patients with HER2$^+$/ER$^+$ disease[47,144]. Beyond HR status, however, the development of additional clinically useful biomarkers has proved challenging, owing in part to the inclusion of chemotherapy in the majority of trials involving patients with HER2$^+$ breast cancer, possibly confounding the results of correlative studies involving tumour specimens from these patients. In this regard, tumour specimens collected as part of chemotherapy-free neoadjuvant trials, such as TBCRC006, TBCRC023, PAMELA and PerELISA, are a valuable resource for correlative biomarker analyses.

Tumours with increased levels of HER2 are functionally dependent on HER2 and, indeed, exemplify the notion of oncogene addiction[49,140,143,144,147]. In addition to the presence or absence of genetic and/or functional aberrations affecting key components of downstream signalling pathways, such as the PI3K–AKT pathway, intratumoural HER2 homogeneity and the magnitude of addiction of tumour cells to HER2 are key determinants of anti-HER2 therapy responses. In the 2018 updated American Society of Clinical Oncology/College of American Pathologists guidelines[148], HER2$^+$ breast cancers are defined as those with an *ERBB2*:chromosome enumeration probe 17 (CEP17) fluorescence in situ

hybridization (FISH) ratio of ≥2, an *ERBB2* copy number of ≥6 or a HER2 immunohistochemistry (IHC) score of 3+ (defined as homogeneous and intense membrane staining of >10% of tumour cells). With these updated cut-offs, previously equivocal HER2$^+$ tumours are now considered HER2$^-$. The results of the NSABP B-47 trial confirmed that patients with HER2 IHC 1+ or 2+ breast cancer and a *ERBB2*:CEP17 FISH ratio <2 do not benefit from HER2-targeted therapy[149]. As opposed to the existing guidelines that intend to identify patients who are likely to benefit from chemotherapy-inclusive anti-HER2 treatment regimens, higher cut-offs might be needed to identify true HER2-addicted tumours that are amenable to treatment with chemotherapy-free regimens. In an analysis of the TBCRC006 trial[143], none of the patients who achieved pCR without chemotherapy had an *ERBB2*:CEP17 FISH ratio <4 and/or an *ERBB2* copy number <10, whereas 29% of those with a pCR had an *ERBB2*:CEP17 ratio ≥4 and/or an *ERBB2* copy number ≥10. These findings support the use of higher cut-offs for identifying patients with truly HER2-addicted tumours who are likely to derive the greatest benefit from chemotherapy-free HER2-targeted therapy[143].

Five intrinsic subtypes of HER2$^+$ tumours can be identified using the PAM50 gene expression assay: luminal A, luminal B, HER2-enriched (HER2-E), basal-like, and normal-like[150]. About 10–15% of all breast cancers are HER2-E, characterized by high levels of *ERBB2* and EGFR/HER2-regulated gene expression[150]. Thus, this tumour subtype has highly active HER2 signalling and, therefore, might be most responsive to HER2 inhibition[150]. In retrospective analyses of data from the NeoSphere and CALGB 40601 trials, the HER2-E subtype was associated with higher pCR rates to HER2-targeted therapy combined with chemotherapy than other subtypes of HER2$^+$ breast cancer[92,138]. In the CALGB 40601 trial[71], 70% of patients with HER2-E tumours had a pCR compared with 35% of those with other HER2$^+$ disease subtypes. The PAMELA trial investigators evaluated the HER2-E subtype as a predictor of response to neoadjuvant dual HER2-targeted therapy with trastuzumab and lapatinib, without chemotherapy[49]. Significantly higher pCR rates were observed in patients with HER2-E tumours than in those with non-HER2-E subtypes (41% versus 10%; OR 6.2, 95% CI 2.3–16.8; $P = 0.0004$)[49]. Interestingly, the association between HR status and pCR was lost upon

Table 5 | **Key phase II–III trials of CDK4/6 inhibitors or immunotherapies combined with anti-HER2 therapy**

Clinical trial	Phase	HR status	Treatment setting	Anti-HER2 therapy	Concurrent therapies	Results
CDK4/6 inhibitors						
NA-PHER2 (NCT02530424)[170]	II	ER$^+$	Neoadjuvant	T+P	Palbociclib ± fulvestrant	pCR rate 27%; mean Ki67 index 31.9 at baseline versus 4.3 at week 2 ($n = 25$; $P < 0.0001$) and 12.1 at surgery ($n = 22$, $P = 0.013$)
PALTAN (NCT02907918)	II	ER$^+$	Neoadjuvant	T	Palbociclib + letrozole (+ goserelin in premenopausal women)	Ongoing (recruiting)
PATRICIA 2 (NCT02448420)[171]	II	ER$^+$	Metastatic	T	Palbociclib ± letrozole	Ongoing (recruiting)
PATINA (NCT02947685)[172]	III	ER$^+$	Metastatic	T+P	Palbociclib + endocrine therapy	Ongoing (recruiting)
monarcHER (NCT02675231)[173]	II	ER$^+$	Metastatic	T	Abemaciclib ± fulvestrant	Ongoing (active, not recruiting)
NCT03530696	II	ER$^+$ or ER$^-$	Metastatic	T-DM1	Palbociclib	Ongoing (recruiting)
TOUCH (NCT03644186)	II	ER$^+$	Neoadjuvant	T+P	Palbociclib + letrozole	Ongoing (recruiting)
Immune-checkpoint inhibitors						
PANACEA (NCT02129556)[174]	I/II	ER$^+$ or ER$^-$	Metastatic	T	Pembrolizumab	Objective response achieved in 6 (15%) of 40 patients with PD-L1-positive disease, but none in patients with PD-L1-negative disease
neoHIP (NCT03747120)[175]	II	ER$^+$ or ER$^-$	Neoadjuvant	T+P	Pembrolizumab	Ongoing (recruiting)
NCT03199885	III	ER$^+$ or ER$^-$	Metastatic	T+P	Atezolizumab	Ongoing (recruiting)
NCT03417544	II	ER$^+$ or ER$^-$	Metastatic	T+P	Atezolizumab	Ongoing (recruiting)
KATE2 (NCT02924883)[176]	II	ER$^+$ or ER$^-$	Metastatic	T-DM1	Atezolizumab	Atezolizumab + T-DM1 did not demonstrate a clinically significant PFS benefit over T-DM1 monotherapy; however, a numerically higher PFS was observed with atezolizumab + T-DM1 in PD-L1-positive patients

For some trials, ER status actually reflects the hormone receptor status (that is, positive or negative for ER and/or progesterone receptor expression). ER, oestrogen receptor; HR, hormone receptor; P, pertuzumab; pCR, pathological complete response; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; T, trastuzumab; T- DM1, trastuzumab emtansine.

accounting for intrinsic subtype in multivariate analyses (OR 2.27, 95% CI 0.93–5.55; $P=0.26$)[49].

The level of *ERBB2* mRNA is emerging as an additional candidate predictive biomarker. A combined analysis by Prat et al.[140] of five trials of neoadjuvant chemotherapy-free HER2-targeted treatment regimens revealed that HER2-E subtype and tumours defined as *ERBB2*-high were associated with higher pCR than non-HER2-E and *ERBB2*-low tumours; together, these characteristics were associated with a pCR rate of 45%. Thus, both variables seem to provide valuable information about the degree of HER2 addiction of the tumour.

The PI3K–AKT pathway is a major component of downstream HER2 signalling; aberrant activation of this pathway via activating *PIK3CA* mutations or low PTEN levels has been implicated in resistance to HER2-targeted therapy[143]. Findings from a pooled analysis of data from five trials of neoadjuvant trastuzumab plus lapatinib demonstrated that approximately 22% of HER2$^+$ breast cancers harbour *PIK3CA* mutations and that these mutations are associated with inferior pCR rates (16.2% compared with 29.5% in patients with *PIK3CA*-wild-type tumours; $P<0.001$), particularly in the HR$^+$ subgroup (7.6% versus 24.2% ($P<0.001$) compared with 27% versus 36% in the HR$^-$ subgroup ($P=0.125$); interaction test between these two subgroups, $P=0.036$))[151]. Low levels of PTEN occur in approximately 20–25% of HER2$^+$ tumours and have also been associated with inferior responsiveness to HER2-targeted therapy[139,143,152]; however, this association has been inconsistent across clinical trials[144,153–155], perhaps owing to the lack of standardized methods to quantify PTEN levels. Furthermore, concurrent administration of chemotherapy in these trials might have confounded the results, considering that chemotherapy might be active against tumours with PI3K pathway aberrations. Molecular analysis of baseline tumour specimens from patients included in the chemotherapy-free TBCRC006 trial showed inferior pCR rates in patients with PI3K pathway-dysregulated tumours, defined by *PIK3CA* mutations or low PTEN levels, compared with those without such aberrations (4% versus 39%; $P=0.0133$)[143]. The results of combined analyses demonstrated that tumours with an *ERBB2*:CEP17 FISH ratio ≥4 and an intact PI3K pathway were associated with a superior pCR rate (44% versus 4% for tumours without both of these features; $P=0.0031$)[143].

A future molecular classifier combining HER2 levels and intratumour heterogeneity, measured at the DNA level (for example, using *ERBB2*:CEP17 FISH), the RNA level (using PAM50 or assays specific for *ERBB2* mRNA) or the protein level (by HER2 IHC), and PI3K pathway status in order to better predict sensitivity to HER2-targeted therapy will be a gateway to successful treatment de-escalation. In tumours with intratumour heterogeneity in HER2 expression, chemotherapy will still need to be combined with anti-HER2 therapy, until the molecular drivers of the non-HER2 amplified and addicted cell populations have been elucidated[142].

Finally, the stromal and tumour immune milieu of HER2$^+$ breast cancers is receiving increased attention as a potential determinant of treatment responses and disease progression, particularly considering the role of the immune system in the therapeutic activity of anti-HER2 antibodies[74,75,156–159]. Sophisticated quantification methods and appropriate cut-offs are needed to facilitate investigations of the predictive and/or prognostic value of tumour-infiltrating lymphocytes (TILs) in patients with HER2$^+$ breast cancer.

Conclusions

Advances in the treatment of HER2$^+$ breast cancer have transformed the natural course of this disease. The focus of many trials has been on potentiating the efficacy of chemotherapy and trastuzumab with additional HER2-targeted agents in order to further improve patient outcomes. The majority of patients, however, benefit only modestly from these additional treatments, which come with added medical and financial toxicities. As our knowledge of the genomic features and the molecular and mutational evolution of HER2$^+$ breast cancer deepens, the field is undeniably heading towards precision medicine. Indeed, focus should be placed on differentiating patients who stand to benefit from additional therapy from those who will do equally well with less therapy, thus moving away from a one-size-fits-all approach to the treatment of this highly heterogeneous disease. Importantly, however, omission of chemotherapy must not compromise the favourable outcomes achieved with currently approved treatment regimens and with any new, more effective HER2-targeted treatments that emerge in the future, considering that our understanding of the optimal dual HER2-targeted drug combination is continually evolving.

The available data demonstrate that the timing of systemic therapy relative to surgery does not influence patient outcomes[160]. Currently, the National Comprehensive Cancer Network (NCCN)[161] and the St Gallen International Expert Consensus[162] guidelines recommend the use of neoadjuvant therapy for patients with clinical stage II–III HER2$^+$ breast cancer. The clinical response to neoadjuvant therapy provides valuable information about tumour biology, serves as a better predictor of an individual's risk of disease recurrence, can help in adapting adjuvant therapy and has the potential to minimize the extent of axillary surgery and subsequent postoperative complications[117,163].

Unlike in patients with ER$^+$ tumours, for whom multigene assays are available to estimate recurrence risk, the recurrence risk of patients with HER2$^+$ tumours is largely determined by clinicopathological characteristics, especially nodal status and tumour size. To more accurately risk-stratify patients up-front and accordingly deploy refined therapeutic strategies, factors beyond clinical stage need to be considered. This risk stratification should include molecular features, such as measures of HER2 addiction, the genomic and molecular make-up of the tumour, intratumour heterogeneity and the immune milieu, all of which can determine whether patients will benefit from escalated HER2-targeted therapy, standard HER2-targeted therapy and chemotherapy or HER2-targeted therapy alone. Whether such a molecular classifier, when combined with conventional clinicopathological characteristics, will help to further refine patient stratification remains

to be explored in prospective clinical trials. Additionally, emerging technologies to explore the potential utility of circulating tumour cells and cell-free tumour DNA in therapeutic monitoring and surveillance after neoadjuvant therapy and surgery might become valuable tools for prognostication in the future[164].

The use of chemotherapy-free regimens in routine clinical practice requires a validated predictive biomarker and, therefore, this approach remains investigational; however, great strides towards the clinical implementation of such regimens have undoubtedly been made and the future of this strategy looks promising. Biomarker studies have provided important insights into the molecular characteristics, prognosis and therapeutic sensitivity of HER2$^+$ breast cancer subtypes. The refinement and validation of predictive and prognostic biomarkers will enable accurate identification and triage of patients with HER2$^+$ disease, either ER$^-$ or ER$^+$, who will respond to targeted therapy alone, with the goal of reducing or entirely eliminating the use of chemotherapy in a sizeable proportion of patients, thus avoiding the associated debilitating — and often long-term — toxicities. Prospective clinical trials testing a risk-stratified, biomarker-driven, de-escalated treatment approach are needed to pave the path towards such a personalized treatment approach.

Published online: 13 December 2019

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Acknowledgements
The work of the authors is supported, in part, by the Department of Defense grants W81XWH-17-1-0579 (to M.F.R.) and W81XWH-17-1-0580 (to R.S.), the NIH SPORE grant P50 CA186784 (to R.S., C.K.O. and M.F.R.); the Cancer Center grant P30 CA125123 (principal investigator C.K.O.); the Breast Cancer Research Foundation grant BCRF-17-143 (to R.S and C.K.O); the Cancer Prevention & Research Institute of Texas grant CPRIT RP 140102 (to C.De A.); and the Translational Breast Cancer Research Consortium (TBCRC).

Author contributions
K.G., J.V., M.F.R., and R.S wrote the manuscript. All authors made substantial contributions to researching data for the manuscript and to discussions of content, and reviewed and/or edited the manuscript prior to submission.

Competing interests
C.K.O. has received research funding from AstraZeneca and GlaxoSmithKline, has served on advisory boards for AstraZeneca, Genentech and Tolmar Pharmaceuticals, has been a data monitoring committee member for Eli Lilly, and is a stockholder of GeneTex. M.F.R. receives research support from GlaxoSmithKline via his institution and has been a consultant for Daiichi, Genentech, Macrogenics and Novartis. R.S. has received research funding from AstraZeneca, Gilead Sciences, GlaxoSmithKline and PUMA Biotechnology, and has been a consultant or advisory committee member for Eli Lilly and Macrogenics. The other authors declare no competing interests.

Peer review information
Nature Reviews Clinical Oncology thanks the anonymous reviewers for their contribution to the peer review of this work.