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The management of HER2-positive early breast cancer: Current and future therapies

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Abstract

Advances in human epidermal growth factor receptor 2 (HER2)-directed therapies have revolutionised the care of patients with HER2-positive breast cancer. While adjuvant trastuzumab in combination with chemotherapy has dramatically improved the prognosis for patients with early-stage disease, up to a quarter of patients will develop recurrent disease. The standard-of-care treatment paradigm has evolved with the introduction of newer HER2-directed therapies and increasing use of neoadjuvant systemic therapy, the latter providing us with important functional data to HER2-directed therapies and impacting subsequent adjuvant therapy decisions. However, these new strategies come at a cost of increased toxicity and economic burden, and only a subset of patients benefit from such approaches. Thus, ongoing work is required to identify predictive biomarkers of response, to de-escalate treatment in patients who may do just as well with less therapy, and new therapeutic approaches for patients who do not respond to currently used therapies. In this review, we will examine the current therapeutic landscape, summarise the latest evidence, and list the current treatment algorithms for early stage HER2-positive breast cancer.

KEYWORDS
adjuvant therapy, breast cancer, HER2-directed therapy, HER2 positive, neoadjuvant therapy

1 | BACKGROUND

Human epidermal growth factor 2-amplified (HER2-positive) breast cancer is characterised by an overexpression of HER2 and accounts for 15%–20% of breast cancers.[1] Prior to the routine use of HER2-directed therapies, this subtype conferred an aggressive phenotype and poor prognosis.[2,3] Since the introduction of the first humanised anti-HER2 monoclonal antibody, trastuzumab, nearly two decades ago, the outcomes of patients with HER2-positive breast cancer have dramatically changed. HER2-directed therapy should therefore be considered standard of care in patients who have HER2 positivity defined by immunohistochemistry (3+) or amplified on the basis of in situ hybridization (ratio > 2.0 or average HER2 copy number ≥ 6.0).[4]

However, despite significant improvement in both disease-free survival (DFS) and overall survival (OS) associated with the addition of trastuzumab to chemotherapy in early-stage HER2-positive breast disease, long-term follow-up data have shown that approximately 25%–30% of patients will develop recurrent disease, indicating the need for treatment escalation for a subset of patients.[5,6] By contrast, there is also emerging evidence that a subset of patients can de-escalate treatment without compromising their outcomes, with the added benefit of reduced toxicities and treatment costs.[7] HER2-positive breast cancer is a heterogenous disease,[8] and hence, the approach to treatment needs to be individualised, and there is an imperative for predictive biomarkers to guide treatment decisions.

This review provides an overview of the current evidence for the management of HER2-positive early-stage breast cancer and describes approaches for its management in an Australian context.

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2 | AN OVERVIEW OF CURRENT HER2-DIRECTED THERAPIES

HER2 is a member of the human epidermal growth factor receptors (EGFR) family and is a major oncogenic driver of breast tumours that overexpress this protein.[9] The amplification of the HER2 gene results in cell proliferation and differentiation through a signal transduction cascade mediated by activation of cellular signalling cascades including the PI3K/AKT and RAS/MAPK pathways.[10]

A number of anti-HER2 agents have been developed and approved for clinical use in HER2-positive breast cancers. Their mechanisms of action and indication for use are summarised in Table 1. There are broadly three classes of agents: monoclonal antibodies, tyrosine kinase inhibitors and antibody-drug conjugates. Trastuzumab and pertuzumab are monoclonal antibodies which bind to the HER2 juxtamembrane domain IV and heterodimerization domain II, respectively. They inhibit ligand-independent HER2 signalling, downregulate HER2 expression and trigger antibody-dependent cellular cytotoxicity.[11–13] Tyrosine kinase inhibitors such as lapatinib, neratinib and tucatinib bind to the intracellular tyrosine kinase domain of HER2 and other HER members to suppress downstream signalling involving the MAPK/ERK1/2 and PI3K/AKT pathways.[14,15] Ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) are antibody-drug conjugates in which a cytotoxic agent is linked with an anti-HER2 antibody. After binding to HER2, the conjugate is internalised and the cytotoxic agent is released within the cell, resulting in cell death and toxic effects on surrounding cells.[16,17]

3 | CURRENT ADJUVANT SYSTEMIC THERAPIES FOR HER2-POSITIVE BREAST CANCER

3.1 | Standard 1-year anti-HER2-based treatment

Adjuvant trastuzumab in combination with chemotherapy was shown to reduce the relative risk of recurrence by up to 40% and relative risk of death by up to 30% in the pivotal HERA, BCIRG-006, NSABP B-31 and NCCTG N9831 trials.[6,18–21] The benefit of trastuzumab was across all subgroups and independent of patient and tumour characteristics.[5,6]

These early pivotal trials primarily used an anthracycline-based chemotherapy backbone and 1 year of adjuvant trastuzumab. In the BCIRG-006 trial, patients were randomised to receive doxorubicin and cyclophosphamide followed by docetaxel (AC-T), the same regimen plus trastuzumab (AC-TH) or a non-anthracycline-based regimen of docetaxel and carboplatin with trastuzumab (TCH).[20] Although the study was not powered to directly compare AC-TH with TCH, the DFS and OS in these two arms were comparable. However, there was a higher risk of cardiac toxicity in the AC-TH arm (2% vs. 0.4%). Factors associated with increased cardiac risk include age, existing cardiac dysfunction, hypertension and diabetes.[22] Hence the TCH regimen is considered a reasonable alternative regimen for patients at increased risk of cardiac toxicity.

One year of adjuvant trastuzumab in combination with 3–6 months of chemotherapy remains the current standard of care for adjuvant systemic therapy. The HERA trial compared DFS between 1 and 2 years of trastuzumab treatment.[18,23] At a median follow-up of 11 years, 2 years of trastuzumab treatment did not demonstrate additional benefit over 1 year of therapy. Two years of therapy was associated with a higher rate of cardiac toxicity, defined as a clinically significant left ventricular ejection fraction (LVEF) drop of ≥10% from baseline or absolute LVEF < 50%, compared with 1 year of treatment (7.3% vs. 4.4%).

3.2 | De-escalation of anti-HER2-based therapy and chemotherapy

Several trials have evaluated the efficacy of reduced duration of adjuvant anti-HER2 treatment. The Short-HER and SOLD trials evaluated 9 weeks versus 1 year of trastuzumab.[24,25] Non-inferiority in the 9-week course could not be demonstrated for DFS for both studies. While DFS in the 9-week arm was minimally inferior to the 1-year arm in Short-HER (hazard ratio (HR) 1.13, 90% CI 0.89–1.42), it was statistically inferior in the SOLD trial (HR 1.39, 90% CI 1.12–1.72). A post hoc analysis of the Short-HER trial at a median follow up of 8.7 years showed favourable long term DFS in patients with low (HR 0.91, 90% CI 0.60–1.38) and intermediate risk of relapse (HR 0.88, 90% CI 0.63–1.21), suggesting that this de-escalation strategy may potentially be suited to these lower risk patient subgroups.[26] The PHARE trial evaluated 6 months compared to 12 months of trastuzumab and failed to demonstrate non-inferiority in the 6-month arm.[27]

The largest of these studies was the phase 3 PERSEPHONE trial of 4089 patients, which compared 6 months as a non-inferior treatment to 12 months of trastuzumab. After a median follow-up of 5.4 years, the 4 year DFS was 89.4% in the 6-month and 89.8% in the 12-month treatment arms (HR 1.07, 90% CI 0.93–1.24), meeting its primary endpoint with a non-inferiority margin of 3%.[28] The 6-month treatment was associated with less severe adverse events and cardiotoxicity. However, this trial included a predominantly low risk group with 60% of patients having node-negative disease, in contrast with the HERA and BCIR006 trials that established 1 year as standard of care, which included a higher risk population, and approximately 70% of patients had node-positive disease. The OS reported in PERSEPHONE marginally favoured 12 months of trastuzumab (94.8% vs. 93.8% at 4 years). In summary, 1 year of adjuvant trastuzumab-based therapy still remains the current standard of care.

Another approach to de-escalating therapy is to decrease the amount of concurrent chemotherapy given in combination with trastuzumab. The APT trial was a single arm study in patients with ≤3 cm, node-negative tumours, who received 12 weeks of adjuvant paclitaxel in combination with trastuzumab for 12 months.[7] The 7-year rates of invasive disease-free survival (iDFS) and OS were 93% and 95%, respectively.[29] Treatment was well-tolerated with low rates of

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TABLE 1 HER2-targeted agents used in the current treatment of breast cancer

Drug Monoclonal antibodies	Mechanism of action	Indication	Current availability in Australia
Trastuzumab	Binds to HER2 juxtamembrane domain IV	In combination with chemotherapy for neoadjuvant and adjuvant early stage disease[18,20] Alone or in combination with chemotherapy for advanced disease[77]	PBS-funded for early and advanced HER2+ breast cancer
Pertuzumab	Binds to HER2 heterodimerisation domain II	In combination with trastuzumab and chemotherapy in neoadjuvant/adjuvant treatment of early stage disease[31,51] In combination with trastuzumab and chemotherapy in advanced disease[78]	PBS-funded for first line advanced HER2+ breast cancer TGA approved but not PBS funded for early HER2+ breast cancer
Margetuximab	Binds to HER2 heterodimerisation domain II	In combination with trastuzumab and chemotherapy for pretreated advanced disease (NCT02492711)	In clinical trials
Tyrosine kinase inhibitors			
Neratinib	Pan-HER inhibitor	Extended adjuvant treatment of early triple positive disease after trastuzumab-based therapy[34] In combination with capecitabine for pretreated advanced disease[79]	TGA approved but not PBS funded for early HER2+ breast cancer
Lapatinib	HER1 and HER2 inhibitor	In combination with capecitabine for pretreated advanced disease[80]	PBS funded for pretreated advanced HER2+ breast cancer
Tucatinib	Selective HER2 inhibitor	In combination with capecitabine and trastuzumab for pretreated advanced disease[69]	In clinical trials
Pyrotinib	HER1 and HER2 inhibitor	In combination with capecitabine in pretreated advanced disease[81]	In clinical trials
Antibody-drug conjugates			
Trastuzumab emtansine	Trastuzumab covalently linked to DM1	Treatment of pretreated advanced disease[82] Adjuvant treatment of residual disease after neoadjuvant treatment with trastuzumab and chemotherapy[59]	PBS funded for adjuvant treatment of residual disease after neoadjuvant treatment and 2nd line treatment of advanced HER2+ breast cancer
Trastuzumab deruxtecan	Humanised HER2 antibody and topoisomerase I inhibitor	Treatment of pretreated advanced disease[17,68]	In clinical trials

Abbreviations: PBS, pharmaceutical benefits scheme; TGA, therapeutic goods administration.

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severe toxicities. In particular, the rate of cardiotoxicity was low at 0.5%. Although it was a single arm study, these results provide evidence to support a de-escalation of chemotherapy strategy in patients with lower risk disease and are now routinely used. Finally, efficacy of adjuvant trastuzumab with and without chemotherapy was evaluated in older patients in the RESPECT trial. [30] While the primary endpoint of non-inferiority was not met, the survival difference between the two groups was <1 month at 3 years, with a favourable toxicity and quality of life profile in the chemotherapy-free arm. Hence this approach can be considered for selected older patients.

3.3 | Intensification of anti-HER2-based therapy

Intensification of adjuvant treatment using dual anti-HER2 blockade has been evaluated in patients with higher risk HER2-positive disease. In the phase 3 APHINITY trial, 4800 patients were randomised to receive chemotherapy plus trastuzumab with or without pertuzumab for 12 months.[31] The 3-year iDFS rate was marginally higher in the pertuzumab arm (94.1% vs. 93.2%, HR 0.81; 95% CI 0.66–1.00; $p = 0.045$). Patients with node-positive disease derived a small benefit from the addition of pertuzumab (92% vs. 90.2%), while no additional benefit was seen in the node-negative group. At 6 years of follow up, similar results were shown for iDFS while OS data remains immature with 95% of patients still alive.[32] Although statistically significant, this approach is not routinely used due to the small clinical benefit and is not funded in Australia by the Pharmaceutical Benefits Scheme for this indication. It should be considered for patients with high risk disease, such as node positivity. Dual adjuvant HER2 blockade using other combinations such as lapatinib and trastuzumab have shown no improvement in outcomes with increased toxicity and hence are not used in clinical practice.[33]

3.4 | Extended anti-HER2-based adjuvant therapy

Another escalation strategy for higher risk patients is to extend adjuvant HER2-directed therapies. The phase 3 ExteNET trial examined the efficacy and safety of 1 year of extended adjuvant neratinib or placebo in patients who had completed 1 year of adjuvant trastuzumab.[34–36] This trial demonstrated an improved 5-year iDFS of 90.2% in the neratinib arm, compared with 87.7% in the placebo arm (HR 0.73, 95% CI 0.57–0.92). Interestingly, subgroup analysis showed an absolute benefit of 5.1% in iDFS (HR 0.58, 95% CI 0.41–0.82) in patients with hormone receptor-positive disease with neratinib (90.8% vs. 85.7%). No benefit was observed in patients with hormone receptor-negative disease (88.9% vs. 88.8%). The 8-year OS rate was numerically improved in hormone receptor-positive patients who received neratinib but this did not reach statistical significance (HR 0.79, 95% CI 0.55–1.13).

Diarrhoea was the most common toxicity with neratinib, affecting 95% of patients without loperamide prophylaxis. Severe diarrhoea (grade 3 or 4) affected 40% of patients in the neratinib arm, leading to dose reduction in 26% and treatment discontinuation in 17%. Prophylaxis with loperamide alone and in combination with colestipol or budesonide for 1–2 cycles reduces the rate of diarrhoea; however, severe diarrhoea remains a significant issue, affecting 20%–30% of patients on prophylaxis.[37] A dose escalation strategy combined with loperamide has been trialled and shown to be effective in reducing the severity and duration of neratinib-associated diarrhoea.[38] The incidence of grade 3 diarrhoea was lower at 13.3%, and the median cumulative duration was 2.5 days. This strategy is hence recommended to improve the tolerability of this treatment. Neratinib is not routinely used, nor is it currently funded by the Pharmaceutical Benefits Scheme for this indication.

4 | NEOADJUVANT SYSTEMIC THERAPY FOR HER2 POSITIVE BREAST CANCER

Neoadjuvant therapy is now a well-established approach for the treatment of early breast cancer with ≥T2 or node-positive HER2-positive breast tumours.[39,40] Pathological response at surgery correlates with patient outcomes and importantly, it can guide subsequent systemic adjuvant therapy.[40] Multiple randomised trials have shown significantly higher rates of pathological complete response (pCR) when trastuzumab is added to primary chemotherapy in the neoadjuvant treatment of HER2-positive early-stage breast cancer.[41–44] The attainment of a pCR represents a surrogate marker of improved long-term outcome in HER2-positive disease,[45,46] and this approach has increasingly been used in the clinical trial evaluation of novel targeted therapies.[47]

Several trials have assessed the efficacy of neoadjuvant lapatinib, as a single anti-HER2 agent in combination with chemotherapy, and in combination with trastuzumab.[8,48,49] Overall these trials demonstrated that lapatinib as a single HER2-directed therapy was not only inferior to trastuzumab in terms of pCR rates, but also associated with significantly more toxicity. In contrast, dual blockade in combination with trastuzumab produced a significant improvement in pCR rates compared to trastuzumab alone. However, this strategy has not translated into an improvement in event-free survival.[33] Hence lapatinib is not routinely used in the neoadjuvant treatment of HER2-positive early breast cancer.

Neoadjuvant dual HER2 blockade with pertuzumab and trastuzumab was evaluated in the NeoSphere trial and several other phase 2 trials. The NeoSphere trial reported a significantly higher pCR rate with dual HER2 blockade plus docetaxel compared with the trastuzumab plus docetaxel (45.8% vs. 29%, $p = 0.0141$). The pCR rates for the other two arms, pertuzumab plus docetaxel and pertuzumab plus trastuzumab, were inferior. The rates of serious adverse events were similar for all chemotherapy containing treatments, with no additional cardiotoxicity in arms with dual HER2 blockade.[50] The addition of pertuzumab to trastuzumab and docetaxel also improved DFS, although the study was not powered to formally test this hypothesis.[51]

In the TRYPHAENA and BERENICE trials, neoadjuvant dual HER2 blockade with standard anthracycline and non-anthracycline chemotherapy regimens showed pCR rates between 57% and 66%, with pCR rates up to 84% in the hormone receptor-negative

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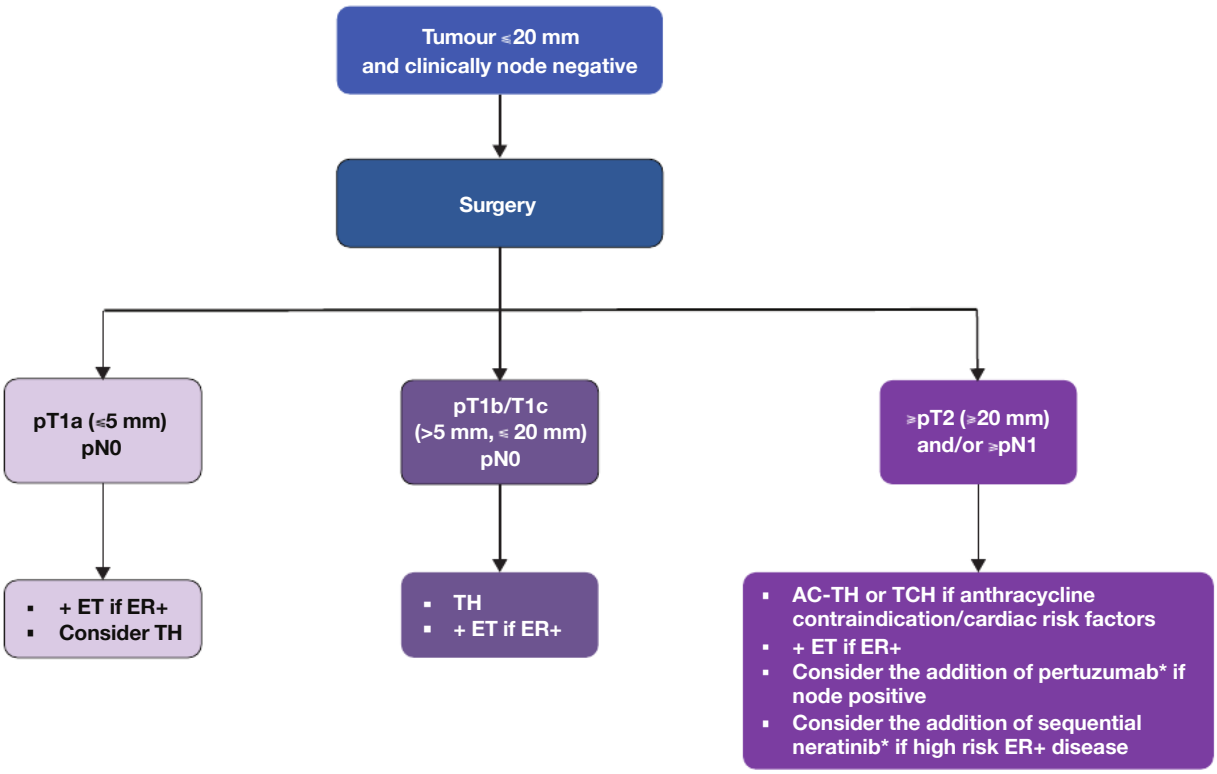

FIGURE 1 Treatment algorithm for stage I HER2-positive breast cancer.
*Pertuzumab and neratinib are not PBS listed; they can be self-funded.
Abbreviations: AC-TH, doxorubicin and cyclosphosphamide followed by paclitaxel and trastuzumab; ER+, estrogen-receptor positive; ET, endocrine therapy; pN0, no regional lymph node metastases; pN1, metastases to movable ipsilateral level I, II axillary lymph node(s); pT, pathologic primary tumour TNM stage; TCH, docetaxel, carboplatin and trastuzumab; TH, paclitaxel and trastuzumab

subgroup.[52,53] The TRAIN-2 study reported comparable rates of pCR using anthracycline and non-anthracycline chemotherapy in combination with pertuzumab and trastuzumab.[54] No difference in EFS and OS was observed at 3-years of follow up, supporting a de-escalation strategy in neoadjuvant therapy with a non-anthracycline regimen.[55] The WSG-ADAPT trial evaluated the efficacy of 12 weeks of neoadjuvant pertuzumab and trastuzumab with or without paclitaxel in the hormone receptor-negative subgroup, and demonstrated an impressive pCR rate of 90.5% with dual HER2 blockade plus chemotherapy.[56] More recently, the KRISTINE trial reported results of neoadjuvant T-DM1 plus pertuzumab compared with TCH plus pertuzumab (TCPH). TDM-1/pertuzumab resulted in lower pCR rates (44% vs. 56%) and a higher risk of locoregional progression events before surgery.[57,58]

In summary, dual blockade with pertuzumab and trastuzumab in combination with chemotherapy currently represents the optimal combination to achieve a pCR and therefore should be considered for patients with HER2-positive early breast cancer who meet criteria for neoadjuvant therapy. Pertuzumab is currently not funded by the Pharmaceutical Benefits Scheme for this indication in Australia, limiting its access in the early stage breast cancer setting. There are currently no data to support the use of neoadjuvant dual HER2 therapy for clinical T1N0 disease.[40]

5 | ADJUVANT THERAPY FOR PATIENTS WHO DO NOT ACHIEVE A PATHOLOGICAL COMPLETE RESPONSE TO NEOADJUVANT SYSTEMIC THERAPIES

With the increasing use of neoadjuvant systemic therapy for patients with HER2-positive breast cancer, there has been significant change to the treatment algorithms for subsequent adjuvant therapies (Figure 1, **Stage I disease** and **Figure 2, Stage II/III disease**). Patients who do not obtain a pCR with neoadjuvant therapy have significant higher rates of recurrence, and the functional assessment of treatment response with neoadjuvant therapy provides us with an opportunity to escalate treatment in these patients.

T-DM1 was evaluated as an adjuvant therapy in patients who had residual disease after neoadjuvant treatment with a trastuzumab and a taxane-based chemotherapy in the KATHERINE trial.[59] In this trial, patients were randomised to receive 14 cycles of T-DM1 or complete 1 year of trastuzumab. At 3 years, the iDFS was significantly higher in the T-DM1 arm compared with trastuzumab (88.3% vs. 77%, HR 0.50, 95% CI 0.39–0.64, $p < 0.0001$). Distant recurrence as the first invasive-disease event occurred in 10.5% of patients in the T-DM1 arm and 15.9% in the trastuzumab arm. The benefit of T-DM1 was observed irrespective of clinicopathological features and type of neoadjuvant

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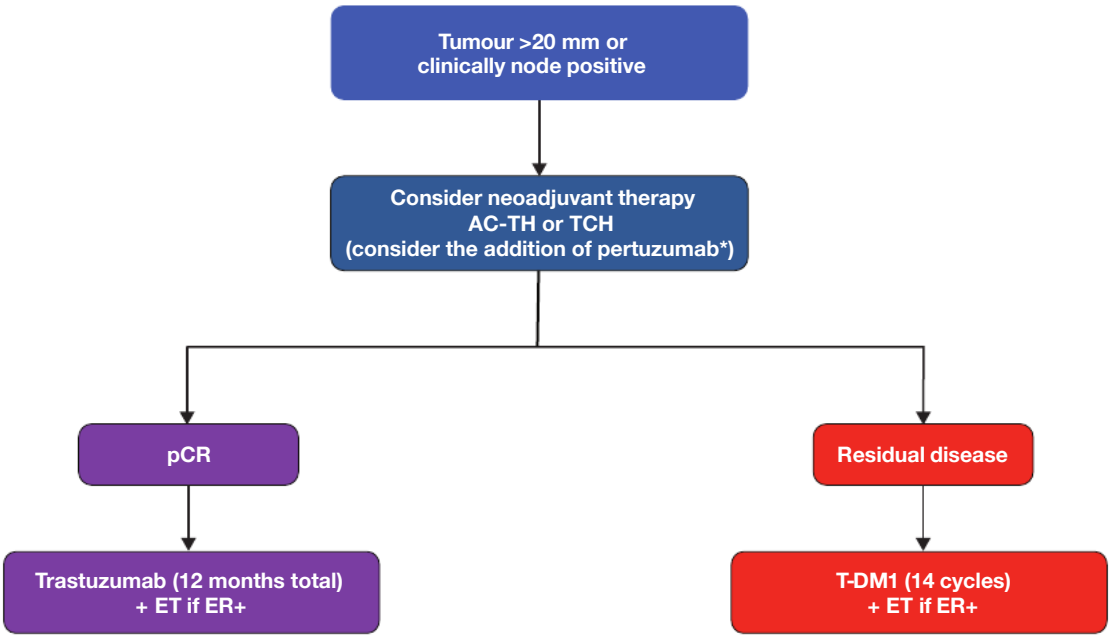

FIGURE 2 Treatment algorithm for stage II/III HER2-positive breast cancer.
*Pertuzumab is not PBS listed; it can be self-funded.
Abbrevviations: AC-TH, doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab; ER+, estrogen-receptor positive; ET, endocrine therapy; pCR, pathologic complete response; TCH, docetaxel, carboplatin and trastuzumab

treatment received. The rate of grade 3 or higher toxicities including thrombocytopenia and peripheral neuropathy was higher in the T-DM1 arm, but the overall toxicity profile was consistent with T-DM1 use in the metastatic setting. The results of this trial established a new standard of care for patients who do not achieve pCR after neoadjuvant therapy.

6 | NOVEL THERAPEUTIC APPROACHES IN METASTATIC HER2-POSITIVE BREAST CANCER AND FUTURE DIRECTIONS

HER2-positive breast cancer is a biologically heterogeneous disease with different patterns of response and recurrence. Currently, HER2 overexpression is the only clinically proven biomarker to predict response to HER2-targeted therapies. Baseline anatomic risk and response to neoadjuvant therapy are used to select patients for treatment de-escalation/escalation. More advanced tools, such as HER2DX, which integrates clinico-pathological and genomic data, have been explored.[60] Initial results provide early hope for a tool that may allow personalisation of treatment but further clinical validation is required before incorporating these into clinical practice.

Patients with luminal HER2-positive disease may benefit from addition of endocrine therapy to their neoadjuvant treatment to improve pCR rates. The cyclin D1-CDK4/6 pathway has been shown to mediate treatment resistance in HER2-positive breast cancer.[61] CDK 4/6 inhibitors have been demonstrated to be efficacious in combination with endocrine therapy for advanced hormone-receptor positive disease.[62–64] A number of clinical trials are evaluating the utility of CDK4/6 inhibitors plus endocrine therapy in HER2-positive breast cancer and potential scope for a non-chemotherapy approach (PATINA NCT02947685; PATRICIA NCT02448420;[65] MonarcHER NCT02675231;[66] PALTAN NCT02907918).

Several novel HER2-directed agents are currently being investigated in clinical trials in advanced breast cancer with promising results. One notable example is trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate comprised of a humanised monoclonal antibody attached by a cleavable peptide-based linker to a potent topoisomerase I inhibitor payload, which is 10 times more potent than the active metabolite of the topoisomerase I inhibitor, irinotecan.[67] Together with a high drug-to-antibody ratio, it is designed to maximise efficient delivery of the payload to tumour while reducing potential toxicities. The phase 2 DESTINY-Breast01 trial demonstrated a high response rate of 60.9% with a median response duration of 14.8 months in patients with HER2-positive breast cancer who have progressed on T-DM1.[17,68] Clinical trials are currently underway to assess the efficacy of this agent in other clinical settings, including early disease (Destiny-Breast05 NCT04622319).

Another promising agent is tucatinib, which is a highly potent HER2-selective tyrosine kinase inhbitor. In the phase 3 HER2Climb study, tucatinib in combination with trastuzumab and capecitabine significantly improved PFS and OS in a heavily pretreated patient population, including a significant proportion with cerebral metastases.[69] The PFS at 1 year was 33.1% in the tucatinib combination group compared to 12.3% in the capecitabine and trastuzumab group (HR 0.54, 95% CI 0.42–0.71, $p < 0.001$), and median OS was 21.9 and 17.4

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months, respectively. These results have led to FDA approval for this combination, but it is currently still not available in Australia. Follow-up trials are currently underway to compare the efficacy of adjuvant tucatinib in combination with T-DM1 in patients with residual disease post-neoadjuvant treatment (CompassHER2 NCT04457596) and in the metastatic setting (HER2CLIMB-02 NCT03975647).

A number of therapies targeting alternative biological pathways are currently being investigated. The *PIK3Cα* gene mutation has been shown to reduce responsiveness of HER2-positive tumours to anti-HER2 therapy.[70,71] A genomic analysis of tumours from the NCCT-N9831 trial has shown an association between immune-enriched tumours and favourable outcome when treated with trastuzumab.[72] Similarly, immune signatures were significantly correlated with higher pCR rate and better relapse-free survival in the CALGB-40601 trial.[73] HER2-directed vaccines are currently under various phases of investigation.[74]

Finally, immune check point inhibitors have been explored in combination with anti-HER2 agents in the metastatic setting. However, early phase trials to date demonstrated limited efficacy in HER2-positive subgroups.[75,76] There is some suggestion that patients with PD-L1 positive tumours may derive some benefit but this requires further confirmation. The role of immune check point blockade in early disease is unknown and is being investigated in studies such as APTneo (NCT03595592) and NeoHIP (NCT03747120).

7 | CONCLUSIONS

HER2-targeted therapies in the neoadjuvant and adjuvant settings have dramatically improved the outcomes of patients with HER2-positive early breast cancer, and transformed our treatment algorithms where a neoadjuvant approach is now used for the majority of patients. While trastuzumab remains effective as a HER2-directed therapy, there are an increasing number of HER2-directed therapies that have shown increased efficacy when added to a traditional trastuzumab-based systemic therapy backbone. This has in turn led to improving outcomes for patients. With therapies such as pertuzumab and T-DM1 being now moved forward into the early breast cancer treatment algorithm, their use in the advanced stages of disease following recurrence of disease following prior exposure is less clear.

With an increase in the number of treatment protocols used, it is clear that a traditional escalation strategy should not be used for every patient, and it is imperative that one considers the balance of risks and benefits when considering escalation or de-escalation strategies to personalise treatment for patients. Further research is needed to better understand predictors of response and resistance to the currently used therapies, which in turn will improve the precision of treatment and develop new strategies to overcome treatment resistance.

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CONFLICT OF INTEREST

Julia Chen has nothing to declare. Maree Colosimo declares honoraria for participating in advisory boards for Pfizer and Specialised Therapeutics. Elgene Lim received research funding from Novartis and Bayer, and honoraria for participating in advisory boards for Roche, Lilly, Novartis, Pfizer and Specialised Therapeutics have been paid to the Garvan Institute.

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