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# HER2-targeted treatment for older patients with breast cancer: An expert position paper from the International Society of Geriatric Oncology

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ABSTRACT

HER2-positive (HER2+) breast cancer (BC) affects older women nearly as frequently as younger ones. Many older patients have cardiovascular comorbidity and risk greater toxicity from therapy. Treatment therefore requires careful consideration, especially since trials include few patients over 65 and so provide limited guidance. A multidisciplinary task force of the International Society of Geriatric Oncology conducted a literature review to make specific recommendations. In the absence of impaired left ventricular ejection fraction, older patients with HER2+ advanced or metastatic BC (MBC) should receive HER2-targeted therapy adjusted to their general condition. Although trastuzumab combined with pertuzumab and docetaxel or paclitaxel is recommended first-line in fit patients, taxanes are difficult in vulnerable ones, making a better-tolerated chemotherapy partner highly desirable. Hormonal therapy with anti-HER2 treatment is an alternative with hormone sensitive tumours. T-DM1 is the standard for fit trastuzumab- and taxane-exposed patients. Lapatinib activity differs from trastuzumab and causes more side effects and drug interactions that are at higher risk in older patients. For fit HER2+ early BC (EBC) patients, chemotherapy plus one year trastuzumab is standard, dual blockade being restricted to high risk and fit patients. Although there is a low level of evidence, using trastuzumab alone (omitting chemotherapy) or enhancing its action through multiple blockade of HER2 and/or the oestrogen receptor pathway may suit vulnerable and frail MBC and EBC patients. Introducing adjuvant therapy lasting less than one year or harnessing neoadjuvant exposure to assess tumour sensitivity and adjust potential rescue treatment accordingly are other key approaches for older patients. These would be particularly helpful for less robust patients or in health systems with limited resources but need further evaluation.



**Contents**



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## 1. Introduction

Around 40% of breast cancers (BC) occur in women aged 65 and older and 20% in women over 75 [1]. The prevalence of Human Epidermal Growth Factor Receptor 2 positive (HER2+) BC in older patients is only slightly lower than the 15–20% rate in younger patients [2]: 10–15% of BC patients older than 65 have tumours that overexpress HER2 [3–6]. In the era before targeted agents, HER2 + was associated with poor prognosis [5,7]. Anti-HER2 therapies, especially when combined with chemotherapy, have dramatically improved survival [8].

Despite accounting for 40% of BC patients, few older women are included in pivotal trials: only 16% of patients in the key studies of adjuvant trastuzumab were 60 and above [9,10]. A further problem is that older patients in trials are fitter than the wider population of older patients. The lack of trial guidance for older patients has resulted in both over-treatment (given the higher risk of toxicities and competing causes of mortality) and under-treatment (because of age-based restrictions). Given the prevalence of comorbidities and the cardiotoxic nature of therapy, older patients with HER2+ disease merit specific consideration [11]. A multidisciplinary task force convened by the International Society of Geriatric Oncology reviewed the evidence in the literature on anti-HER2 treatments for patients over 70, highlighting unmet clinical needs and reaching recommendations.

## 2. Methodology

The task force conducted a literature search of Cochrane and PubMed starting at the year 2000 using key words relevant to BC and HER2 receptor status (see eMethod & eFigure 1). This was supplemented by personal knowledge of the literature and updated to include data from the most recent congresses. Papers were assessed by at least two authors (NdG, EB).

Particular attention was paid to randomized clinical trials (RCTs) reporting efficacy and toxicity data for older patients subsets. Given the relative lack of data from controlled studies in older patients, large "real-world data" population cohorts were included. In the text, the data with a focus on older persons were presented following a pragmatic clinical rule, per setting [metastatic or (neo)adjuvant] then per type of drug. For tables, studies were selected based on their clinical relevance for the addressed question.

The final step was to establish recommendations for clinical practice in older patients, using as reference the broad-based National Comprehensive Cancer Network (NCCN) guidelines for HER2+ BC in the general population [12]. The authors aimed to define peculiarities for the older patients and to propose accordingly concrete statements for clinicians treating such population. By interpreting the available data, recommendations were proposed by EB and HW to the whole group, then adapted with input from all authors until consensus was achieved. Therefore our recommendations carry an appropriate degree of caution, but we refer whenever possible to level of evidence as defined in reference 13 (see eTable 1).

Of note, the general health status assessed by geriatric assessment is of paramount importance when taking clinical decisions in older patients, also if they have HER2+ BC. We refer to extensive review papers for details [14]. Although the terms "fit", "vulnerable" and "frail" are often used to make clinical categories, no consensus exists regarding their definitions, frailty being considered more as a cumulative deficits disorder. Therefore we decided to use these terms in our text as generic, without arbitrary definitions. We acknowledge this hampers the generation of robust recommendations per frailty category, but the available data do not allow making these as evidence-based.

## 3. Metastatic Breast Cancer

Table 1 lists major trials of anti-HER2 agents. The median age of patients is in the early to mid-fifties. In the pivotal publications there is generally no subgroup analysis of efficacy or toxicity by age, although some follow-up papers addressed this issue.

### 3.1. Trastuzumab

Taxanes were established as the standard partner for the monoclonal HER2 antibody trastuzumab, causing less cardiac dysfunction than anthracyclines [15–17]. Increasing age at baseline was a significant risk factor for cardiotoxicity [15]. One trial with vinorelbine first-line challenged taxanes by showing less toxicity [18]. Another, with capecitabine as a partner second-line, also had an attractive safety profile [19]. But few patients above 70 years were included in either study.

Trastuzumab was also investigated in combination with endocrine therapy in the TAnDEM trial in post-menopausal women whose cancers were both HER2+ and oestrogen receptor (ER)-positive (ER+) [20]. The combination significantly improved progression free survival (PFS) compared with anastrozole alone (4.8 vs 2.4 months). Despite the lack of analysis by age and the parallel emergence of the dual HER2 blockade-based strategy (see below), the endocrine plus anti-HER2 approach is still reasonable in older patients with strongly hormone sensitive low volume/slowly progressive disease, and in the fragile and vulnerable.

With the 2% rate of cardiotoxicity confined to patients with prior cardiac disease, single-agent trastuzumab may also suit frail older ones with ER- tumours if chemotherapy is contraindicated. However, it is less active alone than with chemotherapy [21] and should generally be discouraged as primary treatment.

### 3.2. Lapatinib

When BC has progressed on first-line trastuzumab and chemotherapy, combination of the HER2 tyrosine kinase inhibitor (TKI) lapatinib

**Table 1**
Metastatic breast cancer: key trials involving anti-HER2 agents.

| Study | Age of pts: medians across treatment groups and range; or n (%) in age groups | Treatment groups (for explanation see text) | N | Overall efficacy (TTP/PFS and OS, months) | Efficacy in older patients | Cardiotoxicity |
|---|---|---|---|---|---|---|
| 1st line | | | | | | |
| Slamon et al. [15] | 51-54y; (25–77) | CT + T vs CT alone<br>CT for pts. with no adjuvant A was AC; for pts. with prior A, CT was with PXT | 235<br>234 | TTP 7.4 vs 4.6<br>OS 25 vs 20 | No subgroup data given by age | NYHA III-IV CHF:<br>AC + T: 27%; AC 8%<br>PTX + T: 13%; PTX 1%<br>Overall, n = 22 (10%) cases of CHF with CT + T vs 5 (2%) with CT alone<br>Baseline age was the only significant CHF risk factor with AC + T |
| Marty et al. [16] | 53-55y; (24–80) | DTX + T vs DTX | 92<br>94 | TTP 11.7 vs 6.1<br>OS 31[a] vs 23 | RR benefit from combination at least as great in pts. aged >50 as in younger pts | LVEF decline<br>17% vs 8% |
| HERTAX<br>Hamberg et al. [17] | 50-54y; (32–74) | Combination DTX + T vs T followed by DTX | 53<br>46 | PFS 9.4 vs 9.9<br>OS 31.5 vs 19.7 | No subgroup data by age | LVEF decline (% pts)<br>36% vs 28% |
| HERNATA<br>Andersson et al. [18] | 56y; (29–72) | DTX + T vs VNR + T | 143<br>141 | TTP 12.4 vs 15.3<br>OS 35.7 vs 38.8 | Among 108 pts. aged >60 y, HR for TTP was not different between groups | Extent and proportion of pts. with LVEF decline not different between groups |
| TAnDEM<br>Kaufman et al. [20] | 54-56y (27–85) | ANA+T vs ANA | 103<br>104 | PFS 4.8 vs 2.4 | No subgroup data by age | Cardiac events 14 vs 2<br>Cardiac discontinuations 5 vs 0 |
| Schwartzberg et al. [25] | 59-60y; (44–87) | LET+L vs LET | 111<br>108 | PFS 8.2 vs 3.0 | PFS benefit in pts. aged >65 similar to that in younger ones | Fall in LVEF of at least 20% and to below normal limit: 3 vs 1 |
| CLEOPATRA<br>Swain et al. [26]; Miles et al. [28] | <65y = 682<br>≥65 = 127 (16%) | DTX + T+ placebo vs DTX + T + P | 808 | PFS 12.4 vs 18.5<br>OS 40.8 vs 56.5 | P improves outcome, irrespective of age;<br>Placebo vs P<br>PFS<br>- HR 0.72 (0.61–0.86) in <65y; in ≥65y HR 0.50 (0.32–0.77)<br>- HR 0.69 (0.58–0.81) in <75y group; in ≥75y HR 0.62 (0.16–2.40)<br>OS<br>- HR 0.70 (0.56–0.87) in <65y group; in ≥65y HR 0.53 (0.31–0.90)<br>- HR 0.68 (0.55–0.83) in <75y group; in ≥75y HR 0.85 (0.26–2.73) | Combination of P + T did not increase risk of cardiac dysfunction; no evidence of late or cumulative toxicity up to one year<br>Older pts. were at increased risk of CHF, but no significant correlation between cardiac dysfunction and age |
| MARIANNE<br>Perez et al. [39] | 52-55y; (22–88) | T-DM1 + P vs T-DM1 + placebo vs taxane+T | 1095 | PFS 15.2 vs 14.1 vs 13.7 | No age analysis | No cardiac data in abstract |
| PERTAIN<br>Rimawi et al. [40] | 33% ≥ 65 | AI +T vs AI +T + P | 258 | PFS 15.8 vs 18.9 | No difference in benefit across age groups | Decrease in LVEF 0.8% vs 2.4%<br>NYHA class II LV dysfunction 0% vs 1.6% |
| ALTERNATIVE<br>Johnston et al. [41] | 54-57y; (30–84); 20% ≥ 65 | L + T + AI vs T + AI vs L + AI | 355 | PFS 11 vs 5.7 vs 8.7 | No efficacy analysis by age | Cardiac events 7% vs 3% vs 2%<br>Any LVEF decrease 59% vs 65% vs 65%<br>Treatment discontinuation due to LVEF decrease or cardiogenic shock 1 vs 3 vs 2 pts |
| EORTC 75111<br>Wildiers et al. [37] | 76.7y; (61–91) | TP vs TPM<br>T-DM1 on progression | 39<br>41 | PFS 5.6 vs 12.7 | | Lymphopenia grade 3–4 5% vs 33%, but no FN case<br>Other toxicities were comparable<br>No relevant difference in functional evolution between TP and TPM |
| PERNETTA<br>Huober et al. [42] | 58y; (26–85) | T + P vs T + P + weekly PTX or VNR<br>T-DM1 on progression | 210 | 3y OS 73% vs 73% | No subgroup data by age | No cardiotoxicity data<br>CT added haematologic, gastrointestinal, neurological toxicities and alopecia |
| 2nd/3rd line | | | | | | |
| EGF100151<br>Cameron et al. [22] | 51-54y; (26–83) | cape+L vs L | 207<br>201 | TTP 6.2 vs 4.3<br>OS 19 vs 16[a] | No subgroup data by age | 4 pts. in each arm met criteria for serious decline in LVEF, but no case symptomatic |
| EGF 104900<br>Blackwell et al. | 51–52 y; (26–81) | L + T vs L | 148<br>148 | PFS 2.8 vs 2.0<br>OS 14 vs 9.5[b] | No subgroup data by age | |

(continued on next page)

**Table 1** (*continued*)

| Study | Age of pts: medians across treatment groups and range; or n (%) in age groups | Treatment groups (for explanation see text) | N | Overall efficacy (TTP/PFS and OS, months) | Efficacy in older patients | Cardiotoxicity |
|---|---|---|---|---|---|---|
| [38] | | | | | | |
| EMILIA<br>Verma et al. [33] | 54 y; (24–84)<br><65y = 853<br>65-74y = 113 (11%)<br>≥75y = 25 (3%) | T-DM1 vs cape+L | 495<br>496 | PFS 9.6 vs 6.4<br>OS 31 vs 25 | HR according to age for PFS<br><65y: 0.62 (0.52–0.74)<br>65-74y: 0.88 (0.43–1.45)<br>≥75y: 3.51 (1.22–10.13) | In both groups, <2% of pts. had decline in LVEF (fall of 15% to <50%) |
| TH3RESA<br>Krop et al. [34] | <65y = 509<br>65-74y = 74 (12%)<br>≥75y = 19 (3%) | T-DM1 vs physicians' choice | 404<br>198 | PFS 6.2 vs 3.3<br>OS 22.7[a] vs 15.6 | HR according to age for PFS<br><65: 0·55 (0·44–0·70)<br>65–74: 0·42 (0·22–0·80)<br>≥ 75: 0·14 (0·02–0·79) | Cardiac events not mentioned in abstract<br>Significant decline in LVEF rare (1% in both arms)<br>No age subanalysis reported |
| GBG 26/BIG 03–05<br>von Minckwitz et al. [19] | MBC after T failure | cape+T vs cape | 78<br>78 | PFS 8.2[a] vs 5.6<br>OS 24.9 vs 20.6 | No subgroup data by age | |

A, anthracyclines; AC, doxorubicin+cyclophosphamide; AI, aromatase inhibitor; ANA, anastrozole; cape, capecitabine; CHF, congestive heart failure; CT, chemotherapy; DTX, docetaxel; FN febrile neutropenia; HR hazard ratio; L, lapatinib; LET, letrozole; LVEF, left ventricular ejection fraction; OS, overall survival; P, pertuzumab; PFS, progression free survival; pts., patients; PTX, paclitaxel; RR, response rate; T, trastuzumab; TPM, trastuzumab+pertuzumab+metronomic cyclophosphamide; TTP, time to progression; VNR, vinorelbine; y, years.

[a] Indicates statistically significantly superior results.

[b] After some crossover.

with capecitabine prolongs time to progression (TTP) vs capecitabine alone [22]. The only influence of age seems on risk of diarrhoea: in a combined analysis of 11 trials, grade 3 events were more frequent in patients aged over 70 (33% vs 19%) [23]. However, enthusiasm for lapatinib decreased following the head to head comparison suggesting inferiority to trastuzumab-based treatment [24] and the introduction of new drugs. The difficulty in managing lapatinib side effects may also have contributed to reduced usage.

Compared with letrozole alone, adding lapatinib to endocrine therapy for ER+ MBC led to >5 month longer PFS irrespective of age [25]. This combination might be appropriate in frail older patients with few symptoms, provided diarrhoea is actively prevented.

### 3.3. Pertuzumab

The monoclonal antibody pertuzumab targets a different HER2 epitope than trastuzumab, blocks HER2 dimerization, and may synergise with trastuzumab. In CLEOPATRA, docetaxel plus both antibodies gave longer PFS and OS than trastuzumab alone [26], with more diarrhoea and febrile neutropenia but no increase in left ventricular ejection fraction (LVEF) dysfunction. The lack of prior adjuvant trastuzumab in 89% of patients fueled the debate on cost [27], though the triple therapy has become the new standard irrespective of prior adjuvant trastuzumab.

Although a pre-defined subanalysis showed that survival benefits were similar before or after age 65, data were less conclusive after 75 [28]. Diarrhoea, asthenia, fatigue, anorexia, vomiting and dysgeusia (any grade) were more frequent from age 65. This was also true of grade ≥ 3 diarrhoea and peripheral neuropathy, but neutropenia and febrile neutropenia were less frequent. This was probably because only 12% and 31% of patients aged 65 and older had escalation or reduction of dose from the initial 75 mg/m$^2$ docetaxel, respectively. Of note, only 2% of patients in this study were 75+, and these were highly selected. In addition, 20–30% required granulocyte-colony stimulating factor (G-CSF).

For the wider older population, docetaxel 3-weekly may be difficult [29]. Although paclitaxel or vinorelbine might be more tolerable and better suit older patients [30,31], they can still induce clinically relevant toxicity and adversely impact quality of life [32].

### 3.4. Trastuzumab Emtansine (T-DM1)

T-DM1 is a stable conjugate of trastuzumab with DM1, a microtubule inhibitor, allowing targeted delivery of the cytotoxic to HER2+ cells and potentially improving the therapeutic index.

In patients in the EMILIA trial, who had prior trastuzumab and taxane, T-DM1 monotherapy significantly prolonged PFS and OS when compared with lapatinib plus capecitabine [33]. The conjugate was also less toxic, albeit with a confidence interval for hazard ratio (HR) in patients 65–75 years that was too wide to show conclusive benefit; and the toxicity comparison was unfavourable in women above 75 years.

In a more advanced population who had progressed after a taxane, lapatinib and trastuzumab (TH3RESA), T-DM1 doubled PFS compared to physicians' choice and increased OS by 6.9 months [34]. Grade 3–4 adverse events (AEs) were fewer (32% vs 43%). Unfortunately, only 15% of patients were aged over 65 and only 3% over 75. In a safety analysis based on 6 studies, the rate of grade ≥3 AEs increased by an absolute 8% in patients >65 years (52% vs 44%) [35].

Although more women aged 65 and over were enrolled in the Kamilla safety study, they still represented fewer than 20%. [36] Discontinuation due to AEs was 14.3% in patients older than 65 vs 9.5% in younger ones, and the overall rate of AEs was higher. The proportion of patients experiencing a decline in LVEF to below 45% was 2.2% vs 1.3%. The rate of AEs associated with T-DM1 (thrombocytopenia, liver toxicity, haemorrhage) was similar.

T-DM1 was investigated specifically in the old/frail population in the EORTC 75111 study [37] where a subgroup of patients (n = 29) received it after failure of trastuzumab and pertuzumab without (TP) or with metronomic cyclophosphamide (TPM). Median PFS was 5.0 months after TPM and 6.7 months after TP, while toxicities were mild and as previously observed.

T-DM1 has become the preferred second line therapy after taxane and trastuzumab (± pertuzumab). Though relevant in fit older patients, further investigations in frail patients are warranted.

### 3.5. Novel Approaches

There is great interest in trials investigating whether dual blockade alone may be sufficient, thereby avoiding the need to combine anti-HER2 therapy with a cytotoxic partner and the accompanying burden of side effects.

The pioneer EGF 104900 trial investigated a chemotherapy-free option for heavily pre-treated HER2+ patients progressing on trastuzumab, seeking to profit from dual intracellular and extracellular targeting of the HER2 receptor [38]. Compared with lapatinib alone, lapatinib plus trastuzumab gave a 4.5 month longer median overall survival (OS). However, there are no age-specific data, and the lapatinib-only comparator is now considered obsolete.

Disappointingly, an intermediate approach, that of using less toxic chemotherapy (T-DM1) combined with pertuzumab, failed to show a PFS benefit over standard trastuzumab plus taxane in MARIANNE [39].

The recent randomized phase II PERTAIN study evaluated 258 HER2 + MBC patients (33% and 19% aged ≥65 or ≥75 years respectively) who were treated first line with an AI and trastuzumab with or without additional pertuzumab [40]. Induction chemotherapy with taxanes was allowed and was used in 57% of patients. On the primary endpoint, stratified PFS was 18.9 months (95% CI, 14.1 to 27.7 months) in the dual blockade group versus 15.8 months (95% CI, 11.0 to 18.6 months) in the single trastuzumab arm (stratified HR, 0.65; 95% CI, 0.48 to 0.89; $p = 0.007$), with no difference across age groups. This suggests that the addition of pertuzumab is helpful, though this study does not answer the central question of whether an up-front chemotherapy combination is indispensable. As in Cleopatra, diarrhoea, which can be debilitating for older individuals, was more frequent with pertuzumab (all grades 55% versus 36%).

Similarly, the ALTERNATIVE trial evaluated 355 HER2+ MBC patients (19% and 4% aged 65–74 or ≥75 respectively) treated with first line endocrine therapy randomized to trastuzumab, lapatinib, or both [41]. Median PFS was 5.7, 8.3 and 11.0 months in the three arms respectively, significantly favouring dual blockade over single-agent trastuzumab ($p = 0.036$). As expected, the rate of diarrhoea (any grade) was higher with dual blockade (69%) than with single trastuzumab (9%) or lapatinib (51%). No detailed age analysis is available so far. As with PERTAIN, the high rate of diarrhoea may be problematic for older individuals, and this needs to be monitored closely.

The EORTC recently published a trial (EORTC 75111-10114) specifically in women aged 70 years and older or those aged 60 and older with defined functional limitations or comorbidities by the Charlson Index [37]. Patients received TP, a chemo-free regimen with dual HER2 blockade (trastuzumab + pertuzumab), or TPM, the same with metronomic cyclophosphamide (50 mg per day continuously). In cases of progressive disease, treatment with T-DM1 was allowed in both arms. The majority of the population (71%) had a geriatric risk profile according to the G8 screening test. Median PFS was 12.7 months for TPM and 5.6 months for TP. Metronomic cyclophosphamide added very little toxicity to TP: lymphopenia grade 3–4 was higher (33% for TPM vs 5% for TP), but no febrile neutropenia cases occurred. Other toxicities were comparable, and there was no relevant difference in functional evolution between TP and TPM. Nine (31%) of 29 deaths were not BC-related. In conclusion, TPM followed by T-DM1 after progression may delay or supersede taxane chemotherapy in this routine non-highly selected population.

The randomized phase II PERNETTA/SAKK 22/10 trial investigated a similar chemotherapy-free strategy by comparing trastuzumab and pertuzumab with or without paclitaxel or vinorelbine in a population not selected according to age [42]. Median PFS was 8.4 months in the chemotherapy-free arm and 23.3 months with chemotherapy. Despite this major difference, chemotherapy did not confer a benefit in OS, the primary endpoint.

Taken together, these data suggest that the question of optimum use of dual blockade and chemotherapy remains open and is challenged by endocrine therapy combinations in ER+ disease.

### 3.6. Summary and Recommendations

According to the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and the European School of Oncology, patients with HER2+ MBC should receive anti-HER2 therapy [43,44]. Those with congestive heart failure (CHF) or severely reduced LVEF need individual evaluation. These recommendations hold for older patients, but only if fit according to a geriatric assessment. Different approaches may be needed for non-fit older patients (Table 2).

**Table 2**
Recommendations for the treatment of HER2+ metastatic breast cancer in older patients.

| | Grade of recommendation/description |
|---|---|
| First line | |
| Docetaxel 3-weekly + G-CSF or weekly paclitaxel, trastuzumab and pertuzumab is 1st line standard of care in fit older patients only | 1B |
| In frail older patients, metronomic cyclophosphamide, vinorelbine or capecitabine with dual blockade can be considered | 2C |
| Trastuzumab monotherapy, or dual anti-HER2 combinations (pertuzumab and trastuzumab, lapatinib and trastuzumab) without chemotherapy should be reserved for frail older patients at high risk of side effects and used in combination with endocrine therapy for hormone-sensitive tumours | 2C |
| Second line | |
| T-DM1 is recommended for second or later lines in fit older patients. Further investigations in frail patients are warranted. | 2C |
| Further lines | |
| Lapatinib side effects are increased in older patients making early and close monitoring crucial | 1B |

## 4. Adjuvant and Neoadjuvant Therapy

In the early-stage setting, a balance must be achieved between the likelihood of preventing recurrence – influenced by tumour characteristics – and toxicity and the risk of death unrelated to BC. This calls for evaluation of life expectancy through geriatric assessment [14] and for the development of specific algorithms such as PREDICT [45].

### 4.1. Key Adjuvant Trials

Trastuzumab, pertuzumab and neratinib are approved for (neo) adjuvant therapy. Table 3 shows relevant studies.

In the combined analysis of NCCTG 9831 and NSABP B-31, the benefit of adding trastuzumab to adjuvant chemotherapy was essentially independent of age [46]. Although an upper age limit was not specified, these studies excluded patients with angina, left ventricular hypertrophy and poorly controlled hypertension. Benefit independent of age was also found at 11 year follow-up of HERA, [47]. Eight year follow-up of HERA confirmed a low incidence of cardiac events in patients who had trastuzumab for 1–2 years following chemotherapy [48]. Adverse changes were generally reversible, but doubled with two years' exposure without any incremental outcome benefit. This ended interest in trastuzumab administration beyond 1 year.

In BCIRG 006, trastuzumab was combined either with doxorubicin and cyclophosphamide (AC) followed by docetaxel or with docetaxel and carboplatin (TCH regimen) [49]. Although not meeting the non-inferiority criteria, outcome was similar in the two trastuzumab-containing arms, and the carboplatin one was associated with less cardiotoxicity and fewer cases of leukaemia. However this study excluded patients aged over 70; and potential toxicity makes giving carboplatin at an AUC of 6 unrealistic in the oldest patients.

The PACS 04 trial randomly assigned patients under 65 who had received adjuvant anthracyclines ± docetaxel to either sequential trastuzumab for 1 year or observation [50]. Compared with previous trials, its negative results suggest that concomitant administration is important to achieve the benefit of trastuzumab.

Indeed, establishing the standard adjuvant trastuzumab regimen in older patients is difficult since the accompanying chemotherapy remains poorly defined. The sequential chemotherapy used in younger adults has been little investigated in older patients, as highlighted in the most recent Early Breast Cancer Trialists Collaborative Group

**Table 3**
Early-stage breast cancer: key trials involving anti-HER2 agents.

| Study | Age of pts: medians across treatment groups and range; or n (%) in age groups | Treatment groups (for explanation see text) | N | Overall efficacy (DFS/OS, months) | Efficacy in older patients | Cardiotoxicity |
|---|---|---|---|---|---|---|
| HERA<br>Piccart-Gebhart [9]<br>De Azambuja [48]<br>Cameron [47] | Median 49 y<br><35y = 251<br>35-49y = 1490<br>50-59y = 1091<br>≥60y = 549 (16%) | After completion of adjuvant CT: T for one year vs observation | 1694<br>1693 | Events 127 vs 220 | At 11 year follow up:<br>HR for DFS<br>≥60y: 0.82 (0.62–1.08)<br>50-59y: 0.81 (0.65–1.01)<br>35-49y: 0.71(0.59–0.85)<br><35y: 0.75 (0.50–1.11) | Severe cardiotoxicity in 0.8% of T patients (no differences by age in cardiac events or CHF) |
| NSABP B-31 and NCCTG N9831<br>Perez [46]<br>Romond [10] | Median age 49y; (19–79)<br><40y = 654<br>40-49y = 1373<br>50-59y = 1336<br>≥60y = 683 (17%) | AC followed by PTX + T, then T to complete 1y<br>AC followed by PTX | 2028<br>2018 | 10y OS<br>84% vs 75.2% | HR for death significantly reduced in all age groups<br>≥60y: HR 0.51<br>40-49y: HR 0.65<br>50-59y: HR 0.68<br>< 40y: HR 0.67 | Increased risk of cardiac events<br>≥ 60y vs < 50y = x 2.7 (1.0–7.3) (NSABP B-31) or x 3.2 (1.55–6.81) (N9831)<br>≤ 50y vs > 50y = x 3 (1.5–6.1) (combined analysis NSABP B-31+ N9831)<br>6y cumulative incidence of cardiac events 3.4% vs 0.6%<br>In arms containing T, risk factors for cardiac event: ≥60y; baseline LVEF ˚65%; anti-hypertensive treatment<br>late cardiac events very infrequent; LVEF recovered in the majority of pts. long term |
| BCIRG 006<br>Slamon et al. [49] | 53% pts. < 50y<br>None eligible >70y | AC-DTX<br>AC-DTX + T<br>DTX-carboplatin+T | 3222 | 10y DFS<br>78.7% vs 85.9% vs 83.3% | No subgroup data by age | CHF and cardiac dysfunction significantly higher with AC-DTX + T than with DTX-carboplatin+T |
| Short duration studies | | | | | | |
| Finher<br>Joensuu H et al. [59] | 50y; (26–65) | DTX or VNR ± T 9 weeks followed by FEC | 232 | HR of death 0.41 (p = 0.07) in pts. given T | No pts. ≥ 65 | No cases of CHF<br>LVEF preserved with T |
| PHARE<br>Pivot X et al. [60] | 55 y; (21–86)<br>33% ≥ 60y | CT + T<br>12 months vs 6 months | 1691 | 2y DFS<br>93.8% vs 91.1% | No subgroup data by age | CHF 0.65% vs 0.53% (p > 0.05)<br>Cardiac dysfunction 5.7% vs 1.9% (p = 0.0001) |
| SOLD<br>Joenssu et al. [62] | 56y | CT + T 9 weeks vs CT + T 18 weeks | 2174 | 5y DFS 88.0% vs 90.5%, HR 1.39<br>5y OS 94.7% vs 95.9% | No subgroup data by age | Cardiac AEs 2% vs 4%<br>Mean LVEF 63% vs 61% |
| PERSEPH-ONE<br>Earl et al. [63] | | CT + T 6 months vs CT + T 12 months | 4089 | 4y DFS 89% vs 89% | No subgroup data by age | Discontinuation due to cardiac AEs 4% vs 8% |
| Others | | | | | | |
| APHINITY<br>von Minckwitz et al. [77] | 13% ≥ 65y | CT + T + P vs CT + T | 4805 | Recurrence 7.1% vs 8.7% | Benefit independent of age | CHF or cardiac death 0.7% vs 0.3%<br>Asymptomatic or mildly symptomatic LVEF decline 2.7% vs 2.8% |
| RESPECT<br>Sawaki et al. [68] | 73.5; (70–80) | CT + T vs T alone (no CT)<br>(Endocrine therapy when indicated) | 266 | 3y DFS 94.8% vs 89.2%<br>(HR = 1.42; 95% CI, 0.68 to 2.95, P = 0.35)<br>Difference in RMST <1 month | | LVEF dysfunction grade 1–2 6.9% vs 8.1% |

AC, doxorubicin+cyclophosphamide; CHF, congestive heart failure; CT, chemotherapy; DFS, disease-free survival; DTX, docetaxel; HR hazard ratio; LVEF, left ventricular ejection fraction; OS, overall survival; P, pertuzumab; pts., patients; PTX, paclitaxel; RMST, restricted mean survival time; T, trastuzumab; VNR, vinorelbine; y, years.

meta-analysis [51]. The only validated treatments supported by a high level of evidence are the old-fashioned 4 AC and 6 cyclophosphamide/methotrexate/fluorouracil (CMF) regimens. In general, only very fit older patients can be treated with sequential regimens used in younger patients. The 40–50% of potentially unfit patients found by G8 frailty screening in women aged 70 and older with EBC suggests that many patients are unsuited to this approach [52]. Therefore anthracycline-free regimens are attractive for older patients with low-risk tumours or who are predisposed to cardiotoxicity.

In older patients with HER2-negative EBC, docetaxel plus cyclophosphamide (TC) is the best documented non-cardiotoxic regimen that is superior to AC. This has been demonstrated irrespective of age, with a specific subgroup analysis in 65+ patients [53]. Subsequent studies [54,55] showed also that TC can be given and completed in >90% of older (70+) patients, the latter recovering from slight decline in quality of life and functionality after 1 year of follow-up [55]. Moreover, cardiac toxicity of the anthracycline-free TC regimen is definitely lower than with AC, with increased benefit in the older population which is at higher risk. The main caveat is that TC should be given with prophylactic G-CSF, to keep the rate of febrile neutropenia below 5–10%. Thus it is an attractive candidate for combination with trastuzumab in older patients although age-specific data are limited: in patients up to 75 years (most node negative), there was <3% rate of recurrence at three years [56].

In a single-arm study, patients with low risk HER2+ node-negative BC received weekly paclitaxel x12 and trastuzumab [57]. Invasive DFS at 7 years was 99.3%; there were 23 relapses but only 4 were distant. This regimen has not been evaluated in older patient with cancer specifically or in higher risk patients, but given its safety profile, it is an attractive option.

Of note, as with the historical AC × 4 protocol, these regimens based on taxanes only (TC × 4 q3w; paclitaxel qw × 12) are shorter than sequential chemotherapy (12 versus 18–24 weeks), conferring much

lower risk of grade 3–5 AEs according to the CARG-BC predictive model [58]. This consideration strongly supports the strategy of adjusting treatment in older patients, rather than uncritically applying a regimen developed for different and younger populations. However further research according to frailty status is required since such predictive model still defines the low risk group as being below the significant 20%-threshold for grade 3–5 AEs.

The FinHer trial also investigated alternative chemotherapy regimens, including vinorelbine and a shorter duration of trastuzumab, in an effort to minimize toxicity [59]. Interestingly, when compared to no trastuzumab, nine weeks of trastuzumab achieved a relative benefit similar to that with 1 year of trastuzumab in other trials, and did not adversely affect cardiac function. This might well address cardiac concerns in the older patient.

The FinHer finding led to further trials of short-duration trastuzumab such as PHARE and PERSEPHONE (6 months vs 1 year) or SOLD and SHORT-HER (9 weeks vs 1 year). PHARE [60], Short-HER [61] and SOLD [62] failed to show the non-inferiority of shorter duration of trastuzumab. On the other hand, PERSEPHONE did find that 6 months trastuzumab was non-inferior to 12 months [63]. All these studies showed a lower rate of cardiac dysfunction with the shorter duration arm, but CHF was rare in general, and cardiac toxicity mostly reversible. The fact that patients with small node-negative tumours do not seem to derive extra benefit from extending trastuzumab beyond 6 months suggests that treatment duration might be adjusted according to prognostic factors [64]. This is especially relevant in older patients at increased cardiac risk.

A Cochrane review of eight studies showed the addition of trastuzumab highly significantly improved OS compared with placebo (HR 0.66, $p < 0.00001$) [2]. On this basis, guidelines from St Gallen [65], ESMO [66], and the NCCN [12] recommend chemotherapy and trastuzumab in patients (including older patients) with tumours of 0.5–1 cm or greater, or lymph node involvement. This agrees with the most comprehensive review of RCTs in the older patients, which included 1084 patients aged over 60 years [67].

Guidelines also state, with cautious wording, that trastuzumab without chemotherapy, or with endocrine therapy in the case of ER+ tumours, is an option, especially for unfit patients. Of note, new data regarding this strategy have been recently reported: the Japanese RESPECT phase III study randomized 266 EBC patients aged 70–80 between adjuvant single agent trastuzumab and the standard combination of chemotherapy and trastuzumab [68]. DFS at 3 years was 94.8% (12 events) in the trastuzumab + chemotherapy group vs 89.2% (18 events) in patients treated with trastuzumab alone. The standard treatment resulted in more ($p < 0.005$) all grade anorexia (44.3% vs 7.4%) and alopecia (71.8% vs 2.2%), and grade 3/4 haematological and non-haematological AEs (17% vs 0% and 29.8% vs 11.9%), impairing quality of life. Although underpowered to achieve a robust conclusion, these results challenge the usual recommendation that combination with chemotherapy is preferable whenever possible and call for strategies adjusted to frailty status.

### 4.2. Adjuvant Therapy in Routine Practice

Real-life data provide useful and sometimes contrasting information when compared with RCTs, underlining the effect of trials' strict eligibility criteria, especially in relation to the older patient.

Recent American data show that adjuvant trastuzumab is underused in up to 50% of older women (especially black women) with HER2+ EBC and locally advanced disease [69]. Surveillance, Epidemiology and End Results (SEER) data also show that patients >65, especially octogenarians and those with comorbidities, often receive incomplete (≤ 9 months) treatment [70,71]. Delay or cessation was seen in 15–40% of cases. Thirty percent of patients developed an LVEF decrease ≥10%, and 3–11% were hospitalized for cardiac events within 1–2 years of follow up. However, a major Canadian series suggests the true interaction between age and treatment on risk of CHF is uncertain, even if the cumulative incidence of cardiotoxicity is higher in patients ≥65 years [72].

In this context, there is interest in Reeder-Hayes et al.'s recent use of SEER data to compare outcomes among women aged over 65 years treated with two adjuvant regimens frequently used in the USA, namely sequential AC followed by weekly paclitaxel and trastuzumab (ACTH), and the carboplatin-based TCH regimen [73]. In this retrospective analysis, the two regimens were found to have non-significantly different rates of AEs; and there were no significant differences in BC-specific survival or OS at five years, despite the fact that fewer patients receiving ACTH completed their course of trastuzumab. We need to be cautious with these data, as severe selection bias was probably present. It is also worth noting that there may be different attitudes towards use of these chemotherapy regimens in the USA compared with other parts of the world. Although ACTH and TCH are standard regimens used in the general US population, they have significant toxicity, and are probably only suitable for a highly selected fit older population.

### 4.3. Novel Adjuvant Approaches

Route of administration may have an important impact on quality of life and resource use. Subcutaneous trastuzumab has the same efficacy and safety profiles as the standard iv formulation and is often preferred by patients [74]. If approved for administration at home, it would help older patients avoid the need to travel to hospital.

Neratinib, an irreversible TKI of HER1, HER2 and HER4, has been explored as extended treatment after trastuzumab [75]. Despite being approved on the basis of a significant benefit on DFS, mainly in the hormone sensitive subgroup, the 41% rate of grade 3–4 diarrhoea makes it unlikely such a strategy will suit the general older population.

As in MBC, dual blockade is an attractive strategy and was investigated in the ALTTO programme combining lapatinib and trastuzumab with chemotherapy [76]. The combination was not superior in DFS, while being more toxic. Disappointingly this study had no greater success than previous RCTs in enrolling patients >65.

Given the results of CLEOPATRA in MBC, anti-HER2 duets such as pertuzumab and trastuzumab might prove more successful. There has therefore been great interest in the APHINITY trial (BIG 4–11), a placebo-controlled comparison of one year's chemotherapy plus trastuzumab versus chemotherapy plus trastuzumab plus pertuzumab in 4804 women (13% aged 65 or older) with EBC [77]. The addition of pertuzumab significantly improved survival free of invasive disease without causing additional safety concerns but the absolute differences were small. This seemed true irrespective of age. Rates of CHF or cardiac death were low (0.7% vs 0.3% in the placebo arm), as were rates of asymptomatic or mildly symptomatic LVEF decline (2.7% vs 2.8%). However, grade 3 or higher diarrhoea was more frequent with pertuzumab (9.9% vs 3.7%). The addition of pertuzumab for older patients is probably only to be considered in case of very high risk tumours where the patient is willing to accept, and able to tolerate, additional risk, mainly of diarrhoea.

The crucial research question remains whether HER2+ EBC can be adequately treated by adjuvant anti-HER2 therapy alone, as explored in the RESPECT trial [68].

This mirrors the equivalent question in the metastatic setting of whether dual blockade (with endocrine agents if indicated) might be sufficiently effective in eradicating micrometastatic disease that chemotherapy is no longer needed. But this still needs to be demonstrated. T-DM1 is also an interesting agent in this setting because of its clear activity and favorable safety profile in MBC, although it does not avoid chemotherapy.

### 4.4. Neoadjuvant Therapy

The neoadjuvant approach in older patients can be difficult since this strategy generally involves chemotherapy rather than endocrine

treatment, possibly jeopardizing subsequent surgery by causing a deterioration of health status.

However the neoadjuvant context may also be the most appropriate setting in which to investigate dual HER2 inhibition. The NeoSphere trial included patients up to 80 years of age and showed that pertuzumab plus trastuzumab in the absence of chemotherapy could eradicate tumours in a significant proportion of patients (up to 27% if ER-) while causing very limited toxicity [78]. Similarly, the ADAPT trial [79] evaluated T-DM1 versus T-DM1 plus endocrine therapy versus trastuzumab plus endocrine therapy in hormone sensitive HER2 positive EBC, and showed that the pathological complete response (pCR) rate was much higher in the T-DM1 arms (41.0%, 41.5%, and 15.1% respectively) while the addition of endocrine therapy to T-DM1 did not seem to improve efficacy.

The KRISTINE study [80] compared standard chemotherapy TCH and pertuzumab (TCHP) to T-DM1 plus pertuzumab with pCR rates of 55.7% and 44.4% respectively. Subgroups of patients can probably avoid classical chemotherapy and this would greatly benefit older patients. However more research is needed to identify those patients. This kind of approach should be investigated further in both adjuvant and neoadjuvant settings.

Finally, the neoadjuvant model provides gives a unique opportunity to assess early markers of response (e.g. biomarkers, functional imaging) as surrogates for pCR. This should lead to a revision of the non-consensual (if not unfavourable) position for such an approach in older patients. In the same way as their younger counterparts, they may derive great benefit from a targeted strategy, avoiding long periods of treatment with modest efficacy or selecting rescue treatment. In the KATHERINE study [81], patients with no pCR after standard trastuzumab-based neoadjuvant chemotherapy and randomly assigned T-DM1 in post-neoadjuvant setting showed a major improvement of outcome compared with standard extension of trastuzumab for 1 year. The fact that older patients were clearly underrepresented (8% aged ≥65 years) resulted in a wider confidence interval for outcome HR should not lessen the promise of such an approach, irrespective of age.

### 4.5. Summary and Recommendations

Adjuvant trastuzumab reduces mortality by a third and relapse by 40% [2]. However, of >20,000 women included in trials of adjuvant trastuzumab, only about 1000 were 60 years or older. This makes it difficult to draw reliable conclusions outside a highly selected group, especially since impaired baseline cardiac function was generally an exclusion criterion. Adjuvant therapy in older patients with HER2+ EBC should take into account risk of relapse, life expectancy (assessed through geriatric assessment), expected tolerability (including cardiac), and patient preference. Table 4 summarises our recommendations.

If neoadjuvant treatment is considered, the same recommendations can be employed as in the adjuvant setting and for younger patients. Less toxic options need further investigation.

**Table 4**
Recommendations on adjuvant (and neoadjuvant) therapy in older patients with HER2+ early-stage breast cancer.

| (NEO) Adjuvant setting | Grade of recommendation/description |
|---|---|
| Regimen | |
| Only very fit older patients can receive classical adjuvant sequential chemotherapy (anthracylines ➔ taxanes) + G-CSF + trastuzumab 1 year | 2B |
| Trastuzumab can be combined with the TC regimen, which is the best documented regimen in older patients, but G-CSF is required to avoid febrile neutropenia | 2A |
| In frail older patients and/or those with low-risk tumours, weekly paclitaxel is the preferred regimen to combine with trastuzumab | 2C |
| Trastuzumab without chemotherapy or with endocrine therapy only in the case of hormone-sensitive tumours can be considered, especially for unfit patients | 2C |
| Dual blockade with trastuzumab and pertuzumab combined with sequential anthracycline- and taxane-based chemotherapy, or extended anti-HER2 treatment after trastuzumab with neratinib, can only be considered in very fit and high-risk patients. Be aware of the higher risk of side effects | 2C |
| Duration | |
| The standard duration of trastuzumab is 1 year, but the threshold for shorter duration can be low in cases of side effects, increased cardiovascular risk, or lower risk tumours. | 2B |
| Neoadjuvant strategy | |
| Neoadjuvant therapy can help in the individualizing of treatment (before or after surgery), from which older patients should derive great benefit | 2C |

## 5. Cardiac Safety

Trials provide relatively little safety data specific to the older patients and include predominantly patients who are generally healthy [82]. Toxicity may be more frequent in unselected patients, but safety information can be supplemented by observational data.

The main concern with trastuzumab is cardiac. Overall, it can increase the risk of cardiomyopathy five fold and double the risk of decline in LVEF, especially in the older adults [72,73]. In a large and recent meta-analysis of randomized and cohort studies including 29,000 women, cardiotoxicity increased from 2.3% in individuals <50 years to 3.5% and 4.9% in those 50–59 years and >60 years of age [83]. However numbers are insufficient to identify subgroups that might not benefit particularly from trastuzumab treatment, or those at particular risk of AEs.

Cardiotoxicity should be carefully considered in older women at low risk of BC recurrence or with cardiac risk factors. In a model that estimates risk of severe CHF using NSABP B-31 data, age was a major predictive factor (HR 2.73 in patients aged 60 or more vs below 50) [84]. Combining age with LVEF at baseline allowed the development of a Cardiac Risk Score. At seven year follow-up, 4% of the 944 trastuzumab-treated patients had developed a cardiac event vs 1.3% in controls. This seems reversible: LVEF returned to within normal limits in the majority of patients who had experienced dysfunction once trastuzumab was stopped.

Before starting trastuzumab in patients with low/borderline baseline LVEF, cardiac function should be optimized – in collaboration with cardiologists – using angiotensin converting enzyme inhibitors and/or beta-blockers. LVEF in older patients should be checked every three months using echocardiography or MUGA, though data suggest that this advice is not routinely implemented [85].

Compared with trastuzumab, trastuzumab plus pertuzumab did not seem to increase cardiac risk in the older patients [28], but recent data suggest the rate of dysfunction may reach >10% in patients ≥65 [32].

### 5.1. Recommendations

Trastuzumab is well tolerated in older patients. Cardiac toxicity is generally reversible but it is essential that cardiac function is adequately monitored. Patients included in cohort studies, who more closely resemble women in real-life settings than those enrolled in RCTs, are at higher risk of developing cardiac events. The rate of treatment interruption is difficult to interpret since it may depend on the accompanying chemotherapy. The newer anti-HER2 compounds generally also have a favorable toxicity profile, but caution is warranted since there are as yet no firm data on toxicity and quality of life in vulnerable or frail patients.

In patients with impaired LVEF or CHF at baseline, non-cardiotoxic chemotherapy without anti-HER2 drug remains the safest strategy. However, after the advice of a cardiologist and with a close and cautious cardiac monitoring, anti-HER2 treatment combined with non-cardiotoxic chemotherapy might be considered in individual cases when there is a high clinical need to increase the chance of tumour response.

## 6. Discussion

Though 40% of BC patients are 65 years and over, our understanding of treatment effects is hampered by lack of evidence from RCTs in this population. Attempts are being made to consider the particular circumstances of older patients, notably their susceptibility to toxicity. In relation to cardiotoxicity, establishing the optimal duration of adjuvant anti-HER2 treatment is of particular concern. Individualization of treatment based on a comprehensive geriatric assessment and multidisciplinary management are appropriate.

BC biology may differ in the older patients [11] who generally receive less intensive treatment, resulting potentially in higher disease-specific mortality [86]. Tolerance of treatment may be reduced [11], and there are competing risks of death [82]. Life expectancy and risk of relapse with time are key considerations and, together with issues of safety, guide our recommendations.

Cost also remains a challenge, and cost-effectiveness is negatively affected by age [87]. Only adjuvant trastuzumab given for 1 year and as first-line therapy for MBC is regarded as cost-effective [27], highlighting the potential role of biosimilars (20–30% cheaper), especially in low income countries.

Trials should be conducted in patients whose age distribution is more representative of the wider population. It is encouraging that some such trials are now taking place, and that, along with tumour response, they include endpoints particularly relevant to the older patients [88]. Also encouraging is the recent Canadian ASCO recommendation that adjuvant treatment of HER2+ BC takes into account estimated life expectancy and validated geriatric assessment instead of relying solely on chronologic age and comorbidities [89].

## Author Contributions

Conception and design: Etienne Brain, Hans Wildiers
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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
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## Declaration of Conflict of Interests

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## Appendix A. Supplementary data

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