Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group

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Summary

Background Despite the high incidence of metastatic breast cancer and its related mortality in the elderly population, our knowledge about optimal treatment for older patients with cancer is far from adequate. We aimed to evaluate the efficacy of dual anti-HER2 treatment with or without metronomic chemotherapy in older patients with HER2-positive metastatic breast cancer.

Methods We did a multicentre, open-label, randomised, phase 2 trial in 30 centres from eight countries in Europe, in patients with histologically proven, HER2-positive metastatic breast cancer, without previous chemotherapy for metastatic disease, who were 70 years or older, or 60 years or older with confirmed functional restrictions defined by protocol, and had a life expectancy of more than 12 weeks and a performance status according to WHO scale of 0–3. Eligible patients were randomly assigned (1:1) by an online randomisation system based on the minimisation method to receive metronomic oral cyclophosphamide 50 mg per day plus trastuzumab and pertuzumab, or trastuzumab and pertuzumab alone. Trastuzumab was given intravenously with a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks. Pertuzumab was given intravenously with a loading dose of 840 mg, followed by 420 mg every 3 weeks. Patients were stratified by hormone receptor positivity, previous HER2 treatment, and baseline geriatric screening. The primary endpoint was investigator-assessed progression-free survival at 6 months as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A difference of 10% or greater between the two groups was sought. Efficacy analyses were by intention to treat; safety was assessed in all patients who received at least one dose of study treatment. In case of progression, all patients were offered trastuzumab emtansine. This trial is registered with ClinicalTrials.gov, number NCT01597414, and is completed.

Findings Between July 2, 2013, and May 10, 2016, 80 patients, of whom 56 (70%) had a potential frailty profile according to the geriatric screening G8 score (≤14), were randomly assigned to receive trastuzumab and pertuzumab (n=39) or trastuzumab and pertuzumab plus metronomic oral cyclophosphamide (n=41). Estimated progression-free survival at 6 months was 46·2% (95% CI 30·2–60·7) with trastuzumab and pertuzumab versus 73·4% (56·6–84·6) with trastuzumab and pertuzumab plus metronomic oral cyclophosphamide (hazard ratio [HR] 0·65 [95% CI 0·37–1·12], p=0·12). At a median follow-up of 20·7 months (IQR 12·5–30·4), the median progression-free survival was 5·6 months (95% CI 3·6–16·8) with trastuzumab and pertuzumab versus 12·7 months (6·7–24·8) with the addition of metronomic oral cyclophosphamide. The most frequent grade 3–4 adverse events were hypertension (in six [15%] of 39 patients in the trastuzumab and pertuzumab group *vs* five [12%] of 41 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group), diarrhoea (four [10%] *vs* five [12%]), dyspnoea (two [5%] *vs* four [10%]), fatigue (three [8%] *vs* two [5%]), pain (two [5%] *vs* two [5%]), and a thromboembolic event (0 [0%] *vs* four [10%]). Severe cardiac toxicities were occasionally observed in both groups. In the trastuzumab and pertuzumab group four patients died without progression, due to cardiac arrest during treatment (n=1), peritoneal infection (n=1), respiratory failure (n=1), and sudden death without a specified cause (n=1). In the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group, one patient died from heart failure.

Interpretation Addition of metronomic oral cyclophosphamide to trastuzumab plus pertuzumab in older and frail patients with HER2-positive metastatic breast cancer increased median progression-free survival by 7 months compared with dual HER2 blockade alone, with an acceptable safety profile. Trastuzumab and pertuzumab plus metronomic oral cyclophosphamide, followed by trastuzumab emtansine after disease progression, might delay or supersede the need for taxane chemotherapy in this population.

Funding F Hoffmann-La Roche.

Lancet Oncol 2018

Published Online
February 9, 2018
http://dx.doi.org/10.1016/S1470-2045(18)30083-4

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(18)30084-6

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Research in context

Evidence before this study

We searched PubMed using the terms "trastuzumab", "pertuzumab", "HER2 positive", and "metastatic breast cancer" for articles published between Jan 1, 2000, and Dec 31, 2012. Results were manually sorted and restricted to landmark findings about the appropriate treatment of HER2-positive metastatic breast cancer. Results of the phase 3 CLEOPATRA study, published in 2012, established docetaxel plus trastuzumab and pertuzumab as a new first-line standard of care for this population. However, docetaxel is a chemotherapeutic agent with well known and clinically relevant toxicity, affecting quality of life. It was also known that metronomic chemotherapy with oral cyclophosphamide is an active chemotherapy regimen with minor toxicity and is thus suitable for older patients. There were, however, no relevant data for the effects of metronomic cyclophosphamide combined with anti-HER2 therapy in patients with HER2-positive metastatic breast cancer. The present study started recruitment on July 2, 2013, to investigate whether anti-HER2 blockade alone could be adequately effective in this population or whether addition of a milder type of chemotherapy is required.

Added value of this study

The results of this study indicate that the benefit of avoiding the side-effects of chemotherapy with the use of dual anti-HER2 blockade alone does not compensate for the substantial loss of activity in the metastatic breast cancer setting. Antitumour activity seems to be higher when a low-intensity chemotherapy such as oral cyclophosphamide is added.

Implications of all the available evidence

The phase 2 EORTC 75111-10114 study provides a scientific framework in support of more specific trials in the older population of patients with HER2-positive metastatic breast cancer. Further evaluation of trastuzumab and pertuzumab plus metronomic oral cyclophosphamide compared with trastuzumab and pertuzumab alone in a randomised phase 3 study should be considered, although financial support for such studies in the older population remains a challenge.

Introduction

Worldwide, nearly a third of breast cancer cases occur in patients older than 65 years, and in high-income countries this proportion rises to more than 40–50%.[1] Despite the high incidence of cancer and its related mortality in the older population, our knowledge about ageing and cancer and about optimal treatment for older patients is far from adequate. The International Society of Geriatric Oncology (SIOG) has established guidelines on breast cancer treatment in older patients, but confirms that solid evidence is absent in many areas.[2,3] This is largely because of a paucity of evidence-based data for older patients with breast cancer as a result of their under-representation in clinical trials.[4] Many breast cancer clinical trials have tended to exclude older individuals on the basis of age, comorbidity, or both. However, older patients are just as willing as younger patients to participate in clinical trials if given the opportunity.[5]

HER2-positive metastatic breast cancer is an aggressive disease if left untreated, but important advancements in HER2-directed drug development have led to substantial improvements in outcomes. In the phase 3 CLEOPATRA study, addition of pertuzumab to trastuzumab and docetaxel significantly improved median progression-free survival (from 12·4 months to 18·5 months; hazard ratio [HR] 0·65 [95% CI 0·54–0·78]; p<0·001) and median overall survival (from 40·8 months to 56·5 months; HR 0·68 [0·56–0·84]; p<0·001] with limited additional toxicity, establishing a new first-line standard of care for this population.[6] The addition of adjuvant pertuzumab to trastuzumab and chemotherapy has shown a small benefit in patients with early HER2-positive disease.[7]

Docetaxel is a chemotherapeutic agent with well known and clinically relevant toxicity, including alopecia, neutropenia, neuropathy, and fatigue, affecting quality of life. Because of age-related changes in drug pharmacokinetics and pharmacodynamics,[8] tolerance of chemotherapeutic drugs such as docetaxel might decrease in the older population[9] and affect quality of life.[10] In a palliative setting such as metastatic breast cancer, maintenance of quality of life and avoidance of substantial toxicity might be as important as improving survival. Introduction of HER2-directed therapies to classical chemotherapy raises the question of whether it is possible to treat patients with HER2-positive metastatic breast cancer with HER2-directed regimens without classical chemotherapy. In the neoadjuvant setting, the dual blockade of HER2 with pertuzumab plus trastuzumab has shown substantial antitumour activity.[11] Metronomic chemotherapy refers to treatment at regular, close intervals without prolonged breaks at doses substantially lower than the maximum tolerated dose.[12] Metronomic chemotherapy regimens, including oral cyclophosphamide, have been tested in metastatic breast cancer[13,14] and showed clear antitumour activity with minimal toxicity. Trastuzumab emtansine is an antibody–drug conjugate targeting HER2 by trastuzumab binding, followed by intracellular delivery of the cytotoxic agent emtansine, which has become the standard second-line therapy after the combination of a taxane plus trastuzumab with or without pertuzumab in patients with metastatic breast cancer based on major antitumour activity with minimal toxicity.[15,16] Although the above mentioned regimens without classical chemotherapy are not age-specific, the fact that they are associated with

clear antitumour activity and manageable toxicity makes them suitable for older patients.

One of the major characteristics of older patients with cancer treated in clinical practice is the major heterogeneity observed among patients of the same chronological age. Geriatric assessment is a procedure developed by geriatricians to evaluate older patients' functional and global health status, to identify and manage age-related problems, allowing clinicians to select patients more appropriately for therapy and to avoid futile therapy or overtreatment as well as undertreatment.[17] The present study integrates geriatric assessment to better define the study population, to evaluate the prognostic capacity of geriatric assessment, and to evaluate geriatric functional evolution during therapy.

Given the need to develop new treatment strategies with limited toxicity for older patients with breast cancer, we aimed to examine the safety and activity of dual anti-HER2 treatment with or without metronomic chemotherapy in this population.

Methods

Study design and participants

EORTC 75111-10114 was an open-label, randomised, investigator-initiated, phase 2, selection trial done in 30 centres from eight countries in Europe (appendix p 11).

Eligible patients had histologically proven HER2-positive (immunohistochemistry 3+ [with a score ranging from 0 to 3+] or *HER2* gene amplification by fluorescence, silver, or chromogenic in-situ hybridisation, based on local pathology assessment) metastatic breast cancer, a life expectancy of more than 12 weeks, and a performance status according to WHO scale of 0–3. Patients had not received previous chemotherapy for metastatic disease and were 70 years or older or 60 years or older with functional restriction defined as limitation in at least two of eight Instrumental Activities of Daily Living (IADL), one of six Activities of Daily Living (ADL), or a Charlson Comorbidity Index (CCI) score of more than 2 if they were aged 65–69 years, or a limitation in at least three of eight IADL, two of six ADL, or a CCI of more than 3 if they were aged 60–64 years. Treatment with up to one line of anti-HER2 therapy (trastuzumab or lapatinib) in combination with endocrine therapy (if hormone-sensitive) was allowed. Patients were also required to have measurable disease as per Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST 1.1) or evaluable disease; and a left ventricular ejection fraction (LVEF) of 50% or greater. Patients with a history of significant cardiac disease defined as symptomatic congestive heart failure (classes II–IV according to the New York Heart Association classification) were not eligible for inclusion. Additionally, patients were excluded if they had a history of high-risk uncontrolled arrhythmias (ie, atrial tachycardia with a heart rate >100 beats per min at rest), significant ventricular arrhythmia such as ventricular tachycardia or higher grade atrioventricular block (ie, second degree atrioventricular block type 2 or third degree), history of previous myocardial infarction within 6 months before randomisation, clinically significant valvular heart disease, and angina pectoris requiring treatment. Patients with current, uncontrolled hypertension defined as persistent systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 100 mm Hg, or both, with or without medication were also excluded. Previous exposure to anthracyclines could not exceed 360 mg/m² for doxorubicin or liposomal doxorubicin, 720 mg/m² for epirubicin, 120 mg/m² for mitoxantrone, and 90 mg/m² for idarubicin. In cases where another anthracycline or more than one anthracycline were administered, the cumulative dose could not exceed the equivalent of 360 mg/m². Essential laboratory tests were done to assess an adequate haematological function (defined as an absolute neutrophil count of >1500 cells per mm³, platelet count of >100 000 cells per mm³, and haemoglobin of >85·0 g/L), adequate renal function (defined as glomerular filtration rate ≥30 mL/min), and adequate hepatic function (defined as a total bilirubin of ≤1·5 times the upper limit of normal, and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase concentrations [in the absence of bone metastases] of ≤2·5 times the upper limit of normal).

See Online for appendix

The protocol review committee of the European Organization for Research and Treatment of Cancer (EORTC) and the ethics committee at each participating site approved the study. The study was done in accordance with the protocol, good clinical practice guidelines, and the provisions stated in the Declaration of Helsinki. All patients provided written informed consent. The full protocol is available in the appendix.

Randomisation and masking

Patients were randomised (1:1) to receive either trastuzumab plus pertuzumab or trastuzumab and pertuzumab plus metronomic oral cyclophosphamide. Randomisation was stratified by hormone receptor positivity (oestrogen receptor [ER] or progesterone receptor [PgR] positive, or both ER and PgR positive, *vs* both negative), previous HER2 treatment (none *vs* adjuvant *vs* metastatic), and baseline geriatric screening by G8 geriatric assessment screening tool (G8≤14 *vs* G8>14). The randomisation procedure was centrally generated and transferred by the EORTC online randomisation system on the basis of the minimisation method. Neither patients nor investigators were masked to treatment allocation.

Procedures

Patients received metronomic oral cyclophosphamide 50 mg per day without interruption plus intravenous trastuzumab (loading dose of 8 mg/kg, followed by

6 mg/kg every 3 weeks) and intravenous pertuzumab (loading dose of 840 mg, followed by 420 mg every 3 weeks), or the same dose of trastuzumab and pertuzumab alone until disease progression or unacceptable toxicity. Dose reductions were not allowed. In case of treatment delay of 3 weeks or more, the patient would discontinue the protocol-specified treatment. Tumour evaluation was done every 9 weeks, independently of treatment delays. After disease progression, all patients could be treated as per standard practice at the physician's discretion, but they were also given the option of receiving intravenous trastuzumab emtansine as part of the protocol treatment at the registered dose of 3·6 mg/kg every 3 weeks and continuing tumour evaluation every 9 weeks. Dose reductions were allowed during trastuzumab emtansine treatment (two dose levels from 3·6 mg/kg to 3·0 mg/kg and 2·4 mg/kg). Treatment cycles were defined as a 3-week period. During the study, cardiac monitoring was done with regular evaluation of LVEF every 9 weeks with the same method used at screening. This procedure was repeated if it was clinically indicated at any time during the study. For patients with progressive disease limited to the brain, a protocol amendment implemented in July 4, 2014, allowed continuation on the protocol treatment after local brain therapy.

The geriatric and functional assessments covered in this analysis are the G8 geriatric assessment screening tool (G8),[18] CCI, IADL, ADL, Short Physical Performance Battery (SPPB), social situation, and Geriatric Depression Scale-4 (GDS-4).[19] Quality of life was evaluated by the EORTC Quality of Life Questionnaire Core 30 items version 3.0 (QLQ-C30) and the EORTC Quality of Life Questionnaire Elderly Cancer Patients Core 14 items (QLQ-ELD-14). Assessments were done at baseline, and 9 weeks, 27 weeks, and 1 year after treatment initiation independently of treatment evolution or change. Decline in functionality was defined as at least a 1-point decline in IADL (score range 0–8) or in ADL (score range 0–6) at 1 year after treatment initiation. Geriatric assessment details can be found in the protocol (appendix).

Adverse events were recorded from randomisation until 30 days after the last protocol treatment; thereafter only treatment-related serious adverse events were collected. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, was used for reporting of adverse events. Imaging was done every 9 weeks regardless of drug delays, interruptions, or discontinuations, and response was based on RECIST version 1.1 as assessed by local investigator review. Tumour assessment included an evaluation of all disease sites and a CT or MRI scan of the chest and abdomen. Follow-up for any treatment-related toxicity, LVEF evaluation, geriatric assessment, and quality of life was done 28 days after the last study treatment. After stopping study treatment, patients were followed up for survival assessment every 3 months until death or loss to follow-up.

Outcomes

The primary endpoint was investigator-assessed progression-free survival at 6 months by RECIST version 1.1, defined as the proportion of patients who progressed or died from any cause in 6 months from the date of randomisation. Secondary endpoints were overall survival (defined as the time from the date of randomisation to the date of death from any cause), breast-cancer specific survival (defined as the time from randomisation to the time of death due to breast cancer; deaths from causes other than breast cancer were analysed as competing risks), and the proportion of patients who achieved a tumour response (defined as the proportion of patients with complete or partial response or stable disease as per RECIST 1.1 best response).

Other prespecified exploratory endpoints included the evolution of geriatric assessment during treatment, which used G8, IADL, and ADL scores plus social situation at different timepoints (baseline, 9 weeks, 27 weeks, and 1 year after treatment initiation) regardless of treatment delays, interruption, or drug discontinuation. Decline in functionality was defined as at least a 1-point decline in IADL or at least a 1-point decline in ADL at 1 year after treatment initiation.

Progression-free survival outside the brain was defined similarly to progression-free survival (with brain lesion measurements not taken into account) and calculated from the time of brain-only progression. In the trastuzumab emtansine population, progression-free survival was defined as the time from the start of trastuzumab emtansine treatment to further disease progression or death, and tumour response after starting trastuzumab emtansine was defined as the proportion of patients with complete or partial response or stable disease as per RECIST version 1.1 as best response.

Additional assessments included the predictive value of geriatric assessments for toxicity. Quality of life parameters will be reported elsewhere.

Statistical analysis

The trial followed a Sargent and Goldberg screening design.[20] Both treatment groups were compared for progression-free survival at 6 months with the aim of assessing whether one of the groups seemed superior and promising for further development. If the difference in the estimate of progression-free survival at 6 months was 10% or more, the more promising group would be selected as the most favourable treatment for the primary hypothesis. Assuming that progression-free survival at 6 months for one group is 55%, and for the other group 40%, a sample size of 40 patients per group would result in an estimated probability of selecting the better treatment group of 0·81. With this design, there was a 63·5% chance of observing at least a 10% difference favouring the best regimen.

Efficacy analyses were done on the intention-to-treat population (all randomised patients) and safety analyses

were done on the safety population (all patients who received at least one dose of study treatment). Progression-free survival was summarised by the empirical distribution function for interval censored data.[21] If death or disease progression were observed, the patient was censored on the date of the last follow-up examination. In the case of individual null survival time values, which hinder a correct estimation with the interval-censored method, exclusion of the corresponding patients was applied. Post-hoc sensitivity analyses were done to ensure consistency of the primary results by considering the compromising time values as 0·5 instead of zero. Overall survival was summarised with the Kaplan-Meier approach, while breast-cancer-specific survival referred to the cumulative incidence method with non-breast-cancer-related deaths analysed as competing risks. Responses were calculated according to RECIST version 1.1 on the corresponding per-protocol population (defined as all patients who started their allocated treatment) with measurable disease at baseline. Progression-free survival outside the brain after brain-only relapse was restricted to patients who progressed only in the brain and continued their current treatment (trastuzumab and pertuzumab alone, trastuzumab and pertuzumab plus metronomic oral cyclophosphamide, or trastuzumab emtansine). Evolution of geriatric assessment scores was evaluated through the estimated mean and corresponding 95% CIs at each timepoint. No formal comparative analysis was done.

Multivariable analyses were done on the intention-to-treat population to identify potential prognostic factors related to progression-free survival (interval-censored regression models) and overall survival (Cox regression models). The baseline prognostic factors initially considered were: age, WHO performance status, ER status, PgR status, previous HER2 treatment, organ involvement (lymph nodes, soft tissue, visceral, and skeletal involvement), baseline scores for all geriatric assessments (GDS-4 score, G8 score, CCI score, ADL score, IADL score, SPPB score), and social situation. Factors included in the final multivariable model were identified by a backward selection procedure removing, one at a time, the covariates with a Wald test p value greater than 0·10.

Analyses were done with SAS software, version 9.4.

This trial is registered with ClinicalTrials.gov, number NCT01597414.

Role of the funding source

F Hoffmann-La Roche provided the study drugs and provided financial support, but had no other role in the study. The EORTC as the sponsor of the study was involved in protocol development, data collection, and statistical analysis. The statistician (NT) and KT had full access to the raw data. The first draft of the manuscript was prepared by HW and reviewed by all co-authors and the funder. All authors equally contributed to data collection, data analysis, data interpretation, and writing, reviewing, and approving the final version of the manuscript. The corresponding author had full access to the data and in agreement with the EORTC had final responsibility for the decision to submit for publication.

Results

Between July 2, 2013, and May 10, 2016, 80 patients were enrolled, randomly assigned, and started their allocated

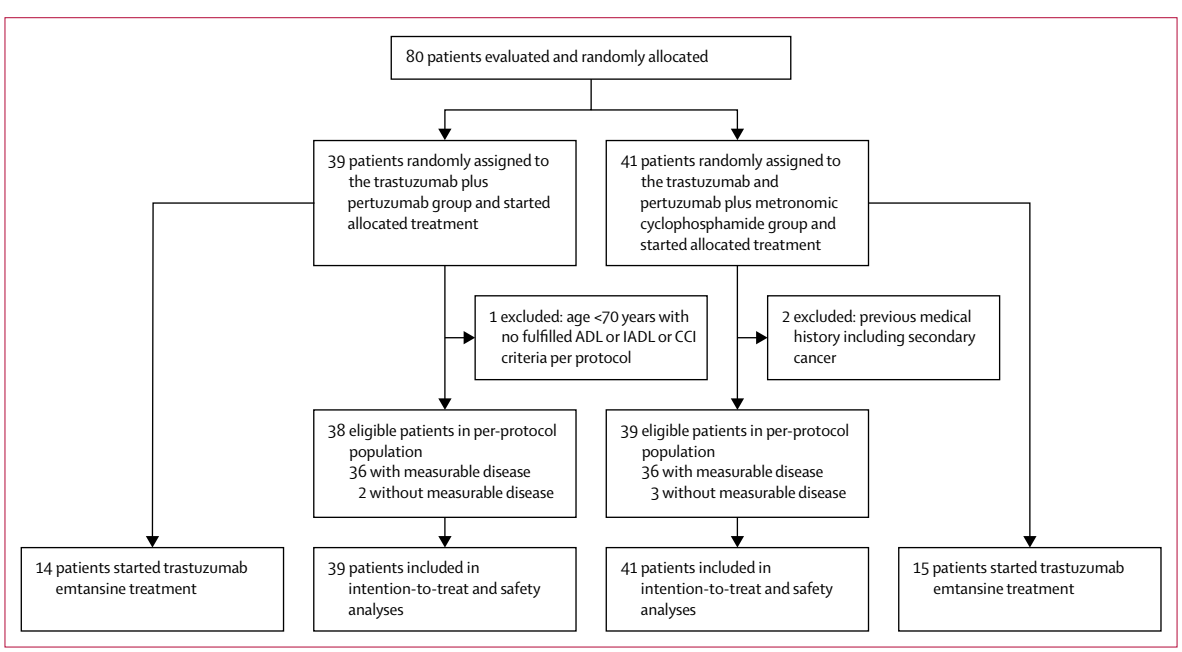

Figure 1: **Trial profile**
ADL=Activities of Daily Living. IADL=Instrumental Activities of Daily Living. CCI=Charlson Comorbidity Index.

	Trastuzumab plus pertuzumab group (n=39)	Trastuzumab and pertuzumab plus metronomic cyclophosphamide group (n=41)
Median age, years (IQR); range	76·2 (71·3–81·4); 61·4–91·4	77·3 (72·8–89·6); 67·7–89·6
WHO performance status (physical examination)		
0	10 (26%)	17 (42%)
1	17 (44%)	17 (42%)
2	8 (21%)	7 (17%)
3	4 (10%)	0
Hormone receptor positivity		
ER-negative and PgR-negative	12 (31%)	13 (32%)
ER-positive or PgR-positive, or both	27 (69%)	28 (68%)
Previous (neo)adjuvant chemotherapy* or anti-HER2 therapy		
No previous line	29 (74%)	35 (88%)
≥1 lines	10 (26%)	5 (13%)
Data missing	0	1
Previous anti-HER2 therapy for metastatic breast cancer		
No	36 (92%)	36 (90%)
Yes	3 (8%)	4 (10%)
Data missing	0	1
Previous adjuvant endocrine therapy		
No	24 (62%)	31 (78%)
Yes	15 (39%)	9 (23%)
Data missing	0	1
Previous endocrine therapy for metastatic breast cancer		
No	33 (87%)	35 (88%)
Yes	5 (13%)	5 (13%)
Data missing	1	1
Previous breast surgery		
No	17 (44%)	22 (54%)
Palliative intent	1 (3%)	2 (5%)
Curative intent	21 (54%)	17 (42%)
Visceral involvement		
No	1 (3%)	4 (10%)
Yes	38 (97%)	36 (90%)
Data missing	0	1
G8 score at baseline		
≤14	28 (72%)	28 (70%)
>14 (normal)	11 (28%)	12 (30%)
Data missing	0	1
CCI score at baseline		
0 (normal)	20 (51%)	27 (68%)
1 or 2	15 (39%)	10 (25%)
>2	4 (10%)	3 (8%)
Data missing	0	1
ADL score at baseline		
≤3	4 (10%)	2 (5%)
4 or 5	9 (23%)	10 (25%)
6 (normal)	26 (67%)	28 (70%)
Data missing	0	1
IADL score at baseline		
≤3	6 (15%)	7 (18%)
4 or 5	7 (18%)	5 (13%)
6–8 (normal)	26 (67%)	28 (70%)
Data missing	0	1
SPPB score at baseline		
Frail (≤7)	20 (59%)	17 (47%)
Pre-frail (8–9)	9 (27%)	11 (31%)
Normal (10–12)	5 (15%)	8 (22%)
Data missing	5	5
Social situation		
At home by myself	14 (38%)	19 (49%)
At home with someone	19 (51%)	19 (49%)
Institutional care	4 (11%)	1 (3%)
Data missing	2	2
GDS-4 score at baseline		
0 (normal)	9 (23%)	16 (41%)
1	12 (31%)	14 (36%)
2	7 (18%)	7 (18%)
3–4	11 (28%)	2 (5%)
Data missing	0	2

Data are n (%) unless otherwise stated. Percentages may not add up to 100% because of rounding. The displayed percentages do not include missing values. ER=oestrogen receptor. PgR=progesterone receptor. G8=G8 geriatric assessment screening tool. CCI=Charlson Comorbidity Index. ADL=Activities of Daily Living. IADL=Instrumental Activities of Daily Living. SPPB=Short Physical Performance Battery. GDS-4=Geriatric Depression Scale 4 items. *With or without anti-HER2 therapy.

Table 1: **Baseline characteristics**

treatment: 39 in the trastuzumab and pertuzumab group and 41 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group (figure 1). Three (4%) of 80 patients were not eligible according to the protocol: two patients because of previous medical history including secondary cancers and one patient younger than 70 years with no fulfilled ADL, IADL, or CCI criteria as per protocol. Baseline characteristics were well balanced between the treatment groups at baseline (table 1). A potential frailty profile was present in 56 (71%) of 79 patients based on geriatric screening with G8 (≤14), and in 57 (81%) of 70 patients based on SPPB (≤9).

The median number of trastuzumab and pertuzumab cycles received was six (range 1–42) in the trastuzumab and pertuzumab group and 13 (1–50) in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group; the median number of metronomic oral cyclophosphamide cycles administered in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group was 13 (1–45; appendix p 3). At the time of clinical

cutoff (Jan 1, 2017), 20 (25%) of 80 patients were still on treatment (nine in the trastuzumab and pertuzumab group and 11 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group). In the trastuzumab and pertuzumab group, 12 (31%) of 39 patients required a trastuzumab and pertuzumab dose delay. In the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group, 16 (39%) of 41 patients required a trastuzumab and pertuzumab dose delay, and 22 (54%) a cyclophosphamide interruption. 29 (36%) of 80 patients received trastuzumab emtansine as second-line treatment, 14 after trastuzumab and pertuzumab and 15 after trastuzumab and pertuzumab plus metronomic oral cyclophosphamide (figure 1); 11 (38%) of 29 patients required dose reduction of trastuzumab emtansine (four previously in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group, seven previously in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group).

Efficacy outcomes are summarised in table 2. In the intention-to-treat population, overall median follow-up was 20·7 months (IQR 12·5–30·4). Estimated progression-free survival at 6 months was 46·2% (95% CI 30·2–60·7) for trastuzumab and pertuzumab versus 73·4% (56·6–84·6) for trastuzumab and pertuzumab plus metronomic oral cyclophosphamide (HR 0·65 [95% CI 0·37–1·12]; p=0·12; figure 2A), leading to a difference of 27·2% with the addition of metronomic oral cyclophosphamide and reaching the 10% difference threshold required by the protocol primary hypothesis. Progression-free survival did not differ significantly between the two groups, but this study design was not powered for a direct treatment comparison. Median progression-free survival is shown in table 2. In the trastuzumab and pertuzumab group, 23 (59%) of 39 patients progressed and four (10%) died without progression. In the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group, 23 (56%) of 41 patients had progressive disease and one (2%) died without progression. One patient from the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group was not included in the progression-free survival analysis because this patient stopped treatment because of an infusion-related reaction and was lost to follow-up at that timepoint, leading to a null survival value, which is not compatible with the interval-censored method. Sensitivity analyses were done by considering the patient as being lost to follow-up at 0·5 days instead of zero— allowing survival function estimation on all patients— and indicated that this exclusion did not change the primary conclusion (appendix p 14).

Overall survival at 1 year was similar between the two groups (83·8% [95% CI 67·3–92·4] for trastuzumab and pertuzumab plus metronomic oral cyclophosphamide *vs* 67·3% [49·4–80·0] for trastuzumab and pertuzumab;

	Trastuzumab plus pertuzumab group	Trastuzumab and pertuzumab plus metronomic cyclophosphamide group
Starting from protocol treatment administration		
Number of patients per group	n=39	n=41
Median follow-up, months (95% CI)	23·1 (3·6–16·8)	16·6 (6·7–24·8)
Progression-free survival status		
Alive (no progression)	12 (31%)	17 (42%)
Progression (followed or not followed by death of any cause)	23 (59%)	23 (56%)
Death without progression	4 (10%)	1 (2%)
Progression-free survival at 6 months* (95% CI)	46·2% (30·2–60·7)	73·4% (56·6–84·6)
Median progression-free survival, months* (95% CI)	5·6 (3·6–16·8)	12·7 (6·7–24·8)
Overall survival status		
Alive	24 (62%)	27 (66%)
Death (all cause)	15 (39%)	14 (34%)
Overall survival at 1 year (95% CI)	67·3% (49·4–80·0)	83·8% (67·3–92·4)
BCSS status		
Alive	24 (62%)	27 (66%)
Death from breast-cancer-specific causes	9 (23%)	11 (27%)
Death from non-breast-cancer causes	6 (15%)	3 (7%)
BCSS cumulative incidence at 1 year (95% CI)	23·4% (8·0–38·7)	16·5% (4·3–28·7)
Response†, n/N	16/36 (44%)	19/36 (53%)
Complete response	1 (3%)	1 (3%)
Partial response	15 (42%)	18 (50%)
Stable disease	12 (33%)	12 (33%)
Progressive disease	4 (11%)	4 (11%)
Early death	2 (6%)	0
Not evaluable	2 (6%)	1 (3%)
Starting from trastuzumab emtansine administration		
Number of patients per group	n=14	n=15
Median follow-up from trastuzumab emtansine administration, months (95% CI)	23·7 (3·5–29·5)	16·3 (8·3–18·4)
Progression-free survival status		
Alive (no progression)	5 (36%)	5 (33%)
Progression (followed or not followed by death of any cause)	7 (50%)	8 (53%)
Death without progression	2 (14%)	2 (13%)
Progression-free survival at 6 months (95% CI)	55·5% (25·7–77·5)	43·9% (18·1–67·3)
Median progression-free survival, months (95% CI)	6·7 (1·8–15·2)	5·0 (2·5–15·9)
Response‡, n/N	2/14 (14·3%)	2/15 (13·3%)
Partial response	2 (14%)	2 (13%)
Stable disease	4 (29%)	3 (20%)
Progressive disease	1 (7%)	0
Early death	7 (50%)	9 (60%)
Not evaluable	0	1 (7%)

Data are n (%), unless otherwise stated. Estimations for progression-free survival were calculated by the interval-censored method, overall survival by use of the Kaplan-Meier method, and breast-cancer-specific survival (BCSS) by use of the cumulative incidence method for competing risks. *One patient in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group was excluded from the interval-censored analysis because she had received trastuzumab and pertuzumab treatment during the first day but immediately stopped because of toxicity and withdrew consent. †On all per-protocol patients with measurable disease at baseline. ‡On all patients who had measurable disease at the start of trastuzumab emtansine administration.

Table 2: **Efficacy outcomes**

HR 0·92 [95% CI 0·44–1·91], p=0·83; table 2, figure 2B), as was breast-cancer-specific survival cumulative incidence at 1 year (23·4% [95% CI 8·0–38·7] for trastuzumab and pertuzumab *vs* 16·5% [4·3–28·7] for trastuzumab and pertuzumab plus metronomic oral cyclophosphamide; HR 1·10 [95% CI 0·47–2·58], p=0·83; table 2; appendix p 8). Of the 15 observed deaths in the trastuzumab and pertuzumab group, nine (60%) were due to breast cancer progression and six (40%) from other causes not related to breast cancer. Of the 14 observed deaths in the trastuzumab and pertuzumab plus metronomic cyclophosphamide group, ten (71%) were due to breast cancer progression, one (7%) due to potential toxicity, and three (21%) from other causes not related to breast cancer.

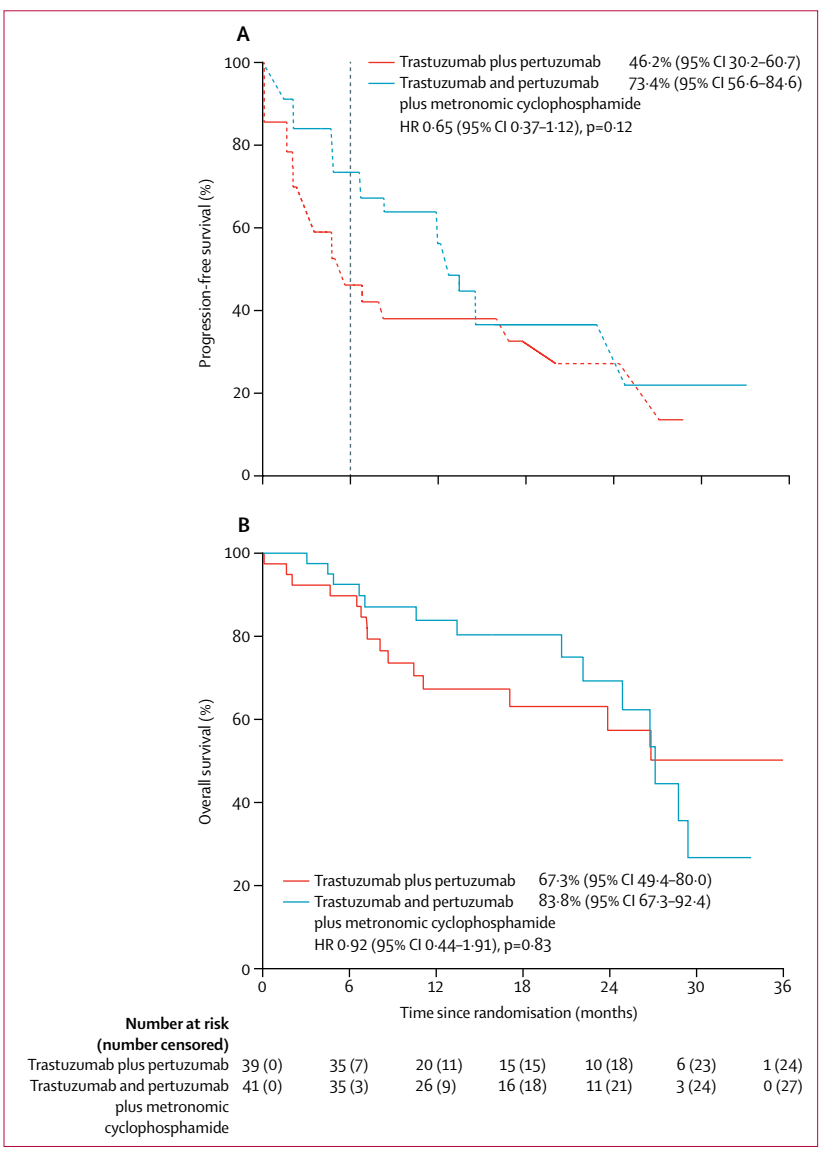

***Figure 2*: Progression-free survival and overall survival**
(A) Ratios correspond to progression-free survival at 6 months (95% CI) as per investigator's assessment. Estimated by use of the interval-censored method, which is unable to display numbers of patients at risk at an exact timepoint. (B) Ratios correspond to overall survival at 1 year (95% CI). HR=hazard ratio.

The proportion of patients who had an overall response among those with measurable disease was 44% (16 of 36) in the trastuzumab and pertuzumab group and 53% (19 of 36) in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group (table 2). One (3%) complete response was achieved in each group.

29 (36%) of 80 patients received trastuzumab emtansine as second-line treatment (14 previously treated in the trastuzumab and pertuzumab group and 15 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group), with an overall progression-free survival at 6 months of 49·5% (95% CI 29·2–66·9) and a median progression-free survival of 5·0 months (95% CI 2·5–12·5) after starting trastuzumab emtansine. The overall response, progression-free survival at 6 months, and median progression-free survival after starting trastuzumab emtansine for patients in each first-line therapy group are shown in table 2. 15 (52%) of 29 patients progressed after trastuzumab emtansine administration, of whom 12 (80%) died afterwards (table 2). Of the 16 patients who died in the trastuzumab emtansine cohort, four (25%) died from causes not related to breast cancer. 17 (37%) of 46 patients who progressed during protocol treatment did not receive subsequent trastuzumab emtansine within the study. Among these 17 patients, 12 (71%) received subsequent antitumour therapies including chemotherapy (n=4, 24%), radiotherapy (n=5, 29%), hormone therapy (n=3, 18%), and targeted therapy (n=5, 29%).

Evolution of geriatric assessment over time is shown in figure 3. Among patients with ADL or IADL information at 1 year, no relevant difference in functional evolution between treatment groups was observed; five (45%) of 11 patients in the trastuzumab and pertuzumab group and seven (39%) of 18 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group had a decline in functionality.

Based on multivariable analyses, the final prognostic factors for progression-free survival were IADL score, lymph node involvement, and skeletal involvement (appendix p 4). The final prognostic factors identified for overall survival were social situation, G8 score, IADL score, and visceral involvement (appendix p 6). G8 score, which was also a stratification factor for this study, was prognostic for both progression-free survival and overall survival (appendix pp 12–13); a high score was found to be associated with favourable overall survival (overall survival at 1 year was 100% with G8 score >14 *vs* 67% [95% CI 52–78] with G8 score ≤14; HR 0·12 [95% CI 0·03–0·55], p=0·01). Further details on the prognostic models are shown in the appendix (pp 4–7, 12–13).

Table 3 shows all grade 4 and 5 adverse events, as well as any grade adverse events in 20% or more patients, during protocol treatment in each group as reported by

investigators. In the safety population, at least one grade 3–5 adverse event was reported during protocol treatment in 21 (54%) of 39 patients in the trastuzumab and pertuzumab group and in 23 (56%) of 41 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group. Nine (23%) of 39 patients in the trastuzumab and pertuzumab group and 18 (44%) of 41 in the trastuzumab and pertuzumab plus metronomic

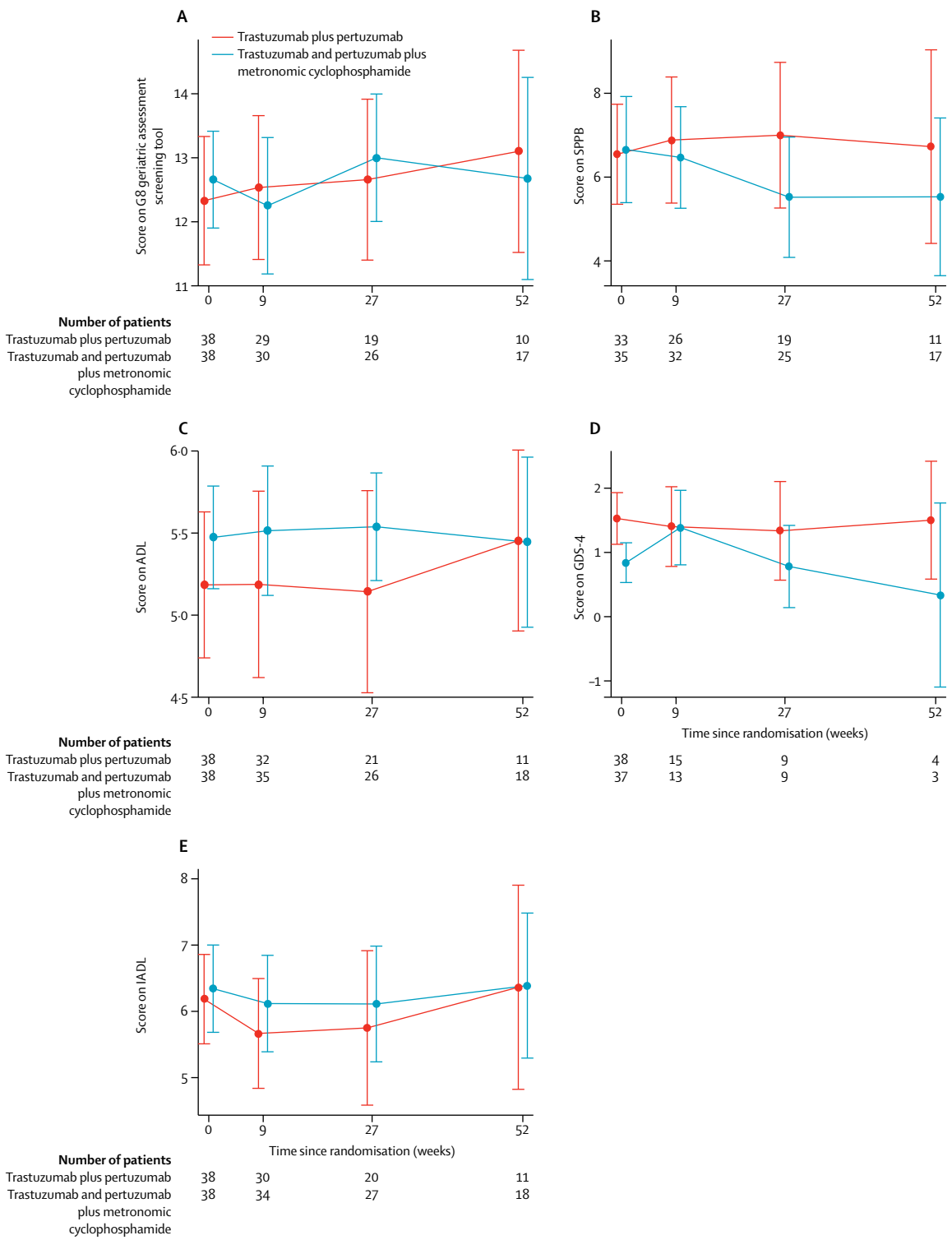

***Figure 3*: Evolution of geriatric assessments by treatment group**
Data are presented as means and error bars are 95% CIs. G8=geriatric assessment screening tool. SPPB=Short Physical Performance Battery. ADL=Activities of Daily Living. GDS-4=Geriatric Depression Scale 4 items. IADL=Instrumental Activities of Daily Living.

	Trastuzumab plus pertuzumab (n=39)					Trastuzumab and pertuzumab plus metronomic cyclophosphamide (n=41)					Trastuzumab emtansine (n=29)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cardiac disorders															
Cardiac arrest	0	0	0	0	1 (3%)	0	0	0	0	0	0	0	0	0	0
Heart failure	0	0	0	0	0	0	0	2 (5%)	0	1 (3%)	0	0	1 (3%)	0	0
Pericardial effusion	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (3%)	0
Pericardial tamponade	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (3%)	0
Gastrointestinal disorders															
Constipation	2 (5%)	0	1 (3%)	0	0	8 (20%)	2 (5%)	0	0	0	4 (14%)	2 (7%)	0	0	0
Diarrhoea	12 (31%)	7 (18%)	4 (10%)	0	0	13 (32%)	11 (27%)	5 (12%)	0	0	5 (17%)	0	1 (3%)	0	0
Oral mucositis	7 (18%)	1 (3%)	0	0	0	5 (12%)	5 (12%)	0	0	0	3 (10%)	0	0	0	0
Nausea	7 (18%)	2 (5%)	0	0	0	16 (39%)	2 (5%)	1 (2%)	0	0	7 (24%)	1 (3%)	0	0	0
General disorders															
Cachexia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (3%)
Fatigue	11 (28%)	11 (28%)	3 (8%)	0	0	18 (44%)	11 (27%)	2 (5%)	0	0	6 (21%)	6 (21%)	2 (7%)	1 (3%)	0
Pain	6 (15%)	1 (3%)	2 (5%)	0	0	9 (22%)	3 (7%)	2 (5%)	0	0	4 (14%)	2 (7%)	0	0	0
Sudden death not otherwise specified	0	0	0	0	1 (3%)	0	0	0	0	0	0	0	0	0	0
Hepatobiliary disorders															
Cholecystitis	0	0	0	0	0	0	0	0	0	0	0	0	1 (3%)	0	0
Hepatic failure	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (3%)	0
Infections and infestations															
Peritoneal infection	0	0	0	0	1 (3%)	0	0	0	0	0	0	0	0	0	0
Skin infection	7 (18%)	0	1 (3%)	0	0	0	1 (2%)	0	0	0	1 (3%)	0	1 (3%)	0	0
Investigations															
Oliguria	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (3%)	0
Metabolism and nutrition disorders															
Anorexia	8 (21%)	3 (8%)	0	0	0	10 (24%)	4 (10%)	2 (5%)	0	0	4 (14%)	3 (10%)	2 (7%)	0	0
Hyperuricaemia	0	0	0	1 (3%)	0	0	0	0	0	0	0	0	0	0	0
Neoplasms benign, malignant, and unspecified															
Myelodysplastic syndrome	0	0	0	0	0	0	0	0	1 (2%)	0	0	0	0	0	0
Nervous system disorders															
Seizure	0	0	0	1 (3%)	0	0	0	0	0	0	0	0	0	0	0
Psychiatric disorders															
Anxiety	2 (5%)	1 (3%)	0	0	0	3 (7%)	1 (2%)	0	1 (2%)	0	0	1 (3%)	0	0	0
Respiratory, thoracic, and mediastinal disorders															
Cough	5 (13%)	1 (3%)	0	0	0	11 (27%)	1 (2%)	0	0	0	0	1 (3%)	0	0	0
Dyspnoea	3 (8%)	2 (5%)	2 (5%)	0	0	4 (10%)	3 (7%)	4 (10%)	0	0	2 (7%)	0	0	1 (3%)	0
Epistaxis	7 (18%)	0	0	0	0	3 (7%)	2 (5%)	0	0	0	5 (17%)	2 (7%)	1 (3%)	0	0
Pleural effusion	1 (3%)	0	2 (5%)	0	0	0	0	1 (2%)	0	0	0	0	0	1 (3%)	0
Pneumonitis	0	0	1 (3%)	0	0	0	0	0	1 (2%)	0	0	0	1 (3%)	0	1 (3%)
Respiratory failure	0	0	0	0	1 (3%)	0	0	0	0	0	0	0	0	0	0

(Table 3 continues on next page)

oral cyclophosphamide group had at least one potential treatment-related grade 3–5 adverse event. In the trastuzumab and pertuzumab group, one patient died during treatment because of cardiac arrest, one died from peritoneal infection, one died from respiratory failure, and one had sudden death without specified cause. In the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group, one patient died from heart failure, which was potentially drug-related. Additional cardiac events were reported in two patients who had a grade 3 heart failure (trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group), two patients with a grade 3 left ventricular systolic dysfunction (one in each group), two patients who developed grade 3 atrial fibrillation (two in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group) and two patients who developed 10% or greater asymptomatic left ventricular ejection fraction decrease to lower than 50% (one in each group). The most frequent grade 3–4 adverse events were hypertension (in six [15%] of 39 patients in the trastuzumab and pertuzumab group *vs* five [12%] of 41 in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group), diarrhoea (four [10%] *vs* five [12%]), dyspnoea (two [5%] *vs* four [10%]), fatigue (three [8%] *vs* two [5%]), pain (two [5%] *vs* two [5%]), and a thromboembolic event (0 [0%] *vs* four [10%]; appendix pp 15–19). Lymphopenia grade 3 or worse was observed in one (3%) patient in the trastuzumab and pertuzumab group versus 15 (37%) in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group. Other grade 3 or worse adverse events reported in at least one patient in both groups were infusion-related reaction, pneumonitis, pleural effusion, urinary tract infection, paresthesia, neurological deficiency, hip fracture, and elevation of the liver enzyme alanine aminotransferase; in the trastuzumab and pertuzumab group only, these were constipation, allergic reaction, bacteraemia, skin infection, hypoglycaemia, seizure, hyperuricaemia, sinus bradycardia, confusion, hallucinations, acute kidney injury, and peripheral ischaemia; and in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group only these were gastroenteritis, myelodysplastic syndrome, muscle weakness of lower limb, bronchial stricture, bronchospasm, anxiety, nausea, aspiration, thoracic pain, anorexia, hyponatraemia, anaemia, and neurological disorders including peripheral motor neuropathy, and cognitive disorders. (appendix pp 15–19). Grade 1–2 adverse events observed during treatment are summarised in the appendix (pp 15–19) and several were considered by the investigators as non-treatment related, since they can be expected in older patients with various comorbidities.

At least one grade 3–5 adverse event was reported in 14 (38%) of 29 patients who received second-line treatment with trastuzumab emtansine. One (3%) patient died because of pneumonitis and one from cachexia. Other grade 3 or worse adverse events reported in more than

	Trastuzumab plus pertuzumab (n=39)					Trastuzumab, pertuzumab plus metronomic cyclophosphamide (n=41)					Trastuzumab emtansine (n=29)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
(Continued from previous page)															
Vascular disorders															
Hypertension	1 (3%)	2 (5%)	6 (15%)	0	0	2 (5%)	2 (5%)	5 (12%)	0	0	0	2 (7%)	0	0	0
Thromboembolic event	0	1 (3%)	0	0	0	0	0	3 (7%)	1 (2%)	0	0	0	1 (3%)	0	0
Laboratory abnormalities															
Alanine aminotransferase*	6 (16%)	2 (5%)	1 (3%)	0	0	7 (18%)	0	1 (3%)	0	0	13 (50%)	0	0	0	0
Aspartate aminotransferase*	10 (27%)	2 (5%)	0	0	0	16 (40%)	1 (3%)	0	0	0	17 (65%)	2 (8%)	0	0	0
Neutropenia*	5 (13%)	1 (3%)	0	0	0	6 (15%)	3 (8%)	0	0	0	5 (19%)	1 (4%)	0	1 (4%)	0
Lymphopenia*	6 (16%)	11 (29%)	1 (3%)	0	0	4 (10%)	17 (43%)	13 (33%)	2 (5%)	0	6 (23)	7 (27%)	3 (12%)	1 (4%)	0
Anaemia*	17 (45%)	3 (8%)	0	0	0	20 (50%)	10 (25%)	1 (3%)	0	0	8 (31%)	7 (27%)	0	0	0
Thrombocytopenia*	4 (11%)	0	0	0	0	7 (18%)	0	0	0	0	9 (35%)	2 (8%)	1 (4%)	0	0

All grade 4 and 5 adverse events, as well as any grade adverse events occurring in 20% or more patients in a specific treatment group or with trastuzumab emtansine are reported as well as laboratory abnormalities. *Because of non-reported laboratory values, missing grades appeared for three patients (two in the trastuzumab plus pertuzumab group, one in the trastuzumab plus pertuzumab plus metronomic cyclophosphamide group) for alanine aminotransferase and aspartate aminotransferase and for two patients (one in the trastuzumab plus pertuzumab group, one in the trastuzumab plus pertuzumab plus metronomic cyclophosphamide group) for neutropenia, lymphopenia, anaemia, and thrombocytopenia during protocol treatment. Missing grades appeared for three patients (two in the trastuzumab plus pertuzumab group, one in the trastuzumab plus pertuzumab plus metronomic cyclophosphamide group) in all laboratory abnormalities during trastuzumab emtansine treatment. Percentages are based on the total number of patients with reported values by group. Two patients developed a ≥10% asymptomatic left ventricular ejection fraction decrease to below 50% (one in each group; not shown).

Table 3: **All grade 4 and 5 adverse events, and all adverse events of any grade in 20% or more patients, occurring during protocol treatment**

one patient during trastuzumab emtansine treatment included lymphopenia (four [15%] of 27 reported laboratory values), fatigue (three [10%] of 29 patients), and anorexia (two [7%] of 29). All other grade 1–3 or worse adverse events reported in these patients are shown in the appendix (pp 15–19).

In 60 (75%) of 80 patients who discontinued protocol treatment, 37 (62%) stopped because of disease progression, nine (15%) because of toxicity, six (10%) because of the patient's decision, three (5%) because of death from other causes, two (3%) because of a secondary malignancy, two (3%) for other reasons, and one (2%) patient was lost to follow-up (appendix p 3).

Toxicity-related reasons for stopping treatment were cardiac (n=2) and diarrhoea (n=1) in the trastuzumab and pertuzumab group, and general decline (n=3), cardiac (n=2), and infusion reaction (n=1) in the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide group. 11 patients (27%) stopped metronomic oral cyclophosphamide definitely before stopping pertuzumab and trastuzumab, because of toxicity (n=8), patient decision (n=1), or unknown reasons (n=2).

Seven (9%) of 80 patients had brain-only relapse during protocol treatment: two (5%) of 39 on trastuzumab and pertuzumab alone, four (10%) of 41 on trastuzumab and pertuzumab plus metronomic oral cyclophosphamide, and one (3%) of 29 on secondary treatment with trastuzumab emtansine (primary therapy trastuzumab plus pertuzumab) who was the only patient to continue current systemic treatment after local brain therapy. No patients permanently discontinued trastuzumab emtansine treatment because of toxicity.

Discussion

Pertuzumab is an approved first-line therapy for patients with HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel. Older patients are at increased risk of chemotherapy-induced toxicity, raising interest in a backbone less toxic than docetaxel, such as metronomic chemotherapy, or chemotherapy-free, dual HER2 blockade regimens. The results of this phase 2 randomised selection study show that the trastuzumab and pertuzumab regimen is active in this setting, with a 6-month progression-free survival of 46·2% (95% CI 30·2–60·7) and median progression-free survival of 5·6 months (95% CI 3·6–16·8). However, the addition of metronomic cyclophosphamide to trastuzumab and pertuzumab increased 6-month progression-free survival to 73·4% (95% CI 56·6–84·6) and median progression-free survival to 12·7 months (6·7–24·8). The study met its primary endpoint, showing a difference of 10% or more in progression-free survival between the two groups. Additionally, subsequent treatment with trastuzumab emtansine in 29 (36%) patients who progressed after trastuzumab and pertuzumab with or without metronomic oral cyclophosphamide was shown to be active and well tolerated, with an overall progression-free survival at 6 months of 49·5% (95% CI 29·2–66·9) and median progression-free survival of 5·0 months (95% CI 2·5–12·5) after starting trastuzumab emtansine.

The results of this study indicate that the benefit of avoiding the side-effects of chemotherapy with the use of dual anti-HER2 blockade only does not compensate for an important loss of activity in the metastatic setting. The trastuzumab plus pertuzumab regimen alone has some antitumour activity, and biomarkers identifying the small subgroup of patients with long-term benefit on this regimen alone would be relevant, but antitumour activity seems to be much higher when chemotherapy—irrespective of type—is added to trastuzumab plus pertuzumab. Metronomic chemotherapy with low-dose cyclophosphamide has been shown to downregulate (immunosuppressive) regulatory T cells,[22] potentially enhancing antibody-dependent cell-mediated cytotoxicity induced by the dual blockade. One could argue that the median progression-free survival of 12·7 months in this study is lower than would be expected compared with the median progression-free survival in the CLEOPATRA study in patients treated with dual HER2 blockage plus docetaxel.[6] However, cross-trial comparisons should be made with caution since patient populations in terms of trastuzumab pre-treatment, age, and levels of frailty were different between the two trials. Of 29 patients who died during first-line protocol treatment, five did so without progression, which also accounts for a progression-free survival event, and occurrence of this type of event is higher in an older study population than in younger cohorts. Moreover, despite the low number of grade 3 toxicity events observed in both groups in this trial, 23 (38%) of 60 patients stopped first-line protocol treatment because of reasons other than progressive disease. In older patients, there could be several reasons for premature treatment withdrawal before progression. Grade 1 or 2 toxicities can be debilitating for older patients;[22] other non-breast-cancer related medical problems might occur and lead to study withdrawal; and there might be social or practical reasons why regular visits to the hospital could become difficult. Therefore, median progression-free survival might be longer with trastuzumab plus pertuzumab and metronomic oral cyclophosphamide in elderly patients capable of continuing the therapy until progression occurs.

The favourable toxicity profile of both trastuzumab and pertuzumab alone and trastuzumab and pertuzumab plus metronomic oral cyclophosphamide are a major asset of these regimens. Quality of life might be even more important than survival duration in older patients. Notably, no grade 3 febrile neutropenia was reported. However, diarrhoea was observed in a high proportion of patients, which might explain some of the premature stopping of trastuzumab and pertuzumab treatment before progression. Continuous grade 1–2 diarrhoea can be debilitating[22] for older patients who are more prone to dehydration, and thus should be followed up more closely

than in younger patients. Notably, toxicity as well as functional and geriatric assessment evolution were similar between both groups; metronomic oral cyclophosphamide therefore seems to increase antitumour activity with limited additional toxicity. An elevated incidence of grade 3–4 lymphopenia (37%) was observed when metronomic oral cyclophosphamide was added, probably related to the effect of cyclophosphamide alone, but it did not have substantial clinical consequences.

The activity and toxicity observed with second-line use of trastuzumab emtansine were as expected from previous studies done in general populations with metastatic breast cancer. No unexpected toxicities have been observed in this older population, making this drug an attractive second-line regimen in this setting.

One of the major strengths of this study was the use of an older population in which clinical frailty was measured and followed up in detail. Most trials in general cohorts include some older patients, but information about the clinical frailty of that sub-population is absent in almost all cases and conclusions made on the basis of these subanalyses cannot be extrapolated to the older population overall. Geriatric assessment in the present study showed a large proportion (more than two-thirds) of potentially frail, older patients in the population enrolled. Unsurprisingly, clinical frailty as estimated by G8 was a strong prognostic factor for overall survival. This kind of tool can thus help clinicians and patients to make individual treatment decisions and future plans. Geriatric evaluation by G8 also allowed stratification of the two groups, avoiding imbalances related to frailty at inclusion. Detailed quality of life analyses and their relation with geriatric evaluation will be reported elsewhere at a later stage.

Unsurprisingly, nine (31%) of 29 observed deaths were not caused by breast cancer. Older people often have comorbidities, as shown by the fact that 32 (41%) of 80 had severe comorbidity according to the CCI score (a score of ≥1), and probably a higher number of patients had other moderate comorbidities not captured by this tool. This finding confirms our hypothesis that starting upfront with less toxic regimens (no classical taxane-based chemotherapy) might delay or even supersede the subsequent use of taxanes in a substantial proportion of older patients.

This study has some limitations. First, this was a selection phase 2 study and further evaluation of trastuzumab and pertuzumab plus metronomic oral cyclophosphamide versus trastuzumab and pertuzumab alone in a randomised phase 3 study is warranted. As such, this study does not provide robust justification for a change in practice. However these findings do give a scientific framework for supporting more specific trials in the older population. We believe a phase 3 trial would be feasible on the basis of the rate of recruitment of our study, which was led in a limited number of centres. Financial support for large phase 3 studies in the older population remains a substantial challenge. The pharmaceutical industry generally does not invest in further development in the more frail or older population after approval of drugs from the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) based on trials in the general population. In some cases, specific trials in older patients might show that new drugs are more harmful than helpful in the older population, being at odds with the classical treatment escalation development model. A second, theoretical, limitation is the absence of a real control group (ie, taxane plus trastuzumab and pertuzumab). Ideally, the trastuzumab and pertuzumab plus metronomic oral cyclophosphamide regimen should be prospectively compared with the current standard treatment in the general population: taxane plus trastuzumab and pertuzumab. However, given the absence of consistency in taking into account age distribution in standard drug development, such a standard control group would be valid only for younger adults or highly selected older adults. In randomised trials of frail, older patients, use of standard treatments as control groups (based on a younger population) could lead to a serious risk of selection bias: physicians, patients, and families can be reluctant to use standard chemotherapy (such as a taxane) for good reasons, and these patients are unlikely to be included in a randomised trial with a possibility of being randomly assigned to receive a taxane. This problem underlines the importance of addressing these issues early in drug development. Older people should be included as much as possible in general population studies, but when the use of standard treatment group becomes challenging or difficult, regulators and developers should recognise the need to design studies with lower intensity treatment groups. Another limitation of this trial was the absence of central review for the primary endpoint and the fact that there was a lot of missing information at the 1-year timepoint in terms of geriatric assessment. Furthermore, only 13% of patients received prior endocrine therapy for metastatic breast cancer before entering the trial, while 69% of tumours were hormone-sensitive. Endocrine therapy alone or with anti-HER2 therapy is not frequently used in HER2-positive metastatic breast cancer, because progression-free survival with this regimen is much shorter than that with docetaxel plus trastuzumab and pertuzumab. Another reason why only a small proportion of the study population received prior endocrine therapy might be that 50 (63%) of 80 patients were recruited in Belgium, where trastuzumab or lapatinib without chemotherapy as first-line therapy are not reimbursed for patients with HER2-positive, hormone-sensitive, metastatic breast cancer, and aromatase inhibitors are only reimbursed after failure of tamoxifen. Oncologists in Belgium thus had the choice of giving first-line tamoxifen (or an aromatase inhibitor in case of contraindication for tamoxifen or progression under tamoxifen), taxane plus trastuzumab and pertuzumab outside of study, or the two treatment regimens within this study.

In conclusion, dual blockade of HER2 plus metronomic chemotherapy seems to provide a better prognosis than HER2 dual blockade alone in an older and frail population with HER2-positive metastatic breast cancer, and has an acceptable safety profile. Trastuzumab and pertuzumab plus metronomic oral cyclophosphamide, potentially followed by trastuzumab emtansine after progression, might delay the need for, or supersede, the use of taxane-based chemotherapy in this population.

Contributors

HW was the coordinator of the EORTC 75111-10114 Elderly Task Force/Breast Cancer Group study and made substantial contributions to the conception and design with the help of EB, FC, KT, and BB. NT, HW, EB, and members from EORTC headquarters developed the methodology. HW, BB, FC, EB, KT, NT, and others from EORTC headquarters wrote the protocol. Statistical analysis, figures, and tables were prepared by NT.

Declaration of interests

HW reports research grants from Roche and personal fees towards his institute from Roche, Amgen, Novartis, Pfizer, Puma, and Celldex. PV reports grants from Roche, outside the submitted work. SW reports non-financial support from Roche Products, during the conduct of the study; personal fees from Eisai; and personal fees and non-financial support from Novartis Pharmaceuticals UK, outside the submitted work. FC reports consulting fees from Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck Sharp & Dohme, Merus BV, Mylan, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, and Teva. All other authors declare no competing interests.

Acknowledgments

In addition to the listed authors, the following principal investigators and participating sites were part of the Elderly Task Force/Breast Cancer Group EORTC 75111-10114 study: Sevilay Altintas (Universitair Ziekenhuis Antwerpen, Belgium), Frank Cornelis (Cliniques Universitaires Saint-Luc, Belgium), Randal D'Hondt (AZ Damiaan, Belgium), Thierry Petit (Centre Paul Strauss, France), Isabelle Desmoulins (Centre Georges-Francois-Leclerc, France), Veronique Servent (Centre Oscar Lambret, France), David Cameron (NHS Lothian—Western General Hospital, UK), Antonio Moreira (IPO Francisco Gentil—Centro De Lisboa, Portugal), Judith R Kroep (Leiden University Medical Centre, Netherlands), Josephine Agnes van de Wouw (VieCuri Medisch Centrum voor Noord-Limburg Locatie Venlo, Netherlands), Zbigniew Nowecki (Maria Sklodowska-Curie Memorial Cancer Centre, Poland), Guy Jerusalem (CHU Sart-Tilman, Belgium), Ellen Copson (University Hospital Southampton NHS Foundation Trust—Southampton General Hospital, UK), Barbro Linderholm (Sahlgrenska Universitetssjukhuset, Sweden), Henrik Lindman (Uppsala University Hospital—Akademiska Sjukhuset, Sweden), Benedicte Petit (Hopital De Jolimont, Belgium), Iain Macpherson (NHS Greater Glasgow and Clyde-Beatson West of Scotland Cancer Centre, Gartnavel General Hospital, UK), Maria Ekholm (Ryhov County Hospital , Sweden), Antonella Brunello (Istituto Oncologico Veneto IRCCS, Italy), Marleen Borms (AZ Groeninge Kortrijk - AZ Groeninge – Oncology Centre, Belgium), Helena Granstam Bjorneklett (Vastmanland Centralsjukhuset Vasteras, Sweden), Ines Deleu (AZ Nikolaas - Campus SM, Belgium), and Karen McAdam (Peterborough and Stamford Hospitals NHS Foundation Trust, Peterborough City Hospital, UK). We thank all the participating patients and their families, sites, and the EORTC Headquarters, with special thanks to all geriatricians and research teams from participating centres involved in the study and to Kim Aalders, Saskia Litière, Coralie Poncet, Bart Meulemans, and Melanie Beauvois for their work on data preparation and analysis. HW is a recipient of a grant of the 'Fonds Voor Wetenschappelijk Onderzoek Vlaanderen' - 1802211N). This publication was supported by Fonds Cancer (FOCA) from Belgium.

References

1 Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127:** 2893–917.
2 Wildiers H, Kunkler I, Biganzoli L, et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol* 2007; **8:** 1101–15.
3 Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* 2012; **13:** 148–60.
4 Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004; **22:** 626–31.
5 Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol* 2003; **21:** 2268–75.
6 Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; **366:** 109–19.
7 von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017; **377:** 122–31.
8 Wildiers H, Highley MS, de Bruijn EA, et al. Pharmacology of anticancer drugs in the elderly population. *Clin Pharmacokinet* 2003; **42:** 1213–42.
9 Loibl S, von Minckwitz G, Harbeck N, et al. Clinical feasibility of (neo)adjuvant taxane-based chemotherapy in older patients: analysis of >4,500 patients from four German randomized breast cancer trials. *Breast Cancer Res* 2008; **10:** R77.
10 Brouwers B, Hatse S, Dal Lago L, et al. The impact of adjuvant chemotherapy in older breast cancer patients on clinical and biological aging parameters. *Oncotarget* 2016; **7:** 29977–88.
11 Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010; **375:** 377–84.
12 Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. *Nat Rev Cancer* 2004; **4:** 423–36.
13 Colleoni M, Orlando L, Sanna G, et al. Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. *Ann Oncol* 2006; **17:** 232–38.
14 Orlando L, Cardillo A, Ghisini R, et al. Trastuzumab in combination with metronomic cyclophosphamide and methotrexate in patients with HER-2 positive metastatic breast cancer. *BMC Cancer* 2005; **6:** 225.
15 Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; **367:** 1783–91.
16 Krop IE, Kim SB, Gonzalez-Martin A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; **15:** 668–89.
17 Wildiers H, Heeren P, Puts M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014; **32:** 2595–603.
18 Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. *Ann Oncol* 2014; **26:** 288–300.
19 Pallis AG, Wedding U, Lacombe D, et al. Questionnaires and instruments for a multidimensional assessment of the older cancer patient: what clinicians need to know? *Eur J Cancer* 2010; **46:** 1019–25.
20 Sargent DJ, Goldberg RM. A flexible design for multiple armed screening trials. *Stat Med* 2001; **20:** 1051–60.
21 Finkelstein DM, Wolfe RA. A semiparametric model for regression analysis of interval-censored failure time data. *Biometrics* 1985; **41:** 933–45.
22 Kalsi T, Babic-Illman G, Fields P, et al. The impact of low-grade toxicity in older people with cancer undergoing chemotherapy. *Br J Cancer* 2014; **111:** 2224–48.