The Breast 64 (2022) 100–111

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Long term outcome data from the EORTC 75111-10114 ETF/BCG randomized phase II study: Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer, followed by T-DM1 after progression☆

Hans Wildiers [a,1,*], Thomas Meyskens [b,1], Sandrine Marréaud [b], Lissandra Dal Lago [c], Peter Vuylsteke [d], Giuseppe Curigliano [e,f], Simon Waters [g], Barbara Brouwers [h], Bart Meulemans [b], Berta Sousa [i], Coralie Poncet [b], Etienne Brain [j]

[a] Department of General Medical Oncology, University Hospitals Leuven and Department of Oncology, KU Leuven, Leuven, Belgium
[b] European Organization for Research and Treatment of Cancer (EORTC) - Headquarters, Brussels, Belgium
[c] Department of Medicine, Institut Jules Bordet, Brussels, Belgium
[d] CHU UCL Namur Sainte Elisabeth, UCLouvain, Namur, Belgium
[e] Division of Early Drug Development, Istituto Europeo di Oncologia, IRCCS, Italy
[f] University of Milano, Milan, Italy
[g] Velindre Cancer Centre, Cardiff, UK
[h] Department of Medical Oncology, AZ Sint-Jan Hospital, Brugge, Belgium
[i] Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal
[j] Department of Medical Oncology, Institut Curie - Hôpital René Huguenin, Saint-Cloud, France

ARTICLE INFO

Keywords:
HER2 positive breast cancer
Older patients
Frail patients
Trastuzumab
Pertuzumab
Metronomic chemotherapy
T-DM1

ABSTRACT

Introduction: Older patients are at higher risk of chemotherapy-induced toxicity, raising interest in less toxic anti-HER2 regimens for older persons with HER2-positive (HER2+) metastatic breast cancer (MBC).
Patients and methods: This phase II study randomized (1:1) patients with HER2+ MBC, aged 70+ or frail 60+, to first line chemotherapy with metronomic oral cyclophosphamide (M) + Trastuzumab (T) and Pertuzumab (P) or TP alone. T-DM1 was offered in case of progression.
Results: In total, 39 and 41 patients were randomized to TP and TPM arm respectively. Median follow-up is 54.0 months. 24-month PFS was 18.7% (95% CI 8.2–32.4) and 28.7% (95% CI 15.8–43.0), respectively. A total of 49 (61.3%) patients died of whom 37 (75.5%) from disease progression; number of deaths per arm was 27 (69.2%) for TP and 22 (53.7%) for TPM. There was no significant difference in OS between the two arms (median OS TP vs TPM: 32.1 vs 37.5 months, p 0.25). Among the 40 patients who have started T-DM1 after disease progression on TP/TPM, PFS rate at 6 months after start of T-DM1 was 43.6% (95% CI: 27.7–58.5) and grade 3 or higher AE occurred in 18 pts (45%).
Conclusions: Metronomic chemotherapy-based dual blockade (TPM), followed by T-DM1 after progression, provides an active and relatively well tolerated treatment option in an older/frail HER2+ MBC population, with a median survival of over 3 years. Nevertheless, the majority of this older/frail population died from breast cancer, highlighting the need for well tolerated and efficacious treatments in these patients.

☆ Twitter handle: @EORTC_BCG

* Corresponding author. Department of General Medical Oncology, University Hospitals Leuven and Department of Oncology, KU Leuven, Herestraat 49, B-Leuven, Belgium.
E-mail address: hans.wildiers@uzleuven.be (H. Wildiers).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.breast.2022.05.004
Received 22 March 2022; Received in revised form 27 April 2022; Accepted 13 May 2022
Available online 20 May 2022

1. Introduction

Approximately one third of all breast cancers are diagnosed in women over 70 years of age. This number is expected to rise due to the increasing life expectancy of the general population [1,2]. More than half of deaths due to breast cancer occur in patients over 65 years of age [3–5].

There is a considerable heterogeneity in the general health status and life expectancy of older patients. Guidelines published by the International Society of Geriatric Oncology (SIOG) recommend screening for frailty in patients aged ≥70 years, and tailoring treatment based on whether patients are grouped as fit, susceptible (pre-frail) or frail [6].

Although the proportion of HER2 positive tumors is generally thought to be lower in older patients, still 10–15% present with breast cancers with HER2 overexpression [7–9]. The prognosis of patients with metastatic HER2+ breast cancer has dramatically improved over the past decade, mainly due to the introduction of more effective HER2-directed therapies [10]. This includes the addition of pertuzumab to trastuzumab and docetaxel as first line treatment and the introduction of trastuzumab emtansine (T-DM1), an antibody drug conjugate targeting HER2, in second and later lines [11–13]. Unfortunately, older women were underrepresented in the pivotal trials for these agents (CLEOPATRA: 16% > 65 y; EMILIA: 14% > 65 y) and those that were included were highly selected and not representative of the wider population of older patients with breast cancer [14].

In the EORTC 75111-10114 study, we investigated the addition of metronomic oral cyclophosphamide to trastuzumab-pertuzumab as first line treatment in older women with HER2+ metastatic breast cancer. The results of the primary analysis have been published previously [15]. The trial met its primary endpoint, with an estimated progression free survival at 6 months of 46·2% (95% CI 30·2–60·7) with trastuzumab and pertuzumab versus 73·4% (56·6–84·6) with trastuzumab and pertuzumab plus cyclophosphamide (hazard ratio [HR] 0·65 [95% CI 0·37–1·12], p = 0·12). Here, we present the final analysis of the long-term outcomes, including outcomes of patients who crossed over on T-DM1 as part of protocol treatment after disease progression on first line treatment.

2. Methods

2.1. Study design and participants

EORTC 75111-10114 was an open-label, 1:1 randomised, investigator-initiated, phase 2, selection trial which involved 30 institutions from eight countries in Europe. The study design has been previously described [15].

Briefly, eligible patients had histologically proven HER2-positive metastatic breast cancer and were either 70 years or older or 60 years or older with functional restrictions according to the Instrumental Activities of Daily Living (IADL), Activities of Daily Living (ADL) or the Charlson Comorbidity Index (CCI) score. Prior chemotherapy for metastatic disease was not allowed, however patients could have received up to one line of anti-HER therapy (trastuzumab or lapatinib) as well as endocrine therapy in case of hormone sensitive metastatic breast cancer.

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; a performance status according to world health organization scale (WHO) of 0–3; a left ventricular ejection fraction (LVEF) of 50% or greater; no history of significant cardiac disease and adequate bone marrow, liver, and renal function.

2.2. Procedures

Patients were randomised 1:1 to receive either 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) (TP) versus the same treatment in combination with metronomic oral cyclophosphamide 50 mg per day without interruption (TPM) until disease progression or unacceptable toxicity. After disease progression, patients were given the option of receiving intravenous trastuzumab emtansine (T-DM1) as part of the protocol treatment at the registered dose of 3·6 mg/kg every 3 weeks. Neither patients nor investigators were masked to treatment allocation.

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. Further procedure information is included in Appendix B.

2.3. Outcomes

The primary endpoint was investigator-assessed progression-free survival at 6 months from the date of randomisation. Other secondary endpoints included overall survival, breast-cancer specific survival and overall response. The purpose of this follow-up analysis is to provide long term follow-up data on the endpoints reported in the primary analysis and to report on endpoints on T-DM1 treatment, including progression free survival on T-DM1 (defined as the time from the start of T-DM1 to further disease progression or death), tumour response on T-DM1 and toxicity. Finally, we also report on prognostic factors. Data on the health related quality of life (HRQoL) are reported separately, based on the database used for the primary analysis [16].

2.4. Statistical analysis

The trial followed a Sargent and Goldberg screening design with 2 arms: TP versus TPM. For the primary analysis, both treatment arms were compared for the progression free survival rate at 6 months, with the aim of assessing whether one of the two treatments seemed superior to the other one. If the difference in estimate of 6-month PFS was 10% or more, the better arm would be selected.

Efficacy analyses were done on the intention-to-treat population (all randomised patients) and safety analyses on the safety population (all patients who received at least one dose of study treatment). Efficacy and safety analyses for T-DM1 were performed in the T-DM1 population (all patients who started T-DM1 as part of protocol treatment).

For this final report, the same statistical analysis plan as for the primary analysis was used including the definition of endpoints and statistical methods. Prognostic factor analysis related to PFS, OS and BCSS were performed on the intention to treat population and included baseline geriatric assessment (G8, IADL, ADL, social situation and SPBB frailty index), together with age, WHO performance status, ER status, PgR status, previous HER2 treatment and organ involvement. Further details on statistical analysis are available in Appendix B.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute).

3. Results

Between July 2, 2013, and May 10, 2016, 80 patients were randomly assigned 1:1 to receive trastuzumab and pertuzumab (n = 39) or trastuzumab and pertuzumab plus metronomic oral cyclophosphamide (n = 41). All patients started their allocated treatment and could thus be analysed for efficacy and safety. After disease progression, 40 patients started T-DM1 as part of the protocol treatment (50%), 18 patients in the TP arm (46.1%) and 22 patients in the TPM arm (53.7%).

At the time of final data cut-off (March 26, 2021), all patients in the TPM group had discontinued their first line treatment, while 1 patient in the TP group remained on treatment. The main reason for treatment discontinuation was progressive disease (65.8% in the TP group and 60.0% in the TPM group). In the T-DM1 population, 1 patient was still on treatment with T-DM1. Most patients in the T-DM1 population discontinued treatment because of progressive disease (71.8%). The

median follow-up from randomisation in the intention to treat population has increased from 20·7 months (IQR: 12·5–30·4) at the time of the primary analysis to 54.0 months (IQR: 39.6–58.2) at final data cut-off. Median follow-up in the T-DM1 population was 33.7 months (IQR: 26.4–38.0) from the start of T-DM1.

Baseline characteristics were generally well balanced between the treatment groups (Table 1). The median age was 76.7 years (range 61.4–91.4), 19 patients had a WHO performance status of 2–3 (23.8%). Geriatric assessment showed a G8-score≤14 in 55 patients (68.8%) and an SBBP score≤9 in 57 patients (71.3%). In patients who discontinued treatment, the median number of cycles of trastuzumab and pertuzumab was 6 in the TP group (range 1–81) and 13.5 in the TPM group (range 1–74). The median number of cycles of cyclophosphamide was 13 in the TPM group (range 1–70) and the median number of cycles of T-DM1 in the T-DM1 population was 7 (range 1–50).

In the updated primary analysis, the estimated progression free survival at 6 months was 43.1% (95% CI 27.1–58.1) in the TP group versus 73.0% (55.8–84.3) in the TPM group, corresponding to a 29.9% absolute difference with the addition of metronomic oral cyclophosphamide and thus still reaching the 10% threshold defined in the protocol. Progression free survival at 12 months was 33.7% (19.3–48.8) in the TP group and 51.9% (34.7–66.5) in the TPM group, while at 24 months this was 18.7% (8.2–32.4) and 28.7% (15.8–43.0) respectively (Fig. 1A). Overall response rate was 44% (16/36) in the TP group and 53% (19/36) in the TPM group, in 72 patients with measurable disease at baseline (Appendix C).

At the time of the final analysis, 27 (69.2%) patients in the TP group had died, in comparison to 22 (53.7%) in the TPM group. Median overall survival was 32.1 months in the TP group and 37.5 months in the TPM group, with no significant difference between the two treatment groups (HR 0.72, 95% CI 0.41–1.26, p = 0.25) (Fig. 1B). Breast cancer specific survival was also similar (HR, 0.92, 95% CI 0.49–1.71) (Appendix D). Amongst the patients who had died, 37 patients (75.5%) died due to disease progression, while the other deaths were attributed to toxicity in one patient (2%), unrelated cardiovascular or other chronic disease in 2 patients (4.1%) and other (non breast cancer related) causes in 7 patients (14.3%).

Table 1
Baseline characteristics.

Baseline characteristics	TP (n = 39)	TPM (n = 41)
Median age, years (range)	76.2 (61.4–91.4)	77.3 (67.7–89.6)
Hormone receptor positivity		
ER and PgR negative	12 (30.8)	13 (31.7)
ER and/or PgR positive	27 (69.2)	28 (68.3)
Prior (neo)adjuvant chemo (±antiHER2) therapy		
No	29 (74.4)	36 (87.8)
Yes	10 (25.6)	5 (12.2)
Prior anti-HER2 therapy for metastatic disease		
No	36 (92.3)	37 (90.2)
Yes	3 (7.7)	4 (9.8)
Visceral involvement		
No	1 (2.6)	4 (9.8)
Yes	38 (97.4)	36 (87.8)
WHO performance status		
0	10 (25.6)	17 (41.5)
1	17 (43.6)	17 (41.5)
2	8 (20.5)	7 (17.1)
3	4 (10.3)	0 (0.0)
G8 score at baseline		
≤14	27 (69.2)	28 (68.3)
>14 (normal)	12 (30.8)	12 (29.3)
Missing	0 (0.0)	1 (2.4)
SPPB score at baseline		
Frail (SPPB≤7)	20 (52.6)	17 (41.5)
Pre-frail (7<SPPB≤9)	9 (23.1)	11 (26.8)
Normal (9<SPPB ≤ 12)	5 (12.8)	8 (19.5)
Unknown	5 (12.8)	5 (12.2)

Data are n (%) unless otherwise stated. TP = trastuzumab, pertuzumab. TPM = trastuzumab, pertuzumab, metronomic cyclophosphamide. ER = oestrogen receptor. PgR = progesterone receptor. HER2 = human Epidermal growth factor receptor 2. G8 = G8 geriatric assessment screening tool. SPPB=Short Physical Performance Battery.

In the patients who started T-DM1, progression free survival was 43.6% (95% CI 27.7–58.5) at 6 months and 34.5% (20.2–49.3) at 12 months (Fig. 2). An objective response was observed in 25% of patients with measurable disease (9/36), all of which were partial responses.

Analysis population restricted to patients who started T-DM1 after disease progression on trastuzumab and pertuzumab with or without metronomic cyclophosphamide (n = 40). Progression-free survival on T-DM1 was estimated by the interval-censored method from the start of T-DM1.

Grade 3-5 adverse events (AE) during first line treatment occurred in 21 (53.8%) patients in the TP group and 24 (58.5%) patients in the TPM group (Table 2). Cardiac toxicity was observed in one (2.6%) patient in the TP group and 4 (9.8%) patients in the TPM group. No new safety signal was detected in comparison to the primary analysis. Three (7.9%) patients in the TP group and 7 (17.5%) patients in the TPM group discontinued treatment because of (non-hematological) toxicity (Appendix E). Additionally, the majority of patients in the TPM group needed a treatment interruption of cyclophosphamide (n = 23, 56.1%), mainly due to non-hematological AE (n = 13, 31.7%) and in 12 patients (29%) cyclophosphamide was discontinued before trastuzumab and pertuzumab.

In the T-DM1 population, grade 3–5 AE were seen in 18 (45%) patients during treatment with T-DM1 (Table 2), with the only toxicities occurring in more than one patient being lymphopenia (n = 6), fatigue (n = 3), anorexia (n = 2), hypertension (n = 2) and AST/ALT increase (n = 2). Two patients (5.1%) experienced a grade 5 AE: one death was considered as related to cachexia and tumour progression; the other to acute pneumonia and renal failure. Treatment interruption occurred in 17 (42.5%) patients, while 12 patients needed at least one dose reduction of T-DM1 (30%). Two patients (5.1%) discontinued T-DM1 due to toxicity.

On multivariate analysis, only the WHO performance status was prognostic for progression free survival (p = 0.037), while the G8 score (p = 0.029) and SPPB score (p = 0.032) were prognostic for overall survival and the G8 score (p = 0.005) and social situation (p = 0.019) for breast cancer specific survival. Details can be found in Appendix F.

4. Discussion

The combination of trastuzumab, pertuzumab and a taxane has been established as the preferred first line treatment for metastatic HER2+ breast cancer since the publication of the CLEOPATRA trial [11]. Although treatment with paclitaxel and docetaxel is generally feasible in fit older patients, it can still be associated with severe acute and long term toxicities, limiting its applicability in those patients that are more frail [14,17]. Alternative treatment options for these patients are needed.

The extended follow-up of the EORTC 75111-10114 trial confirms the activity and safety of a taxane free regimen in this setting, with a greater efficacy when adding metronomic chemotherapy to trastuzumab and pertuzumab in comparison to dual anti-HER2 therapy alone. PFS at 6 months is improved by the addition of metronomic cyclophosphamide, with an absolute difference of almost 30%, and this benefit persists both at 12 and at 24 months. OS and BCSS were similar between both regimens, however it should be noted that this trial was not formally powered for these analyses. Strikingly, even in this generally frail population with multiple comorbidities (41% severe according to the CCI), still the majority of deaths (75.5%) were related to breast cancer, indicating the unmet need for well tolerated and efficacious therapies in this population. Notably, both PFS and OS are lower in the TPM arm than was seen with docetaxel in CLEOPATRA, although cross trial comparisons are difficult since we included a frailer population.

Both regimens were relatively well tolerated, with no apparent

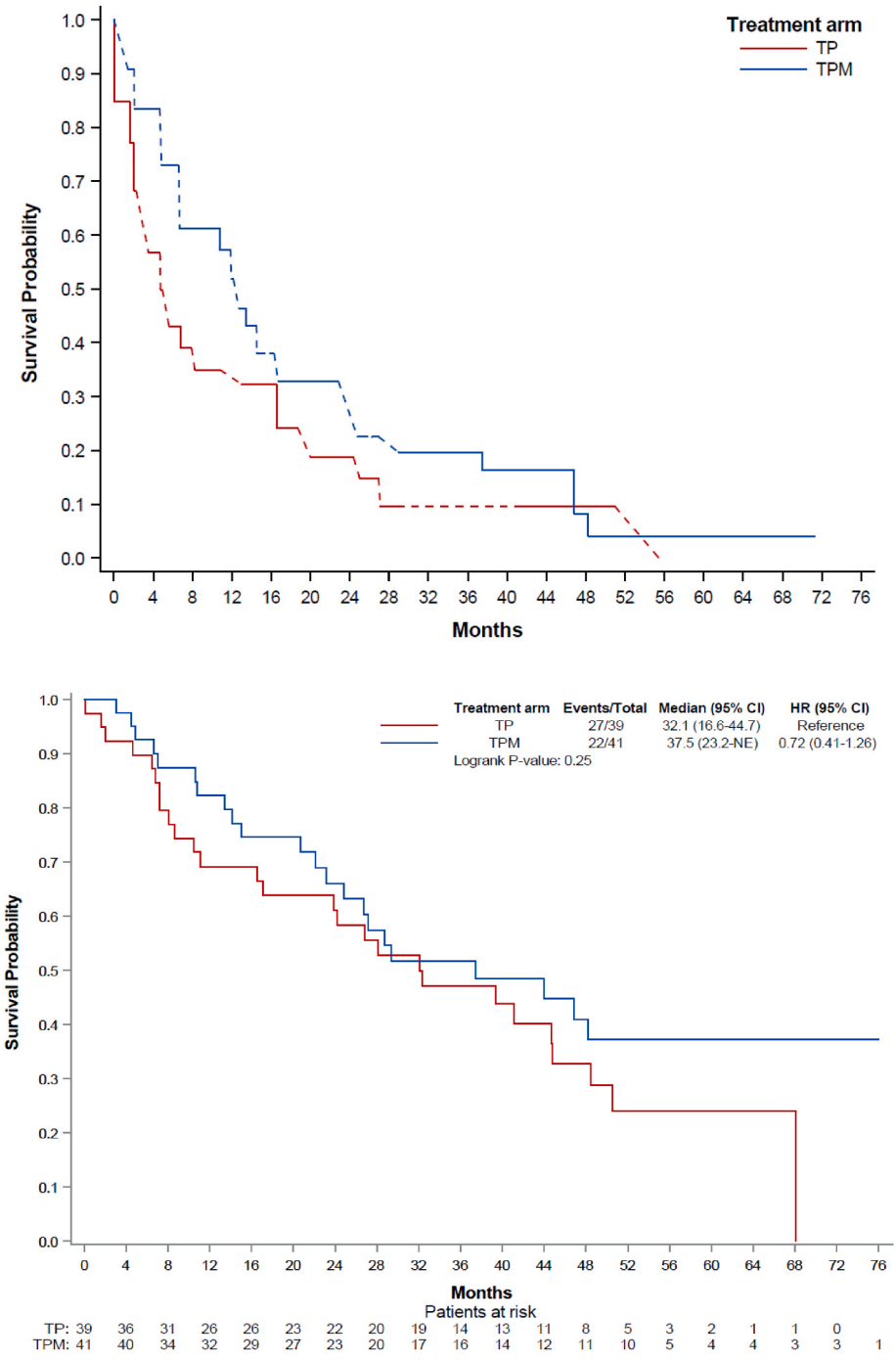


Fig. 1. A. Progression free survival and B. Overall survival after randomisation to trastuzumab/pertuzumab or trastuzumab/pertuzumab with metronomic cyclophosphamide.

increase in high grade toxicity by the addition of metronomic cyclophosphamide. However, premature treatment discontinuation due to toxicity was more frequent in the TPM arm, and a substantial proportion of patients needed at least a temporary interruption of cyclophosphamide. As described in a separate manuscript, HRQoL was similar between the two treatment arms, and so did not appear to be impacted by these interruptions and/or discontinuations [16]. Cardiac toxicity was low, although more frequent in the TPM arm. Cyclophosphamide can cause reversible direct myocardial toxicity and exacerbate underlying myocardial dysfunction, and this risk is greater in older patients [18]. However, this was mainly demonstrated for higher doses of cyclophosphamide (>120–170 mg/kg or 1.55 mg/m2 per day) and has not yet been observed with the metronomic approach.

For patients with ER + HER2+ breast cancer (+- 70% of our population), the addition of an endocrine treatment to dual anti-HER2 blockade could be another alternative to taxane based chemotherapy. This approach has been studied in the PERTAIN trial in an age-unselected population (33% > 65 y), and has shown promising survival outcomes along with manageable toxicity (≥ grade 3 AE in 50.4% of patients for the combination of trastuzumab, pertuzumab and an aromatase inhibitor) [19]. A direct comparison with the results from our trial is again difficult due to differences in patient populations, and as the results of PERTAIN were not known at the time we designed our study, endocrine treatment was not included as a treatment option.

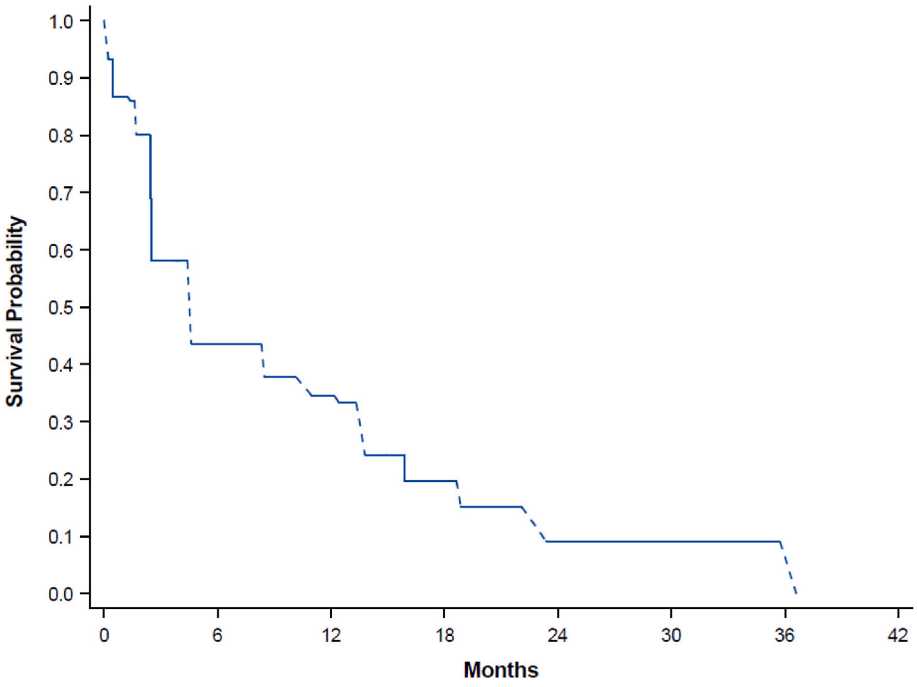


Fig. 2. Progression free survival after starting T-DM1.

Although the efficacy (in terms of PFS) of T-DM1 after disease progression on first line treatment in our population appears slightly lower to what was observed in the pivotal EMILIA trial [12], it is generally in line with the efficacy of T-DM1 in the control arm of more recent trials [20,21]. The rate of grade 3–5 AE we observed was comparable to EMILIA (≥ grade 3 45 vs. 40.8%), with a wide range of AE seen in our trial, also outside those typically associated with T-DM1.

The relatively small sample size is a limitation of this study and highlights the difficulty to set up large randomized phase III trials in an older population. Obstacles are patient and physician worries about trial participation, but certainly also limited financial support by the pharmaceutical industry for trials targeting this specific population. On the other hand, a major strength of our study was that the majority had clear signs of frailty (representing a very poorly studied population), and the long-term follow-up providing insight in death rate and cause of death.

Anticancer drugs are not well tolerated in all older patients with cancer, and extrapolating results from either younger or highly selected fit older patients included in general oncology trials can lead to erroneous conclusions about the safety and efficacy of these treatments in the general older population. Several methods to improve the evidence base for older patients have been suggested. These include study-design elements that promote participation of older adults, such as more inclusive eligibility criteria, and new and composite endpoints relevant to them, for example overall treatment utility [22,23]. Additionally, our study as well as others prove the feasibility of conducting clinical trials specifically in an older frail patient population [24–26]. Moreover, we confirm the prognostic value of geriatric screening instruments in this setting, so that these may potentially be used as stratification factors in future trials.

In conclusion, the combination of trastuzumab-pertuzumab with metronomic cyclophosphamide followed by T-DM1 on progression provides a relatively safe and effective treatment option for HER2+ metastatic breast cancer, especially in frail older patients who might not tolerate a taxane based regimen.

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.

Declaration of interest

- **Hans Wildiers:** Hans Wildiers's institution received financial compensation on his behalf for advisory boards, lecture fees and/or consultancy fees from Immutep Pty, MSD, Astrazenca Ireland, Daiichi, AbbVie, Lilly, PSI CRO AG, KCE, EISAI, Astrazeneca, Roche. Hans Wildiers's institution received an unrestricted research grant on his behalf from Roche and he received travel support from Pfizer and Roche.
- **Thomas Meyskens:** none.
- **Sandrine Marreaud:** none.
- **Lissandra Dal Lago:** Consulting fees from Merck. Educational grants from Novartis, Roche.,
- **Peter Vuylsteke:** Consulting fees from MSD, Roche, Pfizer, Novartis, Lilly, Astra Zeneca. Travel grants from Pfizer, Mundipharma, Roche.
- **Giuseppe Curigliano**: Consulting fees from BMS, Roche, Pfizer, Novartis, Lilly, Astra Zeneca, Daichii Sankyo, Merck, Seagen, Ellipsis.
- **Simon Waters:** none.
- **Barbara Brouwers:** none.
- **Bart Meulemans:** none.
- **Berta Sousa:** none.
- **Coralie Poncet:** none.
- **Etienne Brain**: Receipt of travel supports from Pfizer, Sandoz. Receipt of consultation fees from Daiichi, Eli Lilly, Pfizer, Sandoz. Receipt of honoraria from Eli Lilly, Pfizer, Sandoz, Seagen.

Author contributions

Hans Wildiers: Conceptualization, Methodology, Investigation, Writing – original draft, Supervision, Funding acquisition, **Thomas Meyskens**: Writing – original draft, Visualization, **Sandrine Marréaud**: Methodology, Investigation, Writing – review & editing, Supervision, **Lissandra Dal Lago**: Investigation, Writing – review & editing, **Peter**

Table 2
Toxicity of TPM, TP, and T-DM1.

Toxicity	TP (n = 39)		TPM (n = 41)		T-DM1 (n = 40)	
	All grade	Grade 3-5	All grade	Grade 3-5	All grade	Grade 3-5
All adverse events	39 (97.4)	21 (53.8)	41 (100)	24 (58.5)	35 (87.5)	18 (45)
Gastro-intestinal						
Diarrhea	23 (59)	4 (10.3)	29 (70.7)	5 (12.2)	9 (22.5)	1 (2.5)
Nausea	10 (25.6)	0	20 (48.8)	1 (2.4)	10 (25)	0
Mucositis oral	8 (20.5)	0	10 (24.4)	0	5 (12.5)	0
Constipation	6 (15.4)	1 (2.6)	13 (31.7)	0	10 (25)	0
General disorders						
Fatigue	25 (64.1)	3 (7.7)	33 (80.5)	2 (4.9)	20 (50)	3 (7.5)
Anorexia	14 (35.9)	0	17 (41.5)	2 (4.9)	14 (35)	2 (5)
Pain	10 (25.6)	2 (5.1)	14 (34.1)	2 (4.9)	6 (15)	0
Hypertension	9 (23.1)	6 (15.4)	9 (22)	5 (12.2)	5 (12.5)	2 (5)
Respiratory						
Dyspnea	9 (23.1)	2 (5.1)	12 (29.3)	5 (12.2)	5 (12.5)	1 (2.5)
Epistaxis	8 (20.5)	0	5 (12.2)	0	10 (25)	1 (2.5)
Cough	6 (15.4)	0	13 (31.7)	0	3 (7.5)	0
Liver and kidney function						
AST increase	15 (38.4)	0	18 (43.9)	0	31 (77.5)	1 (2.5)
Serum creatinine increase	13 (33.3)	1 (2.6)	17 (41.5)	0	14 (35)	0
ALT increase	11 (28.2)	1 (2.6)	10 (24.4)	1 (2.4)	21 (52.5)	1 (2.5)
Hematological						
Neutropenia	6 (15.4)	0	9 (21.9)	0	10 (25)	1 (2.5)
Lymphopenia	19 (48.7)	2 (5.1)	36 (87.8)	17 (41.5)	25 (62.5)	6 (15)
Anaemia	22 (56.4)	0	33 (80.5)	1 (2.4)	24 (60)	0
Thrombocytopenia	4 (10.3)	0	8 (19.5)	0	19 (47.5)	1 (2.5)
Special interest						
Heart failure	1 (2.6)		3 (7.3)		0	
Decrease of LVEF (10% and to below 50%)	1 (2.6)		1 (2.4)		0	
Falls	0	0	0	1 (2.4)	4 (10)	1 (2.5)
Peripheral sensory neuropathy	1 (2.6)	0	5 (12.2)	1 (2.4)	2 (5)	0

Data are given as n (%). LVEF = left ventricular ejection fraction. ALT = alanine aminotransferase. AST = aspartate aminotransferase. Adverse events occurring in ≥20% of patients in one treatment group regardless of treatment attribution, as well as adverse events of special interest are described.

Vuylsteke: Investigation, Writing – review & editing, **Giuseppe Curigliano**: Investigation, Writing – review & editing, **Simon Waters**: Investigation, Writing – review & editing, **Barbara Brouwers**: Conceptualization, Methodology, Investigation, Writing – review & editing, **Bart Meulemans**: Data curation, **Berta Sousa**: Investigation, **Coralie Poncet**: Formal analysis, Writing – original draft, Visualization, **Etienne Brain**: Conceptualization, Methodology, Investigation, Writing – review & editing

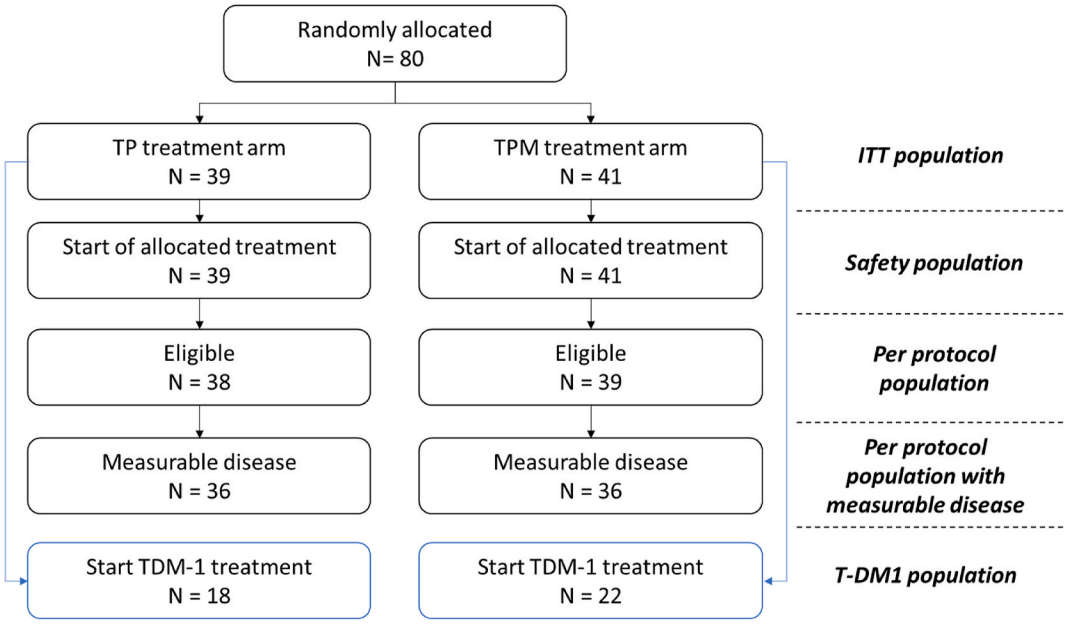
Acknowledgments

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 Bart Meulemans, Melanie Beauvois, Aimé Lambert Uwimana, Taiwo Ajayi and Dunson Ejedepang for their work on data preparation and analysis. Thomas Meyskens, Aimé Lambert Uwimana and Taiwo Ajayi's work as Fellows at EORTC Headquarters was supported by a grant from the EORTC Breast Cancer Group and Dunson Ejedepang's work from the EORTC Lung Cancer Group. We are grateful to F. Hoffmann-La Roche from Switzerland for supporting this study through an educational grant and for providing Trastuzumab, Pertuzumab, and TDM-1 for this study. HW is a recipient of a grant of the 'Fonds Voor Wetenschappelijk Onderzoek Vlaanderen' - 1802211 N). This publication was supported by Fonds Cancer (FOCA) from Belgium.

APPENDIX

.

Appendix A. CONSORT Diagram



Appendix B. Procedures and statistical methods

Procedures.

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. 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.

Statistical methods.

For this final report, the same statistical analysis plan as for the primary analysis was used including the definition of endpoints and statistical methods. PFS was summarized by the empirical distribution function (by treatment arm) for interval censored data. OS was summarized using the Kaplan-Meier method while BCSS was summarized using the cumulative incidence method with non-breast cancer related deaths considered as competing risks.

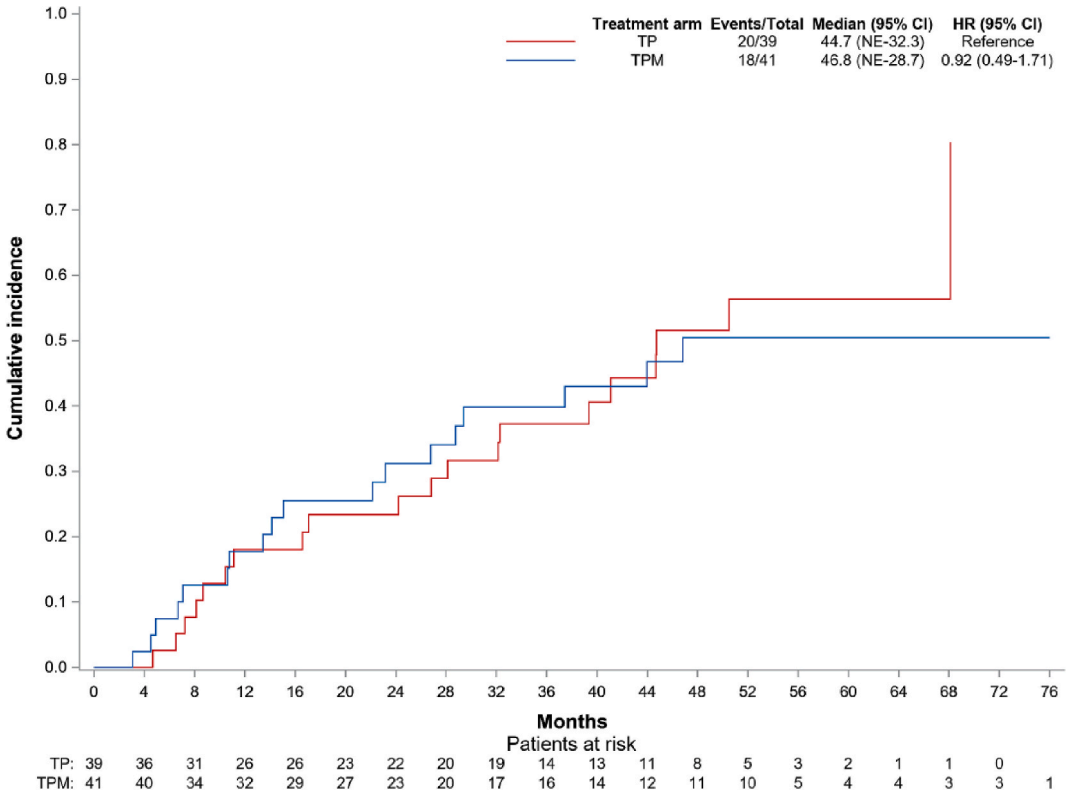
Univariate analyses adjusted for treatment were used to select potential prognostic factors to be entered in the multivariate model at the 10% level. The final multivariate model used a backward variable selection procedure until all remaining factors in the model were significant at 10% level. Treatment was kept in all final multivariate models. The underlying analytical approaches were tailored to the analytical approach used for each endpoint: interval-censored regression model for PFS, Cox regression model for OS and Fine ang Gray model accounting for competing risks for BCSS.

Appendix C. Tumour response

Response rates are calculated on the per protocol population with measurable disease.

Best overall response	TP (n = 36)	TPM (n = 36)	T-DM1 (n = 36)
Complete response	1 (2.8)	1 (2.8)	0
Partial response	15 (41.7)	18 (50.0)	9 (25.0)
Stable disease	12 (33.3)	12 (33.3)	17 (47.2)
Progressive disease	4 (11.1)	4 (11.1)	4 (11.1)
Early death	2 (5.6)	0	3 (8.3)
Not evaluable	2 (5.6)	1 (2.8)	3 (8.3)

Appendix D. Breast cancer specific survival after randomisation to TP or TPM (T = trastuzumab; P = pertuzumab; M = metronomic cyclophosphamide)



Appendix E. Reasons for treatment discontinuation

Main reason for treatment discontinuation	TP (n = 38)	TPM (n = 40)	T-DM1 (n = 39)
Progressive disease	25 (65.8)	24 (60.0)	28 (71.8)
Toxicity	3 (7.9)	7 (17.5)	2 (5.1)
Patient's decision (unrelated to toxicity)	5 (13.2)	4 (10.0)	3 (7.7)
Other malignancy	3 (7.9)	0	0
Death unrelated to malignancy/toxicity	1 (2.6)	2 (5.0)	1 (2.6)
Other	1 (2.6)	2 (5.0)	4 (10.3)
Lost to follow-up	0	1 (2.5)	1 (2.6)

Appendix F. Prognostic factor analyses

These analyses were performed on the intent-to-treat population and included geriatric baseline assessments, together with the usual prognostic factors for metastatic breast cancer.

Prognostic factors for PFS

As a first step, interval censored models for each potential factor were performed adjusting for randomized treatment. All factors which were significant at the 10% level according to the Wald Chi-Square test p-values were kept for the full multivariate prognostic model. Results of the univariate analyses are presented in the table below.

Potential prognostic factors	*P*-value (Wald-test) Adjusted for treatment	Selection for the full multivariate model: 10% threshold (Yes/No)
Age	0.055	**Yes**
WHO performance status	0.037	**Yes**
Estrogen receptor status	0.225	No

(*continued on next page*)

(*continued*)

Potential prognostic factors	*P*-value (Wald-test) Adjusted for treatment	Selection for the full multivariate model: 10% threshold (Yes/No)
Progesteron receptor status	0.503	No
Prior anti-HER2 treatment	0.132	No
Social Situation	0.149	No
GDS-4 score	0.510	No
G8 score	0.231	No
CCI score	0.580	No
ADL score	0.104	No
IADL score	0.055	**Yes**
SPPB score	0.276	No
Lymph node involvement	0.162	No
Soft tissue involvement	0.965	No
Visceral involvement	0.596	No
Skeletal involvement	0.164	No

Among the 80 randomized patients, two patients had missing data on some covariates and were therefore not included in the multivariate models.

A backward model selection procedure was conducted on the ITT cases starting from a full multivariate Interval-Censored regression model using the PFS as outcome and including all the factors retained from the univariate models.

The selection procedure was stopped when all remaining factors in the model are significant at the 10% level according to the Wald Chi-Square test p-values. Treatment variable was retained in the final model regardless of its p-value. Results of the multivariate analysis are presented in the table below.

	Full multivariate interval censored regression model	Backward procedure selection (Yes/No)	Final multivariate interval censored regression model	
	HR (95% CI)		HR (95% CI)	*P*-value (Wald-test)
Treatment				
TP	1.0	**Yes**	1.0	0.085
TPM	0.58 (0.35; 0.96)		0.65 (0.40; 1.06)	
Age category		No		
≤ 69	1.0			
69–75	0.43 (0.15; 1.19)			
≥ 75	0.40 (0.15; 1.03)			
WHO performance status				
0	1.0	**Yes**	1.0	0.037
1	1.73 (0.97; 3.08)		1.74 (0.99; 3.08)	
2–3	1.24 (0.47; 3.25)		2.28 (1.18; 4.38)	
IADL score		No		
≤ 3	1.0			
3–5	0.82 (0.31; 2.20)			
≥ 6	0.48 (0.18; 1.33)			

Only the performance score has a significant effect on progression-free survival (p = 0.037).

Prognostic factors for OS

As a first step, Cox models for each potential factor were performed adjusting for treatment. All factors which were significant at the 10% level according to the Wald Chi-Square test p-values were kept for the full multivariate prognostic model. Results of the univariate analyses are presented in the table below.

Potential prognostic factors	*P*-value (Wald-test) Adjusted for treatment	Selection for the full multivariate model: 10% threshold (Yes/No)
Age	0.705	No
WHO performance status	0.007	**Yes**
Estrogen receptor status	0.188	No
Progesteron receptor status	0.912	No
Prior anti-HER2 treatment	0.018	**Yes**
Social Situation	0.003	**Yes**
GDS-4 score	0.502	No
G8 score	0.002	**Yes**
CCI score	0.019	**Yes**
ADL score	0.135	No
IADL score	0.020	**Yes**
SPPB score	0.001	**Yes**
Lymph node involvement	0.783	No
Soft tissue involvement	0.271	No
Visceral involvement	0.081	**Yes**
Skeletal involvement	0.590	No

Among the 80 randomized patients, two patients had missing data on some covariates and were therefore not included in the multivariate models.

A backward model selection procedure was conducted on the ITT cases starting from a full multivariate Cox model using the OS as outcome and including all the factors retained from the univariate models.

The selection procedure was stopped when all remaining factors in the model are significant at the 10% level according to the Wald Chi-Square test p-values. Treatment variable was retained in the final model regardless of its p-value. Results of the multivariate analysis are presented in the table below.

	Full multivariate Cox regression model	Backward procedure selection (Yes/No)	Final multivariate Cox regression model	
	HR (95% CI)		HR (95% CI)	*P*-value (Wald-test)
Treatment				
TP	1.0	**Yes**	1.0	0.214
TPM	0.75 (0.36; 1.53)		0.69 (0.38; 1.24)	
WHO performance status				
0	1.0	No		
1	0.85 (0.34; 2.16)			
2–3	1.07 (0.25; 4.60)			
Social Situation				
At home by myself	1.0	No		
At home with someone	0.78 (0.37; 1.63)			
Institutional care	0.82 (0.17; 3.99)			
Unknown	7.41 (1.16; 47.94)			
G8 score				
≤ 14	1.0	**Yes**	1.0	0.029
> 14	0.50 (0.18; 1.41)		0.38 (0.16; 0.90)	
Prior anti-HER2 treatment				
None	1.0	No		
Adjuvant/metastatic	1.75 (0.69; 4.45)			
CCI score				
0	1.0	No		
1–2	1.56 (0.77; 3.15)			
> 2	0.59 (0.15; 2.32)			
IADL score				
≤ 3	1.0	No		
3–5	0.62 (0.17; 2.33)			
≥ 6	0.45 (0.12; 1.74)			
SPPB score				
≤ 7	1.0	**Yes**	1.0	0.032
7–9	0.41 (0.15; 1.14)		0.37 (0.15; 0.90)	
9–12	0.82 (0.30; 2.20)		0.67 (0.28; 1.61)	
Unknown	0.61 (0.12; 3.10)		1.92 (0.84; 4.39)	
Visceral involvement				
No	1.0	No		
Yes	1.97 (0.80; 4.82)			

G8 score ($p = 0.029$) and SPPB score ($p = 0.032$) have a significant effect on overall survival.

Breast cancer specific survival

As a first step, Fine and Gray models for each potential factor were performed adjusting for treatment. All factors which were significant at the 10% level according to the Fine and Gray test p-values were kept for the full multivariate prognostic model. Results of the univariate analyses are presented in the table below.

Potential prognostic factors	*P*-value (Fine and Gray) Adjusted for treatment	Selection for the full multivariate model: 10% threshold (Yes/No)
Age	0.449	No
WHO performance status	0.091	**Yes**
Estrogen receptor status	0.123	No
Progesteron receptor status	0.769	No
Prior anti-HER2 treatment	0.106	No
Social Situation	0.0008	**Yes**
GDS-4 score	0.416	No
G8 score	0.002	**Yes**
CCI score	0.752	No
ADL score	0.143	No
IADL score	0.573	No
SPPB score	0.036	**Yes**
Lymph node involvement	0.453	No
Soft tissue involvement	0.108	No
Visceral involvement	0.341	No
Skeletal involvement	0.336	No

Among the 80 randomized patients, two patients had missing data on some covariates and were therefore not included in the multivariate models.

A backward model selection procedure was conducted on the ITT cases starting from a full multivariate Fine and Gray model using the BCSS as

outcome and including all the factors retained from the univariate models.

The selection procedure was stopped when all remaining factors in the model are significant at the 10% level according to the Fine and Gray test p-values. Treatment variable was retained in the final model regardless of its p-value. Results of the multivariate analysis are presented in the table below.

	Full multivariate Fine and Gray regression model	Backward procedure selection (Yes/No)	Final Fine and Gray model	
	HR (95% CI)		HR (95% CI)	*P*-value
Treatment				
TP	1.0		1.0	0.899
TPM	0.97 (0.46, 2.04)		0.96 (0.48; 1.89)	
WHO performance status				
0	1.0	No		
1	0.82 (0.26; 2.60)			
2–3	0.73 (0.16; 3.26)			
Social Situation				
At home by myself	1.0	**Yes**	1.0	0.019
At home with someone	1.04 (0.47; 2.28)		0.99 (0.48; 2.06)	
Institutional care	2.33 (0.82; 6.69)		2.68 (1.31; 5.50)	
Unknown	3.63 (0.52; 25.15)		1.97 (0.24; 16.33)	
G8 score				
≤ 14	1.0	**Yes**	1.0	0.005
> 14	0.27 (0.08; 0.85)		0.24 (0.09; 0.65)	
SPPB score				
≤ 7	1.0	No		
7–9	0.36 (0.09; 1.42)			
9–12	0.72 (0.26; 2.00)			
Unknown	1.10 (0.27; 4.54)			

Social situation **(p = 0.019) and** ***G8 score*** **(p = 0.005)** have a significant effect on breast cancer specific survival.

References

[1] Pilleron S, Sarfati D, Janssen-Heijnen M, Vignat J, Ferlay J, Bray F, et al. Global cancer incidence in older adults, 2012 and 2035: a population-based study. Int J Cancer 2019;144:49–58. https://doi.org/10.1002/ijc.31664.

[2] Aljohar BA, Kilani MA. Breast cancer in europe: epidemiology, risk factors, policies and strategies. A literature review. Global J Health Sci 2018;10:1. https://doi.org/10.5539/gjhs.v10n11p1.

[3] Shachar SS, Hurria A, Muss HB. Breast cancer in women older than 80 years. J Oncol Pract 2016;12:123–32. https://doi.org/10.1200/JOP.2015.010207.

[4] McGuire A, Brown JAL, Malone C, McLaughlin R, Kerin MJ. Effects of age on the detection and management of breast cancer. Cancers 2015;7:908–29. https://doi.org/10.3390/cancers7020815.

[5] DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics. Ca - Cancer J Clin 2019;69:438–51. https://doi.org/10.3322/caac.21583. 2019.

[6] Biganzoli L, Battisti NML, Wildiers H, McCartney A, Colloca G, Kunkler IH, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol 2021;22:e327–40. https://doi.org/10.1016/S1470-2045(20)30741-5.

[7] Laird-Fick HS, Gardiner JC, Tokala H, Patel P, Wei S, Dimitrov NV. HER2 status in elderly women with breast cancer. J Geriatr Oncol 2013;4:362–7. https://doi.org/10.1016/j.jgo.2013.05.007.

[8] Jenkins EO, Deal AM, Anders CK, Prat A, Perou CM, Carey LA, et al. Age-specific changes in intrinsic breast cancer subtypes: a focus on older women. Oncol 2014;19:1076–83. https://doi.org/10.1634/theoncologist.2014-0184.

[9] Van Herck Y, Feyaerts A, Alibhai S, Papamichael D, Decoster L, Lambrechts Y, et al. Is cancer biology different in older patients? Lancet Heal Longev 2021;2:e663–77. https://doi.org/10.1016/s2666-7568(21)00179-3.

[10] Grinda T, Antoine A, Jacot W, Blaye C, Cottu PH, Diéras V, et al. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. ESMO Open 2021;6:100114. https://doi.org/10.1016/j.esmoop.2021.100114.

[11] Swain SM, Baselga J, Kim S-B, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372:724–34. https://doi.org/10.1056/NEJMoa1413513.

[12] Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783–91. https://doi.org/10.1056/NEJMoa1209124.

[13] Krop IE, Kim S-B, Martin AG, LoRusso PM, Ferrero J-M, Badovinac-Crnjevic T, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol 2017;18:743–54. https://doi.org/10.1016/S1470-2045(17)30313-3.

[14] Brain E, Caillet P, de Glas N, Biganzoli L, Cheng K, Lago LD, et al. HER2-targeted treatment for older patients with breast cancer: an expert position paper from the International Society of Geriatric Oncology. J Geriatr Oncol 2019;10:1003–13. https://doi.org/10.1016/j.jgo.2019.06.004.

[15] Wildiers H, Tryfonidis K, Dal Lago L, Vuylsteke P, Curigliano G, Waters S, et al. 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. Lancet Oncol 2018;19:323–36. https://doi.org/10.1016/S1470-2045(18)30083-4.

[16] Dal Lago L, Uwimana AL, Coens C, Vuylsteke P, Curigliano G, Brouwers B, et al. Health-related quality of life in older patients with HER2+ metastatic breast cancer: comparing pertuzumab plus trastuzumab with or without metronomic chemotherapy in a randomised open-label phase II clinical trial. J Geriatr Oncol 2022. https://doi.org/10.1016/j.jgo.2022.01.009.

[17] Biganzoli L, Aapro M, Loibl S, Wildiers H, Brain E. Taxanes in the treatment of breast cancer: have we better defined their role in older patients? A position paper from a SIOG Task Force. Cancer Treat Rev 2016;43:19–26. https://doi.org/10.1016/j.ctrv.2015.11.009.

[18] Page RL, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, et al. Drugs that may cause or exacerbate heart failure. Circulation 2016;134. https://doi.org/10.1161/CIR.0000000000000426.

[19] Rimawi M, Ferrero J-M, de la Haba-Rodriguez J, Poole C, De Placido S, Osborne CK, et al. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2–positive and hormone receptor–positive metastatic or locally advanced breast cancer (PERTAIN): a randomized, open-label phase II tr. J Clin Oncol 2018;36:2826–35. https://doi.org/10.1200/JCO.2017.76.7863.

[20] Emens LA, Esteva FJ, Beresford M, Saura C, De Laurentiis M, Kim S-B, et al. Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial. Lancet Oncol 2020;21:1283–95. https://doi.org/10.1016/S1470-2045(20)30465-4.

[21] Cortés J, Kim S-B, Chung W-P, Im S-A, Park YH, Hegg R, et al. LBA1 Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (Pts) with HER2+ metastatic breast cancer (mBC): results of the randomized phase III DESTINY-Breast03 study. Ann Oncol 2021;32:S1287–8. https://doi.org/10.1016/j.annonc.2021.08.2087.

[22] Bertagnolli MM, Singh H. Treatment of older adults with cancer — addressing gaps in evidence. N Engl J Med 2021;385:1062–5. https://doi.org/10.1056/NEJMp2106089.

[23] Wildiers H, de Glas NA. Anticancer drugs are not well tolerated in all older patients with cancer. Lancet Heal Longev 2020;1:e43–7. https://doi.org/10.1016/S2666-7568(20)30001-5.

[24] Muss HB, Berry DA, Cirrincione CT, Theodoulou M, Mauer AM, Kornblith AB, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 2009;360:2055–65. https://doi.org/10.1056/NEJMoa0810266.
[25] Seymour MT, Thompson LC, Wasan HS, Middleton G, Brewster AE, Shepherd SF, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet 2011;377:1749–59. https://doi.org/10.1016/S0140-6736(11)60399-1.
[26] Hall PS, Swinson D, Waters JS, Wadsley J, Falk S, Roy R, et al. Optimizing chemotherapy for frail and elderly patients (pts) with advanced gastroesophageal cancer (aGOAC): the GO2 phase III trial. J Clin Oncol 2019;37. https://doi.org/10.1200/JCO.2019.37.15_suppl.4006. 4006–4006.