

Randomized Controlled Trial of Trastuzumab With or Without Chemotherapy for HER2-Positive Early Breast Cancer in Older Patients

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abstract

PURPOSE Adjuvant trastuzumab monotherapy has not been compared with trastuzumab + chemotherapy. We investigated the relative value of trastuzumab monotherapy for older patients with breast cancer.

METHODS This study was an open-label, randomized controlled study with a treatment selection design in which a noninferiority criterion was predefined. Patients aged 70-80 years with surgically treated human epidermal growth factor receptor 2–positive invasive breast cancer received trastuzumab monotherapy or trastuzumab + chemotherapy. The primary end point was disease-free survival (DFS) with assessment of prespecified hazard ratio (HR), relapse-free survival (RFS), adverse events (AEs), health-related quality of life (HRQoL), and restricted mean survival time (RMST).

RESULTS The study involved 275 patients (mean age, 73.5 years) who were followed up for a mean of 4.1 years (range, 0.3-8.0 years). The percentages of patients by cancer stage were as follows: I (pT > 0.5 cm), 43.6%; IIA, 41.7%; IIB, 13.5%; and IIIA, 1.1%. Three-year DFS was 89.5% with trastuzumab monotherapy versus 93.8% with trastuzumab + chemotherapy (HR, 1.36; 95% CI, 0.72 to 2.58; *P* = .51). At 3 years, RMST differed by –0.39 months between arms (95% CI, –1.71 to 0.93; *P* = .56). Three-year RFS was 92.4% with trastuzumab monotherapy versus 95.3% with trastuzumab + chemotherapy (HR, 1.33; 95% CI, 0.63 to 2.79; *P* = .53). Common AEs were anorexia (7.4% v 44.3%; *P* < .0001) and alopecia (2.2% v 71.7%; *P* < .0001), and grade 3/4 nonhematologic AEs occurred in 11.9% versus 29.8% (*P* = .0003) for trastuzumab monotherapy versus trastuzumab + chemotherapy, respectively. Clinically meaningful HRQoL deterioration rate showed significant differences at 2 months (31% for trastuzumab monotherapy v 48% for trastuzumab + chemotherapy; *P* = .016) and at 1 year (19% v 38%; *P* = .009).

CONCLUSION The primary objective of noninferiority for trastuzumab monotherapy was not met. However, the observed loss of survival without chemotherapy was < 1 month at 3 years. Therefore, and in light of the lower toxicity and more favorable HRQoL profile, trastuzumab monotherapy can be considered an adjuvant therapy option for selected older patients.

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INTRODUCTION

Trastuzumab with chemotherapy is a standard adjuvant systemic therapy for human epidermal growth factor receptor 2 (HER2)–positive primary breast cancer.¹⁻⁴ Overexpression of HER2 is also associated with potentially more aggressive tumors^{5,6}; consequently, trastuzumab is a key drug for the treatment of HER2-positive primary cancer. Trastuzumab monotherapy used as an adjuvant treatment without chemotherapy avoids toxicity, especially in older patients who are at increased risk of severe chemotherapy-

induced toxicity,⁷⁻⁹ but it is not used in clinical practice, because its benefit has not been investigated.¹⁰ Because even the Early Breast Cancer Trialists' Collaborative Group overview does not arrive at a clear conclusion on the usability of chemotherapy in patients > 70 years of age, due to limited data,¹¹ no standard treatment exists for these patients.

Women in Japan have the highest life expectancy in the world, at 86.8 years.¹² Breast cancer is the most prevalent cancer in women; 95,257 women were diagnosed in 2016, of whom 26.3% were older than

ASSOCIATED CONTENT

Appendix

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To compare trastuzumab with or without chemotherapy in older patients, we carried out a randomized, prospective adjuvant trial comparing trastuzumab monotherapy with trastuzumab + chemotherapy for human epidermal growth factor receptor 2–positive breast cancer, specifically in patients older than 70 years.

Knowledge Generated

The primary objective of noninferiority for trastuzumab monotherapy was not met. However, restricted mean survival time revealed that the observed loss of survival without chemotherapy was < 1 month at 3 years, and health-related quality of life (HRQoL) was better with lower rates of common adverse events.

Relevance

Trastuzumab + chemotherapy remains a standard of care. In patients > 70 years of age who need to avoid chemotherapy because of contraindications or patient preference, especially patients aged > 75 years with performance status 1 disease and estrogen-receptor positivity, we found relatively small influences on chemotherapy effects. With lower toxicity and better HRQoL profile, trastuzumab monotherapy can be a reasonable option for selected older patients with favorable outcomes.

70 years. In the SEER program of the National Cancer Institute, 268,600 women were diagnosed with breast cancer in 2019, of whom 44.1% were > 65 years old. Older adults suffer the majority of cancer diagnoses and deaths, and also make up the majority of cancer survivors; however, the evidence base for treating this population is sparse. ASCO has proposed developing recommendations to improve the evidence base for treating older adults with cancer in response to a critical need.¹³

To address this, we designed a randomized controlled trial to investigate the benefit of trastuzumab monotherapy compared with trastuzumab in combination with chemotherapy on the efficacy, incidence of adverse events (AEs), and quality of life in terms of the noninferiority criterion.

PATIENTS AND METHODS

Patients

The trial protocol is provided in the Data Supplement. We recruited patients aged 70–80 years with HER2-positive breast cancer who had undergone surgery with curative intent. Inclusion criteria comprised the following: invasive breast cancer histologically diagnosed as HER2 positive according to the ASCO and College of American Pathologists guidelines¹⁴; stage I (pathologic tumor size > 0.5 cm), IIA, IIB, or IIIA cancer; and left ventricular ejection fraction (LVEF) ≥ 55%. Other eligibility criteria and exclusion criteria are listed in the Data Supplement.

This study was reviewed and approved by the appropriate independent ethics committees and institutional review boards. This study conformed with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research of Japan's Ministry of Health, Labor, and Welfare. Written informed consent was obtained from all patients. The protocol

was registered at the University Hospital Medical Information Network, Japan (protocol ID: UMIN000002349), on September 1, 2009, and with ClinicalTrials.gov (identifier: [NCT01104935](https://clinicaltrials.gov/ct2/show/study/NCT01104935)) on November 6, 2009.

Trial Design and Oversight

This was an open-label, randomized, parallel group, comparative study with a treatment selection design in which a determining criterion was defined in advance and used to demonstrate clinical benefit between two groups in terms of efficacy. Patients were randomly assigned in a 1:1 ratio to receive either trastuzumab monotherapy or trastuzumab + chemotherapy. Randomization was performed at the data center after confirming patient eligibility with assignment adjustment factors, as follows: age (70–75 v 76–80 years), performance status (0 v 1), hormone receptor status (positive [≥ 10%] v negative), pathologic nodal status (positive v negative), and participating institution.

We hypothesized that (1) trastuzumab monotherapy is not markedly inferior to trastuzumab + chemotherapy in terms of disease-free survival (DFS), and (2) trastuzumab monotherapy is superior in terms of safety and health-related quality of life (HRQoL).

Trastuzumab + chemotherapy treatment comprised a loading dose of trastuzumab at 8 mg/kg and a maintenance dose of 6 mg/kg every 3 weeks for 1 year. Chemotherapy was selected from the following regimens prespecified in the protocol, based on a joint decision by physician and patient:

1. Paclitaxel 80 mg/m² for 12 weeks.
2. Docetaxel 75 mg/m² for 4 cycles.
3. Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² for 4 cycles.

4. Epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² for 4 cycles.
5. Cyclophosphamide 75-100 mg orally, methotrexate 40 mg/m², and 5-fluorouracil 500-600 mg/m² (CMF) intravenously for 6 cycles.
6. Docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² (TC) for 4 cycles.
7. Docetaxel 60-75 mg/m², carboplatin area under the curve 5-6 mg/ml/min trastuzumab loading dose 4 mg/kg, 2 mg/kg (TCbH) for 6 cycles.

Patients treated with trastuzumab monotherapy received the same dose of trastuzumab. Details, including dose modifications, are provided in the protocol (Data Supplement).

End Points

The primary end point was DFS, comparing treatment arms by hazard ratio (HR), and calculating restricted mean survival time (RMST) for each arm as a supplementary analysis. Secondary end points were overall survival (OS), relapse-free survival (RFS), adverse events (AEs), HRQoL, and comprehensive geriatric assessment (CGA).

Assessment

The protocol required assessment of LVEF at registration, every 3 months during trastuzumab administration, and every 6 months after completion of trastuzumab treatment. The HRQoL of the study population was assessed using the Functional Assessment of Cancer Therapy-general (FACT-G) scale at baseline, 2 months, 1 year, and 3 years. FACT-G is a validated, brief yet sensitive, 28-item general cancer HRQoL measure.¹⁵ The analysis of HRQoL was FACT-G total score, and a ≥ 5 -point change from baseline score was considered meaningful.¹⁶ After completion of the protocol treatment, clinical examinations were required at each hospital visit.

Statistical Analysis

The primary end point required 120 events in total, given a power of 80% and a threshold HR of 1.69. Given that the probability of 3 years' DFS in the study population was 68%-72%, and assuming that the survival time follows an exponential distribution, a total of 260 patients registered over 4 years and followed-up for 3 years was necessary to assess 120 events.

To evaluate the clinical position of each treatment, the estimated HR was compared with a threshold HR of 1.69. This threshold for "addition of chemotherapy is determined to be a definite advantage" was based on the results of a questionnaire in advance answered by physicians of this medical field (Data Supplement). The threshold was used to determine whether trastuzumab treatment was definitely equivalent (not inferior) to trastuzumab + chemotherapy with regard to DFS. An upper limit of the 95% CI of the HR for trastuzumab monotherapy relative to trastuzumab + chemotherapy, calculated by applying the proportional

hazards model, not exceeding 1.69, would demonstrate the marked noninferiority of trastuzumab monotherapy, making this a possible treatment option.

In this study, RMST was calculated as a supplementary analysis because blinded annual monitoring on September 1, 2015, showed that the number of events was far fewer than expected, and the statistical power of the noninferiority test based on HR was not assured. The conventional procedure for evaluating long-term treatment effects on survival is the log-rank test and HR. However, if the number of events is too small in a noninferior study to give sufficient information regarding the two treatment arms, RMST can be an option to qualify survival benefit in a comparative oncology clinical study.¹⁷⁻¹⁹ All collected data were analyzed using SAS, version 9.4 (SAS Institute, Cary, NC). Details of the end points, assessment, and the statistical analysis are provided in the Data Supplement.

RESULTS

Patients

The CONSORT diagram is shown in [Figure 1](#). From October 2009 through November 2014, a total of 275 patients aged 70-80 years with HER2-positive invasive breast cancer were enrolled from 99 institutions. Nine patients (3.3%) were excluded, leaving 266 for full-set analysis (trastuzumab monotherapy [$n = 135$] and trastuzumab + chemotherapy [$n = 131$]). Characteristics of the patients at baseline are listed in [Table 1](#). The median age of patients was 73.5 years (range, 70-80 years) and the median follow-up time was 4.1 years (range, 0.3-8.0 years). Most patients (43.6%) had stage I disease, 41.7% had stage IIA, 13.5% had IIB, and 1.1% had IIIA. Chemotherapy regimens were paclitaxel (35.1%), anthracycline (22.9%), CMF (19.8%), docetaxel (14.5%), or TC (3.1%). The relative dose intensity (RDI) values are shown in [Appendix Table A1](#) (online only). The RDI of trastuzumab was 84.4% with trastuzumab monotherapy and 81.8% with trastuzumab + chemotherapy. Concurrent infusion of trastuzumab was allowed when combined with paclitaxel, docetaxel, or CMF, as received by 93.5%, 94.7%, and 46.2% of patients, respectively. Selective estrogen receptor (ER) modulators were administered to 14.2% of patients and aromatase inhibitors were administered to 69.3%. Partial mastectomy was performed in 80 patients (30.0%), of whom 9 received irradiation of the breast.

DFS, RFS, and OS

The data cutoff date was October 31, 2017. The planned analysis showed that 3-year DFS was 89.5% (95% CI, 82.9 to 93.6) with trastuzumab monotherapy versus 93.8% (95% CI, 87.9 to 96.8) with trastuzumab + chemotherapy (HR, 1.36; 95% CI, 0.72 to 2.58; $P = .51$; [Fig 2](#)). The cumulative total number of events in DFS was 18 with trastuzumab monotherapy and 15 with trastuzumab + chemotherapy. Details are listed in [Appendix Table A2](#).

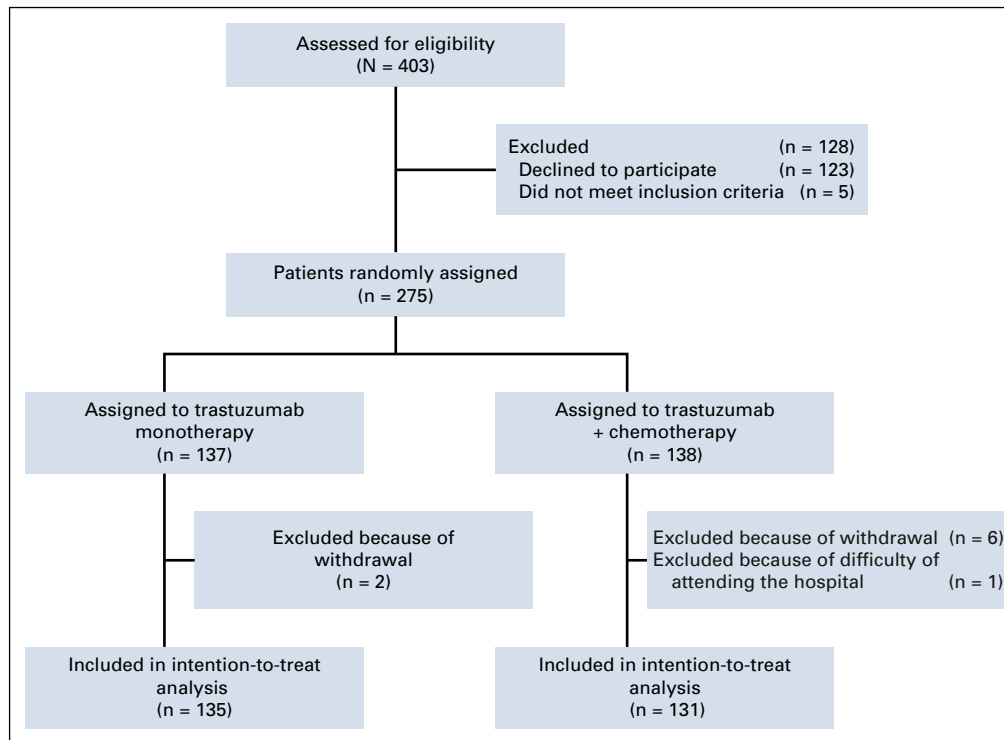


FIG 1. CONSORT diagram for the RESPECT study. Patients were randomly assigned to receive adjuvant treatment either with trastuzumab monotherapy or with trastuzumab + chemotherapy (investigator's selection from regimens specified on the protocol: paclitaxel, docetaxel, doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²; epirubicin 90 mg/m² and cyclophosphamide 600 mg/m²; fluorouracil 500 mg/m², epirubicin 75 mg/m², and cyclophosphamide 500 mg/m²; cyclophosphamide 75-100 mg orally, methotrexate 40 mg/m², and 5-fluorouracil 500-600 mg/m²; docetaxel 75 mg/m² and cyclophosphamide 600 mg/m²; or docetaxel 60-75 mg/m², carboplatin area under the curve 5-6 mg/ml/min, trastuzumab loading dose 4 mg/kg, 2 mg/kg for 6 cycles).

Distant metastasis occurred in nine patients who received trastuzumab monotherapy and eight patients who received trastuzumab + chemotherapy. The posterior probability that the HR was < 1.69 was estimated at 74.5%. The difference in RMST for DFS between the study arms at 3 years was -0.39 months (95% CI, -1.71 to 0.93; $P = .56$). The 3-year RFS was 92.4% (95% CI, 86.3 to 95.8; $n = 17$ events with seven deaths) with trastuzumab monotherapy versus 95.3% (95% CI, 89.7 to 97.8; $n = 12$ events with six deaths) with trastuzumab + chemotherapy (HR, 1.33; 95% CI, 0.63 to 2.79; Fig 3). The difference in RMST for RFS between arms at 3 years was -0.41 months (95% CI, -1.51 to 0.68; $P = .53$). Three-year OS was 97.2% (95% CI, 91.2 to 99.1) with trastuzumab monotherapy versus 96.6% (95% CI, 89.5 to 98.9) with trastuzumab + chemotherapy (HR, 1.07; 95% CI, 0.36 to 3.19; Fig 4). Distant DFS at 3 years was 93.1% with trastuzumab monotherapy versus 96.8% with trastuzumab + chemotherapy (HR, 1.42; 95% CI, 0.64 to 3.17; $P = .39$; Appendix Fig A1, online only). Breast cancer-specific survival at 3 years was 99.2% with trastuzumab monotherapy versus 99.2% with trastuzumab + chemotherapy (HR, 0.20; 95% CI, 0.02 to 1.67; $P = .14$; Appendix Fig A2).

Subgroup analysis of DFS is shown in Table 2. On the basis of the Cox model prespecified subgroup analyses for background or prognostic factors conducted to estimate HR with 95% CI, age > 75 years, performance status 1 (PS1), and ER positivity had relatively small effects on the outcome of chemotherapy, which were not significant.

Safety

All patients who underwent the protocol treatment were included in the safety analysis. Common AEs are listed in Table 3. Common AEs were neutropenia (9.6% with trastuzumab monotherapy v 42.0% with trastuzumab + chemotherapy; $P < .0001$), anorexia (7.4% v 44.3%; $P < .0001$), and alopecia (2.2% v 71.7%; $P < .0001$). No grade 4 hematologic AEs occurred with trastuzumab monotherapy but were reported with trastuzumab + chemotherapy (0% v 13.7%; $P < .0001$). Similarly, some grade 3 or 4 nonhematological AEs occurred with trastuzumab monotherapy but the rate more than doubled with trastuzumab + chemotherapy (11.9% v 29.8%; $P = .0003$). In patients who received the most-used regimen, paclitaxel + trastuzumab, neuropathy-sensory AEs of any grade occurred in 65.2% of patients. No patients discontinued trastuzumab treatment because of toxicity. All serious AEs resolved.

TABLE 1. Baseline Characteristics of the Full Analysis Set (N = 266)

Characteristic	Trastuzumab Monotherapy (n = 135)	Trastuzumab + Chemotherapy (n = 131)	P
Mean age, years (SD)	73.9 (2.8)	73.9 (3.0)	.79
Performance status			.76
0	126 (93.3)	121 (92.4)	
1	9 (6.7)	10 (7.6)	
Pathologic tumor size			.57
T1b	10 (7.4)	11 (8.4)	
T1c	55 (40.7)	54 (41.2)	
T2	64 (47.4)	64 (48.9)	
T3	6 (4.4)	2 (1.5)	
Lymph node metastasis			.39
Negative	111 (82.2)	103 (78.6)	
Positive	23 (17.0)	24 (18.4)	
Unknown	1 (0.7)	4 (3.1)	
Stage			.8
I	58 (43.0)	58 (44.3)	
IIA	56 (41.5)	55 (42.0)	
IIB	20 (14.8)	16 (12.2)	
IIIA	1 (0.7)	2 (1.5)	
Surgery			.2
Mastectomy	97 (71.9)	87 (66.4)	
Partial mastectomy	36 (26.7)	44 (33.6)	
Others	2 (1.5)	0 (0.0)	
Hormone receptor status			.55
ER+ and/or PgR+	62 (45.9)	65 (49.6)	
ER– and PgR–	73 (54.1)	66 (50.4)	
Major comorbidity			
Hypertension			.83
Absent	76 (56.3)	72 (55.0)	
Present	59 (43.7)	59 (45.0)	
Diabetes			.52
Absent	119 (88.1)	112 (85.5)	
Present	16 (11.9)	19 (14.5)	
Osteoporosis			.13
Absent	117 (86.7)	121 (92.4)	
Present	18 (13.3)	10 (7.6)	
Hyperlipidemia			.67
Absent	101 (74.8)	95 (72.5)	
Present	34 (25.2)	36 (27.5)	

NOTE. Data presented as No. (%).

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; SD, standard deviation.

LVEF decreases occurred in 11 patients (8.1%) in the trastuzumab monotherapy group and in nine patients (6.8%) in the trastuzumab + chemotherapy group ($P = .647$).

All patients recovered after appropriate medication containing a diuretic agent. Hypertension of grade 3/4 occurred in five patients (3.7%) who received trastuzumab monotherapy and nine patients (6.9%) who received trastuzumab + chemotherapy ($P = .043$). No congestive heart failure (CHF) occurred in either group.

HRQoL

Among study patients, 116 who received trastuzumab monotherapy and 115 who received trastuzumab + chemotherapy who achieved the baseline response were analyzed. We detected a significant difference between treatment groups in clinically meaningful HRQoL deterioration rate using the FACT-G at 2 months (31% for trastuzumab monotherapy ν 48% for trastuzumab + chemotherapy; $P = .016$), and at 1 year (19% ν 38%; $P = .009$), and in clinically meaningful HRQoL improvement rate at 2 months (38% for trastuzumab monotherapy ν 15% for trastuzumab + chemotherapy; $P < .01$), and at 1 year (43% ν 25%; $P = .021$). There was no significant difference between the two arms at 3 years.

DISCUSSION

To our knowledge, this is the first randomized prospective adjuvant trial to compare trastuzumab monotherapy with trastuzumab + chemotherapy for HER2-positive breast cancer. The primary end point was not met on HR, although prespecified analysis was performed supplementary to investigation of RMST. To our knowledge, it is also the first study to specifically enroll patients older than 70 years. DFS at 3 years was 93.8% in the trastuzumab + chemotherapy group but 89.5% with less toxicity and a better HRQoL profile in the trastuzumab monotherapy group.

Trastuzumab without chemotherapy has not been assessed in the adjuvant setting, as far as we are aware. In the metastatic setting, trastuzumab monotherapy has efficacy with low toxicity,^{20,21} although combination chemotherapy with trastuzumab is generally preferred.²² In the neoadjuvant setting, trastuzumab + pertuzumab without chemotherapy was tested, but chemotherapy was administered after surgery.²³

With regard to trastuzumab AEs, cardiac dysfunction and CHF have been reported.²⁴⁻²⁶ A long-term assessment found that the incidence of decreased LVEF was 3.6%, whereas that of severe CHF was 0.8%.²⁷ The cardiac event rate was highest in patients who received anthracycline (1.9%-3.8%)²⁸ and lowest in patients who received a TCbH regimen (0.4%).⁴ Independent predictors of cardiac events were age > 50 years and a low LVEF.²⁹ Among older patients, a systematic review indicated that cardiac events occurred in 5% of patients.³⁰ A large observational study indicated that the risk of cardiac function toxicity was 5.7%³¹ and that this risk was associated with age,^{31,32} although it remained manageable³¹ and the risks associated with trastuzumab were outweighed by the benefits.^{30,31} In our

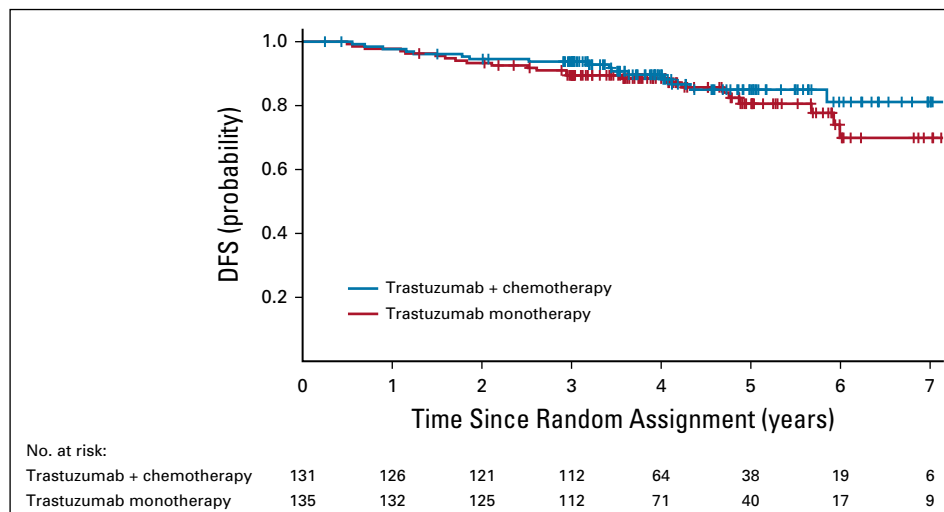


FIG 2. Kaplan-Meier estimates of disease-free survival (DFS). DFS at 3 years was 89.5% (95% CI, 82.9 to 93.6) in the trastuzumab monotherapy group versus 93.8% (95% CI, 87.9 to 96.8) in the trastuzumab + chemotherapy group (HR, 1.36; 95% CI, 0.72 to 2.58; $P = .51$). The difference in restricted mean survival time for DFS between the study arms at 3 years was -0.39 months (95% CI, -1.71 to 0.93 ; $P = .56$). Tick marks indicate censored data.

trial, cardiac events occurred in 7.5% of patients, but because this was a prospective study, LVEF was routinely evaluated and, as a result, decreases in LVEF were detected, and no CHF occurred. Our results thus provide safety data on trastuzumab with or without chemotherapy for older patients.

In older patients, HRQoL is important in addition to the incidence of AEs, because chemotherapy causes significant deterioration of HRQoL.³³ The European Society for Medical Oncology proposed a Clinical Benefit Scale incorporating toxicity and HRQoL as outcomes of living better with adjuvant therapy,³⁴ although there is no definitive consensus on how to assess and interpret risks and benefits. The findings of our study on short-term toxicity and the impact on HRQoL are useful for treatment selection in older patients. Older adults do not differ from their younger counterparts regarding chemotherapy acceptance, but

they do differ in terms of willingness to trade survival for current QoL.³⁵ Consequently, HRQoL deterioration, even if temporary, is important when deciding whether to receive chemotherapy. In our trial, the upper threshold of HR of 1.69, an inferior margin defined in advance, was set based on a questionnaire among physicians, because older patients may not accept a small absolute benefit if treatment carries a high risk of AEs, loss of independence, and cognitive impairment.

For a more definitive answer to anti-HER2 therapy without chemotherapy, biomarkers will be important in selecting a suitable population to optimize benefit. Meanwhile, we await the results from other studies of de-escalation. In the ATEMPT trial comparing paclitaxel + trastuzumab with trastuzumab emtansine (T-DM1), the latter was associated with a low rate of recurrence, although it did not meet the preplanned relative reduction in toxicity.³⁶ The ATOP trial

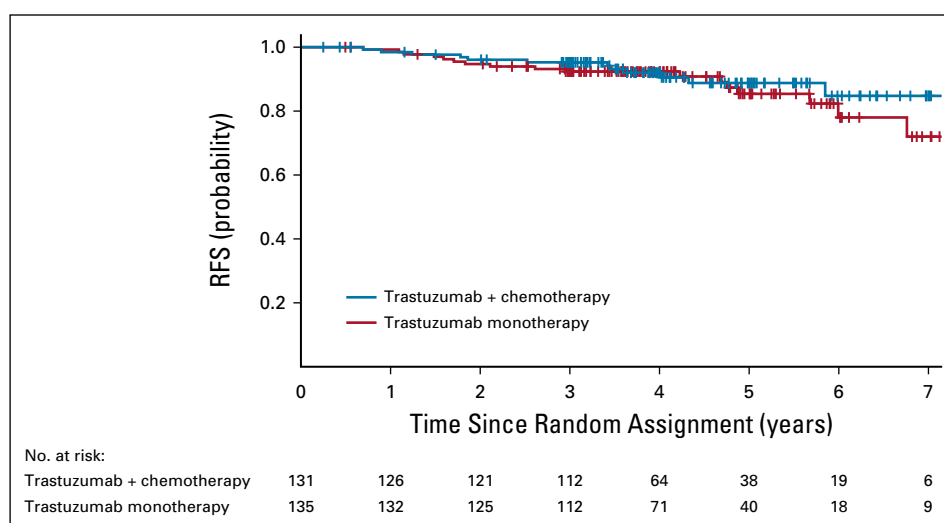


FIG 3. Kaplan-Meier estimates of relapse-free survival (RFS). RFS at 3 years was 92.4% (95% CI, 86.3 to 95.8, 17 events with seven deaths) in the trastuzumab monotherapy group versus 95.3% (95% CI, 89.7 to 97.8, 12 events with six deaths) in the trastuzumab + chemotherapy group (HR = 1.33; 95% CI, 0.63 to 2.79). The difference in restricted mean survival time for RFS between the study arms at 3 years was -0.41 months (95% CI, -1.51 to 0.68 ; $P = .53$). Tick marks indicate censored data.

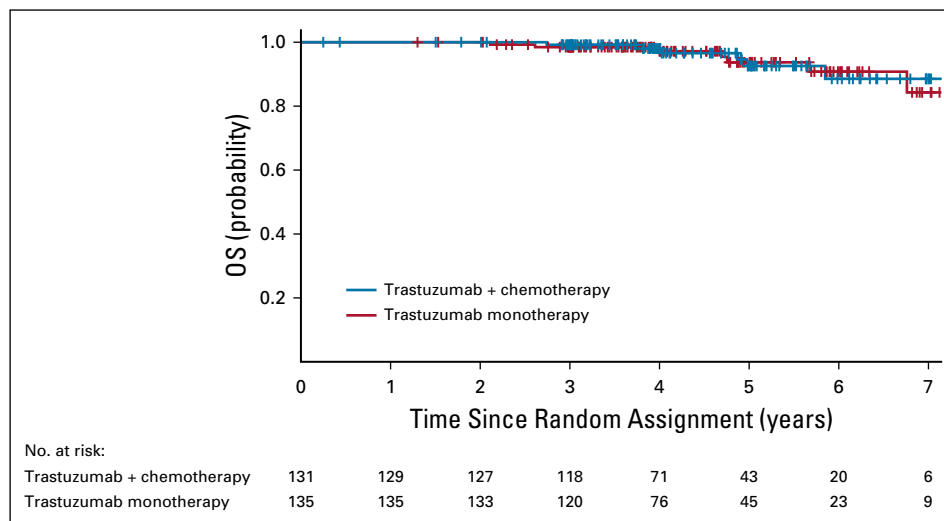


FIG 4. Kaplan-Meier estimates of overall survival (OS). OS at 3 years was 97.2% (95% CI, 91.2 to 99.1) in the trastuzumab monotherapy group versus 96.6% (95% CI, 89.53 to 98.9) in the trastuzumab + chemotherapy group (HR, 1.07; 95% CI, 0.36 to 3.19). Tick marks indicate censored data.

(ClinicalTrials.gov identifier: [NCT03587740](https://clinicaltrials.gov/ct2/show/study/NCT03587740)) is a single-arm study of T-DM1 in patients > 60 years of age. Short duration of trastuzumab combined with chemotherapy was associated with worse outcome despite a favorable cardiotoxicity.³⁷ In our subgroup analysis, we found age > 75 years, PS1, and ER positivity had relatively small influences on the effects of chemotherapy. There might be a difference in the impact of chemotherapy between pure-HER2 and luminal-HER2 type,²³ and ER positivity affected

the timing of DFS events and patterns, providing prognostic information.³⁸

Limitations of this study include, first, that although 266 patients were treated according to the protocol, the primary end point was not met on HR, because of the low numbers of events consequent to an underpowered analysis. As a result, no definitive conclusions regarding trastuzumab without chemotherapy in this setting can be made. The prognosis of patients in both arms was better than expected

TABLE 2. Subgroup Analysis of Disease-Free Survival

Subgroup	Treatment	No. of Patients	No. of Events (%)	Hazard Ratio	95% CI		P
					Upper	Lower	
Age group, years							
70-75	Trastuzumab monotherapy	96	14 (14.6)	1.85	0.75	4.58	.31
	Trastuzumab + chemotherapy	89	7 (7.9)				
76-80	Trastuzumab monotherapy	39	9 (23.1)	1.04	0.41	2.61	.94
	Trastuzumab + chemotherapy	42	9 (21.4)				
Performance status							
0	Trastuzumab monotherapy	126	22 (17.5)	1.62	0.81	3.21	.17
	Trastuzumab + chemotherapy	121	13 (10.7)				
1	Trastuzumab monotherapy	9	1 (11.1)	0.32	0.03	3.09	.32
	Trastuzumab + chemotherapy	10	3 (30.0)				
Lymph node metastasis							
Negative	Trastuzumab monotherapy	106	18 (17.0)	1.62	0.75	3.52	.22
	Trastuzumab + chemotherapy	97	10 (10.3)				
Positive	Trastuzumab monotherapy	29	5 (17.2)	0.91	0.28	2.99	.87
	Trastuzumab + chemotherapy	34	6 (17.6)				
Hormone receptor							
Positive	Trastuzumab monotherapy	62	9 (14.5)	1.19	0.44	3.19	.74
	Trastuzumab + chemotherapy	65	7 (10.8)				
Negative	Trastuzumab monotherapy	73	14 (19.2)	1.48	0.64	3.43	.36
	Trastuzumab + chemotherapy	66	9 (13.6)				

TABLE 3. Common Adverse Events in All Patients (N = 266)

Adverse Event	Trastuzumab Monotherapy AE Grade (n = 135)					Trastuzumab + Chemotherapy AE Grade (n = 131)					P
	1	2	3	4	3 or 4	1	2	3	4	3 or 4	
	No. of Patients					%	No. of Patients				
Hematologic											
Neutrophils	6	7	0	0	0.0	7	25	9	14	17.6	< .0001
Leukocytes	15	10	0	0	0.0	21	29	12	8	15.3	< .0001
Platelets	20	0	0	0	0.0	30	1	0	1	0.8	.026
Hemoglobin	37	7	0	0	0.0	46	25	8	3	8.4	< .0001
Nonhematologic											
Left ventricular systolic dysfunction: LVEF	8	3	0	0	0.0	7	2	0	0	0.0	.647
Hypertension	9	19	5	0	3.7	10	27	9	0	6.9	.043
Diarrhea	4	0	1	0	0.7	17	3	1	0	0.8	.004
Fatigue	18	7	0	1	0.7	43	19	8	1	6.9	< .0001
Anorexia	8	2	0	0	0.0	33	17	8	0	6.1	< .0001
Alopecia	3	0	NA	NA	NA	35	59	NA	NA	NA	< .0001
Oral cavity mucositis (clinical examination)	6	1	0	0	0.0	29	9	1	0	0.8	< .0001
Taste alteration (dysgeusia)	5	0	NA	NA	NA	39	8	NA	NA	NA	< .0001
Vomiting	0	1	0	0	0.0	9	4	0	0	0.0	.0037
Nausea	9	1	0	0	0.0	26	7	4	0	3.1	< .0001
Edema: limb	10	1	0	0	0.0	18	4	0	0	0.0	.026
Neuropathy: motor	1	1	2	0	1.5	2	2	1	0	0.8	.966
Neuropathy: sensory	8	1	0	0	0	30	12	4	0	3.1	< .0001

Abbreviations: AE, adverse event; LVEF, left ventricular ejection fraction, NA, not applicable.

because > 80% of patients enrolled had stage I or stage IIA disease. In view of patients' baseline risk, it is not always possible to apply results to all HER2-positive older patients. It was assumed that enlarging the sample size to increase the number of events would have rendered the study unfeasible because of the relatively smaller proportion of HER2-positive older patients and their heterogeneity.³⁹ We could have extended the follow-up period to detect more events, but it was assumed that non-breast cancer deaths, as well as recurrences, would accumulate in both arms over the 8 years that had passed since the first patient was enrolled. However, a longer follow-up period is needed to shed light on patient prognosis. Second, patients aged 70-80 years still had only a modest number of comorbidities, with LVEF \geq 55%; in other words, they were healthy patients with good performance. In fact, the majority of these patients received > 80% of the RDI. These healthy patients were able to tolerate standard chemotherapy with trastuzumab, which results in the best prognosis, as supported by the results of the APT trial.⁴⁰ Chronological age by itself is not a stand-alone biomarker; thus, fit older patients who are

deemed suitable may be offered standard treatment. To distinguish between fit or vulnerable older persons, CGA may be useful.⁴¹ In this study, we selected as many patients as possible who could be treated at least with trastuzumab as monotherapy, with optional chemotherapy regimens at the physician's discretion. We did not exclude less-fit older patients but included both fit and vulnerable patients. After analyzing CGA data, we hope to create predictive tools for AEs or prognosis. In the field of geriatric oncology, the inclusion of functional end points is needed, which can aid in shared decision-making by physicians and patients.⁴² In older patients considered fit for chemotherapy, standard treatment can be offered, but such decisions could be individualized by weighing competing risks.

In conclusion, the primary objective of noninferiority for trastuzumab monotherapy was not met. However, the observed loss of survival without chemotherapy was < 1 month at 3 years. Therefore, and in light of the lower toxicity and more favorable HRQoL profile, trastuzumab monotherapy can be considered an adjuvant therapy option for selected older patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Randomized Controlled Trial of Trastuzumab With or Without Chemotherapy for HER2-Positive Early Breast Cancer in Older Patients**

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APPENDIX

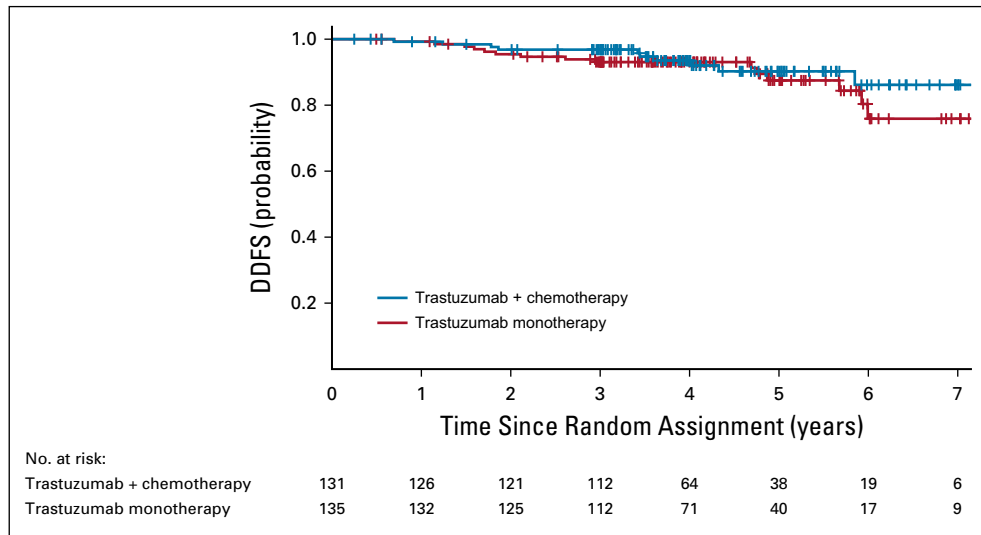


FIG A1. Kaplan-Meier estimates of distant disease-free survival (DDFS). DDFS at 3 years was 93.1% in the trastuzumab monotherapy group versus 96.8% in the trastuzumab + chemotherapy group (HR, 1.42; 95% CI, 0.64 to 3.17; $P = .39$). Tick marks indicate censored data.

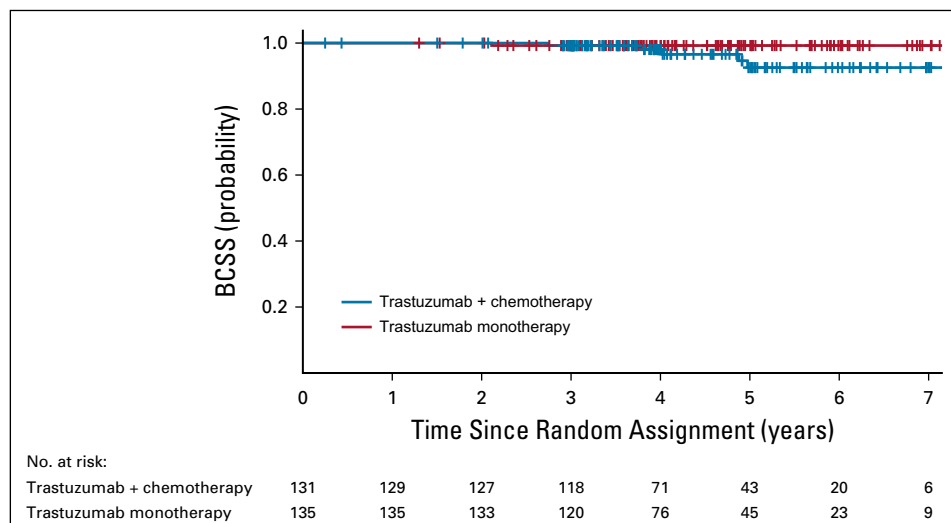


FIG A2. Kaplan-Meier estimates of breast cancer-specific survival (BCSS). BCSS at 3 years was 99.2% in the trastuzumab monotherapy group versus 99.2% in the trastuzumab + chemotherapy group (HR, 0.20; 95% CI, 0.02 to 1.67; $P = .14$). Tick marks indicate censored data.

TABLE A1. Chemotherapy Regimen Received and Relative Dose Intensity in the Trastuzumab Plus Chemotherapy Group (n = 131)

Chemotherapy Regimen	No. (%) (n = 131)	Relative Dose Intensity (%)
Paclitaxel	46 (35.1)	79
Docetaxel	19 (14.5)	87
AC/EC	28 (21.4)	84/97
FEC75	2 (1.5)	62
TC	4 (3.1)	78
CMF	26 (19.8)	84
TCbH	0	—
Unknown	6 (4.6)	

Abbreviations: —, Regimens specified on the protocol, Initial dose; AC, doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m²; CMF, cyclophosphamide 75-100 mg orally, methotrexate 40 mg/m², and fluorouracil 500-600 mg/m²; EC, epirubicin 90 mg/m² + cyclophosphamide 600 mg/m²; FEC75, fluorouracil 500 mg/m², epirubicin 75 mg/m², and cyclophosphamide 500 mg/m²; TC, docetaxel 75 mg/m² + cyclophosphamide 600 mg/m²; TCbH, docetaxel 60-75 mg/m², carboplatin area under the curve 5-6 mg/ml/min, trastuzumab loading dose 4 mg/kg, 2 mg/kg for 6 cycles.

TABLE A2. Events in Disease-Free Survival

Variable	Trastuzumab, No. of Events (n = 135)	Trastuzumab + Chemotherapy, No. of Events (n = 131)
Recurrence	18	15
Ipsilateral breast	1	1
Regional lymph node	4	3
Distant	9	8
Second malignancy	9	4
Death	7	6
Breast cancer specific	1	5
Others	6	1