# Adjuvant Trastuzumab Without Chemotherapy For Treating Early HER2-Positive Breast Cancer In Older Patients: A Cohort Study Accompanying With The RESPECT Trial

**Masataka Sawaki** ( m-sawaki@aichi-cc.jp )
Aichi Cancer Center Hospital https://orcid.org/0000-0002-2927-9258
**Naruto Taira**
Okayama University: Okayama Daigaku
**Yukari Uemura**
National Center for Global Health and Medicine: Kokuritsu Kenkyu Kaihatsu Hojin Kokuritsu Kokusai Iryo Kenkyu Center
**Tsuyoshi Saito**
Japanese Red Cross Saitama Hospital
**Shinichi Baba**
Sagara Hospital
**Kokoro Kobayashi**
The Cancer Institute Hospital of the Japanese Foundation for Cancer Research
**Hiroaki Kawashima**
Aomori City Hospital
**Michiko Tsuneizumi**
Shizuoka General Hospital: Shizuoka Kenritsu Sogo Byoin
**Noriko Sagawa**
Kyoundo Hospital
**Hiroko Bando**
University of Tsukuba: Tsukuba Daigaku
**Masato Takahashi**
National Hospital Organisation Hokkaido Cancer Center: Hokkaido Gan Center
**Miki Yamaguchi**
JCHO Kurume General Hospital
**Tsutomu Takashima**
Osaka City University Graduate School of Science Faculty of Science: Osaka Shiritsu Daigaku Daigakuin Rigaku Kenkyuka Rigakubu
**Takahiro Nakayama**
Osaka International Cancer Institute: Osaka Kokusai Gan Center

**Masahiro Kashiwaba**
Adachi Breast Clinic
**Toshiro Mizuno**
Mie University Hospital: Mie Daigaku Igakubu Fuzoku Byoin
**Yutaka Yamamoto**
Kumamoto University: Kumamoto Daigaku
**Hiroji Iwata**
Aichi Cancer Center Hospital
**Tatsuya Toyama**
Nagoya City University Graduate School of Medical Sciences and Medical School: Nagoya Shiritsu Daigaku Daigakuin Igaku Kenkyuka Igakubu
**Koichiro Tsugawa**
St.Marianna Universitiy School of Medicine
**Takuya Kawahara**
The University of Tokyo Hospital: Tokyo Daigaku Igakubu Fuzoku Byoin
**Hirofumi Mukai**
National Cancer Center-Hospital East: Kokuritsu Gan Center Higashi Byoin

---

**Research Article**

**Keywords:** Breast cancer, older, HER2, trastuzumab, without chemotherapy

**Posted Date:** August 11th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-766187/v1



---

# Abstract

**Purpose** To gauge the effects of treatment practices on prognosis for all older patients with HER2-positive breast cancer, particularly to determine whether adjuvant trastuzumab alone can offer benefit over no adjuvant therapy. This report accompanies the RESPECT study, a randomized-controlled trial (RCT) comparing trastuzumab monotherapy with trastuzumab-plus-chemotherapy for early HER2-positive breast cancer.

**Patients and methods** Patients who declined the RCT were treated based on the physician's discretion. We studied the (1) trastuzumab-plus-chemotherapy group, (2) trastuzumab-monotherapy group, and (3) non-trastuzumab group (no therapy or anticancer therapy without trastuzumab). The primary endpoint was disease-free survival (DFS), which was compared using the propensity-score method.

**Results** We enrolled 398 eligible patients, aged over 70 years, with HER2-positive invasive breast cancer, of whom 275 (69%) were in the RCT, and 123 (31%) were in this cohort group. The median age was 74.5 years. Among cohort group treatment categories were as follows: (1) trastuzumab-plus-chemotherapy group (n = 36, 30%), (2) trastuzumab-monotherapy group (n = 52, 43%), and (3) non-trastuzumab group (n = 32, 27%). A total of 73% of patients received trastuzumab-containing regimens, with or without chemotherapy. The 3-year DFS was 92.3% in the trastuzumab-plus-chemotherapy group, 89.2% in the trastuzumab-monotherapy group, and 82.5% in the non-trastuzumab group. DFS in the non-trastuzumab group was lower than in the trastuzumab-plus-chemotherapy and trastuzumab-monotherapy groups (propensity-adjusted HR: 3.29; 95% CI: 1.15–9.39; $P = 0.026$). The relapse-free survival in the non-trastuzumab group was lower than in the trastuzumab-plus-chemotherapy and trastuzumab monotherapy groups (propensity-adjusted HR = 7.80; 95% CI: 2.32–26.2, $P < 0.0001$). Chemotherapy with trastuzumab or trastuzumab monotherapy did not affect health-related quality of life (HRQoL) at 36 months.

**Conclusions** Trastuzumab-treated patients had better prognoses than patients not treated with trastuzumab without deterioration of HRQoL. Thus, trastuzumab monotherapy can be considered for patients who reject chemotherapy.

**Trial registration number** The protocol was registered on the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID: UMIN 000028476).


# Introduction

This study accompanied the RESPECT study [1], which is a randomized controlled trial (RCT) designed to compare the value of trastuzumab monotherapy with the standard combination treatment with the value of chemotherapy in patients over 70 years, with human epidermal growth factor receptor type 2 (HER2)-positive invasive breast cancer, who received curative surgery. This study aimed to determine the overall prognosis of older patients with HER2-positive breast cancer, including patients who did not agree to participate in the RCT despite meeting the eligibility criteria, and to compare the efficacies of trastuzumab

monotherapy and trastuzumab-plus-chemotherapy. Particularly, we aimed to determine whether adjuvant trastuzumab alone can offer benefit over no adjuvant therapy. Before starting this RCT, we questioned whether acquiring consent to participate in this RCT might be difficult in older patients, because of the possibility of emphasizing treatment in accordance with the patient's wishes, considering the potential adverse events (AEs) of chemotherapy. It is currently unknown whether adjuvant trastuzumab therapy alone can offer a benefit over no adjuvant therapy. Although we sought to directly compare trastuzumab monotherapy with no treatment in older patients, we were concerned that such a study would not be feasible because some patients might refuse to participate in an arm without trastuzumab, despite having HER2-positive disease. In addition, only healthy patients can participate in the RCT. Thus, we designed a non-interventional cohort study in addition to the RCT to gauge the effects of treatment practices on prognosis for all older patients with HER2-positive breast cancer.

# Patients And Methods

### Patients

The trial protocol is described within the full text of this article. We recruited patients, aged 70–80 years old, with HER2-positive invasive breast cancer who underwent curative surgery. The patient-inclusion criteria were as follows: patients with invasive breast cancer histologically diagnosed as HER2-positive breast cancer, who underwent curative surgery for stage I (pathological tumor size > 0.5 cm), IIA, IIB, or IIIA disease. HER2-positivity was defined by the ASCO/CAP guidelines [2], which lay down the following criteria: immunohistochemical staining of 3+ (uniform, intense membrane staining of > 30% of invasive tumor cells) and a fluorescence-*in situ* hybridization (FISH) result of more than six HER2 gene copies per nucleus or a FISH ratio (HER2 gene signal: chromosome 17 signal) of more than 2.2. Other key eligibility criteria were as follows: a baseline left ventricular-ejection fraction of ≥55% (measured by echocardiography) within 4 weeks of registration, an Eastern Cooperative Oncology Group performance status (PS) score of 0 or 1, and sufficient organ function that meets the prescribed criteria in laboratory tests performed within four weeks of registration. The key exclusion criteria were as follows: the presence of active multiple primary cancer (synchronous multiple primary cancer and invasive cancer of other organs); ≥4 histological axillary lymph node metastases; no histological evaluation of axillary lymph nodes; a histologically confirmed positive margin found during breast-conservation surgery; a history of drug-related allergy that could hinder planned treatment; any history of or complication following cardiac disorders; a history of congestive heart failure; cardiac infarction; complications requiring treatment, such as ischemic cardiac disorder, arrhythmia, valvular-heart disease, poorly-controlled hypertension, and poorly controlled diabetes; difficulty in regularly attending a medical institution due to a deterioration in the ability to perform the activities of daily living; difficulty participating in the trial because of a psychiatric disorder or psychiatric symptoms; or ineligibility for enrollment according to the decision of an investigator based on contacts and locations.

### Trial design and oversight

In general, the physicians involved in this study explained and encouraged patients to participate in the RCT. Patients who did not agree to participate in the RCT (despite meeting the eligibility criteria and being given an explanation of the RCT by the investigator) were included in the cohort study with written informed consent. Patients who consented to participate in the RCT were randomly assigned at a 1:1 ratio to the trastuzumab monotherapy group or trastuzumab-plus-chemotherapy group [1]. In this cohort study, treatment was chosen based on the discretion of the treating physician and the patients' wishes without intervention, and patients were prospectively surveyed based on routine medical records. The cohort group was divided into 1) the trastuzumab-plus-chemotherapy group, 2) the trastuzumab-monotherapy group, and 3) a group that received no therapy at all or received any anticancer therapy without trastuzumab (the non-trastuzumab group). The purpose of this prospective cohort study was to assess the overall effect of adjuvant therapy on HER2-positive primary breast cancer in older patients (≥ 70 years) and to investigate the efficacy and safety of trastuzumab-plus-chemotherapy, trastuzumab monotherapy, and non-trastuzumab treatment.

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

### End points

The primary endpoint of the cohort study was disease-free survival (DFS), and the secondary endpoints were overall survival (OS), relapse-free survival (RFS), AEs, and health-related quality of life (HRQoL). DFS was defined by the occurrence of any of the following: a diagnosis of recurrence after breast-conservation therapy, local (ipsilateral chest wall) recurrence, regional lymph node recurrence or distant organ metastasis; a diagnosis of metachronous breast cancer or secondary cancer (not including cutaneous basal cell carcinoma, squamous cell cancer, or endometrial intraepithelial carcinoma); and all deaths (regardless of cause). RFS was defined by the occurrence of any of the following: any local recurrence (including local recurrence after breast-conservation therapy), regional lymph node recurrence or distant organ metastasis (not including metachronous breast cancer or secondary cancer), and death (regardless of cause). HRQoL was assessed using the Functional Assessment of Cancer Therapy-general (FACT-G) scale [3].

### Assessment

In the cohort group, patients were surveyed using routine medical records without interventions, such as prospective treatment and testing. Tumor grades and types of AEs were determined according to Common Terminology Criteria for Adverse Events v3.0. The survival data and AEs were reviewed every year, beginning from the time of first enrollment to the end of the study. HRQoL of the study population was assessed at registration, and after 36 months.

### Statistical analysis

The target sample size for the cohort group was set to 200–400 patients. The survey of the clinical trial group indicated the presence of approximately 200 HER2-positive patients (aged ≥ 70 years) each year, who could potentially participate in either the RCT or the cohort group. Assuming that 40–50% of patients would provide consent for participating in the RCT and that approximately 70% would provide informed consent for the cohort study, we expected that approximately 50–65 patients would be included in the observational studies each year. Thus, it was considered possible to include 200 patients in the RCT over 4 years. The DFS was set as the primary endpoint, as was done for the RCT of the RESPECT study [1]. The DFS and other endpoints among trastuzumab-plus-chemotherapy, trastuzumab-monotherapy, and non-trastuzumab groups were compared using propensity score-based covariate adjustments by the Cox regression model. The propensity score was estimated for each participant using a multinomial regression model, based on the age (70–75 versus 76–80 years), hormone receptor status (positive versus negative), pathologic nodal status (positive versus negative), and PS (0 or 1) in the model. Group comparisons of FACT-G total and subdomain scores were performed using an Analysis of Co-Variance (ANCOVA). This model used scores at 36 months as an outcome, and the adjusted covariates were scored at baseline in addition to the same factors in the survival analysis (i.e., age, hormone receptor status, pathologic nodal status, and PS). The estimated score difference at 36 months from trastuzumab-plus-chemotherapy (as a reference) in the trastuzumab-monotherapy group and the non-trastuzumab group, 95% confidence interval (CI), and *p*-value were calculated.

All collected data were analyzed using SAS® version 9.4 (SAS Institute, Inc). A *p*-value of < 0.05 was considered to reflect a statistically significant difference. The end points, assessments, and statistical analyses are described in detail in the protocol.

# Results

### Patients

We enrolled 398 eligible patients, aged over 70 years, with HER2-positive invasive breast cancer, from 114 institutions, between October 2009 and October 2014, of whom 275 (69%) were in the RCT group and 123 (31%) were in the cohort group. The CONSORT diagram is presented in Figure 1. All 275 patients who were randomly assigned to the RCT group were registered for full-set analysis: trastuzumab monotherapy (n = 137), and trastuzumab-plus-chemotherapy (n = 138). In the cohort group, three patients (2.4%) were excluded because all efficacy data was missing, leaving 120 patients for a full-set analysis; the treatment categories were as follows: 1) the trastuzumab-plus-chemotherapy group (n = 36, 30%), 2) the trastuzumab-monotherapy group (n = 52, 43%), and 3) the non-trastuzumab group (n = 32, 27%). A total of 73% of patients received trastuzumab-containing regimens, with or without chemotherapy. The patients' characteristics of the full analysis set are shown in Table 1 (n = 395). P values were assessed by chi squared test. The mean ages of the patients in the RCT and cohort groups at entry were 73.9 and 74.6, respectively, and the numbers of patients in the categories (<75 or ≥75) were different (*P* = 0.03). The groups had no differences in terms of the cancer stage, estrogen receptor (ER) and/or progesterone receptor (PgR) positivity, surgical procedure, lymph node metastasis, and co-morbidities (hypertension,

diabetes mellitus, osteoporosis, or hyperlipidemia). The characteristics of the patients in the cohort group are shown in Table 2, according to the treatment options (n = 120). P values were assessed by chi squared test. Among the three subgroups in the cohort group, ER and/or PgR positivity were higher in the non-trastuzumab group (81.3% versus 48.1% in the trastuzumab group, 47.2% in the trastuzumab-plus-chemotherapy group; *P* = 0.005). No differences existed among the groups in terms of the age category, stage, surgical procedure, lymph node metastasis, or co-morbidities.

**Table 1. Baseline characteristics of the entire cohort (n = 395)**

| | | RCT group (n = 275) | Cohort group (n = 120) | |
|---|---|---|---|---|
| | | n (%) | n (%) | *P* |
| Age | <75 | 191 (69.5) | 70 (58.3) | 0.03 |
| | ≧75 | 84 (30.5) | 50 (41.7) | |
| Stage | I | 118 (42.9) | 51 (42.5) | 0.68 |
| | IIA | 116 (42.2) | 49 (40.8) | |
| | IIB | 37 (13.5) | 16 (13.3) | |
| | IIIA | 4 (1.5) | 4 (3.3) | |
| Surgery | Mastectomy | 189 (68.7) | 82 (68.3) | 0.99 |
| | Partial mastectomy | 84 (30.5) | 37 (30.8) | |
| | Others | 2 (0.7) | 1 (0.8) | |
| Lymph node metastasis | Negative | 211 (76.7) | 82 (68.3) | 0.08 |
| | Positive | 64 (23.3) | 38 (31.7) | |
| Pathology | Invasive ductal carcinoma | 256 (93.1) | 112 (93.3) | 0.56 |
| | Invasive lobular carcinoma | 9 (3.3) | 2 (1.7) | |
| | Special type | 10 (3.6) | 6 (5.0) | |
| ER+ and/or PgR+ | Positive | 133 (48.4) | 68 (56.7) | 0.13 |
| | Negative | 142 (51.6) | 52 (43.3) | |
| Performance status | 0 | 254 (92.4) | 109 (90.8) | 0.61 |
| | 1 | 21 (7.6) | 11 (9.2) | |
| Major comorbidity | | | | |
| Hypertension | No | 156 (56.7) | 74 (61.7) | 0.38 |
| | Yes | 118 (42.9) | 46 (38.3) | |
| Diabetes | No | 239 (86.9) | 105 (87.5) | 0.94 |
| | Yes | 35 (12.7) | 15 (12.5) | |
| Osteoporosis | No | 246 (89.5) | 108 (90.0) | 0.95 |
| | Yes | 28 (10.2) | 12 (10.0) | |
| Hyperlipidaemia | No | 204 (74.2) | 95 (79.2) | 0.31 |
| | Yes | 70 (25.5) | 25 (20.8) | |

Table 2. Patient characteristics in the cohort group according to the treatment options (n = 120)

| | | Trastuzumab-plus-chemotherapy group (n = 36) | Trastuzumab-group (n = 52) | Non-trastuzumab group (n = 32) | |
|---|---|---|---|---|---|
| | | n (%) | n (%) | | *P* |
| Age | <75 | 26 (72.2) | 27 (51.9) | 17 (53.1) | 0.13 |
| | ≧75 | 10 (27.8) | 25 (48.1) | 15 (46.9) | |
| Stage | I | 14 (38.9) | 20 (38.5) | 17 (53.1) | 0.43 |
| | IIA | 16 (44.4) | 22 (42.3) | 11 (34.4) | |
| | IIB | 4 (11.1) | 9 (13.7) | 2 (6.3) | |
| | IIIA | 1 (2.8) | 1 (1.9) | 2 (6.3) | |
| | N.A | 1 (2.8) | 0 (0) | 0 (0) | |
| Surgery | Mastectomy | 22 (61.1) | 37 (71.2) | 23 (71.9) | 0.99 |
| | Partial mastectomy | 14 (38.9) | 15 (28.8) | 9 (28.1) | |
| Lymph node metastasis | Negative | 23 (63.9) | 35 (67.3) | 23 (71.9) | 0.88 |
| | Positive | 12 (33.3) | 17 (32.7) | 9 (28.1) | |
| | N.A | 1 (2.8) | 0 (0) | 0 (0) | |
| Pathology | Invasive ductal carcinoma | 32 (88.9) | 49 (94.2) | 31 (96.9) | 0.85 |
| | Invasive lobular carcinoma | 1 (2.8) | 3 (5.8) | 1 83.1) | |
| | Special type | 3 (8.3) | 0 (0) | 0 (0) | |
| ER+ and/or PgR+ | Positive | 17 (47.2) | 25 (48.1) | 26 (81.3) | 0.005 |
| | Negative | 19 (52.8) | 27 (51.9) | 6 (18.8) | |
| Performance Status | 0 | 34 (94.4) | 45 (86.5) | 30 (93.8) | 0.36 |
| | 1 | 2 (5.6) | 7 (13.5) | 2 (6.3) | |
| Major Comorbidity | | | | | |
| Hypertension | No | 23 (63.9) | 30 (57.7) | 21 (65.6) | 0.73 |
| | Yes | 13 (36.1) | 22 (42.3) | 11 (34.4) | |
| Diabetes | No | 31 (86.1) | 48 (92.3) | 26 (81.2) | 0.32 |
| | Yes | 5 (13.9) | 4 (7.7) | 6 (18.8) | |
| Osteoporosis | No | 32 (88.9) | 47 (90.5) | 29 (90.6) | 0.97 |
| | Yes | 4 (11.1) | 5 (9.6) | 3 (9.4) | |
| Hyperlipidaemia | No | 27 (75.0) | 41 (78.8) | 27 (84.4) | 0.64 |
| | Yes | 9 (25.0) | 11 (21.2) | 5 (15.6) | |
| N.A: Non available | | | | | |

## DFS, RFS, and OS

The data cut-off date was October 31, 2017. The median follow-up time was 3.2 years (range: 0.9–7.0 years) in the cohort group. The details of DFS events are listed in Appendix Table A1. The DFS at 3 years was 96.7% in the trastuzumab-plus-chemotherapy group, 89.2% in the trastuzumab-monotherapy group, and 82.5% in the non-trastuzumab group (Figure 2). In the non-trastuzumab group, 26 of 32 patients (81.3%) were ER-positive; hormone therapy was initiated for 25 patients (78.1%), and breast irradiation was performed for four patients (12.5%). The DFS of patients in the non-trastuzumab group was lower than that of patients in the trastuzumab-plus-chemotherapy and trastuzumab monotherapy groups (propensity-adjusted HR = 3.29; 95% CI: 1.15–9.39, $P = 0.026$). DFS of the non-trastuzumab group also showed a worse prognosis than that of the trastuzumab-monotherapy group (propensity-adjusted HR: 2.15; 95% CI: 1.20–3.93, $P = 0.012$). The RFS of patients in the non-trastuzumab group was lower than that of patients in the trastuzumab-plus-chemotherapy and trastuzumab monotherapy groups (propensity-adjusted HR = 7.80; 95% CI: 2.32–26.2, $P < 0.0001$) (Figure 3). The OS of patients in the non-trastuzumab group was marginally lower than that of patients in the trastuzumab-plus-chemotherapy and trastuzumab monotherapy groups (propensity-adjusted HR = 3.44; 95% CI: 0.75–15.67, $P = 0.11$) (Figure A1).

## Safety

Patients who registered for the cohort group (n = 120) were included in the safety analysis. The incidences of grade 3 or 4 non-hematological AEs were higher in the RCT group than in the cohort group (18.5% versus 10.8%, $P = 0.05$). All serious AEs resolved. Common AEs are listed in Table A2.

## HRQoL

Mean scores and 95% CI for the FACT-G total and sub-domain at each survey point are presented in Appendix Table A3 and Figure 4. ANCOVA showed that there were no significant differences in FACT-G total score after 36 months between the trastuzumab-plus-chemotherapy and trastuzumab monotherapy groups, and the trastuzumab-plus-chemotherapy and non-trastuzumab groups (Appendix Table A4). The only difference between the groups was that the social and family well-being (SFWB) score at 36 months between the trastuzumab-plus-chemotherapy group and the trastuzumab monotherapy group (estimated value = -5.5, $P$ = 0.036), and SFWB score of trastuzumab-plus-chemotherapy group at 36 months was better than that of trastuzumab monotherapy group.

# Discussion

The RESPECT study is the first randomized adjuvant trial comparing trastuzumab monotherapy with trastuzumab-plus-chemotherapy for patients with HER2-positive breast cancer [1]. The RESPECT study was accompanied by a cohort study for patients who refused to participate in the RCT. By adding the cohort group to the RCT, we could evaluate the overall efficacy of adjuvant therapy for HER2-positive breast cancer in 398 patients over 70 years of age in detail, which enabled us to determine the prognoses of patients who did not receive trastuzumab prospectively, despite meeting the criteria for the RCT. We found that the DFS of the non-trastuzumab group was significantly lower than that of the trastuzumab-plus-chemotherapy and the trastuzumab-monotherapy groups. Trastuzumab with chemotherapy has been approved as a standard adjuvant therapy for HER2-positive primary breast cancer based on previous studies that compared chemotherapy with trastuzumab-plus-chemotherapy [4–7]. Since 2005, no data have been generated through clinical trials regarding (i) trastuzumab without chemotherapy, and (ii) no trastuzumab treatment, because all patients receive trastuzumab.

Here, for the first time, we added an implication to this issue as prospective data with propensity-adjustment analysis in a non-interventional cohort study group. In a previous study, trastuzumab-plus-pertuzumab was tested in a neoadjuvant setting as a treatment regimen without chemotherapy [8], but chemotherapy was administered after surgery, and the study lacked a no-treatment arm without anti-HER2 therapy. Recent retrospective data obtained using the National Cancer Database revealed no significant difference in survival by administering HER2 to patients who did not receive chemotherapy [9]. Data from a large observational study suggested that trastuzumab-plus-chemotherapy should remain the preferred option for all patients indicated for adjuvant treatment, and that a low proportion of patients need an alternative treatment approach, either because of contraindications or the patient's preference. Trastuzumab monotherapy might be a reasonable option [10], but to our knowledge, no prospective data exist to suggest that prospective adjuvant trastuzumab alone can offer a benefit over no adjuvant therapy.

The RESPECT study was designed to investigate whether older patients with HER2-positive breast cancer should undergo chemotherapy; however, before starting the trial, we were concerned that the consent rate for participation might be low. We expected it to be 40–50%, although almost 70% of the patients provided informed consent to participate in the RCT. The RCT employs a standard method for

determining a standard therapy, but it remains controversial as to whether patients would benefit from participating in the RCT. Some findings showed improved outcomes in trial participants as compared to those in non-participants, including those with breast cancer [11–13] whereas other findings revealed no improvement in outcomes [14, 15]. A systematic review indicated that insufficient data were available to conclude positive trial outcomes [16]. Notably, the rate of ER-positivity was higher in the cohort group, suggesting that ER expression in patients with HER2-positive breast cancer may have influenced their decision to participate in the study or to choose hormonal therapy as a treatment option. In the non-trastuzumab group, ER-positivity was 81.3%, and the patients only received hormonal therapy, although it was associated with a worse prognosis compared to the chemotherapy-plus-trastuzumab, and trastuzumab groups. Older patients are at an increased risk for severe chemotherapy-induced toxicity [17–19]. Regarding the safety of trastuzumab in older patients, the results of a large observational study indicated that the risk of cardiac function toxicity was 5.7% [20] and that it was associated with age [20, 21], although it remained manageable [20], and the risks associated with trastuzumab were outweighed by the benefits [20, 22]. In terms of the balance between benefit and harm, we recommend trastuzumab monotherapy if the patients do not receive chemotherapy, based on our current findings. Besides the incidence of AEs, HRQoL is also important, because chemotherapy causes significant deterioration of HRQoL in older patients [23, 24]. We observed a clinically significant HRQoL rate of deterioration between 2 months and 1 year into the RCT, which recovered after 3 years [1, 25]. As a result of the QoL evaluation in this cohort study, chemotherapy with trastuzumab or trastuzumab monotherapy as postoperative adjuvant therapy did not affect global QoL at 36 months. We also observed the impact of chemotherapy on cognitive functioning in the RCT [26], the information would be important to share decision making between clinicians and patients.

Comprehensive geriatric-assessment (CGA) screening tools for older patients can be useful for predicting severe AE [27], and it is important to intensify supportive care and develop modified treatment regimens in vulnerable patients who may subsequently experience greater toxicity [28]. For the RCT group, we developed a CGA screening tool at baseline and at each point to analyze the relationship between AEs and DFS.

This study has a few limitations. Although 275 patients in the RCT group and 120 patients in the cohort group were treated and assessed, no definitive conclusions regarding trastuzumab without chemotherapy (compared with trastuzumab-plus-chemotherapy) can be made, because there were fewer events than expected because > 80% of the patients enrolled had stage I or stage IIA breast cancer. Even in the non-trastuzumab arm of the cohort group, the 3-year DFS was over 80%. Although more patients were needed for a higher number of events, it was difficult to complete enrollment, because of the low number of older HER2-positive patients and disease heterogeneity [29]. 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, because eight years passed after the first patient was enrolled. However, a longer follow-up period is needed to shed light on patient prognosis.

In conclusion, we found that patients who received any trastuzumab-containing regimen, even trastuzumab monotherapy, had a better prognosis than those who were not treated with trastuzumab, without deterioration of HRQOL. Although trastuzumab-plus-chemotherapy remains a standard of care, trastuzumab monotherapy could be considered for selected older patients, even if the patients are not willing to receive chemotherapy.

# Declarations


### Acknowledgments

We acknowledge Toru Watanabe and Yasuo Ohashi for valuable advice on the research plan. We thank the patients who participated in this trial and their families and caregivers, all investigators involved in this study, and all members of the independent data-monitoring committee for their contributions to the study.


**Author contributions** Study concept and design: MS, NT, YU, HB, TN, MK, TM, YY, HI and HM. Provision of study material or patients: TS, SB, KK, HK, HM, MT, NS, MT, MY, TT, KT and TT. Data and statistical analysis: YU and TK. Manuscript preparation: MS, NT, YU, and TK. Manuscript editing: MS and NT. Manuscript review: All authors.


### Funding

This study was funded by the Comprehensive Support Project for Oncology Research (CSPOR) of the Public Health Research Foundation, Japan. All decisions concerning the planning, implementation, and publication of this study were made by the executive committee of this study. The corporate and individual sponsors of this study are listed on the CSPOR website (http://www.csp.or.jp/cspor/kyousan_e.html).


**Data availability** The datasets analyzed during the current study are available from the corresponding author on reasonable request.

**Code availability** The codes used to analyze the datasets during the current study are available from the corresponding author on reasonable request.

**Conflict of interest** YU reports honoraria for consulting from Chugai pharmaceutical Co., Ltd. TT reports honoraria for lectures from Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Eisai Co., Ltd., Pfizer Japan Inc., Novartis Pharma K.K., AstraZeneca K.K., Takeda Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., and Daiichi Sankyo Co., Ltd. TN reports fees for Non-CME services and honoraria for lectures from Chugai pharmaceutical Co., Ltd., AstraZeneca K.K., Novartis Pharma K.K., Eli Lilly Japan K.K., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited, and Eisai Co., Ltd. TM reports fees for non-CME services and honoraria for lectures from AstraZeneca K.K., Chugai pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Daiichi Sankyo Co., Ltd., Nippon Kayaku Co., Ltd., and Pfizer Japan Inc. HI reports honoraria for

lectures from Chugai pharmaceutical Co., Ltd. HM reports honoraria from AstraZeneca K.K., Pfizer Japan Inc, Takeda Pharmaceutical Company Limited, Daiichi Sankyo Co., Ltd and Taiho Pharmaceutical Co., Ltd; and research grants from the Japanese government, Daiichi Sankyo Co., Ltd, Eisai Co., Ltd, Nippon Kayaku Co., Ltd and Pfizer Japan Inc, outside the submitted work.

**Ethical approval** The trial protocol was approved by the institutional review boards of all participating institutions.

**Informed consent** All patients provided written informed consent.

# References

1. Sawaki M, Taira N, Uemura Y, Saito T, Baba S, Kobayashi K, Kawashima H, Tsuneizumi M, Sagawa N, Bando H, Takahashi M, Yamaguchi M, Takashima T, Nakayama T, Kashiwaba M, Mizuno T, Yamamoto Y, Iwata H, Kawahara T, Ohashi Y, Mukai H (2020) Randomized Controlled Trial of Trastuzumab With or Without Chemotherapy for HER2-Positive Early Breast Cancer in Older Patients. J Clin Oncol 38:3743-3752. doi: 10.1200/jco.20.00184

2. Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM, Hayes DF (2007) American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol 25:118-145. doi: 10.1200/JCO.2006.09.2775

3. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 11:570-579. doi: 10.1200/jco.1993.11.3.570

4. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Lang I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Ruschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353:1659-1672. doi: 353/16/1659 [pii] 10.1056/NEJMoa052306

5. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353:1673-1684. doi: 353/16/1673 [pii] 10.1056/NEJMoa052122

6. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, Goldhirsch A, Untch M, Mariani G, Baselga J (2007) 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive

breast cancer: a randomised controlled trial. The Lancet 369:29-36. doi: 10.1016/s0140-6736(07)60028-2

7. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buyse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J (2011) Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-1283. doi: 10.1056/NEJMoa0910383

8. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagussa P (2012) Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 13:25-32. doi: 10.1016/s1470-2045(11)70336-9

9. Nguy S, Wu SP, Oh C, Gerber NK (2021) Outcomes of HER2-positive non-metastatic breast cancer patients treated with anti-HER2 therapy without chemotherapy. Breast Cancer Res Treat 187:815-830. doi: 10.1007/s10549-021-06115-9

10. Dall P, Koch T, Gohler T, Selbach J, Ammon A, Eggert J, Gazawi N, Rezek D, Wischnik A, Hielscher C, Schleif N, Cirrincione U, Hinke A, Feisel-Schwickardi G (2018) Trastuzumab without chemotherapy in the adjuvant treatment of breast cancer: subgroup results from a large observational study. BMC Cancer 18:51. doi: 10.1186/s12885-017-3857-5

11. Davis S, Wright PW, Schulman SF, Hill LD, Pinkham RD, Johnson LP, Jones TW, Kellogg HB, Jr., Radke HM, Sikkema WW, et al. (1985) Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. Cancer 56:1710-1718. doi: 10.1002/1097-0142(19851001)56:7<1710::aid-cncr2820560741>3.0.co;2-t

12. Udell JA, Wang TY, Li S, Kohli P, Roe MT, de Lemos JA, Wiviott SD (2014) Clinical trial participation after myocardial infarction in a national cardiovascular data registry. JAMA 312:841-843. doi: 10.1001/jama.2014.6217

13. Ohno S, Mukai H, Narui K, Hozumi Y, Miyoshi Y, Yoshino H, Doihara H, Suto A, Tamura M, Morimoto T, Zaha H, Chishima T, Nishimura R, Ishikawa T, Uemura Y, Ohashi Y (2019) Participants in a randomized controlled trial had longer overall survival than non-participants: a prospective cohort study. Breast Cancer Res Treat 176:631-635. doi: 10.1007/s10549-019-05276-y

14. Tanai C, Nokihara H, Yamamoto S, Kunitoh H, Yamamoto N, Sekine I, Ohe Y, Tamura T (2009) Characteristics and outcomes of patients with advanced non-small-cell lung cancer who declined to participate in randomised clinical chemotherapy trials. Br J Cancer 100:1037-1042. doi: 10.1038/sj.bjc.6604982

15. Keizman D, Rouvinov K, Sella A, Gottfried M, Maimon N, Kim JJ, Eisenberger MA, Sinibaldi V, Peer A, Carducci MA, Mermershtain W, Leibowitz-Amit R, Weitzen R, Berger R (2016) Is there a "Trial Effect" on Outcome of Patients with Metastatic Renal Cell Carcinoma Treated with Sunitinib? Cancer Res Treat 48:281-287. doi: 10.4143/crt.2014.289

16. Peppercorn JM, Weeks JC, Cook EF, Joffe S (2004) Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. The Lancet 363:263-270. doi: 10.1016/s0140-6736(03)15383-4

17. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH (2007) Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol 25:3808-3815. doi: 10.1200/JCO.2006.10.4976

18. Patt DA, Duan Z, Fang S, Hortobagyi GN, Giordano SH (2007) Acute Myeloid Leukemia After Adjuvant Breast Cancer Therapy in Older Women: Understanding Risk. J Clin Oncol 25:3871-3876. doi: 10.1200/jco.2007.12.0832

19. Du XL, Xia R, Liu CC, Cormier JN, Xing Y, Hardy D, Chan W, Burau K (2009) Cardiac toxicity associated with anthracycline-containing chemotherapy in older women with breast cancer. Cancer 115:5296-5308. doi: 10.1002/cncr.24621 [doi]

20. Dall P, Lenzen G, Gohler T, Lerchenmuller C, Feisel-Schwickardi G, Koch T, Eggert J, Heilmann V, Schindler C, Wilke J, Tesch H, Selbach J, Wohlfarth T, Eustermann H, Hinke A (2015) Trastuzumab in the treatment of elderly patients with early breast cancer: Results from an observational study in Germany. J Geriatr Oncol 6:462-469. doi: 10.1016/j.jgo.2015.06.003

21. Vaz-Luis I, Keating NL, Lin NU, Lii H, Winer EP, Freedman RA (2014) Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol 32:927-934. doi: 10.1200/JCO.2013.51.1261

22. Brollo J, Curigliano G, Disalvatore D, Marrone BF, Criscitiello C, Bagnardi V, Kneubil MC, Fumagalli L, Locatelli M, Manunta S, Goldhirsch A (2013) Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: a systematic review of randomized controlled trials. Cancer Treat Rev 39:44-50. doi: 10.1016/j.ctrv.2012.03.009

23. Muss HB, Berry DA, Cirrincione CT, Theodoulou M, Mauer AM, Kornblith AB, Partridge AH, Dressler LG, Cohen HJ, Becker HP, Kartcheske PA, Wheeler JD, Perez EA, Wolff AC, Gralow JR, Burstein HJ, Mahmood AA, Magrinat G, Parker BA, Hart RD, Grenier D, Norton L, Hudis CA, Winer EP (2009) Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 360:2055-2065. doi: 10.1056/NEJMoa0810266

24. Kornblith AB, Lan L, Archer L, Partridge A, Kimmick G, Hudis C, Winer E, Casey R, Bennett S, Cohen HJ, Muss HB (2011) Quality of Life of Older Patients With Early-Stage Breast Cancer Receiving Adjuvant

Chemotherapy: A Companion Study to Cancer and Leukemia Group B 49907. J Clin Oncol 29:1022-1028. doi: 10.1200/jco.2010.29.9859

25. Taira N, Sawaki M, Uemura Y, Saito T, Baba S, Kobayashi K, Kawashima H, Tsuneizumi M, Sagawa N, Bando H, Takahashi M, Yamaguchi M, Takashima T, Nakayama T, Kashiwaba M, Mizuno T, Yamamoto Y, Iwata H, Ohashi Y, Mukai H, Kawahara T (2021) Health-related quality of life with trastuzumab monotherapy versus trastuzumab plus standard chemotherapy as adjuvant therapy in older patients with HER2-positive breast cancer. J Clin Oncol 20.02751, in press.

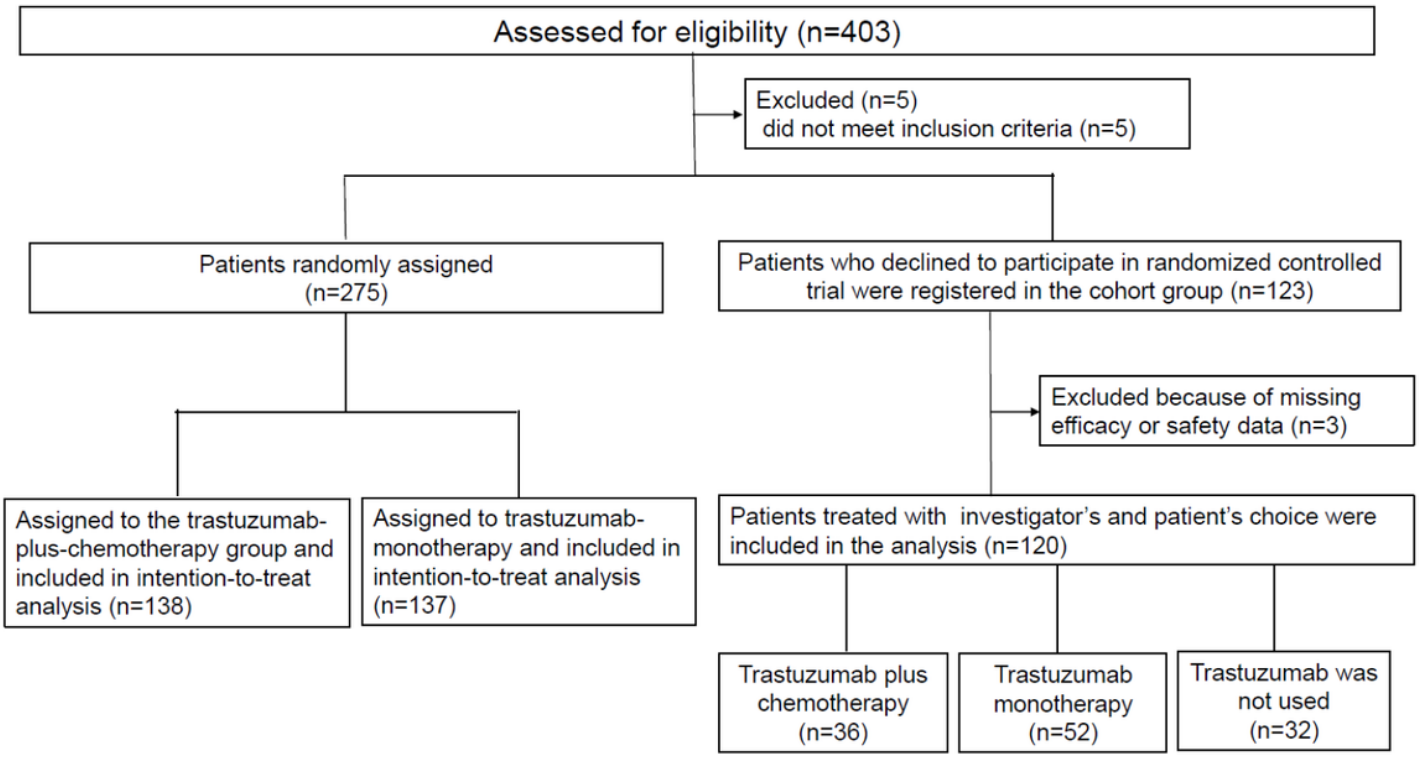
26. Hagiwara Y, Sawaki M, Uemura Y, Kawahara T, Shimozuma K, Ohashi Y, Takahashi M, Saito T, Baba S, Kobayashi K, Mukai H, Taira N (2021) Impact of chemotherapy on cognitive functioning in older patients with HER2-positive breast cancer: a sub-study in the RESPECT trial. Breast Cancer Res Treat 188:675-683. doi: 10.1007/s10549-021-06253-0

27. Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, Feng T, Smith D, Sun CL, De Glas N, Cohen HJ, Katheria V, Doan C, Zavala L, Levi A, Akiba C, Tew WP (2016) Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. J Clin Oncol 34:2366-2371. doi: 10.1200/JCO.2015.65.4327

28. Magnuson A, Sedrak MS, Gross CP, Tew WP, Klepin HD, Wildes TM, Muss HB, Dotan E, Freedman RA, O'Connor T, Dale W, Cohen HJ, Katheria V, Arsenyan A, Levi A, Kim H, Mohile S, Hurria A, Sun CL (2021) Development and Validation of a Risk Tool for Predicting Severe Toxicity in Older Adults Receiving Chemotherapy for Early-Stage Breast Cancer. J Clin Oncol 39:608-618. doi: 10.1200/jco.20.02063

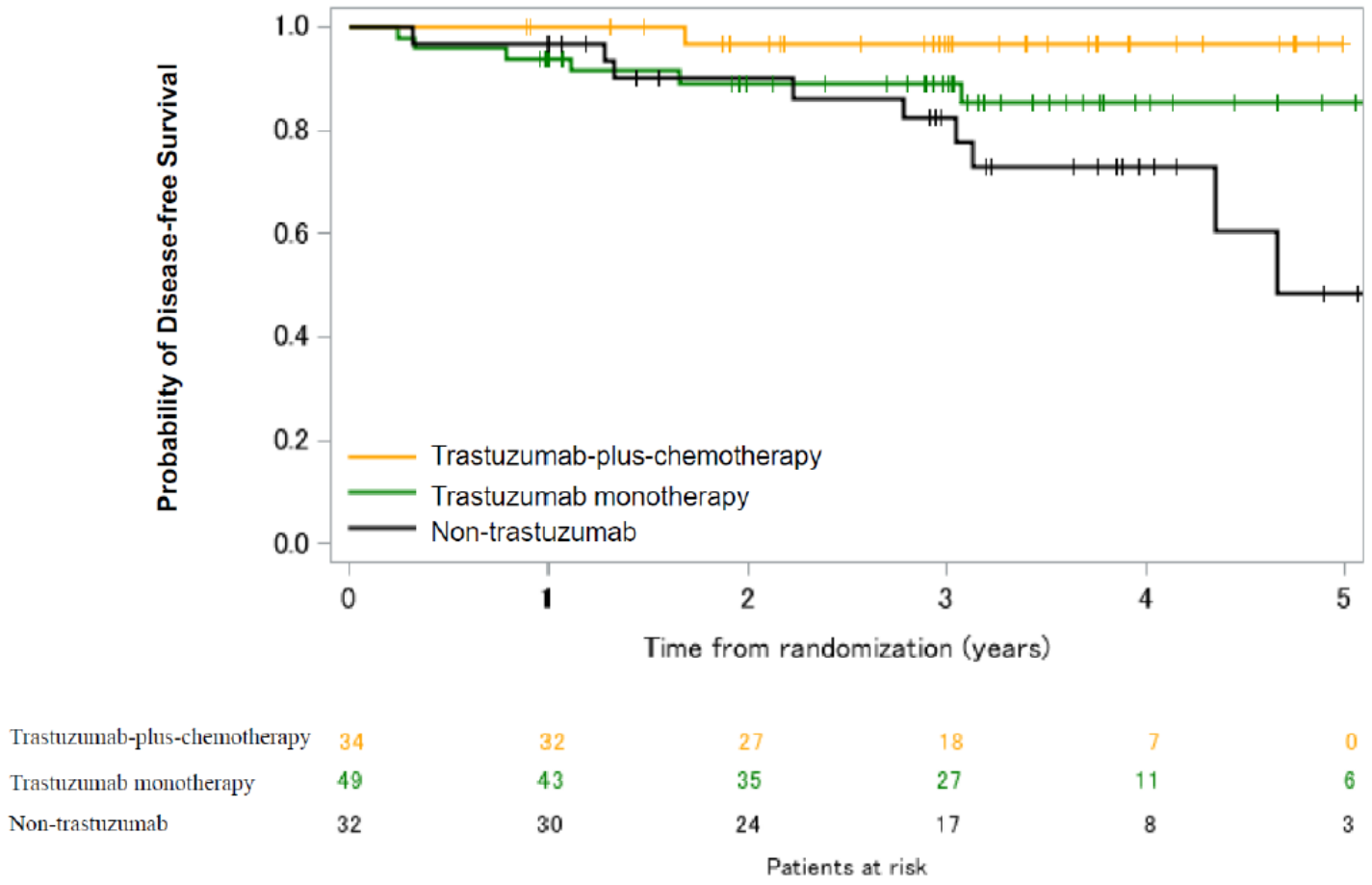
29. Leonard R, Ballinger R, Cameron D, Ellis P, Fallowfield L, Gosney M, Johnson L, Kilburn LS, Makris A, Mansi J, Reed M, Ring A, Robinson A, Simmonds P, Thomas G, Bliss JM (2011) Adjuvant chemotherapy in older women (ACTION) study - what did we learn from the pilot phase? Br J Cancer 105:1260-1266. doi: 10.1038/bjc.2011.377

# Figures



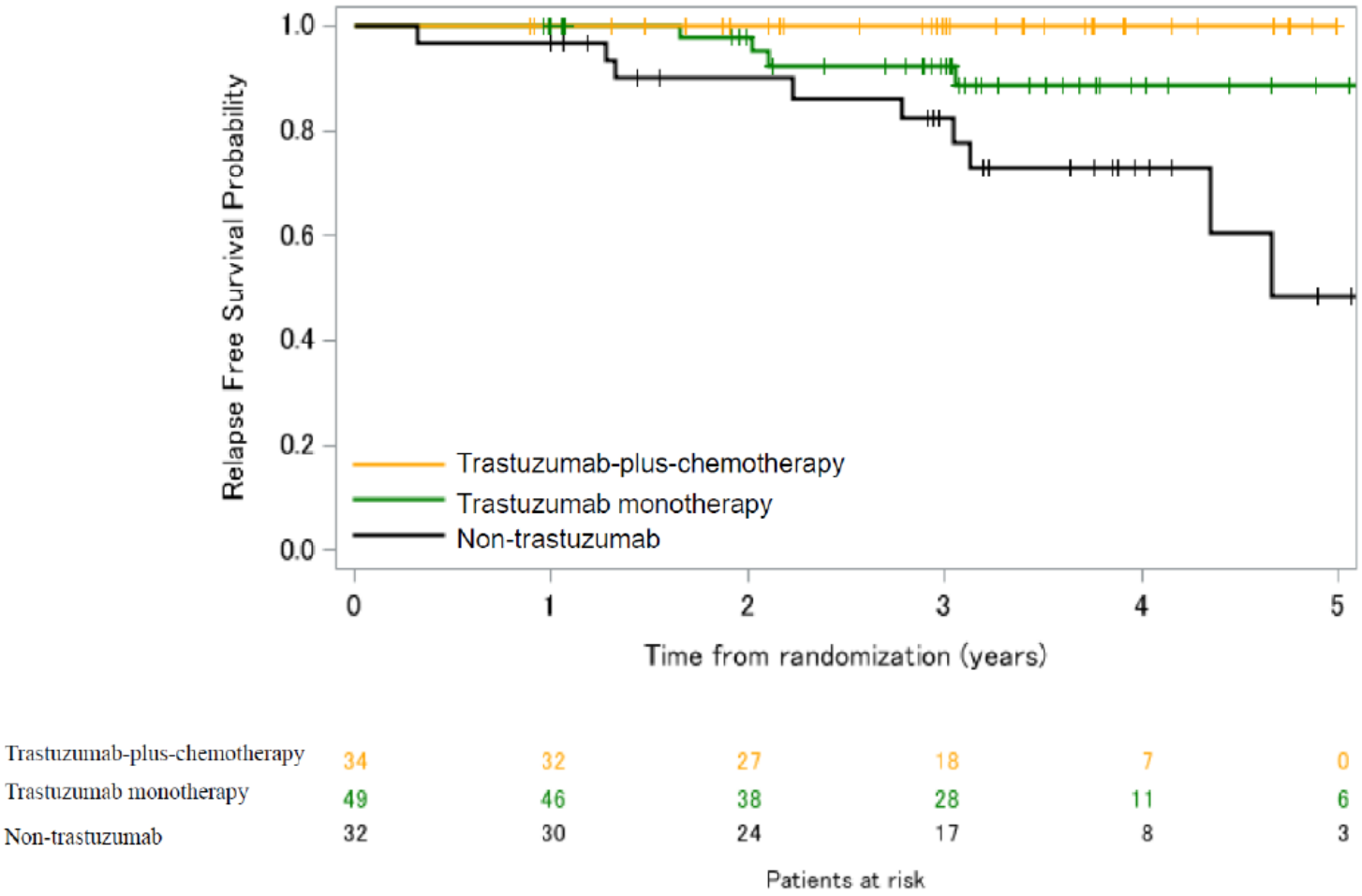

## Figure 1

CONSORT diagram for the RESPECT study. Patients who provided informed consent to participate in the randomized controlled trial (RCT) were assigned, at a 1:1 ratio, to the trastuzumab monotherapy and trastuzumab-plus-chemotherapy groups. Patients who met the eligibility criteria but did not agree to participate in the RCT were included in the cohort group with written informed consent. In the RCT group, treatment was selected for each patient based on the discretion of the treating physician and the patient's wishes, without intervention.




## Figure 2

Kaplan–Meier estimates of disease-free survival (DFS). The DFS at 3 years was 96.7% in the trastuzumab-plus-chemotherapy group, 89.2% in the trastuzumab-monotherapy group, and 82.5% in the non-trastuzumab group. The DFS period of the non-trastuzumab group was lower than that of the trastuzumab-plus-chemotherapy and the trastuzumab monotherapy groups (propensity-adjusted HR: 3.29; 95% CI: 1.15–9.39; P = 0.026). The DFS in the non-trastuzumab group also showed a worse prognosis compared with the trastuzumab monotherapy group (propensity-adjusted HR: 2.15; 95% CI: 1.20–3.93; P = 0.012). Tick marks indicate censored data.




## Figure 3

Kaplan–Meier estimates of relapse-free survival (RFS). The RFS of patients in the non-trastuzumab group was lower than that of patients in the trastuzumab-plus-chemotherapy and trastuzumab monotherapy groups (propensity-adjusted HR = 7.80; 95% CI: 2.32–26.2, P < 0.0001). Tick marks indicate censored data.

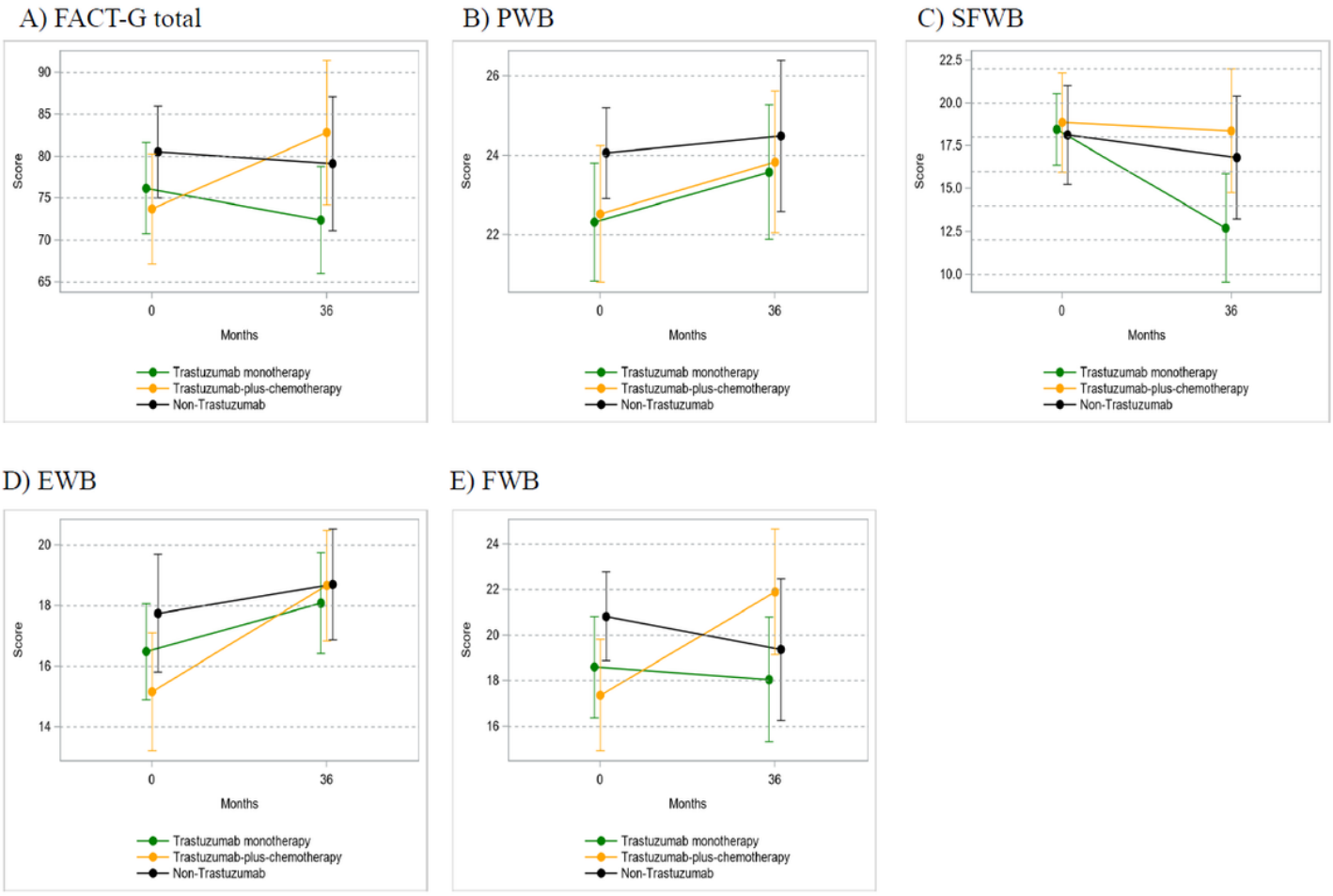



**Figure 4**

Means and 95%CI of FACT-G scores at each survey point. Mean value and 95% confidential interval (95%CI) of A) Functional Assessment of Cancer Therapy-general (FACT-G) total, B) physical well-being (PWB), C) social and family well-being (SFWB), D) emotional well-being (EWB) and E) functional well-being (FWB) scores at baseline, and after 36 months in each group.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AppendixTable.docx
- FigA1.png