

# Patient-reported outcomes with trastuzumab monotherapy versus trastuzumab plus standard chemotherapy as a postoperative adjuvant therapy in HER2-positive elderly breast cancer patients (RESPECT): a randomized, open-label, phase 3 clinical trial

P2-13-02

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## BACKGROUND

Trastuzumab with chemotherapy is standard adjuvant systemic therapy for human epidermal growth factor receptor type-2 (HER2)-positive primary breast cancer. However, adjuvant trastuzumab monotherapy without concurrent or preceding chemotherapy is not used in clinical practice since its benefit has not been investigated in elderly patients.

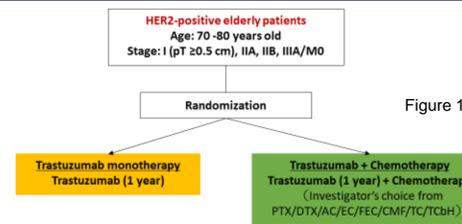
## OBJECTIVE

The RESPECT trial (NCT01104935) compared 1-year trastuzumab monotherapy with trastuzumab plus standard chemotherapy as postoperative adjuvant therapy in elderly patients with HER2-positive breast cancer. The planned analysis showed that the restricted mean survival time between the two groups at 3 years differed by 0.45 months (reported by Sawaki at ASCO2018). This report assesses the patient-reported outcomes (PROs) and health-related quality of life (HRQoL) in the RESPECT trial.

## METHODS

### Study Design

Elderly women (70 to 80 years old) with stage I-IIIa HER2-positive breast cancer after surgery were randomly assigned to receive 1-year trastuzumab (group H) or 1-year trastuzumab plus standard chemotherapy (group H+CT) (Figure 1). The primary endpoint was disease-free survival (DFS), and the PROs/HRQoL was investigated as one of the secondary endpoints in this trial<sup>1</sup>.



### PROs/HRQoL Assessment

Patients completed questionnaires at baseline, 2 months, 1 year, and 3 years after protocol treatment started. The questionnaire consisted of the following scales:

**Functional Assessment of Cancer Therapy-General (FACT-G):** The FACT-G is validated as a sensitive 28-item general cancer HRQoL measure [7 for physical well-being (PWB), 8 for social and family well-being (SFWB), 6 for emotional well-being (EWB), and 7 for functional well-being (FWB)]. Scores range from 0 to 108 and a higher score indicates better HRQoL.

**Philadelphia Geriatric Center Morale Scale (PGCMS):** The PGCMS includes 17 items and is used for assessment of morale, PWB, and HRQoL in the elderly. Scores range from 0 to 17 and a higher score indicates a higher level of morale.

**The Hospital Anxiety and Depression Scale (HADS):** The HADS is a 14-item scale that generates ordinal data. Seven of the items relate to anxiety and 7 relate to depression. Each item on the questionnaire is scored from 0-3; therefore, a score between 0 and 21 indicates possible anxiety or depression. Higher scores indicate greater anxiety and depression.

**Patient Neurotoxicity Questionnaire (PNQ):** The PNQ is composed of two questions about sensory and motor neurotoxicity. PNQ grades range from grade A (no neurotoxicity) to grade E (very severe neurotoxicity). PNQ grades A-C indicate the absence of symptoms interfering with activities of daily living, whereas grades D and E indicate that symptoms of chemotherapy-induced peripheral neurotoxicity are interfering with activities of daily living.

**Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC):** The TMIG-IC was developed as a comprehensive evaluation of the activity capacity of healthy older adults living in the region. It is a multidimensional 13-item scale that includes three subscales: IADL (five items), intellectual activity (four items), and social role (four items).

The FACT-G total score was used to measure the primary endpoint of PROs/HRQoL, with a change in FACT-G total score of  $\geq 5$  points considered to be meaningful.

### Characteristics of the Subjects

135 patients were assigned to group H and 131 to group H+CT. Among these patients, 116 in group H and 115 in group H+CT obtained a baseline response and were selected as the analysis group.

Clinical characteristics of subjects are presented in Table 1.

The response rates at 2 months, 1 year, and 3 years were 89.7%, 79.1% and 89.4% in group H, and 91.7%, 78.9% and 84.2% in group H+CT.

Table 1. Clinical characteristics of subjects

Item	Group H (n=116)	Group H+CT (n=115)	p value
Age (mean, SD)	73.9 2.8	73.7 3.0	0.660
Performance Status			
0	107 92.2%	107 93.0%	0.815
1	9 7.8%	8 7.0%	
Pathological tumor size			
T1	56 48.3%	60 52.2%	0.343
T2	54 46.6%	53 46.1%	
T3	6 5.2%	2 1.7%	
Lymph node metastasis			
Negative	90 77.6%	87 75.7%	0.728
Positive	26 22.4%	28 24.3%	
Stage			
I	51 44.0%	55 47.8%	0.730
IIA	46 39.7%	45 39.1%	
IIB	18 15.5%	13 11.3%	
IIIA	1 0.9%	2 1.7%	
Surgery			
Mastectomy	88 75.9%	74 64.3%	0.038
Breast-conserving surgery	26 22.4%	41 35.7%	
Others	2 1.7%	0 0.0%	
Hormone receptor status			
ER-positive and/or PgR-positive	52 44.8%	58 50.4%	0.394
ER- and PgR-negative	64 55.2%	57 49.6%	
Major comorbidity #			
Absent	45 38.8%	48 41.7%	0.648
Present	71 61.2%	67 58.3%	

# Major comorbidity, including hypertension, diabetes, osteoporosis, and hyperlipidemia

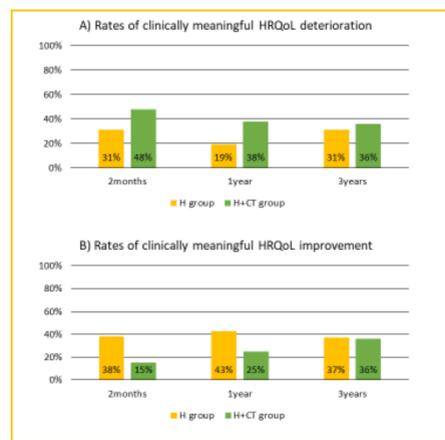


Figure 2. Clinically meaningful A) deterioration and B) improvement in HRQoL were defined as an A) decrease or B) increase of 5 points or more in FACT-G total score compared to that at baseline. Fisher's exact test

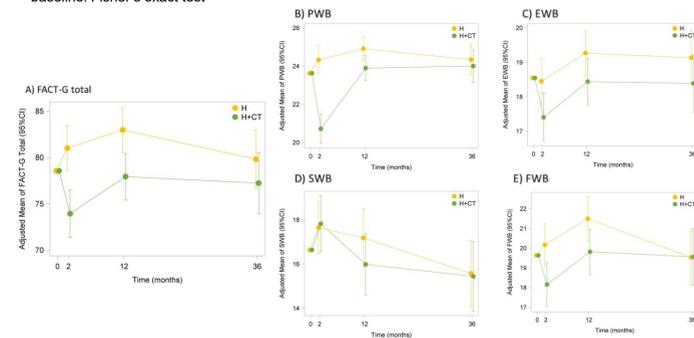


Figure 3. Adjusted means of A) FACT-G total score, B) PWB subscale score, C) EWB subscale score, D) SWB subscale score, and E) FWB subscale score (95% CI)

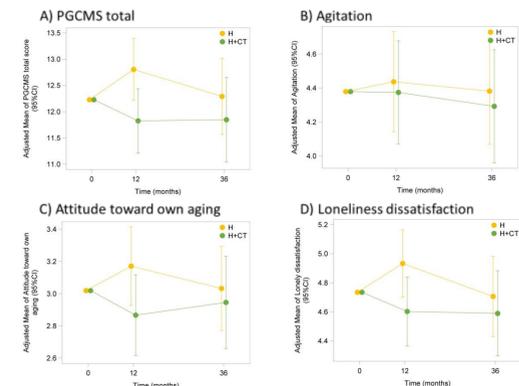


Figure 4. Adjusted means of A) PGCMS total score, B) agitation subscale score, C) attitude toward own aging subscale score, and D) loneliness dissatisfaction subscale score (95% CI)

## RESULTS

**FACT-G:** Significant differences in the rates of clinically meaningful HRQoL deterioration at 2 months (31% (group H) vs. 48% (group H+CT);  $p=0.016$ ) and 1 year (19% vs. 38%;  $p=0.009$ ); and in clinically meaningful HRQoL improvement at 2 months (38% vs. 15%;  $p<0.01$ ) and 1 year (43% vs. 25%;  $p=0.021$ ) (Figure 2).

Significant differences in **FACT-G total score** at 2 months (81.0 vs. 74.0;  $p<0.001$ ) and 1 year (83.0 vs. 78.0;  $p=0.004$ ); **PWB** at 2 months (24.3 vs. 20.7;  $p<0.001$ ) and 1 year (25.0 vs. 23.9;  $p=0.025$ ); **EWB** at 2 months (18.5 vs. 17.4;  $p=0.035$ ); and **FWB** at 2 months (20.2 vs. 18.2;  $p=0.011$ ) and 1 year (21.5 vs. 19.8;  $p=0.039$ ) (Figure 3).

**PGCMS:** Significant difference in **PGCMS total score** at 1 year (12.8 (group H) vs. 11.8 (group H+CT);  $p=0.024$ ) (Figure 4).

**HADS:** Significant differences between **HADS total score** (8.9 (group H) vs. 10.79 (group H+CT);  $p=0.003$ ), **anxiety subscale** (4.9 vs. 5.8;  $p=0.029$ ), and **depression subscale** (4.1 vs. 5.0;  $p=0.009$ ) at 2 months (Figure 5).

**PNQ:** Significant difference in the proportion of cases with **severe sensory neurotoxicity** (grades D and E) at 2 months (2% (group H) vs. 14% for (group H+CT);  $p=0.001$ ) (Figure 6).

**TMIG-IC:** Significant differences in **TMIG-IC total score** (12.0 (group H) vs. 11.5 (group H+CT);  $p=0.042$ ) and **IADL score** (4.9 vs. 4.7;  $p=0.038$ ) at 1 year (Figure 7).

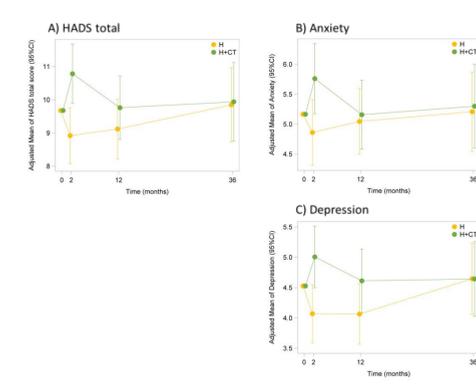


Figure 5. Adjusted means of A) HADS total score, B) Anxiety subscale score, and C) Depression subscale score (95% CI)

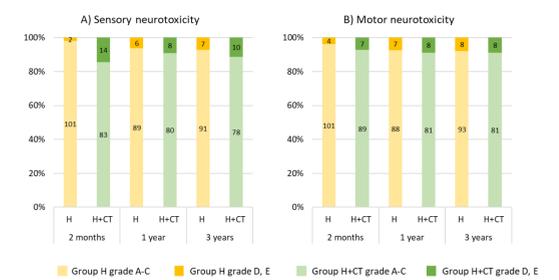


Figure 6. Distribution of PNQ grades. A) sensory neurotoxicity, B) motor neurotoxicity

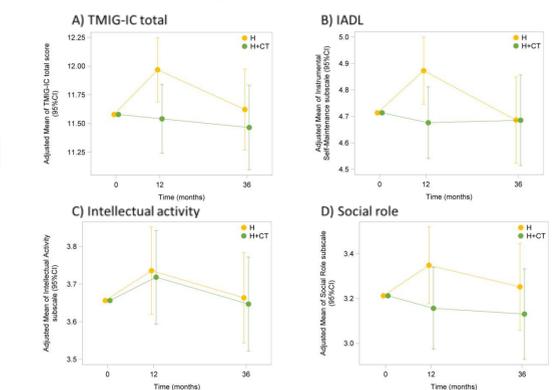


Figure 7. Adjusted means of A) TMIG-IC total score, B) IADL subscale score, C) intellectual activity subscale score, and D) social role subscale score (95% CI)

## DISCUSSION and CONCLUSION

Postoperative chemotherapy for elderly patients with breast cancer resulted in decreases in PWB, EWB, subjective morale, IADL, and global HRQoL from the early stage to the first year after the start of chemotherapy.

At 3 years, there was no difference between the groups. These findings supported recent articles that suggested that a negative change in QoL was short-lived during adjuvant chemotherapy for some elderly patients with breast cancer<sup>2</sup>.

Given the small advantage of adjuvant trastuzumab plus chemotherapy compared to trastuzumab monotherapy for elderly women with HER-2-positive breast cancer, decisions about treatment should be informed by the risk for adverse health effects associated with chemotherapy.

## ACKNOWLEDGEMENT

We wish to thank all of our patients who participated in the RESPECT study. This study was funded by the Comprehensive Support Project (CSP) of the Public Health Research Foundation.

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