Health-related quality of life (HRQOL) and psychological distress in Japanese postmenopausal women with breast cancer treated with tamoxifen, exemestane or anastrozole for adjuvant endocrine therapy: a final analysis for HRQOL in National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 04

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Introduction

TEAM Trial

"Tamoxifen (TAM) and Exemestane (EXE) Adjuvant Multicenter (TEAM)" trial is a phase III, randomized, and open-label trial that compares an efficacy and tolerability of adjuvant 5 years **of EXE with 2.5 to 3 years of TAM followed by EXE for a total of 5 years**. **Adjuvant EXE as an** upfront use of at least 2.5 years had a superior efficacy to TAM in terms of disease free survival of postmenopausal women with hormone-receptor positive, invasive breast cancer.

N-SAS BC 04

National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) 04 is a Japan sub-study of the TEAM trial. It consisted of two protocols as follows.

- TEAM Japanese protocol
  To evaluate the relative impact of EXE, TAM, and anastrozole (ANA) on lipid metabolism, bone mineral density (BMD), and bone turnover markers as primary end points, and blood coagulation, HRQOL, and psychological distress as secondary end points.
- TEAM International protocol
  To evaluate the relative impact of EXE and TAM on blood coagulation, HRQOL, and **psychological distress as secondary end points**.

We reported interim analyses of N-SAS BC 04 for HRQOL and psychological distress at San Antonio Breast Cancer Symposium in 2006 and 2007. The final analysis is reported here.

Objective

To evaluate the impact of adjuvant EXE, TAM, and ANA on HRQOL and psychological distress in postmenopausal women with hormone receptor positive breast cancer.

Patients

Inclusion criteria

- Postmenopausal women with surgically treated stage I to IIIA estrogen receptor positive and/or progesterone receptor positive invasive breast cancer, and with at least one of following criteria; pathologically ≥3 cm of a maximum tumor size, pathologically positive nodes, nuclear grade **3**, **invasive lobular carcinoma or metaplastic carcinoma**.
- They were required to have adequate hematologic, hepatic, and biochemical functions, and to show Eastern Cooperative Oncology Group performance status of 0 to 1.

Exclusion criteria

- Previous histories of any invasive carcinomas within 5 years, deep vein thrombosis, ischemic heart disease, congestive heart failure, myocardial infarction, current treatments for cerebral infarction, or valvular disease
- Hormone replacement therapy within 4 weeks of enrollment
- Bilateral breast cancer.

Treatment regimens

- Eligible patients who met the following criteria were on the TEAM International protocol, and **were randomly assigned 1:1 to receive EXE or TAM (Figure 1)**.
- Other eligible patients were on the TEAM Japanese protocol, and were randomly assigned 1:1:1 to receive EXE, TAM or ANA (Figure 1).

Figure 1. Patient enrollment and distribution

Screening 1		Treatment of hyperlipidemia	
		Yes	No
Treatment of osteoporosis	Yes	TEAM International	TEAM International
	No	TEAM International	Screening 2

TC, total cholesterol
TG, triglyceride

Screening 2		TC <260mg/dl or TG<300mg/dl	
		Yes	No
BMD (%YAM)	≥70%	TEAM Japanese	TEAM Japanese
	<70%	TEAM Japanese	TEAM International

Treatment doses and durations

- EXE, 25 mg daily for 5 years; TAM, 20 mg daily for 2.5 or 3 years followed by 2 or 2.5 years of EXE for a total of 5 years; ANA, 1 mg daily for 5 years.

Stratification (adjustment factors used in dynamic balancing)

- Chemotherapy (yes or no)
- **Nodal metastasis (node negative**, **1-3 nodes positive**, **or 4 or more nodes positive)**
- Radiation therapy (yes or no)
- Institute.

Measures for HRQOL and Psychological Distress

HRQOL was measured using following questionnaires.

- **The 27 items Functional Assessment of Cancer Therapy-General (FACT-G)**
- The 36 items FACT-Breast (FACT-B) that was FACT-G together with 9 items breast cancer subscale (BCS)
- The 45 items FACT-Endocrine Symptoms (FACT-ES) that was FACT-G together with 18 items endocrine symptom subscale (ES).
- Higher scores indicate better HRQOL.

Psychological distress was analyzed using following questionnaires.

- **The 20**-items **C**enter for **E**pidemiologic **S**tudies **D**epression (**CES**-D) Scale.
- Lower scores indicate better condition of psychological distress.
- Patients were asked to complete all questionnaires at baseline and at 3 months and 12 months after the start of treatment.
- Scores of every item of ES and BCS were analyzed in order to clarify which symptoms affected HRQOL.

Statistical analyses

Baseline characteristics were analyzed by using descriptive statistics that were calculated by the groups and using ANOVA or chi-square tests that to determine imbalance among the groups. HRQOL scores were compared between groups using the mixed effect model with the baseline value as a random covariate.

Results

Patients

- A total of 242 patients from 31 institutes in Japan were eligible and enrolled in N-SAS BC 04. Of these patients, 39 and 37 assigned to receive EXE and TAM, respectively (TEAM International protocol), and 55, 56 and 55 assigned to receive EXE, TAM, and ANA, respectively (TEAM Japanese protocol). These patients were classified and grouped as shown in Table 1.
- **Patient and tumor characteristics at baseline were similar across the 3 TEAM Japanese groups**, and also across the 2 TEAM International groups.
- All patients continued trial treatment through 3 months; however, 7 (7.4%), 3 (3.2%), and 3 (5.5%) of 94, 93, and 55 patients on EXE, TAM, and ANA, respectively, discontinued it between 3 and 12 months.

Table 1. The number of patients of the TEAM International groups and TEAM Japanese groups.

Treatments	EXE	TAM	ANA	
TEAM International protocol	39	37		
TEMA Japanese protocol	55	56	55	→TEAM Japanese groups
Total	94	93	→TEAM International groups	

HRQOL and Psychological Distress

- Percentages of patients who completed the required assessment questionnaires at each time point were consistently over 84% in each group throughout the study period.
- There were no significant between-group differences in baseline scores for any of the scales used to assess HRQOL and psychological distress.
- In the patients on the TEAM International groups, the scores of FACT-B were statistically higher in **the patients on TAM than in the patients on EXE over the period of the study (P=0.047) (Figure 3A)**. The scores of FACT-G, FACT-ES, BCS, ES, and CES-D did not statistically differ between the patients on EXE and TAM over the period of the study (Figure 2A, 4A-7A).
- In the patients on the TEAM Japanese groups, the scores of FACT-B were statistically higher in the patients on TAM than in the patients on EXE or ANA over the period of the study (P=0.045) (Figure 3B). The scores of FACT-G, FACT-ES, BCS, ES, and CES-D did not statistically differ between the patients on EXE, TAM and ANA over the period of the study (Figure 2B,4B-7B).
- Of all items of ES and BCS, TAM was significantly worse than EXE or ANA in terms of scores of **ES4 (I have vaginal discharge); however**, **TAM was significantly better in terms of scores of B8 (I** am bothered by a change in weight) in both the TEAM international groups and the TEAM Japanese groups.

Figure 2. FACT-G scores*

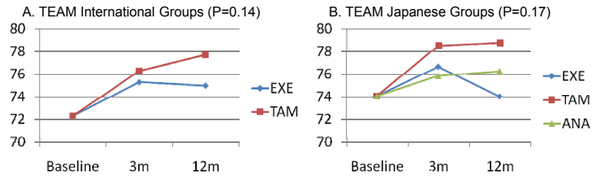


Figure 3. FACT-B scores*

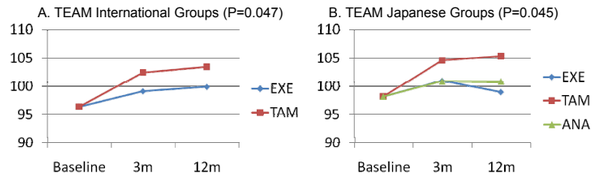


Figure 4. FACT-ES scores*

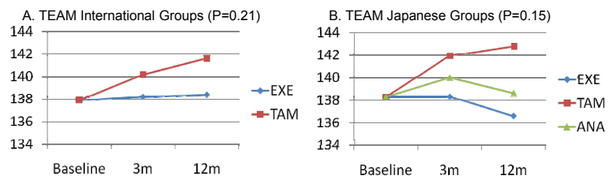


Figure 5. BCS scores*

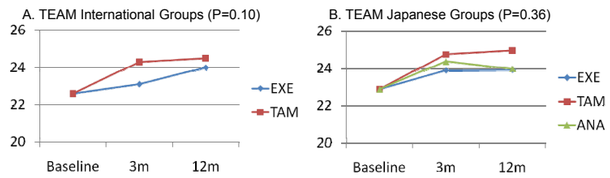


Figure 6. ES scores*

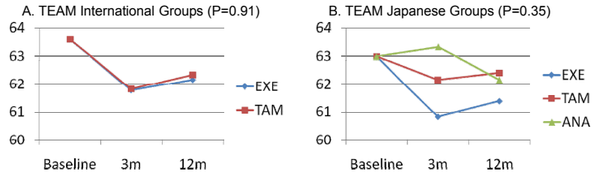
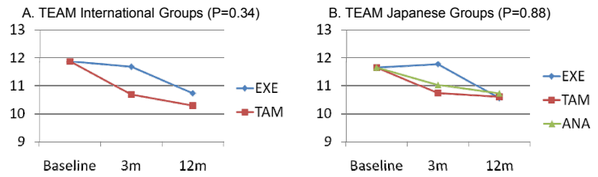


Figure 7. CES-D scores*



***LS(least-squares)means with a common baseline mean are plotted.**

Conclusions

- In Japanese postmenopausal women with breast cancer, HRQOL was better by the initial **adjuvant TAM than EXE or ANA within 12 months after the beginning of these treatments**.
- Psychological distress was similar among three treatments arms.

Discussion

- HRQOL was better in Japanese postmenopausal patients who received a continued TAM than a switched ANA after 1-4 years of TAM in N-SAS BC 03 [1]. In the IES trial a reduction in TOI was **observed within the EXE group and no change in the TAM group; however**, **its reduction** recovered through a short term [2]. In the ATAC trial, no significant difference was observed in QOL scores across treatment groups from baseline during the 2-year period [3].
- In this study HRQOL was better by TAM than EXE or ANA. Of all items of ES and BCS, TAM was worse than EXE or ANA in terms of ES4 (I have vaginal discharge); however, it was better in terms of B8 (I am bothered by a change in weight).
- Some menopausal symptoms or adverse events were reported to be different between ethnic minority women and Caucasians with breast cancer treated with letrozole [4]. It remains to be clarified why better HRQOL was observed in Japanese breast cancer patients who received the initial adjuvant TAM compared to EXE or ANA. A further investigation may be needed in relation to ethnic difference.

References

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