



# Impact of clinical response to neoadjuvant endocrine therapy on patient outcomes: a follow-up study of JFMC34-0601 multicentre prospective neoadjuvant endocrine trial

Takayuki Ueno,<sup>1</sup> Shigehira Saji,<sup>2</sup> Norikazu Masuda,<sup>3</sup> Katsumasa Kuroi,<sup>4</sup> Nobuaki Sato,<sup>5</sup> Hiroyuki Takei,<sup>6</sup> Yutaka Yamamoto,<sup>7</sup> Shinji Ohno,<sup>8</sup> Hiroko Yamashita,<sup>9</sup> Kazufumi Hisamatsu,<sup>10</sup> Kenjiro Aogi,<sup>11</sup> Hiroji Iwata,<sup>12</sup> Takeharu Yamanaka,<sup>13</sup> Hironobu Sasano,<sup>14</sup> Masakazu Toi<sup>15</sup>

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For numbered affiliations see end of article.

**Correspondence to**  
Professor Shigehira Saji; ss-saji@wa2.so-net.ne.jp

## ABSTRACT

**Background** Neoadjuvant endocrine therapy (NET) has been demonstrated to improve breast-conserving rate and is a widely accepted treatment option for postmenopausal patients with hormone receptor-positive breast cancer. There are few reports on the association of NET response and long-term outcomes.

**Objectives** To investigate the prognostic value of clinical response to NET.

**Methods** Long-term outcomes of NET were examined in 107 patients who participated in the multicentre prospective neoadjuvant exemestane study, JFMC34-0601. Patients were treated with 25 mg/day exemestane for 16 weeks followed by an 8-week extension depending on the treatment response.

**Results** Clinical response included partial response (PR) in 58 patients, stable disease in 41 patients and progressive disease (PD) in 8 patients. Clinical response was significantly associated with disease-free survival (DFS), distant disease-free survival (DDFS) and overall survival (OS) ( $P < 0.0001$  for all). Especially, patients with PD showed markedly poor outcomes with median DFS=17.8 months (HR (vs PR): 7.7 (95% CI 1.6 to 33)) and median OS=37.7 months (HR (vs PR): 26.3 (95% CI 2.4 to 655)). Preoperative endocrine prognostic index (PEPI) were associated with DFS and marginally with OS ( $P = 0.022$  and  $0.066$ , respectively). PEPI=0 indicated an excellent prognosis with 95% 5-year DFS (95% CI 73 to 99). In the multivariate analysis including T stage, nodal status and Ki67, clinical response was an independent prognostic factor for DFS, DDFS and OS ( $P = 0.032$ ,  $0.0007$  and  $0.020$ , respectively), whereas PEPI was marginally associated with DFS and OS ( $P = 0.079$  and  $0.068$ , respectively).

**Conclusions** Clinical response to NET showed an independent prognostic value. Patients with PD had markedly poor prognosis, indicating a need of additional therapy. PEPI=0 indicated an excellent prognosis. The integration of clinical response and PEPI would improve decision-making with regard to treatment options for endocrine-responsive breast cancer when these results are validated in a larger clinical trial.

## Key questions

### What is already known about this subject?

- ▶ Clinical response to neoadjuvant endocrine therapy (NET) is associated with surgical outcome, including conversion from mastectomy to breast-conserving surgery.

### What does this study add?

- ▶ Clinical response to NET is an independent predictive marker for long-term survival in postmenopausal patients with endocrine-responsive breast cancer. Especially, patients with progressive disease (PD) during NET showed markedly poor prognosis.

### How might this impact on clinical practice?

- ▶ Integration of clinical response to NET in the decision making for adjuvant treatment will improve the treatment strategy for endocrine-responsive breast cancer. Practically, when patients experienced PD during NET, they would be encouraged to participate in clinical trials that test the effect of intensified adjuvant treatment on outcome of such patients.

**Trial registration number** UMIN C000000345.

## INTRODUCTION

Neoadjuvant endocrine therapy (NET) is a widely accepted treatment option for postmenopausal women with endocrine-responsive breast cancer.<sup>1,2</sup> NET has been shown to reduce tumour volume in 30%–75% of the patients and to increase breast-conserving rate.<sup>3–6</sup> It has also been shown that post-treatment characteristics of tumours including tumour size, nodal status, oestrogen receptor (ER) status and Ki67 are good indicators for patients' long-term outcomes.<sup>5,7,8</sup> Thus, NET

is considered a promising strategy for stratification of prognosis for patients with endocrine-responsive breast cancer.

Response to neoadjuvant systemic therapy can be a surrogate endpoint because of its correlation with patients' prognosis. Pathological response to neoadjuvant treatment, especially pathological complete response (pCR), is a good surrogate marker for long-term outcomes in patients with different types of breast cancer.<sup>9–11</sup> However, pCR is not necessarily associated with long-term survival for patients with endocrine-responsive breast cancer. In addition, pCR rate by NET is relatively low.<sup>3–6</sup> Thus, pCR is not a potential surrogate endpoint for endocrine-responsive breast cancers in chemotherapy or endocrine therapy in the neoadjuvant setting.

Clinical response to NET is associated with surgical outcome, including conversion from mastectomy to breast-conserving surgery (BCS).<sup>12</sup> However, there are few reports examining the association of clinical response to NET with long-term outcomes. In this report, we examined long-term outcomes of patients who received neoadjuvant exemestane treatment for 24 weeks in a multicentre prospective clinical trial and found that clinical response to NET is an independent predictive marker for long-term survival in postmenopausal patients with endocrine-responsive breast cancer.

## PATIENTS AND METHODS

A multicentre prospective neoadjuvant exemestane study, JFMC34-0601, was a single-arm, phase II study to assess treatment response and safety of NET (registration number: UMIN C000000345). The survival analysis in association with clinical response was included in the secondary endpoints. The design of the trial is reported elsewhere.<sup>13–15</sup> Briefly, the eligibility criteria included postmenopausal women aged 55–75 years with histologically confirmed stage II or IIIa invasive breast

cancer with positive ER status ( $\geq 10\%$  nuclear staining). The treatment included 25mg/day exemestane for 16 weeks followed by an 8-week extension depending on the treatment response. Treatment response was assessed every 4 weeks. Patients underwent surgery at 24 weeks. Patients with progressive disease (PD) were withdrawn from the study treatment and offered appropriate alternative therapy such as surgical intervention or other drug therapy. Clinical response was evaluated by investigators as described previously by combining calliper measurement and image modalities including ultrasound, CT and MRI as suggested by the Response Evaluation Criteria in Solid Tumors version 1.0.<sup>14</sup>

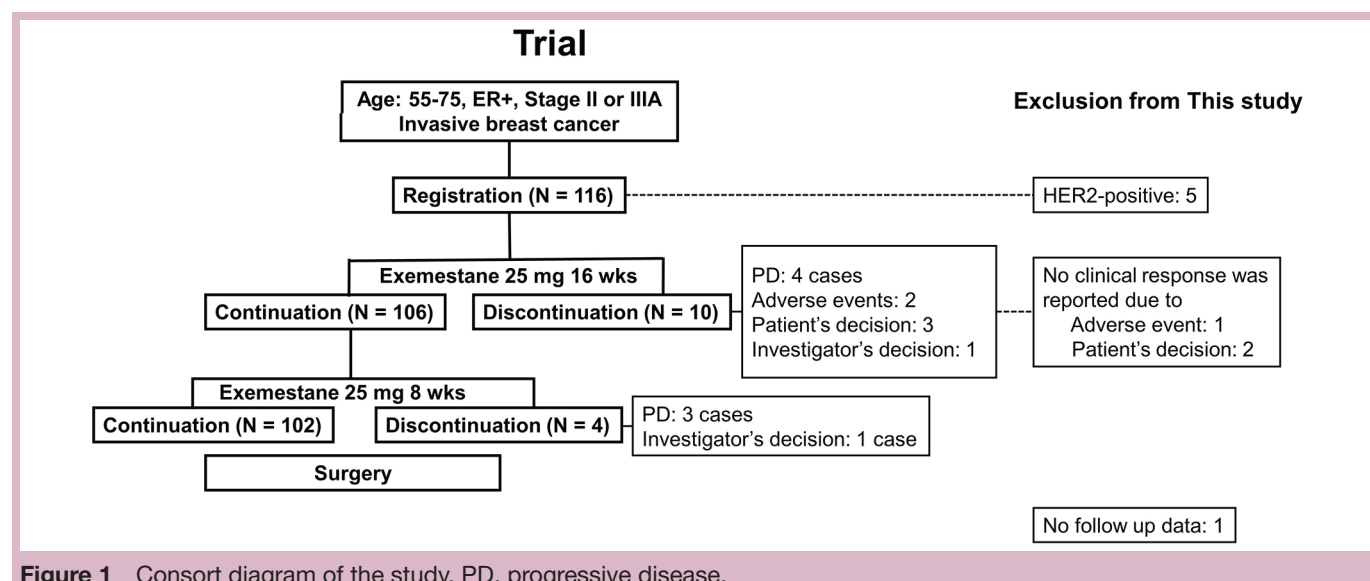
Preoperative endocrine prognostic index (PEPI) was calculated on the basis of tumour characteristics of surgical specimen including tumour size, nodal involvement, ER status and Ki67 according to the method by Ellis *et al.*<sup>8</sup> PEPI for recurrence-free survival (RFS) and breast cancer-specific survival was used for disease-free survival (DFS) and overall survival (OS) analysis, respectively. Distant disease-free survival (DDFS) could not be examined because PEPI for DDFS has not been developed.<sup>8</sup>

After surgery, patients received standard adjuvant therapy including radiation, chemotherapy and endocrine therapy. For patients with complete response (CR), partial response (PR) and stable disease (SD) in the trial, exemestane was continued as an adjuvant therapy after surgery.

Informed consent was obtained from all the patients who participated in this study. The study was performed in accordance with the Declaration of Helsinki.

## STATISTICAL ANALYSIS

Prognosis was analysed by the log-rank test according to individual clinical and pathological parameters. Multivariate analysis was performed by the Cox proportional



**Figure 1** Consort diagram of the study. PD, progressive disease.

**Table 1** Patients' background characteristics

Factor	N
Total	107
Age (years)	
55–59	21
60–69	53
70–79	33
T	
2	102
3	5
N	
0	77
1	28
2	2
Clinical Stage	
IIA	76
IIB	27
IIIA	4
ER	
+	107
–	0
PgR	
+	101
–	6
HER2	
+	0
–	107

ER, oestrogen receptor; PgR, progesterone receptor.

hazards model. The association between clinical response and types of surgery were analysed by the  $\chi^2$  test. All statistical analyses were performed by JMP V.13.2.0.

## RESULTS

The consort diagram for this study is shown in [figure 1](#). One hundred and sixteen patients were registered for the clinical trial. Nine patients were excluded from the analysis because five patients had HER2-positive disease, no clinical response was reported in three patients and no follow-up data were obtained from one patient. Thus, this study included 107 patients whose background information is shown in [table 1](#).

The median follow-up period was 5.5 years. The 2-year and 5-year survival rates were 99% (95% CI 97% to 100%) and 90% (95% CI 84% to 96%), respectively.

### Pretreatment factors and patient outcomes

Conventional prognostic factors including tumour size, nodal status, PgR status and Ki67 were analysed in association with patients' long-term outcomes ([table 2](#)). The magnitude of impact on different prognosis including

DFS, DDFS and OS differed depending on factors. ER could not be analysed for survival because 96% of the patients had tumours with high ER expression (Allred score  $\geq 6$ ).

### Post-treatment factors and patient outcomes

Post-treatment clinicopathological factors were also analysed for survival ([table 2](#)).

PEPI was calculated on the basis of tumour characteristics at the time of surgery. Patients were divided into two groups on the basis of PEPI (0 and  $\geq 1$ ). Patients with PEPI  $\geq 1$  showed a worse prognosis than those with PEPI=0; the difference was significant for DFS and marginal for OS (P=0.022 and 0.066, respectively) ([figure 2A](#)). In particular, PEPI=0 indicated an excellent prognosis (5-year DFS rate: 95% (95% CI 73% to 99%)). When stratified by tumour size and nodal status, PEPI showed marginal prognostic power for DFS in patients with T2N0 tumours (P=0.078) ([figure 2B](#)). Although only a few patients with T2N1 tumours showed PEPI=0, they showed a favourable prognosis ([figure 2B](#)).

### Therapeutic response and patient outcomes

Clinical response included PR in 58 patients, SD in 41 patients and PD in eight patients. No patients showed CR. Clinical response was significantly associated with DFS, DDFS and OS (P<0.0001 for all) ([figure 3A](#)). In particular, patients with PD showed markedly poor outcomes with median DFS=17.8 months (HR (vs PR): 7.7 (95% CI 1.6 to 33)), median DDFS=17.8 months (HR: 16 (95% CI 3.9 to 62)) and median OS=37.7 months (HR: 26.3 (95% CI 2.4 to 655)) ([figure 3A](#)). However, patients with SD showed similarly favourable survival to those with PR in terms of DFS, DDFS and OS. When stratified by tumour size and nodal status, clinical response held prognostic power for DFS in patients with T2N0 and T2N1 tumours (P=0.0053 and 0.0069, respectively) ([figure 3B](#)).

Pathological response was not associated with prognosis (data not shown).

### Types of surgery and patient outcomes

Types of surgery (BCS vs mastectomy) were analysed in association with patient prognosis. No surgery was performed in four patients because two of these patients had PD and received preoperative chemotherapy and the other two patients had PR and refused surgical intervention. Clinical response was correlated with types of surgery. The breast-conserving rate was 87.5% (49/56) for the patients with PR, 87.8% (36/41) for those with SD and 16.7% (1/6) for those with PD (P=0.0008). The types of surgery showed a significant association with DDFS and a marginal association with DFS (P=0.024, and 0.067, respectively) ([figure 3C](#)). No association was observed between the types of surgery and OS.

### Multivariate analysis

Multivariate analysis was performed using baseline characteristics with P value <0.2 in the univariate analysis and a post-treatment index, PEPI, together with clinical

**Table 2** Univariate and multivariate analysis for DFS, DDFS and OS

<b>Univariate analysis (log-rank test)</b>						
	<b>DFS</b>		<b>DDFS</b>		<b>OS</b>	
	$\chi^2$	<b>P value</b>	$\chi^2$	<b>P value</b>	$\chi^2$	<b>P value</b>
<b>Pretreatment factors</b>						
T: T2 versus T3	5.27	<b>0.02</b>	3.31	0.069	4.68	<b>0.03</b>
N: N0 versus N1/2	8.01	<b>0.0047</b>	5.34	<b>0.021</b>	3.39	0.066
PgR (Allred): <3 versus $\geq$ 3	0.39	0.53	0.14	0.71	0.13	0.72
Ki67: $\leq$ 11% versus >11%	4.78	<b>0.029</b>	4.69	<b>0.03</b>	2.03	0.15
<b>Post-treatment factors</b>						
T: T1/2 versus T3	5.79	<b>0.016</b>	2.21	0.14	0.65	0.42
N: negative versus positive	2.20	0.14	1.49	0.22	1.79	0.18
Ki67: $\leq$ 2.7% versus >2.7%	3.34	0.068	3.58	0.059	5.50	<b>0.019</b>
PEPI: 0 vs $\geq$ 1	5.24	<b>0.022</b>	-	-	3.39	0.066
<b>Multivariate analysis (Cox proportional hazards model)</b>						
	<b>DFS</b>		<b>DDFS</b>		<b>OS</b>	
	<b>HR (95% CI)</b>	<b>P value</b>	<b>HR (95% CI)</b>	<b>P value</b>	<b>HR (95% CI)</b>	<b>P value</b>
T: T2 versus T3	0.94 (0.13 to 20)	0.96	0.85 (0.16 to 6.5)	0.86	0.76 (0.069 to 18)	0.84
N: N0 versus N1/2	0.51 (0.18 to 1.5)	0.21	0.49 (0.18 to 1.4)	0.19	0.79 (0.17 to 5.2)	0.79
Ki67: $\leq$ 11% versus >11%	0.59 (0.19 to 1.7)	0.33	0.66 (0.22 to 2.0)	0.45	1.3 (0.21 to 9.9)	0.77
PEPI: 0 versus $\geq$ 1	0.22 (0.012 to 1.2)	0.079	-	-	1.1*10 <sup>-9</sup> (1.4*10 <sup>-300</sup> to 1.2)	0.068
<b>Clinical response</b>		<b>0.032</b>		<b>0.0007</b>		<b>0.020</b>
SD versus PR	2.1 (0.71 to 6.7)		2.3 (0.78 to 7.1)		5.4 (0.78 to 108)	
PD versus PR	7.7 (1.6 to 33)		16 (3.9 to 62)		26.3 (2.4 to 655)	

Post-treatment Ki67 was associated with OS (P=0.019).

Bold means statistically significant.

DFS, disease-free survival; DDFS, distant disease-free survival; OS, overall survival; PD, progressive disease; PEPI, preoperative endocrine prognostic index; PgR, progesterone receptor; SD, stable disease.

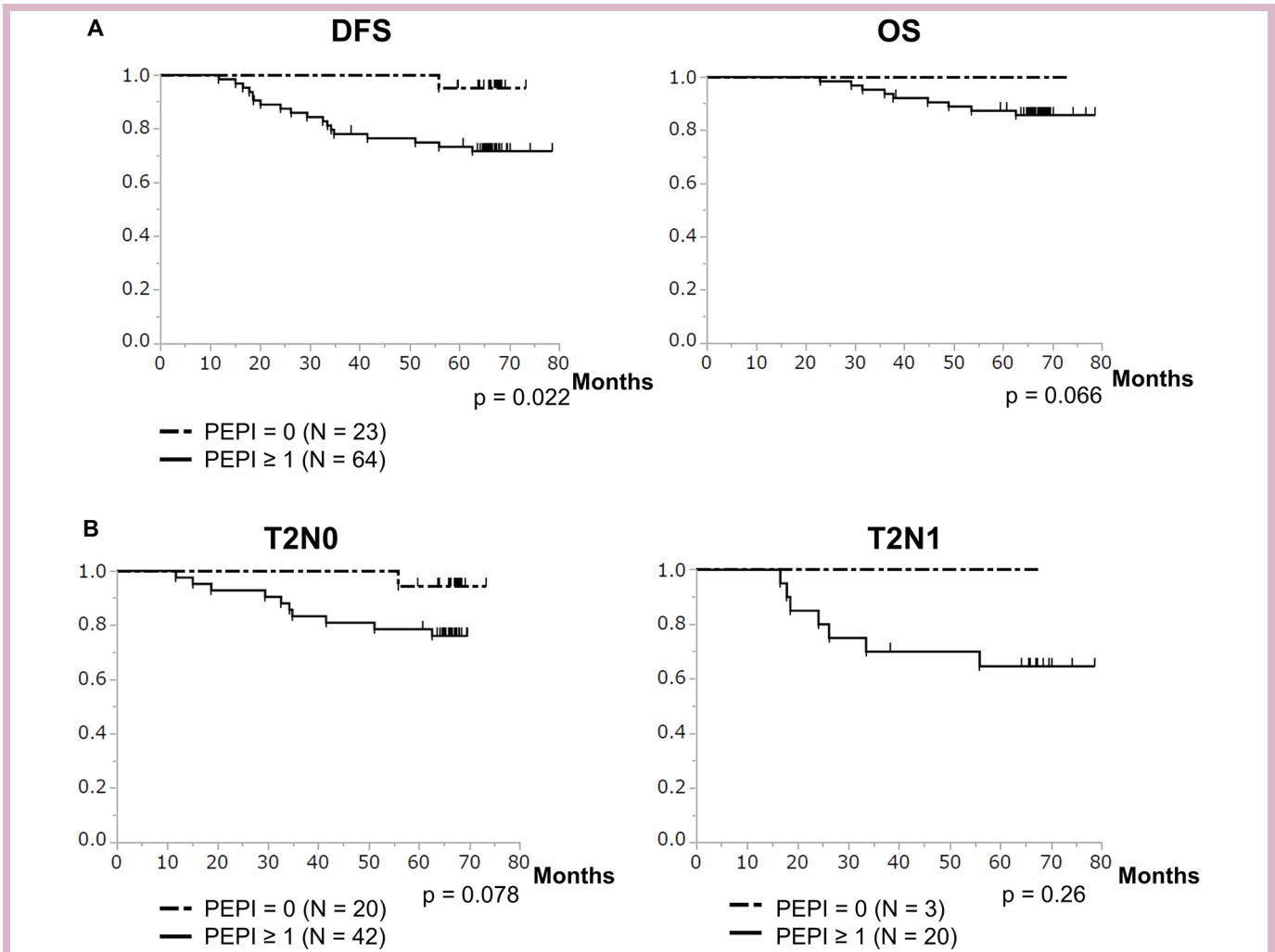
response (table 2). Types of surgery were not included in the analysis because of the close correlation with clinical response. The multivariate analysis revealed that clinical response was an independent prognostic factor for all the survival analyses including DFS, DDFS and OS (P=0.032, 0.0007 and 0.020, respectively) (table 2). PEPI was marginally associated with DFS and OS (P=0.079 and 0.068, respectively). None of the other clinical and pathological factors remain significant.

## DISCUSSION

This study demonstrated that clinical response to NET is an independent prognostic factor for DFS, DDFS and OS. Especially patients with PD showed markedly poor prognosis, which indicates that clinical trials that test the effect of additional treatments in the adjuvant settings need to be considered. One retrospective observational study showed that absence or slow response to NET was

associated with poor RFS and that it was an independent predictor for RFS, which is in accordance with our finding.<sup>16</sup> Interestingly, patients with SD showed similar prognosis to those with PR, which suggests that the effect of NET on prognosis derives from tumour cell death and arrest of tumour cell growth.

Since pCR is not frequent in NET and the prognostic value of pCR for endocrine-responsive breast cancer is not well established, it is of clinical value to clarify the prognostic power of clinical response (CR and PR) to NET. Our study showed 84.1% 5-year DFS rate in patients with clinical response (figure 3A). Even when restricted to T2N0 tumours, it was 89.8%, which is not high enough to rule out chemotherapy (figure 3B). Thus, the clinical response to NET does not seem to yield sufficient results to consider the omission of chemotherapy. Additional research is needed to clarify whether addition of chemotherapy improves prognosis in such patients.



**Figure 2** (A) Disease-free survival (DFS) and overall survival (OS) according to PEPI. PEPI was significantly associated with DFS and marginally with OS ( $P=0.022$  and  $0.066$ , respectively). (B) Disease-free survival according to PEPI stratified by tumour size and nodal status. PEPI, preoperative endocrine prognostic index.

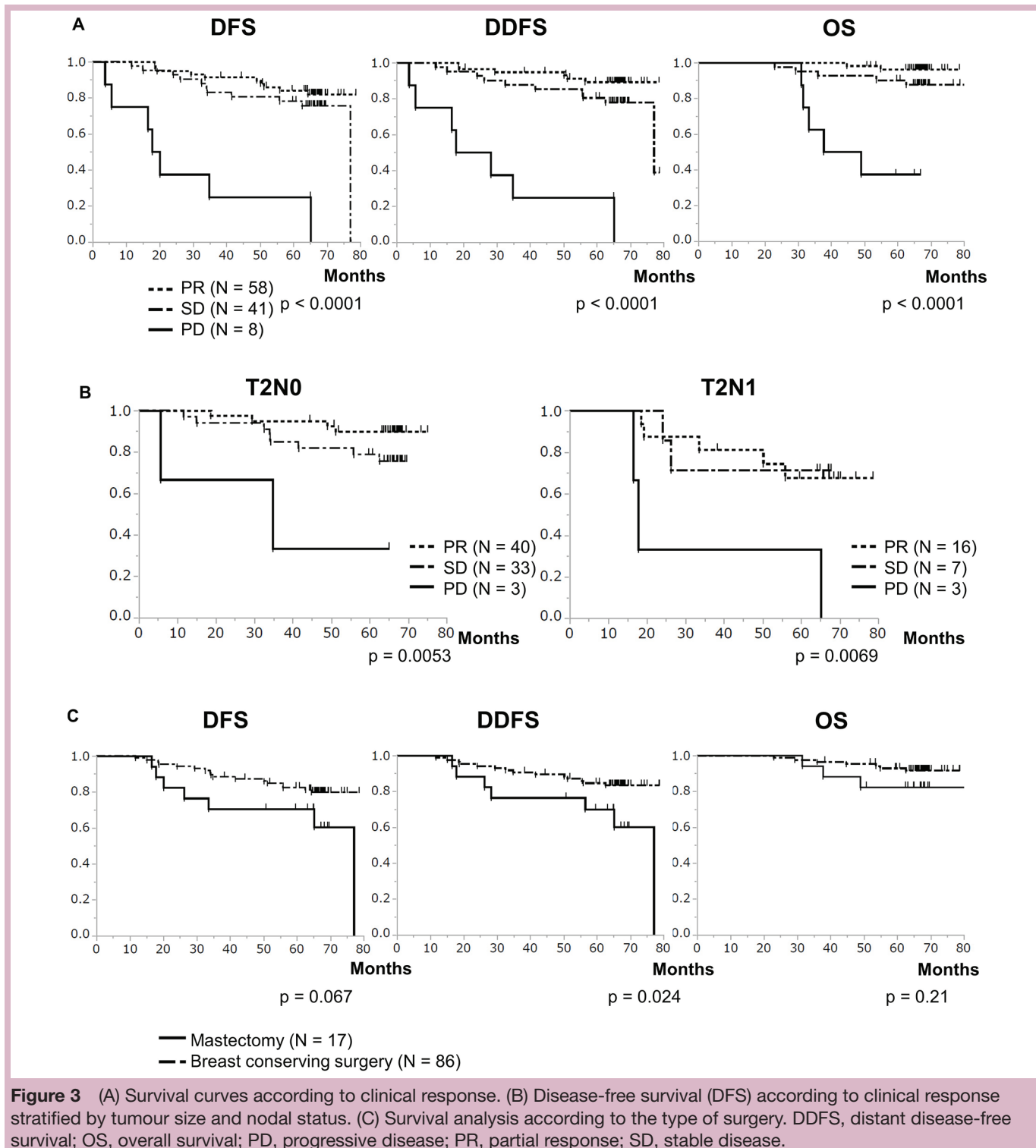
A retrospective observational study by Grassadonia showed that clinical response was strongly correlated with BCS and that BCS was an independent prognostic factor for DFS and OS.<sup>12</sup> Our study showed a correlation between clinical response and the type of surgery; the type of surgery was associated with patient prognosis. These results also align with findings of previous reports. Although the type of surgery was not included in the multivariate analysis due to its close association with clinical response, to the best of our knowledge, this is the first prospective study that showed the prognostic value of clinical response to NET.

In this study, we showed that conventional prognostic factors for endocrine-responsive tumours including tumour size, nodal status and Ki67 held prognostic value following NET. In addition, we confirmed the prognostic value of PEPI, which comprises post-treatment tumour characteristics.<sup>8</sup> PEPI=0 indicated an excellent prognosis (95% 5-year DFS rate), and thus, PEPI=0 seems to be a good indicator for the omission of chemotherapy. However, our study allowed adjuvant chemotherapy after

NET; hence, it is not clear whether PEPI=0 indicates an equally good prognosis with endocrine therapy alone. Further prospective studies are necessary to examine the clinical usefulness of PEPI for chemotherapy indication.

Optimal duration of NET is still an issue of debate. Major clinical trials offered endocrine therapy for 3–4 months.<sup>3–6</sup> A phase II clinical trial, the primary endpoint of which was to establish the optimal duration to attain the maximum response, offered letrozole between 4 months and 12 months.<sup>17</sup> Median times to objective response and maximum response were reported to be 3.9 months (95% CI 3.3 to 4.5) and 4.2 months (95% CI 4.0 to 4.5), respectively; however, 37.1% of the patients achieved the maximum response after 6 months. Another clinical trial, the aim of which was to establish optimal duration to allow BCS for patients with tumours larger than 20 mm, offered letrozole up to 12 months; the median time to achieve BCS was 7.5 months (95% CI 6.3 to 8.5), which was also beyond 6 months.<sup>18</sup> A single institutional trial was conducted to investigate the pCR rates by letrozole for 4 months, 8 months and 12 months.<sup>19</sup>





The pCR rate was more frequent as the duration became longer: 2.5% for 4 months, 5.0% for 8 months and 17.5% for 12 months. The panel at St. Gallen 2015 concluded that NET should continue either for 4–8 months or until maximal response.<sup>20</sup> Our study used 6 month duration of exemestane, and thus, it is unclear whether clinical response will predict long-term outcome when NET continues until maximal response. However, considering that only patients with clinical response or SD continue

NET until maximum response, the prognostic value of clinical response seems to be retained.

There are several limitations in this study. One critical limitation is a small sample size. In particular, subgroup analyses based on tumour size and nodal status require cautious interpretation. Another limitation is a lack of information on adjuvant therapy. Since adjuvant therapy influences long-term outcomes, it would be of clinical importance to analyse prognosis

with detailed information of adjuvant therapy. However, because standard adjuvant therapies including chemotherapy with anthracycline and taxane were indicated in this study, our result may be a representative result of clinical practice. Means to assess clinical response is another issue. We applied the investigators' evaluation based on the combination of calliper measurement and image modalities including ultrasound, CT and MRI. It would be of clinical importance to monitor tumour size centrally by a fixed modality such as MRI in future studies.

In conclusion, we demonstrated that clinical response to NET was an independent prognostic factor for DFS, DDFS and OS and that patients with PD showed markedly poor outcomes. Patients with PEPI=0 showed an excellent prognosis with 95% 5-year DFS rate. Integration of clinical response and PEPI to determine the appropriate options of adjuvant treatment will improve the treatment strategy for endocrine-responsive breast cancer. Further studies are warranted to confirm the clinical utility of NET for the stratification of endocrine-responsive breast cancer.

#### Author affiliations

- <sup>1</sup>Department of Breast Surgery, Breast Oncology Center, The Cancer Institute Hospital, The Japanese Foundation for Cancer Research, Tokyo, Japan
- <sup>2</sup>Department of Medical Oncology, Fukushima Medical University, Fukushima, Japan
- <sup>3</sup>Department of Surgery, Breast Oncology, National Hospital Organization Osaka National Hospital, Osaka, Japan
- <sup>4</sup>Department of Surgery, Tokyo Metropolitan Health and Medical Treatment Cooperation Ebara Hospital, Tokyo, Japan
- <sup>5</sup>Department of Breast Oncology, Niigata Cancer Center, Niigata, Japan
- <sup>6</sup>Department of Breast Surgery, Nippon Medical School, Tokyo, Japan
- <sup>7</sup>Department of Breast and Endocrine Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
- <sup>8</sup>Breast Oncology Center, The Cancer Institute Hospital, The Japanese Foundation for Cancer Research, Tokyo, Japan
- <sup>9</sup>Department of Breast Surgery, Hokkaido University Hospital, Sapporo, Japan
- <sup>10</sup>Oikawa Hospital, Fukuoka, Japan
- <sup>11</sup>National Hospital Organization Shikoku Cancer Center, Ehime, Japan
- <sup>12</sup>The department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, Nagoya, Japan
- <sup>13</sup>Department of Biostatistics, Yokohama City University, Yokohama, Japan
- <sup>14</sup>Department of Pathology, Tohoku University School of Medicine, Sendai, Japan
- <sup>15</sup>Department of Surgery (Breast Surgery), Kyoto University, Kyoto, Japan

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**Contributors** SS and MT have contributed to the conception and design of the study and drafting the study. TU has contributed to the data analysis and manuscript writing. NM, KK, NS, HT, YY, SO, HY, KH, KA and HI have contributed to acquisition of data. TY has contributed to the statistical analysis. HS has contributed to pathological analyses.

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**Patient consent** Obtained.

**Ethics approval** The clinical trial and all the analyses comply with the current law of Japan. The study protocol was approved by the Ethics Committee in each institution.

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