

# Optimal Treatment Duration of Neoadjuvant Endocrine Therapy for Women Aged 60 Years or Older with Estrogen Receptor-Positive, HER2-Negative Invasive Breast Cancer

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**Background:** Neoadjuvant endocrine therapy is not the standard of care for breast cancer, primarily because the optimal treatment duration remains unclear. This phase 2 prospective multicenter study analyzed time to progression, time to maximal response, and time to treatment failure for neoadjuvant exemestane.

**Methods:** Inclusion criteria were women aged  $\geq 60$  years with Stage II or III breast cancer classified as estrogen receptor-positive/human epidermal growth factor receptor 2-negative. Response was defined as a  $\geq 10\%$  and minimum of 3 mm decrease in tumor size, as compared with the most recent or smallest value, and no new lesion. Progression was defined as a  $>10\%$  and minimum of over 3 mm increase in tumor size, as compared with the most recent or smallest value, or a new lesion. Maximal response was defined as the final recorded response.

**Results:** This study included 24 women, most of whom had T2 N0 tumors with high estrogen receptor expression. We initially observed a response in 23 patients (96%); however, 6 patients (25%) later experienced progression. Time to progression, time to maximal response, and time to treatment failure ranged from 7 to 22 months (estimated median, 35), 1 to 22 months (estimated median, 10), and 2 to 22 months (estimated median, 22), respectively. Treatment duration varied widely, but the estimated optimal duration of neoadjuvant exemestane therapy was 22 to 35 months in patients seeking to avoid surgery and 10 months in patients wishing to receive breast-conserving surgery.

**Conclusions:** Neoadjuvant exemestane therapy is long effective for older women with hormone-sensitive breast cancer. (J Nippon Med Sch 2021; 88: 354–360)

**Key words:** neoadjuvant endocrine therapy, aromatase inhibitors, exemestane, progression, response

## Introduction

In women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, initial endocrine therapy (ET) is a

standard treatment<sup>1</sup>. In metastatic, non-curable diseases, it is generally considered that ET is better than chemotherapy because quality of life is meaningful, with no clear evidence that initial chemotherapy can prolong sur-

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vival as compared with ET. In postmenopausal women with operable breast cancer, preoperative or neoadjuvant endocrine therapy (NET) is a treatment choice because in neoadjuvant settings aromatase inhibitors (AIs) were as effective as chemotherapy in terms of breast-conserving surgery (BCS) rates<sup>2,3</sup>. In addition, the efficacy of neoadjuvant AIs was superior to that of tamoxifen<sup>4-6</sup>.

In most previous studies, preplanned treatment durations of NET were 3 to 6 months<sup>7,8</sup>; however, it was reported that some study patients continued to take AIs because of persistent tumor regression<sup>9</sup>. Our Saitama Breast Cancer Clinical Study Group (SBCCSG) conducted a phase II clinical trial (SBCCSG-03) in which the pathological effects of exemestane were analyzed in postmenopausal women with ER-positive, invasive breast cancer after 4 months of treatment. A total of 44 patients were treated with neoadjuvant exemestane for 4 months; however, 6 chose to remain on exemestane without surgery because of estimated persistent tumor shrinkage<sup>10</sup>.

NET is not a standard of care for breast cancer, because its optimal treatment duration has not been determined. In addition, it remains to be clarified whether survival times are improved by NET. The meaning of "optimal" depends on the purpose of treatment. The main purpose of NET is converting an initially necessary mastectomy to BCS. In this setting, optimal treatment duration is identical to time to maximal response (TTMR). Another purpose of NET is to safely avoid surgery during a certain period without progression. For this purpose, optimal treatment duration is identical to time to progression (TTP). TTP is an important index when surgery must be postponed. The last purpose is to discern the sensitivity of ET, which implies prediction of survival time and determination of chemotherapy requirements. TTP is a clinical marker believed to correlate with the sensitivity of ET.

For optimal treatment durations of NET using AIs, TTMR and the time to maximize a conversion rate of mastectomy to BCS were analyzed in previous studies<sup>11-14</sup>; whereas, TTP has never been analyzed. Because the optimal treatment duration for adjuvant ET is 5 years or more<sup>15</sup>, the median TTP of NET might be much longer than the planned treatment durations in previous studies. A phase II multicenter study conducted by SBCCSG analyzed TTP, TTMR, and time to treatment failure (TTF) of NET using the steroidal AI exemestane in women aged 60 years or older with ER-positive, HER2-negative invasive breast cancer. This article is the first report of this study.

## Patients and Methods

### Trial Design

This phase II, multicenter trial of SBCCSG-10 analyzed optimal treatment durations for neoadjuvant exemestane (trial identification, UMIN00000802). The primary endpoint was TTP. Secondary endpoints were TTMR, TTF, clinical tumor response (Response Evaluation Criteria in Solid Tumors, RECIST, version 1.1), pathological tumor response, adverse events, changes in bone mineral density, and changes in Ki67 labeling index. The treatment plan involved neoadjuvant use of exemestane for at least 3 years, unless progression was observed. This trial was approved by the institutional review boards of all hospitals in which patients were recruited. In this manuscript, TTP, TTMR, and TTF were analyzed based on tumor size, as measured by a caliper at preplanned time points.

### Patients

Eligible patients were women aged 60 years or older with core needle biopsy-proven, ER-positive, and HER2-negative invasive carcinoma of the breast, without distant metastases. Eligibility criteria for clinical tumor size and clinical nodal status were T2, T3, or T4b and N0, N1, or N2, respectively, according to the UICC TNM classification. ER positivity was defined as 10% or more positive cells by immunohistochemistry (IHC). HER2 negativity was defined as 0, 1+, or 2+ by the HercepTest; however, 2+ cases with HER2 amplification >1.8 HER2/chromosome 17 centromere (CEP17) ratio by fluorescence in situ hybridization (FISH) were excluded. Eligible performance status (Eastern Cooperative Oncology Group, ECOG) was 0 to 1. Written informed consent was required for all patients.

Exclusion criteria were patients who had received chemotherapy or ET for the present disease, patients who were receiving hormone replacement therapy at diagnosis, and patients who had a previous history of breast cancer or any active invasive cancers.

A total sample size of 23 was determined for this study based on the following analysis. In the SBCCSG-03 trial<sup>10</sup>, a partial response or a minor response was observed in 86% of postmenopausal women with ER-positive invasive breast cancer at 4 months after starting neoadjuvant exemestane. If the effects of neoadjuvant exemestane were consistent with an exponential distribution, the estimated progression-free survival (PFS) rate would be 25% at 3 years. In this trial, the recruited patients were considered more sensitive to neoadjuvant exemestane because they were older than patients in the SBCCSG-03 trial and because HER2-positive disease was

excluded from the SBCCSG-03 trial. Therefore, PFS at 3 years was estimated to be 50% in this trial. To confirm this estimated PFS rate of 50%, 20 patients were required statistically, and the alpha error and beta error were 0.05 and 0.20, respectively. The number of patient withdrawals was estimated at 20%; thus, a total of 25 patients were needed for this trial.

The first patient was registered in August 2007, and a total of 25 patients were registered as of February 2009, when study entry was closed.

#### Treatment and Follow-up

Patients took exemestane 25 mg per day for at least 3 years after starting the treatment, unless progression was observed. The follow-up period was defined as the interval from the beginning of treatment to the last outpatient visit or death from any cause.

#### Clinical Tumor Response

Tumor size was measured by palpation by using a caliper at baseline, at 1, 2, and 3 months after starting treatment, and every 3 months thereafter. Ultrasound and/or mammography were performed at baseline, at 3 and 6 months after starting treatment, and every 6 months thereafter. Tumor size was defined as maximum tumor diameter.

A response was defined as a decrease of  $\geq 10\%$  and minimum of 3 mm in tumor size, as compared with the most recent or smallest value, and no new lesions. Progression was defined as an increase of  $>10\%$  and minimum of over 3 mm in tumor size, as compared with the most recent or smallest value, or a new lesion. No change was defined as a finding outside the above categories. Maximal response was defined as the final recorded response. For tumors that were no longer palpable, tumor size was categorized as 0 mm and defined as maximal response. Tumor response was also classified into 4 categories—complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD)—by RECIST version 1.1<sup>16</sup>. Response was categorized as CR when tumors were nonpalpable.

#### TTP, TTMR, and TTF

TTP and TTMR were defined as the durations from the beginning of treatment to progression and maximal response, respectively. TTF was defined as the duration from the beginning of treatment to the time treatment was stopped for any reason. TTP, TTMR, and TTF were calculated in all patients. The medians of these durations were calculated by the Kaplan-Meier method. Statistical analyses were performed by using BellCurve for Excel (SSRI. Inc. Japan).

Table 1 Patient and tumor characteristics

Age, years	
60-84 (mean and median, 69)	
TNM Stage	N
T2 N0	20 (91.7%)
T2 N1	2 (8.3%)
T4b N0	1 (4.2%)
T4b N2	1 (4.2%)
ER/PgR (0-8, Allred score; +, Score unknown)	
ER 7-8/PgR 7-8	11 (45.8%)
ER 7-8/PgR 5-6	3 (12.5%)
ER 7-8/PgR 0-4	9 (37.5%)
ER+/PgR+	1 (4.2%)
HER2	
2+ (FISH<1.8)	2 (8.3%)
1+	14 (58.3%)
0	8 (33.3%)

#### Results

Twenty-five patients were initially registered in this trial. However, 1 was ineligible because she had a tumor with 2+ HER2 expression by HercepTest and 1.9 ratio of HER2 amplification by FISH. Ultimately, 24 patients with 24 tumors were eligible for this study. Patient age was 60 to 84 years (mean and median, 69.0 years). Tumor size by palpation at baseline was 23 to 50 mm (mean, 33.6 mm). Tumor size, nodal status, ER, progesterone receptor (PgR), and HER2 at baseline are shown in **Table 1**. Most patients were classified as T2 N0 M0, stage IIA, and tumors had high ER expression.

Tumor size as measured by palpation at preplanned time points was analyzed because some ultrasound and mammography data were missing. Of the 24 patients, a response was initially observed in 23 (96%) at 1 to 6 months after starting treatment. No change was observed in 1 patient (4%) until 15 months after starting treatment. Tumor size in relation to baseline tumor size was calculated for each patient at all time points. Mean relative tumor size consistently decreased over time during the entire study period (**Fig. 1**).

Progression was observed in 6 patients (25%), all of whom had an initial response. Time range to progression after starting treatment was 7 to 22 months (**Fig. 2**). In one of the 6 patients, a new lesion was detected in the same breast at 22 months after starting treatment and was classified as progression, although the primary tumor had become nonpalpable. This new lesion was pathologically diagnosed as ER-negative ductal carcinoma in situ. In the other 5 patients, all tumor sizes were

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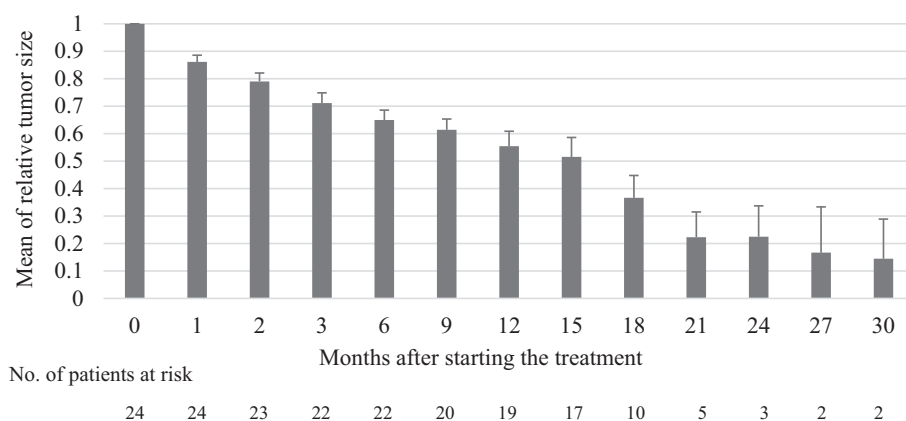


Fig. 1 Mean relative tumor size (with standard error) at preplanned time points.

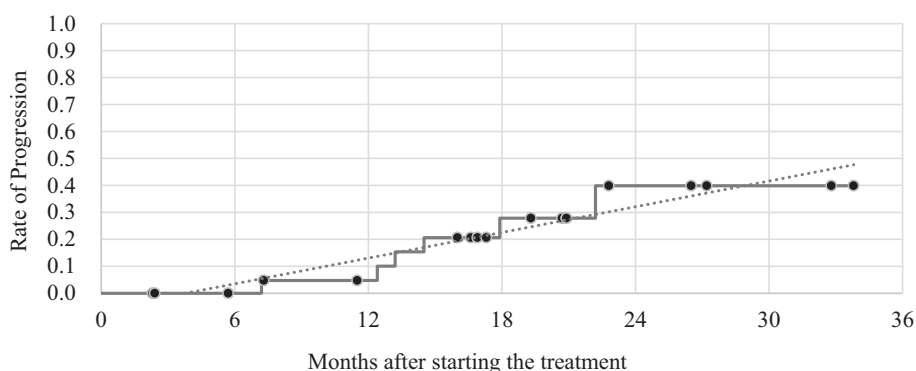


Fig. 2 Time to progression (TTP) calculated by the Kaplan–Meier method. Median TTP was not determined but was estimated to be 35 months from the fitted curve. Closed circles are censored data.

smaller than at baseline, even at the time of progression. No patient developed metastasis to the axilla or distant organs before primary tumor progression. In the 6 patients with progression, 5 underwent surgery and 1 declined surgery because advanced ovarian cancer was detected at the time of progression. Median TTP was not determined; however, from the fitted curve, it was estimated to be about 35 months (Fig. 2). One-year and 2-year PFS rates were 95% and 60%, respectively (Fig. 2). The 3-year PFS rate was estimated to be 50% from the fitted curve (Fig. 2). The 3-year PFS rate of 50% was identical to the estimate made when the study was designed and the sample size was calculated.

Among the 24 patients, maximal response was identified in 18 (75%). In 3 of these 18 patients, the tumors became nonpalpable. TTMR was 1 to 22 months after initiation of treatment (Fig. 3). Median TTMR was 11.9 months, by the Kaplan–Meier method, and about 10 months, according to the fitted curve estimate (Fig. 3).

The neoadjuvant exemestane was discontinued in 13 patients (54%) because of progression ( $n = 6$ ), patient

preference ( $n = 5$ ), and adverse events ( $n = 2$ ). The adverse events were eczema in 1 patient, and arthralgia and amnesia in 1 patient. The TTF was 2 to 22 months after treatment initiation (Fig. 4). Median TTF was 17.9 months, and the fitted curve estimate was 22 months (Fig. 4). Of the 13 patients who discontinued treatment, 12 underwent surgery, but 1 patient with advanced ovarian cancer diagnosed at the time of progression (mentioned above) did not. Of the 12 patients who underwent surgery, 11 (92%) underwent partial mastectomy and 1 (8%) total mastectomy.

According to the RECIST, CR, PR, and SD were the best response in 3 (13%), 14 (58%), and 7 (29%) patients, respectively. PD was observed in 6 patients (25%).

### Discussion

How long can NET safely delay surgery without worsening survival time? In theory, primary tumor cells probably do not metastasize while the tumor is shrinking during NET. Furthermore, NET, if it works, can kill metastatic tumor cells. Therefore, TTP is the duration when

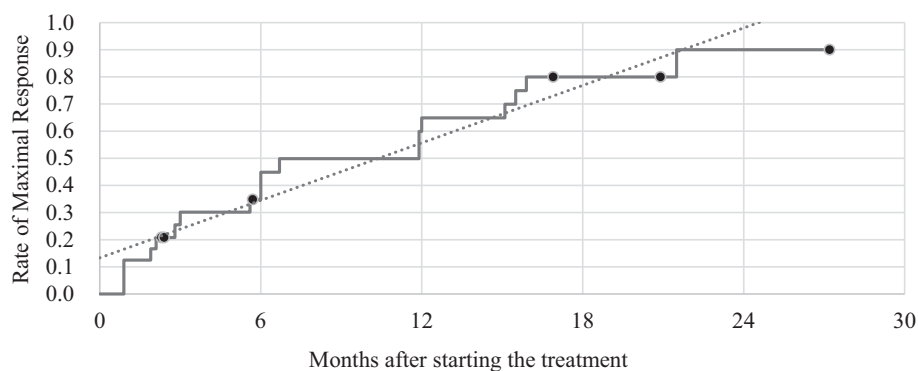


Fig. 3 Time to maximal response (TTMR) calculated by the Kaplan–Meier method. Median TTMR was 12 months and was estimated to be 10 months from the fitted curve. Closed circles are censored data.

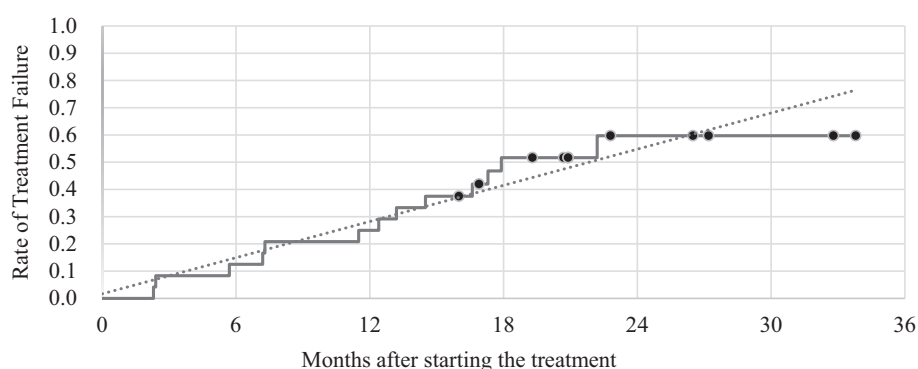


Fig. 4 Time to treatment failure (TTF) calculated by the Kaplan–Meier method. Median TTF was 18 months and was estimated to be 22 months from the fitted curve. Closed circles are censored data.

surgery can be safely delayed. This hypothesis is supported by previous randomized controlled studies of women aged 70 years or older, for whom tamoxifen taken until disease progression had a survival benefit similar to that for surgery alone<sup>17</sup>.

In this study, progression was observed in 6 (25%) of the 24 patients at 7 to 22 months after starting treatment, and median TTP was estimated to be 35 months (Fig. 2). Almost all patients initially responded to exemestane in this study, which suggests that de novo resistance is rare in patients who met the present inclusion criteria. Furthermore, TTP analysis showed that a relatively long interval is needed in order to acquire resistance to neoadjuvant exemestane. However, neoadjuvant exemestane was stopped for various reasons at 2 to 22 months after starting treatment, and median TTF was estimated to be 22 months (Fig. 4). Accordingly, the optimal treatment duration for which surgery can be safely delayed is estimated to be 22 to 35 months, which is a long but wide interval.

NET has the benefit of converting mastectomy to BCS

in postmenopausal women<sup>2-6,8-14</sup>. Generally, BCS is most suitable when a maximal response is observed. Llombart-Cussac et al<sup>12</sup> reported that, in 70 patients preoperatively treated with letrozole for 4 to 12 months, median TTMR was 4.2 months, although 20 patients achieved maximal response within 6 to 12 months. Dixon et al<sup>9</sup> reported that, in patients taking neoadjuvant letrozole, tumor volume continued to decrease between 3 and 6 months (median 50%), 6 and 12 months (median 37%), and 12 and 24 months (median 33%). These results indicate that, in relatively large populations of patients, tumors continued shrinking for 12 to 24 months. In our study, TTMR ranged from 1 to 22 months (median, 10 months; Fig. 3). The results of previous studies strongly support the present results.

Previous studies of BCS rates and treatment duration for neoadjuvant AIs found that BCS rates did not differ for 4 months and >4 months<sup>11,13</sup>. However, another study showed that BCS rates increased from 60% to 72% in patients who continued treatment for longer than 3

months<sup>14</sup>. Furthermore, a multicenter trial of neoadjuvant AI found that median time to BCS was 7.5 months<sup>18</sup>. On the basis of the above results, neoadjuvant AIs required at least 4 or 7.5 months to maximize the BCS rate. The main purpose of BCS is to control local recurrence and achieve a good aesthetic result. The former depends on the surgical margin status and the latter on the volume of breast tissue removed. To achieve negative surgical margins when removing a smaller volume of breast tissue, surgery should be performed at the time of maximal response to NET. All these results, including ours, suggest that the optimal treatment duration to become suitable for BCS was 4 to 10 months; however, the treatment window was wide. For the most appropriate BCS to be performed, it is important to closely monitor tumor size during NET.

One of the purposes of NET is to discern the sensitivity of ET. Sensitivity implies prediction of survival time and determination of chemotherapy requirements. High ER and PgR expressions, negative HER2, and reduction in the Ki67 labeling index are considered surrogate markers of higher sensitivity to NET<sup>10</sup>. In previous analyses of survival time, disease-free survival time was predicted by the Ki67 labeling index at 2 to 4 weeks<sup>19,20</sup> and 3 to 4 months<sup>21</sup> after starting NET. TTP, as defined in this study, is a candidate clinical marker to predict NET sensitivity. Shorter TTP likely correlates with worse survival rates when ET alone is administered, even after tumor progression. In this study, however, survival times were not analyzed in correlation with the TTP. Generally, chemotherapy is recommended in patients whose tumors progress during NET. However, it remains to be clarified whether chemotherapy can prolong survival in cases of progression during NET.

The RECIST criteria are commonly used to evaluate treatment effect. When these criteria were used, a response (cCR or cPR) was observed in 17 (71%) patients. This percentage was much smaller than the 96% initial response rate derived by our study criteria. This suggests that our cut-off levels are more sensitive than those of the RECIST criteria and that the RECIST criteria may be a crude measure for precise evaluation of tumor response by NET.

This study had limitations. First, tumor size was measured by palpation, which was the case in many previous studies. Ultrasound is reported to be the best modality because measured tumor size is close to pathological tumor size<sup>22</sup>. Second, the sample size was small. Third, the Ki67 labeling index was not used in the patient entry criteria

or in correlation analyses with TTP or TTMR. Fourth, survival times after initiation of NET were not analyzed. Despite these limitations, our study contributes to standardizing NET for certain periods in patients with hormone-sensitive, operable breast cancer. In a future study, ET will be taken preoperatively by women with breast cancer for the standardized optimal duration, and changes in the extent of surgery will be prospectively analyzed. In addition, survival time after initiation of treatment will be compared between patients treated with either NET for the standardized period or initial surgery followed by ET, although such studies will require longer follow-up.

The optimal treatment duration for neoadjuvant exemestane in older women with hormone-sensitive breast cancer was about 22 to 35 months in patients seeking to avoid surgery and 10 months in patients wishing to receive BCS; however, treatment duration ranged widely. Because the range of treatment duration depended on individual patients, tumor size should be monitored closely during neoadjuvant treatment with AIs. Accordingly, for a certain period, patients can be safely treated with AIs without surgery, after the period, BCS can be performed appropriately, and chemotherapy requirements can be suitably determined. In conclusion, the present benefits indicate that neoadjuvant exemestane is a long effective strategy for older women with hormone-sensitive breast cancer.

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