# Neoadjuvant endocrine therapy for estrogen receptor-positive primary breast cancer

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**Abstract:** Neoadjuvant endocrine treatment (NAE) for estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative primary breast cancer improves the surgical outcome, and its therapeutic response is useful for predicting prognosis. The indication for NAE is patients who have highly hormone-sensitive breast cancer. The optimal treatment duration depends on the required endpoint. In the case of tumor reduction or introduction to breast-conserving surgery (BCS), a treatment period of at least 6 months is required. Several clinical trials are underway to develop treatment strategies based on short-term responsiveness to NAE to improve the prognosis of hormone receptor (HR)-positive/HER2-negative breast cancer. This article outlines the current status of NAE and new treatment strategies based on the responsiveness during NAE or clinical and biological feature on residual tumor after NAE.

**Keywords:** Neoadjuvant endocrine treatment (NAE); breast cancer; estrogen receptor-positive (ER-positive)

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## Introduction

Hormone receptor (HR)-positive primary breast cancer accounts for 70–80% of all breast cancers (1). Adjuvant endocrine therapy significantly contributes to reducing recurrence and improving survival and has high tolerability in patients with HR-positive breast cancer (2). Neoadjuvant endocrine therapy (NAE) was initially used for inoperable HR-positive locally advanced breast cancer in elderly patients with poor performance status for whom chemotherapy was not tolerable. Recently, NAE has also been used for selected patients with operable HR-positive/human epidermal growth factor receptor 2 (HER2)-negative cancer who opt for breast-conserving surgery (BCS) (3). NAE and neoadjuvant chemotherapy (NAC) require a quite different administration schedule. NAC is often given during the same treatment period as adjuvant chemotherapy. On the other hands, in NAE, a portion (generally 2 weeks to 6 months) of the total (5 to 10 years) endocrine therapy period is given preoperatively and endocrine therapy is given again after surgery for the remainder of the period.

Neoadjuvant systemic treatment is given for several purpose such as improving surgical outcomes through inducing tumor shrinkage, prediction of prognosis based on treatment response or clinicopathological characteristics in residual tumors, improving prognosis by adding postoperative treatment, improving prognosis by starting systemic treatment early and evaluating new drugs early. In this article, we review the current status of NAE for operable breast cancer and discuss its future prospects.

## Clinical significance of NAE

### *Does NAE improve surgical outcome in operable breast cancer?*

*Table 1* shows the tumor response rates and BCS rates for NAE. The rate of clinical response by palpation,

**Table 1** Selected randomized studies on endocrine therapy in neoadjuvant setting

| Study | Study phase | Menopausal status | Primary endpoint | Treatment duration | Treatment arm | No. of patients | Radiological OR | Clinical OR | BCS rates |
|---|---|---|---|---|---|---|---|---|---|
| P024 (4) | IIb/III | Post-menopausal | OR by clinical palpation | 16 weeks | Letrozole; tamoxifen | 154; 179 | 35%; 25%; P=0.042 | 55%; 36%; P<0.001 | 45%; 35%; P=0.02 |
| IMPACT (5) | III | Pre-menopausal | OR by ultrasound | 12 weeks | Anastrozole (A); tamoxifen (T); combination | 113; 108; 109 | 24%; 20%; 28%; n.s. | 37%; 26%; 39%; n.s. | 44%; 31%; 29%; A *vs.* T, P=0.03 |
| PROACT (6) | III | Post-menopausal | OR by ultrasound | 12 weeks | Anastrozole; tamoxifen | [a]163; [a]151 | 36%; 27%; P=0.07 | 50%; 40%; P=0.08 | 43%; 31%; P=0.03 |
| ACOSOG Z1031 (7) | II | Post-menopausal | OR by clinical assessment | 16–18 weeks | Exemestane; letrozole; anastrozole | 124; 128; 125 | NR | 63%; 75%; 69% | 48%; 41%; 64% |
| NEWEST (8) | II | Post-menopausal | Change in Ki-67 LI from baseline to week 4 determined by ACIS | 16 weeks | Fulvestrant 500; fulvestrant 250 | 109; 102 | 22.9%; 20.6% | – | NR |
| STAGE (9) | III | Pre-menopausal | OR by clinical palpation | 24 weeks | Anastrozole + goserelin; tamoxifen + goserelin | 98; 99 | [b]58%, [c]64%; [b]42%, [c]37%; P=0.071; P=0.0009 | 70%; 51%; P=0.009 | 86%; 68% |

[a], Endocrine treatment-only population; [b], OR based on US; [c], OR based on MRI or CT. OR, objective response; BCS, breast-conserving surgery; NR, not reported; ACIS, automated computer imaging system; LI, labelling index.

radiological response by imaging, and BCS, with NAE were 26% to 75%, 24% to 64%, and 29% to 89%, respectively (4-9). Clinical response and BCS rates were higher following treatment with aromatase inhibitors (AIs) than with tamoxifen (4,9,10). Clinical response and BCS rates in patients receiving NAE were similar to those receiving anthracycline- and taxane-based NAC among patients with HR-positive primary breast cancer (10-13) (*Table 2*). In addition, NAE reduced adverse events such as febrile neutropenia, nausea, vomiting, stomatitis, alopecia and cardiac events compared to NAC. According to the exploratory subgroup analysis in GEICAM 2006-03 (12), there was no significant difference between NAE and NAC in terms of clinical response for postmenopausal patients (NAC: 57% *vs.* NAE: 52%). On the other hands, NAC was more effective than NAE in terms of clinical response in premenopausal patients (NAC: 75% *vs.* NAE: 44%, P=0.027). However, for premenopausal women, chemotherapy can exhibit both the direct cytotoxic effects of chemotherapy and the indirect effects of endocrine therapy due to chemotherapy-induced amenorrhea. Therefore, it is reasonable that NAC had a higher tumor response than NAE in the premenopausal setting. It is unclear for endocrine-sensitive premenopausal patients whether an additional effect of chemotherapy on endocrine therapy is needed to improve the surgical outcome.

Of the cases that required mastectomy at baseline, 30% to 70% of the patients were able to undergo BCS after NAE (*Table 3*).

As mentioned above, NAE can improve the surgical outcome through tumor shrinkage in patients with hormone-receptor positive operable breast cancer.

### *Is prognostication possible based on response to NAE?*

Prognostication based on treatment response and the clinicopathological characteristics of residual tumor after NAE may provide important information regarding the postoperative treatment strategy, especially in patients with a poor prognosis. Pathological complete response (pCR) after NAC is a strong prognostic factor in operable breast cancer (15). Although the prognosis of patients with non-

**Table 2** Randomized trials of comparing endocrine treatment with chemotherapy

| Study | Study phase | Menopausal status | Primary endpoint | Treatment duration | Treatment arm | No. of patients | pCR | Radiological OR | Clinical OR | BCS rates |
|---|---|---|---|---|---|---|---|---|---|---|
| Russian study (11) | II | Post-menopausal | OR by clinical palpation | 12 weeks | DOX + PTX; ANA/EXE | 118; 121 | 6%; 3% | NR | 64%; 65% | 24%; 33%; P=0.058 |
| GEICAM 2006-03 (12) | II | Pre- and post-menopausal | OR by MRI | 24 weeks | EC followed by DTX; EXE (+ GOS if premenopausal) | 47; 48 | 0.2%; 0% | 66%; 48%; P=0.075 | NR | 47%; 56% |
| NEOCENT (13) | III | Post-menopausal | Recruitment feasibility and tissue collection | 18–23 weeks | FEC followed by DTX; LET | 22; 22 | 0%; 0% | 54.5%; 59.1% | 77.3%; 90.9% | NR |

No., number; pCR, pathological complete response; OR, objective response; BCS, breast conserving surgery; DOX, doxorubicin; PTX, paclitaxel; ANA, anastrozole; EXE, exemestane; NR, not reported; MRI, magnetic resonance imaging; EC, epirubicin + cyclophosphamide; DTX, docetaxel; GOS, goserelin; NR, not reported; FEC, fluorouracil + epirubicin + cycylophosphamide; LET, letrozole.

**Table 3** Improving of BCS rates after NAE

| Studies | Endocrine therapy | Treatment duration | No. of patients | Mastectomy as surgical candidate before NAE | Successful BCS after NAE | Change rates of from requirement for mastectomy to BCS |
|---|---|---|---|---|---|---|
| IMPACT (5) | ANA (A), TAM (T), combination | 12 weeks | 113; 108; 109 | 46; 36; 26 | 20; 11; 6 | 44%; 31%; 24%; A *vs.* T, P=0.23 |
| PROACT (6) | ANA, TAM | 12 weeks | [a]163; [a]151 | 142; 120 | 61; 37 | 43%; 31%; P=0.04 |
| ACOSOG Z031 (7) | EXE, LET, ANA | 16–18 weeks | 377 | 159 | 81 | 51% |
| JFMC34-0601 (14) | EXE | 24 weeks | 116 | 59 | 40 | 68% |

[a], Endocrine treatment-only population. NAE, neoadjuvant endocrine treatment; BCS, breast-conserving surgery; ANA, anastrozole; TAM, tamoxifen; LET, letrozole; EXE, exemestane.

pCR after NAC is extremely poor, additional postoperative systemic treatment such as capecitabine and trastuzumab emtansine has been shown to improve prognosis in patients with non-pCR after NAC (16,17). On the other hands, the pCR rates after NAE is quite low (<10%) (10), and pCR is not an independent prognostic factor for the patients receiving NAE. However, pCR rates after NAC in patients with luminal A-like tumor also is low (8.1%) and pCR after NAC is not a prognostic indication in those patients (15).

Akashi-Tanaka *et al.* reported preliminary histological findings after NAE based on the General Rules for the Clinical and Pathological Recording of Breast Cancer 2007 (18) correlated with prognosis (19). The prognosis of patients with some histological changes after NAE was better than those without histological changes after NAE (HR: 6.3, 95% CI: 1.6–23.8, P=0.0067).

Dowsett *et al.* showed that Ki-67 labelling index (LI) 2 weeks after NAE initiation had a better prognostic value than that before NAE (20). Ellis *et al.* identified four independent prognostic factors including pathological tumor size, pathological nodal status, Ki-67 LI and ER status, using surgical specimens after NAE. Based on these factors and their prognostic impact calculated by Cox proportional hazards, they developed the preoperative endocrine prognostic index (PEPI) score as a postoperative prognostic tool for patients receiving NAE for 3 to 4 months (21).

Regarding the prognosis based on the clinical efficacy of NAE, Ueno *et al.* demonstrated that the prognosis of patients with progressive disease (PD) following NAE was extremely poor [disease-free survival (DFS): HR: 7.7, 95% CI: 1.6–3.3; overall survival (OS): HR: 26.3 (2.4–65.5)] (22).

Iwata *et al.* have shown similar results in 904 cases treated with letrozole for 6 months as NAE (23). Moreover, the prognosis for PD patients was extremely poor, even though all 46 (5.1%) PD patients on NAE were receiving chemotherapy after NAE or surgery. A novel treatment approach for PD patients on NAE is therefore needed. However, the prognosis based on clinical response is very limited information because of the low frequency of PD cases (<10%) treated with NAE and the inability to stratify the prognosis of PR and stable disease (SD) patients.

Taken together, the clinical response and clinicopathological findings after NAE have prognostic value, suggesting the necessity of a new approach for patients with poor prognosis.

### *Does early initiation of endocrine therapy improve prognosis?*

There is no direct evidence that the effects of NAE and adjuvant endocrine therapy on long-term prognosis are comparable. GRETA, a randomized controlled phase III trial comparing tamoxifen with surgery and adjuvant tamoxifen in patients aged 70 years and older, showed no differences in DFS, breast cancer specific-survival (BCSS), or OS between the two groups (24,25). A similar randomized controlled study in Italy demonstrated no differences in BCSS or OS between tamoxifen alone and optimal surgery plus tamoxifen (26).

As mentioned above, Ki-67 LI 2 weeks after initiation of NAC is important predictor of long-term survival. The POEIC trial was conducted to ascertain whether treatment with a non-steroidal AI 2 weeks before surgery improves long-term prognosis compared to patients who received no systemic treatment before surgery (27). The POETIC study registered 4,486 ER-positive patients. There were no significant differences between the group that received preoperative AI and the group that did not, in terms of the primary endpoint, time to recurrence (TTR) (% TTR event free at 5 years in the perioperative AI group was 90.9% *vs.* the no perioperative AI in which it was 90.3%; HR: 0.91, 95% CI: 0.74–1.12, log-rank P=0.37) (28).

Although no advantage of NAE over adjuvant endocrine therapy has been demonstrated in terms of long-term prognosis, NAE does not impair prognosis.

### *Can NAE be used for early evaluation of new drugs for early clinical application?*

NAC is already using pCR as an indicator for early evaluation of new drugs for early clinical applications. In NAE, complete cell-cycle arrest (CCCA) was defined as a Ki-67 LI less than or equal to 2.7% at 2 weeks after NAE initiation as an indicator for early evaluation of new agents. *Table 4* shows the results of the combination of endocrine treatment and molecular-targeted drugs as NAE (29-36). In most cases, the combination of endocrine therapy and molecular-targeted therapy significantly increased CCCA rates compared to endocrine therapy alone (33,35,36). However, BCS rates were not improved by a combination of endocrine therapy and molecular-targeted therapy (36). There is no early clinical application of new agents based on their early evaluation using NAE.

Taken together, these data show that the clinical significance of NAE at present is improvement of surgical outcome and prognostication based on tumor response and clinicopathological characteristics of residual tumor after NAE.

## Optimal use of NAE

### *Endocrine agents*

In a meta-analysis comparing clinical response and radiological response of patients treated with tamoxifen and AI (10), the rate of BCS was significantly better in the AI group. However, the pCR rate did not differ between the two groups. Therefore, AI is the first-choice drug for use as NAE.

### *Optimal treatment duration*

Optimal treatment duration should be considered for each endpoint such as clinical response, transition to BCS and prediction of long-term outcome. *Table 5* shows the response rate and BCS rate for each duration of NAE (14,37-40). In general, longer durations of NAE resulted in greater tumor response rates and BCS rates compared to shorter durations. Llombart-cussac *et al.* reported that the time to response and the time to maximum effect were 3.9 and 4.2 months, respectively, in 70 cases of a neoadjuvant letrozole trial. The maximum tumor response was also seen 6 to 12 months after treatment in 39% of patients (41). In a neoadjuvant exemestane trial with 116 treated, Toi *et al.* showed 54 cases of SD 4 months after NAE initiation. Among them, 14 (26%) had PR, 35 (63%) had SD, and 6 (11%) had PD. It was shown that the tumor response tended to be determined as the treatment duration was extended (14). If the index of the optimal administration duration is tumor response, a treatment duration of at least 6 months or so is necessary.

**Table 4** Selected randomized trials of endocrine therapy with molecular-targeting therapy

| Studies | Study phase | Menopausal status | Primary endpoint | Treatment duration | Treatment arm | No. of patients | Radiological OR | Clinical OR | Another endpoints |
|---|---|---|---|---|---|---|---|---|---|
| Baselga *et al.* (29) | II | Postmenopausal | OR by clinical palpation | 16 weeks | EVE + LET; LET | 138; 132 | [a]58%; [a]47%; P=0.0352 | 68%; 59%; P=0.0616 | 57%; 30%; in [b]antiproliferative response |
| Guarneri *et al.* (30) | II | Post-menopausal | OR by US | 24 weeks | Lapatinib + LET; LET | 43; 49 | 70%; 63% | 63%; 71% | In lapatinib + LET group, 93% (PIK3CA mut+) *vs.* 63% (PIK3CA wild type); P=0.04 |
| LORELEI (31) | II | Post-menopausal | OR by MRI and pCR | 16 weeks | Taselisib + LET; LET | 166; 168 | 50%; 38%; P=0.049 | NR | – |
| Ma *et al.* (32) | II | Pre- and post-menopausal; PIK3CA mut+ | pCR rate | 16 weeks | ANA (4 weeks) → ANA + MK-2206 (+ GOS if premenopausal) | 13 | NR | NR | pCR rate: 0%; BCS rate: 62% |
| NeoPalAna (33) | II | Pre- and post-menopausal | [c]CCCA rate after 15 days of therapy | 16 weeks | ANA (4 weeks) → ANA + PAL (+ GOS if premenopausal) | 50 | 41% | 80% | CCCA at C1D1: 26%; CCCA at C1D15: 87%; P<0.00001 |
| N007 (34) | II | Postmenopausal | OR, PEPI score | 16 weeks | LET + PAL | 20 | 70% | 85% | PEPI score 0 rate: 5% |
| NeoMONARCH (35) | II | Postmenopausal | Change in Ki-67 from baseline to 2 weeks of treatment | 16 weeks | Abemaciclib + ANA; abemaciclib ANA | 74; 75; 74 | 46% (104/224) | 54% (120/224) | 68%; 58% CCCA at C1D15; 14% |
| PALLET (36) | II | Postmenopausal | OR by US and change in Ki-67 | 14 weeks | LET; LET (2 weeks) → LET + PAL; PAL (2 weeks) → PAL + LET; PAL + LET | 103; 68; 69; 67 | 50%; 49%; 57%; 54% | NR | BCS rates: 14% (LET) *vs.* 14% (PAL + LET); CCCA: 90% (LET) *vs.* 59% (PAL + LET) |

[a], OR based on US; [b], as defined by a reduction in Ki-67 expression to natural logarithm of percentage positive Ki-67 of less than 1 at day 15; [c], defined as the percentage of patients with tumor Ki-67 <2.7%. No., number; OR, objective response; EVE, everolimus; LET, letrozole; MRI, magnetic resonance imaging; pCR, pathological complete response; mut+, mutation positive; ANA, anastorozole; GOS, gosereline; BCS, breast conserving surgery; PAL, palbocicilb; C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; PEPI, perioperative endocrine prognostic index; US, ultrasonography; NR, not reported; CCCA, complete cell cycle arrest.

**Table 5** Tumor response and breast-conserving rate according to duration of NAE

| Authors | No. of patients | Endocrine therapy | Treatment duration | OR rates | BCS rates |
|---|---|---|---|---|---|
| Dixon *et al.* (37) | 182 | Letrozole | 3 months; >3 months | 70%; 83% | 60%; 72% |
| Krainick-Strobel *et al.* (38) | 33 | Letrozole | 4 months; >4 months | 55%; 72% (end of treatment) | 71%; 80% |
| Fontein *et al.* (39) | 102 | Exemestane | 3 months; >3 months | 59%; 68% | 62%; 71% |
| Hojo *et al.* (40) | 52 | Exemestane | 4 months; 6 months | 42%; 48% | 50%; 48% |
| Toi *et al.* (14) | 116 | Exemestane | 4 months; 6 months | 49%; 54% | NR |

No., number; OR, objective response; BCS, breast-conserving surgery; NAE, neoadjuvant endocrine therapy.

Carpenter *et al.* reported that the median time to achieve a tumor response sufficient to allow BCS with NAE was 7.5 months (95% CI: 6.3–8.5 months) with 146 patients receiving letrozole preoperatively (42). If the index of the optimal administration duration is BCS, a treatment duration of at least 6 months is again necessary.

Taira *et al.* examined the health-related quality of life (HRQoL) for 6 months during neoadjuvant letrozole treatment in 497 patients who participated in the NEOS trial. NAE increased endocrine therapy-related side effects, but had no significant effect on global HRQoL, and also improved anxiety, depression, and emotional well-being (43). This showed that the HRQoL of patients undergoing NAE does not decrease during the NAE given to obtain tumor shrinkage, and patients' mental condition is maintained and improved by NAE.

On the other hand, if the index of optimal administration duration is prediction of long-term prognosis, the treatment duration of NAE can be 2 weeks or 3 to 4 months after initiation of NAE. Long-term prognosis can be predicted by evaluating the Ki-67 LI 2 weeks after NAE initiation (20) or by obtaining the PEPI score of residual tumor 3 to 4 months after NAE initiation (21). When checking acquired resistance to endocrine treatment, it is necessary to confirm tumor regrowth during NAE. The progression-free survival after treatment with 1$^{st}$ line endocrine monotherapy is around 12 months. If the index of the optimal NAE duration is acquired resistance of endocrine therapy, NAE duration of at least 6 months or so is necessary.

### *Indication for NAE*

Common indications for NAE are HR-positive/HER2-negative stage II–III primary breast cancer. However, NAE should be avoided in cases with high proliferative activity or low hormone sensitivity. Toi *et al.* reported that if the Ki-67 LI before NAE was 30% or less, there was no PD case after 6 months NAE. On the other hand, if the Ki-67 LI was more than 30%, PD cases appeared after that (14). Ueno *et al.* demonstrated that when Oncotype Dx Recurrence Score (RS) category was high RS, clinical response was significantly worse than low and intermediate RS in the same study (44). Iwata *et al.* conducted a similar study in 295 patients with a tumor diameter of 2 cm or more who participated in the NEOS trial, and confirmed that patients with a high RS had lower tumor response than those with low or intermediate RS (45).

## Development of a treatment strategy using NAE

Treatment responsiveness to NAE and clinicopathological status of residual tumor after NAE strongly predict long-term prognosis. Therefore, an attempt has been made to determine a treatment approach based on tumor responsiveness to NAE as in the POETIC study described above. In the ACOSOG Z1031B study (46), the subsequent systemic treatment was decided based on Ki-67 LI 2 to 4 weeks after neoadjuvant AI. When Ki-67 LI was 10% or less, NAE was continued, and when Ki-67 LI exceeded 10%, it was changed to NAC. The pCR rates after NAC was only 5.7%. This result was far below the pCR rates threshold of 20% in this study. The tumor response on NAC may be limited in cases of low tumor responsiveness to NAE. In the JBCRG-11CPA trial (47), patients were initially treated with neoadjuvant exemestane for 8 to 12 weeks. After that, comprehensive tumor evaluation was performed based on clinical response and measurement of Ki-67 LI. Patients with complete response (CR), partial response (PR) with Ki-67 index ≤5% after treatment, or SD with Ki-67 index ≤5% before and after treatment were defined as responders. Patients with others condition was defined as non-responder. Responders continued exemestane for the

subsequent 24 weeks, while non-responders were treated with a combination of cyclophosphamide and exemestane for 24 weeks. At 36 weeks after NAE initiation, clinical response rates (responder 71% *vs.* non-responder 71%) and Ki-67 LI (responder 3.5% *vs.* non-responder 4.0%) did not differ between two groups. It has been shown that concomitant use of cyclophosphamide and endocrine treatment achieved tumor response equivalent to responders when ineffective tumor response after short-term NAE. The effect of this combination on long-term prognosis has not been reported and this result is expected in the near future.

Although there are several issues to be resolved regarding the selection of treatment using Ki-67 LI, such as intratumoral heterogeneity and analytical validity, this assay is simple and inexpensive and requires validation studies to be undertaken to lead to clinical applications.

## Conclusions

NAE for HR-positive/HER2-negative stage II or III primary breast cancer with high hormone sensitivity improves the surgical outcome, and its therapeutic response is useful for predicting prognosis. Clinical trials are underway to develop more effective treatment strategies based on short-term responsiveness to NAE to improve the prognosis of HR-positive/HER2-negative breast cancer.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki. Ethical approval and informed consent were not required, since this is a review paper.



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