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Comprehensive Support Project

N-SAS BC06: A phase III study of adjuvant endocrine therapy with or without chemotherapy for postmenopausal breast cancer patients who responded to neoadjuvant letrozole (LET): the new primary endocrine-therapy origination study (NEOS).

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Background

- Endocrine therapy alone or chemotherapy followed by endocrine therapy are recommended as adjuvant therapy for highly endocrine-responsive, or incompletely endocrine-responsive and HER2-negative, intermediate-risk breast cancer.
- It has not been established if adjuvant chemotherapy is necessary in patients with intermediate-risk endocrine-responsive postmenopausal breast cancer.
- Sufficient data about the long-term prognosis of patients receiving neoadjuvant endocrine therapy is not available, so the difference in long-term treatment outcome between patients who respond to neoadjuvant endocrine therapy and those who do not, and between those receiving neoadjuvant endocrine therapy and those who do not, are unknown.
- NEOS is a randomized controlled trial designed to verify the need for adjuvant chemotherapy in patients with clinical node-negative, ER-positive, and HER2-negative postmenopausal breast cancer who responded to neoadjuvant endocrine therapy.

Endpoints

- Primary endpoint: Disease-free survival (DFS)
- Secondary endpoints: Overall survival (OS), clinical response rates, pathological response, breast-conserving surgery rate, DFS/OS in subgroups of patients according to clinical response (CR, PR, SD, or PD), safety, health-related quality of life (HRQOL) and cost effectiveness

Key Eligibility Criteria for Primary Registration

- **Inclusion criteria**

1) Postmenopausal women with histologically confirmed primary invasive breast cancer
2) T1c-T2, N0, M0
3) ER-positive (≥10% in IHC)
4) HER2: ≤2+ and FISH negative at registration
5) ≤75 years at primary registration
6) ECOG Performance Status: 0 or 1
7) No previous treatment
8) Adequate organ function
9) Written informed consent

- **Exclusion criteria**

1) Positive sentinel lymph node if biopsy is done before primary registration
2) Synchronous or asynchronous bilateral breast cancer
3) Multiple tumors located in multiple breast segments
4) Double primary invasive cancer untreated or diagnosed within 5 years after completion of treatment for the previous cancer

Key Eligibility Criteria for Secondary Registration

- **Inclusion criteria**

1) Clinical response to the neoadjuvant protocol treatment evaluated as CR, PR or SD
2) Completion of any surgical treatment of breast cancer as scheduled
3) The following lymph node status found after axillary lymph node dissection:
   i. Patients with CR or PR: No lymph node metastasis, or 1 to 3 nodes involved
   ii. Patients with SD: No lymph node metastasis or 1 to 3 nodes involved, and the following criteria are met.
   - Nuclear grade ≤ Grade 2
   - No widespread invasion of the vasculature surrounding the tumor

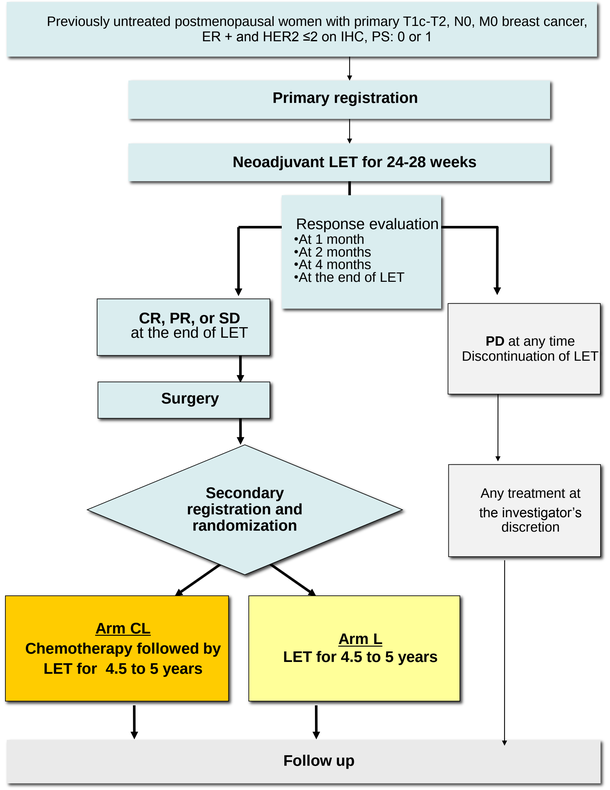
Statistical Considerations

- This study utilizes a randomized selection design.
- The objective of this design is to select the arm with the better outcome.
- A questionnaire was sent to all centers scheduled to participate in this study. The results of the questionnaire survey are as follows:
  - The mean predicted 5-year DFS with LET alone was 85.20%
  - The mean highest 5-year DFS with LET plus chemotherapy that would strongly discourage oncologists to add adjuvant chemotherapy was 86.6% (condition A).
  - The mean lowest 5-year DFS with LET plus chemotherapy that would strongly encourage oncologists to add adjuvant chemotherapy was 92.1% (condition B).
  - Assuming an exponential distribution for DFS, the expected HRs for LET plus chemotherapy relative to LET alone under conditions A and B were calculated to be 0.90 and 0.52, respectively.

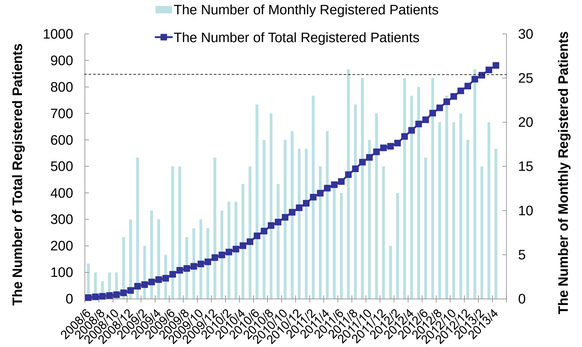
- Although the selection probability was set as 90% when the initial planned sample size was set, the initial purpose was considered almost reachable, even with a selection probability of 80 to 85%. In such a case, approximately 170 events are required in both groups.
- An overall number of approximately 630 patients is required when the 5-year DFS is assumed to be 88%, and the enrollment duration and follow-up period to be 5 and 10 years, respectively (follow-up period will be up to 15 years).
- When approximately 1/4 of the initially enrolled patients are not assumed to be enrolled secondarily, approximately 850 patients are required.

Trial Design

- This trial is a randomized, open-label, multicenter trial, and the aims is to recruit a total of 850 patients.
- Follow-up is planned for 10 years from the final recruitment.



Trial Progress



Related research

- The result of HRQOL during neoadjuvant endocrine therapy in this trial will be published in the General Poster Session of Health Service Research on June 3, ASCO 2013.

  #6588 "Analysis of health-related quality of life during neoadjuvant endocrine therapy with letrozole in postmenopausal breast cancer patients: N-SAS BC06 trial"
- Assessment of overall response by an independent central radiology review committee is ongoing.
- Central pathological review of ER, PgR, HER2, and Ki-67 is also ongoing.
- Correlative translational research using paraffin-embedded tissue is planned.

Conflicts of Interest

This study was funded by the Comprehensive Support Project (CSP) of the Public Health Research Foundation. The corporate and individual sponsors of this study are listed on the CSPOR website (http://www.csp.or.jp/cspor/kyousan_e.html). The pharmaceutical manufacturer/distributor who provided financial contributions as a corporate sponsor took no part in this study other than providing information relevant to the proper use of the study drug(s).

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