Background

Endocrine therapy alone or chemotherapy followed by endocrine therapy are recommended as adjuvant therapy for high-risk 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-negative 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 receive 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.

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

- Exclusion criteria
  1) Previous treatment

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.

Relate-related

- Primary endpoint: Disease-free survival (DFS)
- Secondary endpoints: Overall survival (OS), clinical response rate, 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

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.

- 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) COGQ Performance Status 0 or 1
  7) No previous treatment
  8) Adequate organ function
  9) Written informed consent

- Exclusion criteria
  1) Positive sentinel lymph node 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

- Although the selection probability was set at 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 85%, 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.

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