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Comprehensive Support Project

NEOS: A randomized, open label, phase 3 trial of adjuvant chemotherapy for postmenopausal breast cancer patients who responded to neoadjuvant letrozole: First report of long-term outcome and prognostic value of response to neoadjuvant endocrine therapy

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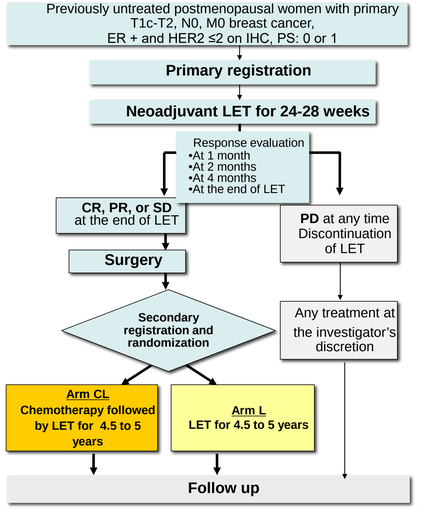
Introduction

- Neoadjuvant therapy (NA) for locally advanced breast cancer has the potential to improve surgical therapeutic outcomes without sacrificing the survival advantages of adjuvant therapy (1).
- Whether adjuvant chemotherapy is required for patients (pts) with intermediate-risk endocrine-responsive postmenopausal breast cancer (BC) remains unknown.
- Sufficient data have not been available about the long-term prognosis of patients with neoadjuvant endocrine therapy (NAET).
- NEOS is a randomized phase III study that assessed the long-term prognosis of estrogen receptor positive (ER+) primary breast cancer (PBC) pts who received neoadjuvant ET with/without adjuvant chemotherapy (Clinical trial information: UMIN000001090)(2)
- We already reported the change the HRQOL during NAET and confirm the feasibility of NAET for early breast cancer pts in NEOS (3)

Trial Design



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 analyses plan

- 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.

Consort diagram

904 patients were enrolled between May 2008 and June 2013 from 100 institutions in Japan (median follow-up: 4.0 years)

904pts at 1st registration

- Withdrawn :24pts
- PD :43pts*
  *All pts were treated by chemotherapy before or after surgery

surgery

- Exclude at 2nd registration: 166pts

Randomized :671pts

Clinical Response

	n	%
CR	16	2
PR	421	48
SD	400	45
PD	43	5
CR+PR	437	50
CR+PR+SD	837	95
Total	880	100

CR: target tumor has disappeared or completely undergone tumor-related secondary changes
PR: largest diameter of the target tumor reduced by ≥30% from baseline
SD: largest diameter of the target tumor by <30% or increased by <20% from baseline
PD: largest diameter of the target tumor increased by ≥20% from baseline

Patient's Characteristics

		Al(880pts)	CR(16pts)	PR(421pts)	SD(400pts)	PD(43pts)
Age Median (SD)		63± 6	64± 6	63± 6	63± 6	62± 7
BMI Mean (SD)		24.0±3.7	24.4±3.8	24.2±3.9	23.8±3.6	22.7±2.9
PS	0	870 (99%)	16 (100%)	413 (98%)	398 (100%)	43 (100%)
	1	8 (1%)	0	7 (2%)	1	0
T	T1c	319 (36%)	9 (56%)	161 (38%)	138 (35%)	11 (26%)
	T2	559 (64%)	7 (44%)	259 (62%)	261 (65%)	32 (74%)
Histological type	IDC	812 (93%)	15 (94%)	397 (95%)	361 (90%)	39 (93%)
	ILC	35 (4%)	1 (6%)	12 (3%)	19 (5%)	3 (7%)
	Other types	30 (3%)	0	11 (3%)	19 (5%)	0
ER	Positive	880 (100%)	16 (100%)	421 (100%)	400 (100%)	43 (100%)
	Negative	0	0	0	0	0
PgR	Positive	691 (79%)	15 (94%)	22 (17%)	48 (33%)	13 (100%)
	Negative	189 (21%)	1 (6%)	104 (83%)	99 (67%)	0
HER2	0	299 (35%)	4 (25%)	131 (33%)	144 (38%)	20 (48%)
	1+	414 (49%)	7 (44%)	206 (51%)	187 (49%)	14 (33%)
	2+	130 (15%)	5 (31%)	64 (16%)	53 (14%)	8 (19%)
Planned operation	BCS	643 (73%)	14 (88%)	309 (74%)	296 (74%)	24 (56%)
	Mastectomy	235 (27%)	2 (13%)	111 (26%)	103 (26%)	19 (44%)
Ki67 in central (mean)		16.9	37.8	17.2	16.2	27.1

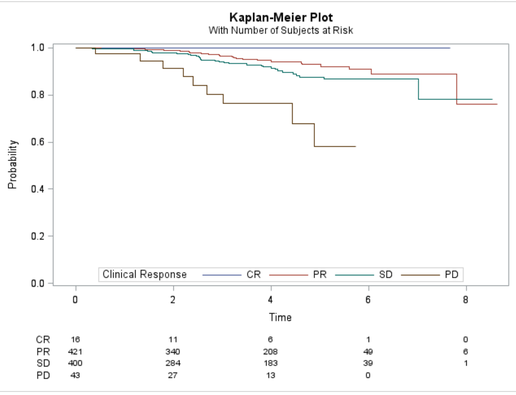
Objective in This Report

- The objectives in this report: To evaluate the long term prognosis (DFS and OS) according to each clinical responses by NAET (secondary endpoint)
- DFS is defined as the time from the date of primary enrollment until the date of the first event (recurrence in the ipsilateral preserved breast, the ipsilateral chest wall, the regional lymph node, or distant organ metastasis, or secondary cancer without cutaneous basal cell carcinoma/spindle cell carcinoma, and uterine carcinoma *in situ* or all-cause deaths)

Events in Each Groups according to Clinical Response

	All(880)	CR(16)	PR(421)	SD(400)	PD(43)
All DFS events	63 (7%)	0 (0%)	23 (5%)	31 (8%)	9 (21%)
Distant organ	22 (3%)	0 (0%)	5 (1%)	10 (3%)	7 (16%)
Recurrence in ipsilateral breast	2	0	1	1	0
Recurrence in ipsilateral chest wall	3	0	1	2	0
Recurrence in regional lymph node	10	0	2	8	0
Secondary cancer	23	0	14	7	2
All cause death	3	0	0	3	0

DFS in Each Groups according to Clinical Response



DFS in PD pts to neoadjuvant ET were statistically significantly worse than CR, PR, SD pts (p<0.0001, hazard ratio 4.7 (95% CI:2.3-9.5).

Conclusion

- This is the first report of DFS in the largest neoadjuvant ET trial (NEOS).
- The DFS of postmenopausal, ER+/HER2-, PBC pts excluding PD pts to neoadjuvant ET is highly good regardless with/without chemotherapy.
- Neoadjuvant ET with utilization of PD response as a prognostic marker can be considered as a standard treatment option for these patients.
- We have plan to present the primary endpoint future

References

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Aknowlegent

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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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