Long-term follow-up of neoadjuvant dual anti-HER2 therapy with trastuzumab and lapatinib plus paclitaxel, with or without endocrine therapy for HER2-positive primary breast cancer: Neo-LaTH (JBCRG-16) study

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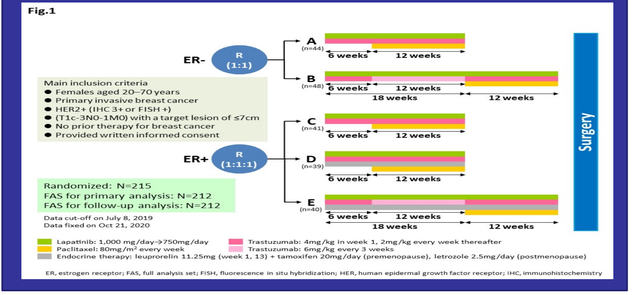
Background:

Human epidermal growth factor receptor 2 (HER2)-positive (+) breast cancer has traditionally been associated with a poor prognosis,[1)] however, with the development of HER2-targeted therapy, the prognosis of HER2-positive breast cancer has markedly improved.[2,3)] Moreover, dual blockade of HER2, such as with trastuzumab and lapatinib, promises an increased pathological complete response (pCR) rate compared with single blockade in the presence of chemotherapy for HER2+ primary breast cancer. We previously reported the results of the Neo-LaTH study (trial no: UMIN 000007576); comprehensive pathological complete response plus ypN0 (CpCRypN0) was confirmed in 46% (98/212) of total patients, and in 62% and 34% of ER-negative (-) and ER-positive (+) patients, respectively.[4)] Long-term 5-year follow-up after surgery has been successful. Here, we report the survival outcome of patients enrolled in the Neo-LaTH study.

Methods:

The randomised phase II, five-arm study was conducted between March 2012 and September 2013 in 16 centers in Japan to evaluate the efficacy and safety of lapatinib and trastuzumab (6 w) followed by lapatinib and trastuzumab plus weekly paclitaxel (12 w) with/without prolonged anti-HER2 therapy prior to chemotherapy (18 vs. 6 w), and in ER+ patients, with/without endocrine therapy, for the treatment of HER2+ primary breast cancer (Fig. 1). For the present follow-up study, the data cut-off was July 8, 2019 and data were fixed on October 21, 2020. After surgery, patients received anthracycline (A)-based regimen according to the physician's choice mainly depending on the efficacy of neoadjuvant treatment, followed by trastuzumab, and in ER+, endocrine therapy. The Kaplan–Meier method was used to assess survival curves.

Fig.1



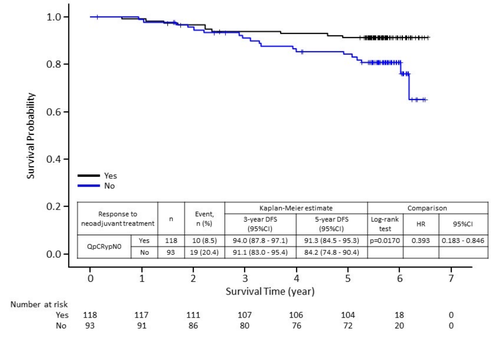
Results:

- Among the followed-up patients (n=212; Table 1), the 5-year disease-free survival (DFS) rate was 87.8% (95%CI, 82.5-91.6); it was higher in patients who achieved CpCRypN0 after neoadjuvant treatment than in those who did not (91.7% vs 85.1%; p=0.0387) (Fig. 2).
- Among non-pCR patients, G2b (defined as only focal invasive tumor residues confirmed in the removed breast tissue; near pCR) was confirmed in 20 patients (9/35 ER- patients and 11/78 ER+ patients).
- The 5-year DFS rate was higher in patients who achieved QpCRypN0 (CpCRypN0 plus near pCR) than in those who did not (91.3 vs 84.2; p=0.0170) (Fig. 3).
- Adjuvant A-based therapy was performed in 48.6% (102/210); 5-year distant DFS was similar between patients with and without adjuvant A. In the ER+ cohort, the 5-year distant DFS rate ranged between 90-93% in patients who did not achieve CpCRyoN0 regardless of use of adjuvant A (Fig. 4).
- Four (T3N1 in 3) patients had brain metastasis; 2 of them had achieved CpCRypN0 and adjuvant A-based therapy was omitted.

Table.1

		Group A n=44	Group B n=48	Group C n=41	Group D n=39	Group E n=40	All n=212
Age, years	Median	56	56	52	53	49	53
	Range	33-69	36-69	32-70	26-66	28-68	26-70
TNM staging before treatment start							
T: primary lesion	cT1	4 (9.1)	6 (12.5)	11 (26.8)	8 (20.5)	11 (27.5)	40 (18.9)
	T2	31 (70.5)	29 (60.4)	26 (63.4)	26 (66.7)	26 (65.0)	138 (65.1)
	T3	9 (20.5)	13 (27.1)	4 (9.8)	5 (12.8)	3 (7.5)	34 (16.0)
N: regional lymph node	N0	22 (50.0)	26 (54.2)	23 (56.1)	22 (56.4)	24 (60.0)	117 (55.2)
	N1	22 (50.0)	22 (45.8)	18 (43.9)	17 (43.6)	16 (40.0)	95 (44.8)
Histological grade (B&R)	1	0	2 (4.2)	1 (2.4)	0	0	3 (1.4)
	2	6 (13.6)	7 (14.6)	13 (31.7)	10 (25.6)	13 (32.5)	49 (23.1)
	3	11 (25.0)	11 (22.9)	9 (22.0)	12 (30.8)	8 (20.0)	51 (24.1)
	Unknown	27 (61.4)	28 (58.3)	18 (43.9)	17 (43.6)	19 (47.5)	109 (51.4)
Lymph node metastasis after surgery	pN0	40 (90.9)	44 (91.7)	33 (80.5)	31 (79.5)	32 (80.0)	180 (84.9)
	pN (+)	4 (9.1)	2 (4.2)	7 (17.1)	6 (15.4)	5 (12.5)	24 (11.3)
	Unknown	0	2 (4.2)	1 (2.4)	2 (5.1)	3 (7.5)	8 (3.8)
Response to neoadjuvant chemotherapy (CpCRypN0)	Yes	29 (65.9)	28 (58.3)	13 (31.7)	13 (33.3)	15 (37.5)	98 (46.2)
	No	15 (34.1)	20 (41.7)	28 (68.3)	26 (66.7)	24 (60.0)	113 (53.3)
	Unknown	0	0	0	0	1 (2.5)	1 (0.5)
Response to neoadjuvant chemotherapy (QpCRypN0)	Yes	34 (77.3)	32 (66.7)	16 (39.0)	15 (38.5)	21 (52.5)	118 (55.7)
	No	10 (22.7)	16 (33.3)	25 (61.0)	24 (61.5)	18 (45.0)	93 (43.9)
	Unknown	0	0	0	0	1 (2.5)	1 (0.5)

Fig.3

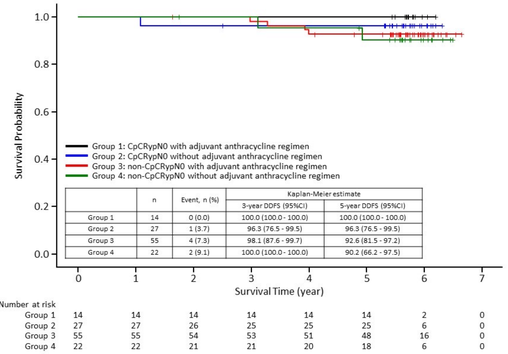


Response to neoadjuvant treatment		n	Event, n (%)	Kaplan-Meier estimate 3-year DFS (95%CI)	Kaplan-Meier estimate 5-year DFS (95%CI)	Comparison Log-rank test	Comparison HR	Comparison 95%CI
CpCRypN0	Yes	118	10 (8.5)	94.0 (87.8 - 97.1)	91.3 (84.5 - 95.3)	p=0.0170	0.393	0.183 - 0.846
	No	93	19 (20.4)	91.1 (83.0 - 95.4)	84.2 (74.8 - 90.4)			

Number at risk

Yes	118	117	111	107	106	104	18	0
No	93	91	86	80	76	72	20	0

Fig.4

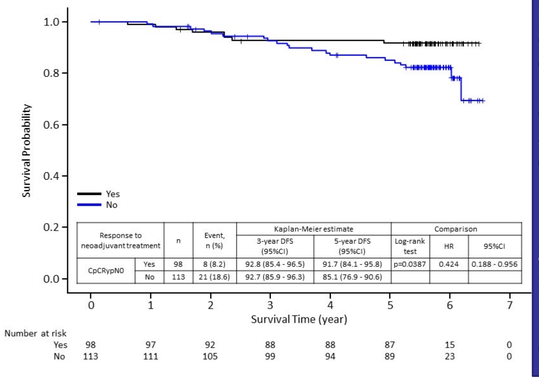


	n	Event, n (%)	Kaplan-Meier estimate 3-year DDFS (95%CI)	Kaplan-Meier estimate 5-year DDFS (95%CI)
Group 1	14	0 (0.0)	100.0 (100.0 - 100.0)	100.0 (100.0 - 100.0)
Group 2	27	1 (3.7)	96.3 (76.5 - 99.5)	96.3 (76.5 - 99.5)
Group 3	55	4 (7.3)	98.1 (87.6 - 99.7)	92.6 (81.5 - 97.2)
Group 4	22	2 (9.1)	100.0 (100.0 - 100.0)	90.2 (66.2 - 97.5)

Number at risk

Group 1	14	14	14	14	14	14	2	0
Group 2	27	27	26	25	25	25	6	0
Group 3	55	55	54	53	51	48	16	0
Group 4	22	22	21	21	20	18	6	0

Fig.2



Response to neoadjuvant treatment		n	Event, n (%)	Kaplan-Meier estimate 3-year DFS (95%CI)	Kaplan-Meier estimate 5-year DFS (95%CI)	Comparison Log-rank test	Comparison HR	Comparison 95%CI
CpCRypN0	Yes	98	8 (8.2)	92.8 (85.4 - 96.5)	91.7 (84.1 - 95.8)	p=0.0387	0.424	0.188 - 0.956
	No	113	21 (18.6)	92.7 (85.9 - 96.3)	85.1 (76.9 - 90.6)			

Number at risk

Yes	98	97	92	88	88	87	15	0
No	113	111	105	99	94	89	23	0

Discussion:

Achieving CpCRypN0 after neoadjuvant treatment is a predictor of good prognosis. We found that achieving QpCRypN0 is also associated with a favorable outcome, as compared with those without pCR. In these patients, a good survival outcome was observed regardless of use of adjuvant A-based therapy, thus, omission of adjuvant A-based therapy may be considered. However, brain metastasis did occur in some cases, even in patients who achieved CpCRypN0. Thus, such risk should be taken into account. Although dual HER2 blockade is generally less effective for ER+ patients, the 5-year distant DFS in ER+ cohort showed a good outcome, regardless of use of adjuvant A-based therapy, suggesting that omission of the A-based regimen may also be considered in cases of CpCRypN0 / QpCRypN0 after neoadjuvant treatment.

Conclusions:

A good prognosis was observed with near pCR. The omission of adjuvant A-based therapy may be considered in patients who had CpCRypN0 / QpCRypN0 after neoadjuvant treatment, however, the risk of brain metastasis should be taken into consideration.

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