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Article

Regional nodal irradiation after breast conserving surgery for early HER2-positive breast cancer: Results of a subanalysis from the ALTTO trial

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Abstract

Background: Two randomized trials recently demonstrated that regional nodal irradiation (RNI) could reduce the risk of recurrence in early breast cancer; however, these trials were conducted in the pre-trastuzumab era. Whether these results are applicable to HER2-positive breast cancer patients treated with anti-HER2 targeted therapy, is unknown.

Patients and Methods: This retrospective analysis was performed on patients with node-positive breast cancer, who were enrolled in the ALTTO phase III adjuvant trial and subjected to BCS. The primary objective of the present study was to examine the effect of RNI on disease-free survival (DFS). A multivariate cox regression analysis adjusted for number of positive lymph nodes, tumor size, grade, age, hormone receptors status, presence of macrometastatis, treatment arm, and chemotherapy timing was carried out to interrogate the relation between RNI and DFS.

Results: 1,664 HER2-positive breast cancer patients were included, of whom 878 (52.8%) had received RNI to the axillary, supraclavicular and/or internal mammary lymph nodes. Patients in the RNI group had higher nodal burden and more frequently tumors larger than 2cm. At a median follow-up of 4.5 years, DFS was 84.3% in the RNI group and 88.3% in the non-RNI group. No differences in regional recurrence (0.9 % vs 0.6 %) and in OS (93.6% vs 95.3%) were observed between the two groups. After adjustment in multivariate analysis, there was no statistically significant association between RNI and DFS (HR=0.96, 95% CI=0.71-1.29).

Conclusion: Our analysis did not demonstrate a DFS benefit of RNI in HER2-positive, node positive patients treated with adjuvant HER2-targeted therapy. The benefit of RNI in HER2-positive breast cancer needs further testing within randomized clinical trials

Introduction

Adjuvant radiation therapy has an important role in the multidisciplinary management of early breast cancer. Whole-breast irradiation (WBI) after breast-conserving surgery (BCS) reduces the rate of breast cancer recurrence and breast cancer-related death, and is considered standard of care for these patients.[1] However, the role of regional nodal irradiation (RNI) has been a persistent source of debate, as studies have been inconsistent in demonstrating benefit from RNI to prevent loco-regional recurrence.[2-4] Moreover, recent studies suggest that neither axillary lymph node dissection (ALND) nor RNI may be necessary for small clinically node-negative breast tumors with one to three positive lymph nodes detected by sentinel lymph node biopsy (SLNB), provided that WBI is administered after BCS.[5, 6] On the other hand, two recently published randomized trials, the MA.20 and the EORTC 22922 trials, have demonstrated a benefit from RNI on the rate of loco-regional recurrence and distant metastases.[7, 8] Both trials included either patients with node-positive disease or node-negative patients considered at high risk of relapse, irrespective of hormone receptor or HER2 status. Although the two trials did not show an overall survival (OS) benefit, they are the first to robustly demonstrate that aggressive regional treatment improve disease-free survival (DFS) in node-positive or high-risk early breast cancer patients.

During the last 15 years, the understanding of the biology of breast cancer has greatly evolved.[9][10] The introduction of anti-HER2 targeted therapies have revolutionized the treatment of HER2-positive breast cancer, with important gains obtained in OS and DFS.[11] An unanswered question is whether adjuvant RNI is associated with the same benefit demonstrated in the MA.20 and EORTC 22922 trials in the context of modern adjuvant treatment including anti-HER2 targeted therapies, which was not administered in these trials.

Recently, the results of the ALTTO trial were reported, which is the largest adjuvant trial to date in the field of HER2-positive breast cancer.[12] The main analysis indicated a statistically non-significant 16% reduction in the DFS hazard rate in patients treated with trastuzumab and lapatinib combination compared to those treated with trastuzumab, both given for one year. In the current analysis, we evaluated the impact of RNI on DFS in HER2-positive node-positive breast cancer patients enrolled in ALTTO.

Methods

Study design and patients

The ALTTO trial is an international open-label randomized phase III adjuvant trial in which centrally confirmed HER2-positive breast cancer patients were randomly assigned to one of four arms: adjuvant intravenous (IV) trastuzumab (T) alone, oral lapatinib (L) alone, sequential IV trastuzumab followed by oral lapatinib (T→L), or concomitant IV trastuzumab and oral lapatinib (L+T), all for a total duration of one year (NCT00490139). The trial was conducted between June 2007 and July 2011 and enrolled 8,381 patients from 44 countries. Investigators could administer anti-HER2 therapy either at the end of completion of all chemotherapy, or combined with a taxane. Further details regarding eligibility criteria and study design are provided in the original publication.[12]

The primary endpoint of the ALTTO trial was DFS, defined as the time from randomization to recurrence of invasive breast cancer, contralateral invasive breast cancer, second non-breast malignancy, or death from any cause, whichever occurred first. Secondary endpoints included OS, safety, cardiac safety, time to recurrence, time to distant recurrence and

time to first brain metastasis. As per inclusion criteria, either upfront ALND or SLNB was to be performed for all patients, and completion of ALND was mandatory for all patients with a positive SLNB.

Per protocol, all patients subjected to BCS had to receive WBI. RNI was administered at the discretion of the local investigator according to institutional guidelines and was not mandated by the ALTTO protocol. However, discretionary recommendations for RNI treatment were included in the protocol: RNI was suggested for patients with 0-3 nodes positive, and strongly recommended for patients with 4 or more nodes positive; RNI to the internal mammary nodes (IMN) was recommended in case of suspicion of IMN involvement by sentinel nodes procedure; three-dimensional conformal radiotherapy was recommended in case of IMN irradiation, to minimize cardiac irradiation. There were no recommendations for doses, fields or radiotherapy technique. Areas treated were reported on the case report as follows: breast, chest wall, axillary nodes, supraclavicular nodes, IMN, and other, with the actual doses and dates of treatment. Boost administration was reported separately.

Definitions and Objectives

For the main analysis, only patients with node-positive disease having been treated with BCS were included. Patients who received neoadjuvant chemotherapy were excluded from the analysis, because of the non-reliability of the pathological lymph node evaluation. RNI was defined as irradiation to the axillary nodes, supraclavicular nodes, and/or IMN site. Patients having received treatment to either one or more of these regions were considered to have received RNI.

The primary objective was to examine the effect of RNI on DFS in patients with lymph nodes positive breast cancer treated with BCS in the ALTTO trial. Secondary objectives were to evaluate the effect of RNI on OS, local and regional recurrences, and distant disease-free survival (DDFS), and to examine the patterns of RNI administration in this population. In a second step, the effect of RNI on DFS was explored in patients with nodes-positive disease treated with mastectomy.

Statistical Analysis

Patient characteristics were summarized for patients treated with BCS who had received or did not receive RNI. The clinical decision to administer RNI is influenced by lymph node status and so this should feature in any formal statistical analysis; therefore, p values were not calculated for **Table 1**. For this reason, an additional table considered those with 1-3 positive lymph nodes and ≥4 positive lymph nodes as two groups; for this table, differences in number of lymph nodes between the RNI and no-RNI groups were tested using the Wilcoxon 2-sample test and all other patient characteristics were tested using Chi-squared tests.

Summaries of type of regional areas treated, number of regions treated and dose administered were calculated as well as a summary of RNI administration by geographical area. Cox proportional hazards models, which included patients' characteristics in univariate models, were fitted to DFS in two separate analyses, one for the BCS group and one for the mastectomy group. The assumption of proportionality was assessed by fitting time-varying covariates, which were interactions between the covariate of interest and time to DFS. All covariates were included in a multivariate model adjusted for age, tumor size, grade, hormone receptor status, presence of

macrometastatis, treatment arm, number of positive lymph nodes, chemotherapy timing, chest wall irradiation (CWI) (only for the mastectomy group) and RNI.

All statistical tests were two-sided and a P value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 1,664 patients (19.8%) met the inclusion criteria for the main analysis (**Table 1**). Approximately half of the patients (878/1664, 52.8%) received RNI. Age, histologic grade, hormone receptor status and treatment allocation were well balanced between the non-RNI and RNI groups. However, the number of patients with ≥ 4 positive lymph nodes was considerably higher in the RNI group (55.2% vs 13.4%). Likewise, numerically more patients in the RNI group had macrometastasis (53.0% vs 43.8%) and tumors larger than 2cm (52.8% vs 44.1%). Because of the substantial imbalance in nodal burden between patients having received RNI or not, we also compared the patients' characteristics after stratification for nodal burden (1-3 positive lymph nodes versus ≥ 4 positive lymph nodes) (**Supplementary Table 1**).

Patterns of RNI administration

Only a third of the patients with 1-3 positive lymph nodes (393/1068, 36.8%) received RNI, while 82.2% of patients with ≥ 4 positive lymph nodes were treated with RNI. Of patients receiving RNI, 60.9% had treatment that targeted only one regional node area, while only 3.9% received RNI targeting the three regional nodal areas. The supraclavicular nodes, axillary nodes

and IMN were treated respectively in 86.8%, 41.1% and 14.9% of patients, with a median cumulative dose of 49-50 Gy for all regional areas (**Table 2**).

Differences in RNI administration were observed across geographical areas. Less than 40% of patients received RNI in Oceania (Australia and New-Zealand) and in Southern Europe (Spain, Greece, Italy, and Slovenia), while approximately half or more of the patients received RNI in the other geographical areas (**Table 3**). The proportion of patient receiving RNI to the IMN was lower than for the other nodal regions in all geographical areas, but the proportion of patients treated was the highest in Western Europe (14.7%) and Scandinavia (14.5%). No patient received IMN irradiation in Africa, Oceania and the United-Kingdom/Ireland.

Efficacy

At a median follow-up of 4.5 years, the total number of DFS events was 230 (13.8%). DFS was 84.3% in the RNI group compared to 88.3% in the non-RNI group (**Table 4**). The number of regional recurrences was very low, with less than 1% of regional recurrence observed in both the RNI (0.9%) and the non-RNI (0.6%) group. There was no difference in local recurrences; however, there was proportionally more distant recurrence in the RNI group (12% vs 5% in non-RNI group). OS was comparable between the two groups (93.6% for the RNI group vs 95.3% for the non-RNI group). The number of DFS events after stratification for nodal burden is provided in **Supplementary Table 2**. Only the tumor size, the hormone receptor status and the number of positive lymph nodes were associated with DFS in multivariate analysis. There was no statistically significant association between RNI and DFS in multivariate analysis (HR=0.96, 95% CI=0.71-1.29, p=0.77) (**Table 5**).

In a second step, we explored the effect of RNI on DFS in the 2658 nodes-positive patients treated with mastectomy in the ALTTO trial. As for the BCS patients, there was numerical imbalance between groups for nodal burden, tumor size, SNLB and macrometastasis (patients characteristics are available in **Supplementary Table 3**). There was more CWI performed in the RNI group (95.7% vs 23.4%). The rate of regional recurrence was also very low for these patients (0.9% for the RNI group and 1.3 for the no-RNI groups). There was no statistically significant association between RNI and DFS in multivariate analysis (HR=0.82, 95% CI=0.63-1.08, *p*=0.15) (**Table 6**)

Discussion

The local treatment of the regional nodal areas after BCS is an area of controversy. While some studies support avoiding any regional treatment for patients with a low nodal burden because of the low risk of loco-regional recurrence,[5] the MA.20 and EORTC 22922 studies demonstrated that RNI can improve the rate of loco-regional as well as distant recurrences in patients with high risk or node-positive disease.[7, 8] However, these trials were conducted before standard application of adjuvant trastuzumab. In our study, we sought-to explore whether the benefit observed in these trials also applies to HER2-positive breast cancer patients treated with anti-HER2 targeted therapies.

Our analysis did not demonstrate a DFS improvement with RNI in the HER2-positive breast cancer population treated with adjuvant chemotherapy and targeted therapies. DFS was poorer in the RNI group, which is likely explained by the higher-risk profile of the patients selected for RNI (higher nodal burden, larger tumors, and more macrometastasis). Interestingly,

the difference observed in DFS was mostly driven by the number of distant recurrences, and not by regional recurrences. However, the number of regional recurrences may be underestimated since there was no routine imaging performed during follow-up except for annual mammography. After adjusting for confounding factors, there was still no trend for association between RNI administration and improved DFS. Although our main analysis focused on patients treated with BCS whom all received WBI, we also explored the effect of RNI in patients treated with mastectomy, some of whom did not received any form of radiation. No statistically significant benefit from RNI was observed in this population as well.

The rationale behind the regional nodal treatment of early breast cancer patients is to eradicate microscopic residual disease to prevent regional recurrence, and eventually the development of distant metastasis. In our cohort, the rate of regional recurrence was very low (1% in both the RNI and non-RNI group). This compares to the regional recurrence rate described in the ACOSOG Z0011 study, a study randomizing clinically T1-T2 N0 M0 breast cancer patients with one to three positive lymph node detected by SLNB to either ALND or no further regional treatment. In the latter study, the regional recurrence rate at a median follow-up of 6.3 years was 0.9% in the "no further treatment" arm and 0.5% in the ALND arm.[5] In the MA.20 and the EBCTCG 22922 trial, the regional recurrence rates in the control group at 10 years were 2.5% and 4.2% respectively despite generally lower nodal infiltration compared to our study (36% with ≥ 4 positive lymph node in our cohort versus 5% and 12.5% in the MA.20 and EORTC 22922 trials, respectively). ER-negative and HER2-positive status has been identified in the past as a risk factors for loco-regional recurrence, and some groups advocated giving RNI preferentially for these patients.[13-17] However, there has been considerable improvement in the adjuvant treatment for HER2-positive early breast cancer in the last years

with the use of more aggressive chemotherapy regimens (with taxanes) and the introduction of adjuvant trastuzumab. In the MA.20 trial, only 25% of patients received taxane-based chemotherapy, and almost none received anti-HER2 targeted therapy. Our study suggests that some HER2-positive node-positive patients may have a very favorable outcome in the era of application of modern systemic adjuvant therapy and that these patients may not benefit from additional regional treatment. Interestingly, the rate of regional recurrence was also very low in mastectomy patients, even though some patients did not receive any form of radiation therapy.

The ALTTO trial was conducted between 2007 and 2011, before the first presentation of the MA.20 and EORTC 22922 results. Before these trials, evidence on the benefit of RNI was scarce for patients with low nodal burden, which may explain why only 37% of the patients with 1-3 positive lymph nodes received RNI.[3, 4, 18] We observed important variability in the pattern of RNI administration according to different geographical areas, which stress the lack of strong consensus in the field. Very few patients received IMN irradiation, since previous trials had shown conflicting results and an increased risk of cardiac toxicities.[2, 18-23] On the contrary, in the EORTC 22922 and MA.20 trials, all patients randomized into the RNI group received IMN irradiation. A recent cohort study by the Danish breast cancer group suggests that IMN irradiation increases overall survival in early breast cancer.[24] Patients with a high axillary nodes burden are at increased risk of IMN involvement[25] and it is plausible that IMN irradiation plays an important role in the effect of RNI observed in the aforementioned trials. Low IMN irradiation rate in our cohort may therefore partly explain our negative results. Nevertheless, with the high 4-year OS observed in HER2-positive breast cancer patients treated with adjuvant trastuzumab and chemotherapy (94% in ALTTO), it is likely that benefit from additional IMN irradiation in this population would be minimal. The wide variability in RNI

administration and low rates of IMN irradiation in our study underscore the need for guidelines in the field such as those recently published for mastectomy patients.[26]

Our study has a few drawbacks that should be pointed out. First, all patients included in our analysis were treated with ALND, so the results may not be applicable for patients approached with SLNB alone. However, it is worth noting that most of the patients included in the MA.20 and EORTC 22922 trials were also treated with ALND. Second, because of the retrospective, non-randomized nature of our analysis, important selection bias was introduced, with patients in the RNI group presenting a more high-risk profile. To control for that, we adjusted for confounding factors in multivariate analysis; however, it is possible that factors unaccounted for in this analysis, such as lympho-vascular invasion or extra capsular node extension, may still have influenced the results. Third, although the ALTTO dataset included detailed information on targeted regional nodal treatment, data on tangential treatment of regional areas was not collected, nor was the radiation therapy technique used, and no quality analysis for radiation therapy was performed during the trial. This may have led to misclassification of some patients. Finally, this analysis was not prospectively powered, as reflected in the wide confidence intervals for the hazard ratios. The follow-up was relatively short, although patients with HER2-positive disease tend to relapse early compared to luminal tumors,[27-29] and thus it is unlikely that the results would differ considerably with longer follow-up. Nevertheless, our study is the first to explore the effect of RNI in HER2-positive breast cancer patients treated with modern systemic therapy. Observational and randomized studies in radiation therapy are very challenging, given the rapid evolution in techniques and large variability in practices.[30] Prospective data addressing the use of RNI in HER2-positive breast cancer may take years to obtain if a clinical trial addressing this question is ever

conducted. On the other hand, RNI is associated with mildly increased toxicities, as was highlighted by the higher rate of acute dermatitis (49% vs 40%, p<0.001),[7] acute pneumonitis (1.2% vs 0.2%, p=0.01),[7] lymphedema (8.4% vs 4.5%, p<0.001),[7] late radiation skin changes (6.9% vs 4.3%, p=0.02),[7] and late pulmonary toxicity (4.4% vs 1.7%, p=<0.001)[8] reported in the MA.20 and EORTC 22922 trials.[7, 8] Although the results of our study are hypothesis generating and have to be interpreted with caution, they highlight the need to identify a subset of patients that may truly benefit from RNI. Our analysis also underscores the importance of characterizing breast cancer subtype in radiation therapy trials.

In conclusion, our study suggests that RNI as administered in the ALTTO trial does not have statistically significant impact on DFS in node-positive, HER2-positive early breast cancer patients treated with BCS, ALND and WBI, especially for patients with low lymph node burden, and that the rate of regional recurrence for this population is very low. In the era of modern systemic therapy of HER2-positive patients, our analysis questions the need to systematically offer RNI to patients with HER2-positive, lymph node positive disease.

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Notes

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The authors have no conflict of interest to declare.

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Table 1. Patients' Characteristics (N=1664)*

Characteristics	No-RNI Group, No. (%) (N = 786)	RNI Group, No. (%) (N=878)	Total (N=1664)
Age			
< 50 years	326 (41.5)	359 (40.9)	685
≥ 50 years	460 (58.5)	519 (59.1)	979
SLNB			
Yes	297 (37.8)	478 (54.4)	775
No	489 (62.2)	400 (45.6)	889
Axillary lymph node status			
1-3 positive lymph nodes	681 (86.6)	393 (44.8)	1074
≥4 positive lymph nodes	105 (13.4)	485 (55.2)	590
Nodal Macrometastasis			
Absence	194 (24.7)	108 (12.3)	302
Presence	344 (43.8)	465 (53.0)	809
Not Measured	243 (30.9)	304 (34.6)	547
Missing	5 (0.6)	1 (0.1)	6
Tumor Size			
≤ 2 cm	434 (55.2)	411 (46.8)	845
> 2 cm	347 (441)	464 (52.8)	811
Missing	5 (0.6)	3 (0.3)	8
Histologic Grade			
G1	18 (2.3)	27 (3.1)	45
G2	258 (32.8)	278 (31.7)	536
G3	499 (63.5)	552 (62.9)	1051
Gx	10 (1.3)	20 (2.3)	30
Missing	1 (0.1)	1 (0.1)	2
Hormone receptor Status			
Negative	289 (36.8)	354 (40.3)	643
Positive	497 (63.2)	524 (59.7)	1021
Planned Treatment			
L	203 (25.8)	222 (25.3)	425
L+T	180 (22.9)	225 (25.6)	405
T	185 (23.5)	210 (23.9)	395
T→ L	218 (27.7)	221 (25.2)	439
Chemotherapy timing			
Sequential	364 (46.3)	449 (51.1)	813
Concurrent	422 (53.7)	429 (48.9)	851

*L = Lapatinib; RNI = Regional nodal irradiation; SLNB = Sentinel Lymph Node Biopsy ; T = Trastuzumab

Table 2. Regional area treated and dose administered (N=878)*

Region	No. (%)	No. of patients with missing dose	Median dose received in Gy (Q1-Q3)
Any Axilla	361 (41.1)	1	50 (46-50.4)
Any Internal Mammary	131 (14.9)	0	49 (46-50)
Any Supraclavicular	762 (86.8)	3	50 (46-50)
Axilla only	95 (10.5)	--	--
Internal Mammary only	12 (1.4)	--	--
Supraclavicular only	428 (48.7)	--	--
Axilla and Internal mammary	6 (0.7)	--	--
Axilla and Supraclavicular	227 (25.8)	--	--
Internal mammary and Supraclavicular	79 (9.0)	--	--
All three regions	34 (3.9)	--	--

*Q1=Lower quartile; Q3=Upper quartile

Table 3. Regional nodal irradiation (RNI) administration per geographical areas (N=1,664)

Geographical Area	N (Total)	Patients treated with RNI N (%)	Axillary nodes N (%)	Internal Mammary nodes N (%)	Supraclavicular nodes N (%)
Africa	14	9 (64.3)	4 (28.6)	0 (0)	8 (57.1)
Asia	244	125 (51.2)	36 (14.7)	9 (3.7)	119 (48.8)
Eastern Europe	165	108 (65.5)	78 (47.3)	11 (6.7)	93 (56.4)
Oceania	51	19 (37.2)	6 (11.8)	0 (0)	18 (35.3)
Scandinavia	69	36 (52.2)	25 (36.2)	10 (14.5)	29 (42.0)
South America	97	61 (62.9)	17 (17.5)	3 (3.1)	58 (59.8)
Southern Europe	200	78 (39.0)	37 (18.5)	2 (1.0)	66 (33.0)
UK & Ireland	68	43 (63.2)	9 (13.2)	0 (0)	38 (55.9)
USA & Canada	159	75 (47.2)	32 (20.1)	8 (5.0)	67 (42.1)
Western Europe	597	324 (54.3)	118 (19.8)	88 (14.7)	269 (45.1)
Total	1664	878 (52.8)	362 (21.7)	131 (7.9)	765 (46.0)

Table 4. Summary of efficacy events

Event	Total (N=1664) No. (%)	No-RNI Group (N=786) No. (%)	RNI Group (N=878) No. (%)
DFS event*	230 (13.8)	92 (11.7)	138 (15.7)
Local recurrence†	47 (2.8)	23 (2.9)	24 (2.7)
Regional recurrence†	13 (0.8)	5 (0.6)	8 (0.9)
Distant recurrence†	146 (8.8)	41 (5.2)	105 (12.0)
Died†	93 (5.6)	37 (4.7)	56 (6.4)

*****The primary endpoint, DFS, is the first recurrence of disease or death, irrespective of type. RNI = Regional nodal irradiation; DFS = Disease free survival

† Represent the sum of all corresponding events, irrespective of the order of occurrence.

Table 5. Multivariate Cox regression analysis for disease free survival for patients treated with breast conserving surgery

Variable	Univariate Analysis			Multivariate Analysis		
	HR	**(95% CI)**	***P*-value***	**HR**	**(95% CI)**	***P*-value***
Age (>=50 years vs < 50)	0.89	(0.69 , 1.16)	0.40	0.85	(0.65 , 1.11)	0.22
Tumor size (> 2cm vs <=2cm)	1.42	(1.10 , 1.85)	0.008	1.35	(1.03 , 1.76)	0.03
Grade (3 vs 1-2)	1.28	(0.97 , 1.70)	0.09	1.19	(0.89 , 1.59)	0.25
Hormone receptor status (Negative vs Positive)	1.50	(1.15 , 1.94)	0.002	1.45	(1.11 , 1.89)	0.006
Macrometastasis (Presence/Unknown vs Absence)	1.58	(1.09 , 2.37)	0.02	1.30	(0.89 , 1.98)	0.20
Treatment arm (L-containing vs T)	1.09	(0.81 , 1.50)	0.58	1.17	(0.86 , 1.62)	0.32
No. positive lymph nodes (≥4 vs 1-3)	1.76	(1.36 , 2.28)	<0.001	1.64	(1.22 , 2.21)	0.001
Chemotherapy (Concurrent vs Sequential)	0.81	(0.62 , 1.06)	0.12	0.82	(0.62 , 1.07)	0.14
RNI (Yes vs No)	1.28	(0.98 , 1.67)	0.07	0.96	(0.71 , 1.29)	0.77

***The *P*-values are from 2-sided Wald test**

CI = Confidence Intervalle ; HR=hazard ratio ; RNI = Regional nodal irradiation; L = Lapatinib; T = Trastuzumab

Table 6: Multivariate Cox Regression for disease free survival for patients treated with mastectomy

Variable	Multivariate Analysis		
	HR	**(95% CI)**	***P*-value***
Age (>=50 years vs < 50)	0.94	(0.79, 1.13)	0.53
Tumor size (> 2cm vs <=2cm)	1.38	(1.11, 1.72)	0.004
Grade (3 vs 1-2)	0.99	(0.82, 1.20)	0.92
Hormone receptor status (Negative vs Positive)	1.25	(1.04, 1.50)	0.02
Macrometastasis (Presence/Unknown vs Absence)	1.38	(0.99, 1.98)	0.07
Treatment arm (L-containing vs T)	1.05	(0.86, 1.30)	0.62
No. positive lymph nodes (≥4 vs 1-3)	2.64	(2.13, 3.29)	<0.001
Chemotherapy (Concurrent vs Sequential)	0.64	(0.53, 0.77)	<0.001
Chest Wall Irradiation (No vs Yes)	0.81	(0.61, 1.07)	0.14
RNI (Yes vs No)	0.82	(0.63, 1.08)	0.15

***The *P*-values are from 2-sided Wald test**

CI = Confidence Intervalle ; HR = hazard ratio ; L = Lapatinib; RNI = Regional nodal irradiation; T = Trastuzumab.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Patients' characteristic with stratification per lymph node (LN) burden

Characteristics	**1-3 positive LN(s)** (N=1074)			**≥ 4 positive LNs** (N=590)		
	No-RNI group, No. (%) (N = 681)	**RNI Group, No. (%)** (N=393)	**P-Value***	**No-RNI group, No. (%)** (N=105)	**RNO Group, No. (%)** (N=485)	**P-Value***
Age, y						
< 50	283 (41.6)	170 (43.3)	0.59	43 (41.0)	189 (39.0)	0.71
≥ 50	398 (58.4)	223 (56.7)		62 (59.0)	296 (61.0)	
SLNB						
Yes	231 (33.9)	176 (44.8)	< 0.001	66 (62.9)	302 (62.3)	0.91
No	450 (66.1)	217 (55.2)		39 (37.1)	183 (37.7)	
Number of positive lymph node						
1	414 (60.8)	184 (46.8)	< 0.001	--	--	--
2	171 (25.1)	121 (30.8)		--	--	--
3	91 (13.4)	87 (22.1)		--	--	--
Missing	5 (0.7)	1 (0.2)		--	--	--
Median (Range)	--	--	--	6 (4-49)	7 (4-60)	0.55
Nodal Macrometastasis						
Absence	184 (27.0)	70 (17.8)	0.003	10 (9.5)	38 (7.8)	0.68
Presence	289 (42.4)	190 (48.3)		55 (52.4)	275 (56.7)	
Not Measured	203 (29.8)	132 (33.6)		40 (38.1)	172 (35.5)	
Missing	5 (0.7)	1 (0.2)		0	0	
Tumor Size						
≤ 2 cm	384 (56.4)	209 (53.2)	0.28	50 (47.6)	202 (41.6)	0.24
> 2 cm	293 (43.0)	183 (46.6)		54 (51.4)	281 (57.9)	
Missing	4 (0.6)	1 (0.2)		1 (1.0)	2 (0.4)	
Histologic Grade						
G1	15 (2.2)	12 (3.0)	0.31	3 (2.9)	15 (3.1)	0.15
G2	218 (32.0)	144 (36.6)		40 (38.1)	134 (27.6)	
G3	438 (64.3)	231 (58.8)		61 (58.1)	321 (66.2)	
Gx	9 (1.3)	6 (1.5)		1 (1.0)	14 (2.9)	
Missing	1 (0.1)	0 (0)		0 (0)	1 (0.2)	
Hormone Receptor Status						
Negative	241 (35.4)	143 (36.4)	0.74	48 (45.7)	211 (43.5)	0.68
Positive	440 (64.6)	250 (63.6)		57 (54.3)	274 (56.5)	
Planned Treatment						
L	182 (26.7)	104 (26.5)	0.47	21 (20.0)	118 (24.3)	0.62
L+T	157 (23.0)	106 (27.0)		23 (21.9)	119 (24.5)	
T	156 (23.0)	88 (22.4)		29 (27.6)	122 (25.2)	
T→ L	186 (27.3)	95 (24.2)		32 (30.5)	126 (26.0)	
Chemotherapy timing						
Sequential	314 (46.1)	206 (52.4)	0.05	50 (47.6)	243 (50.1)	0.64
Concurrent	367 (53.9)	187 (47.6)		55 (52.4)	242 (49.9)	

* Two-sided P-value for differences in number of lymph nodes between the RNI and no-RNI groups were tested using the Wilcoxon 2-sample test and all other patient characteristics were tested using Chi-squared tests. HR = Hormone receptor ; L = Lapatinib; RNI = Regional nodal irradiation; SLNB = Sentinel Lymph Node Biopsy ; T = Trastuzumab.

Supplementary Table 2: Efficacy events with stratification per lymph node (LN) burden*

Event	All patients, No. (%) (N=1664)	1-3 positive LN(s)			≥ 4 positive LNs		
		Total, No. (%) (N=1074)	No-RNI group, No. (%) (N=681)	RNI Group, No. (%) (N=393)	Total, No. (%) (N=590)	No-RNI group, No. (%) (N=105)	RNI Group, No. (%) (N=485)
DFS event	230 (13.8)	119 (11.1)	76 (11.2)	43 (10.9)	111 (18.8)	16 (15.2)	95 (19.6)
Regional recurrence	13 (0.8)	5 (0.5)	5 (0.7)	0 (0)	8 (1.4)	0 (0)	8 (1.6)
Distant recurrence	146 (8.8)	58 (5.4)	32 (4.7)	26 (6.6)	88 (14.9)	9 (8.6)	79 (16.3)
Died	93 (5.6)	40 (3.7)	26 (3.8)	14 (3.6)	53 (9.0)	11 (10.5)	42 (8.7)

*DFS = Disease free survival; RNI = Regional Nodal Irradiation.

Supplementary Table 3: Patients' characteristics for patients treated with mastectomy*

Characteristics	**No-RNI Group, No. (%)** (N = 1184)	**RNI Group, No. (%)** (N=1474)	**Total, No.** (N=2658)
Age			
< 50 years	530 (44.8)	720 (48.8)	1250
≥ 50 years	654 (55.2)	754 (51.2)	1408
SLNB			
Yes	420 (35.5)	363 (24.6)	783
No or missing	764 (64.5)	1111 (75.4)	1872
Axillary lymph node status			
1-3 positive lymph nodes	884 (74.7)	499 (33.8)	1383
≥4 positive lymph nodes	300 (25.3)	975 (66.1)	1275
Nodal Macrometastasis			
Absence	180 (15.2)	119 (8.1)	299
Presence	529 (44.7)	687 (46.6)	1216
Not Measured	469 (39.6)	666 (45.2)	1135
Missing	6 (0.5)	2 (0.1)	8
Tumor Size			
≤ 2 cm	405 (34.2)	379 (25.7)	784
> 2 cm	763 (64.4)	1071 (72.7)	1834
Missing	16 (1.4)	24 (1.6)	40
Histologic Grade			
G1	25 (2.1)	25 (1.6)	50
G2	483 (40.8)	495 (33.6)	978
G3	642 (54.2)	900 (61.1)	1542
Gx	30 (2.5)	48 (3.3)	78
Missing	4 (0.3)	6 (0.4)	10
HR Status			
Negative	532 (44.9)	712 (48.3)	1244
Positive	652 (55.1)	762 (51.7)	1414
Chest Wall Irradiation			
No	907 (76.6)	63 (4.3)	970
Yes	277 (23.4)	1411 (95.7)	1688
Planned Treatment			
L	312 (26.4)	355 (24.1)	667
L+T	301 (25.4)	373 (25.3)	674
T	288 (24.3)	389 (26.4)	677
T→ L	283 (23.9)	357 (24.2)	640
Chemotherapy timing			
Sequential	572 (48.3)	748 (50.7)	1320
Concurrent	612 (51.7)	726 (49.3)	1338

* HR = Hormone receptor ; L = Lapatinib; RNI = Regional nodal irradiation; SLNB = Sentinel Lymph Node Biopsy ; T = Trastuzumab