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ORIGINAL RESEARCH

Final analysis of the ALTTO trial: adjuvant trastuzumab in sequence or in combination with lapatinib in patients with HER2-positive early breast cancer [BIG 2-06/NCCTG N063D (Alliance)]

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Background: Dual anti-human epidermal growth factor receptor 2 (HER2) blockade has improved the outcomes of patients with early and metastatic HER2-positive breast cancer. Here we present the final 10-year analysis of the ALTTO trial.

Patients and methods: The ALTTO trial (NCT00490139) is a prospective randomized, phase III, open-label, multicenter study that investigated the role of adjuvant chemotherapy and trastuzumab alone, in combination or sequentially with lapatinib. The primary endpoint was disease-free survival (DFS) and secondary endpoints included overall survival (OS), time to distant recurrence and safety.

Results: Overall, 6281 patients with HER2-positive early breast cancer were included in the final efficacy analysis in three treatment groups: trastuzumab (T), lapatinib + trastuzumab (L + T) and trastuzumab followed by lapatinib (T→L). Baseline characteristics were well balanced between groups. At a median follow-up of 9.8 years, the addition of lapatinib to trastuzumab and chemotherapy did not significantly improve DFS nor OS. The 10-year DFS was 77% in T, 79% in L + T and 79% in T→L, and the 10-year OS was 87%, 89% and 89%, respectively. The incidence of any cardiac event was low and similar in the three treatment groups.

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Conclusions: With a longer follow-up, no significant improvement was observed in DFS in patients treated with dual anti-HER2 blockade with lapatinib + trastuzumab compared to trastuzumab alone. The 10-year survival rates for the combination group are consistent with other studies that have explored dual anti-HER2 therapy.
Key words: adjuvant chemotherapy, early breast cancer, HER2-positive, lapatinib, trastuzumab

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer represents about 15%-20% of all breast cancers. The prognosis of HER2-positive breast cancer was radically improved by the introduction of trastuzumab (T), a recombinant monoclonal antibody targeting HER2. In early-stage disease, pivotal randomized trials were presented in the early 2000s showing improved outcomes by incorporating trastuzumab to conventional chemotherapy[1] and revealing a significant decrease in recurrence rates with the administration of 1-year adjuvant trastuzumab.[2-4] To overcome resistance, several trials also explored the combination of new agents targeting HER2 through different mechanisms of action. The phase III CLEOPATRA trial demonstrated that the use of trastuzumab and pertuzumab (T + P) with docetaxel improves both progression-free survival and OS in the first-line metastatic setting. More recently, dual anti-HER2 blockade with pertuzumab and trastuzumab has been demonstrated to improve patients' outcomes even in high-risk early breast cancer.[5-7] Lapatinib, approved exclusively in metastatic disease,[8] is an oral tyrosine kinase inhibitor against HER2 and epidermal growth factor receptor. To achieve a synergic effect in HER2-overexpressing breast cancer cells, lapatinib has been evaluated in combination with trastuzumab.[9] The combination of lapatinib plus trastuzumab for dual anti-HER2 inhibition improved the rate of pathological complete response (pCR) in several neoadjuvant trials.[10-13] The updated analysis of NeoALTTO, with a median follow-up of 6.7 years, showed improved pCR rates in the combination arm but no statistically significant differences in long-term outcomes (event-free survival and OS) between the three treatment groups.[14]

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial was the largest phase III trial including patients with HER2-positive early breast cancer and testing whether adjuvant lapatinib alone, in combination (L + T) or in sequence to trastuzumab (T→L) would improve patients' outcomes over trastuzumab. The lapatinib-alone group was inferior and prematurely closed in 2011, leading to three remaining groups. Here we report the final planned efficacy analysis of the three remaining groups with a median follow-up of 9.8 years.

PATIENTS AND METHODS

The ALTTO trial (NCT00490139) is a prospective randomized, phase III, open-label, multicenter study conducted between June 2007 and July 2011 in 946 centers from 44 countries in four different continents. Eligibility criteria were previously reported.[15,16] Briefly, patients with centrally confirmed HER2-positive (3+ by immunohistochemistry and/or FISH-positive) early breast cancer as per the American Society of Clinical Oncology 2007, with either node-positive or node-negative disease with tumor size ≥1 cm were considered eligible. Hematological, renal and hepatic functions were to be adequate, and a left ventricular ejection fraction of ≥50% was required at baseline assessment.

Study design

The trial compared four treatment groups and patients were centrally randomly assigned in a 1 : 1 : 1 : 1 ratio to receive adjuvant T, L, L + T or T→L for a total anti-HER2 treatment duration of 1 year. In group 1, patients received intravenous T during and after chemotherapy; in group 2 they received oral L during and after chemotherapy; in group 3, a sequence of the two agents (T→L) that started with 12 weekly doses of T, followed after a 6-week washout by 34 weeks of L; and in group 4 the combination of the two anti-HER2 agents (L + T).

Investigators could administer anti-HER2 therapies at completion of all chemotherapy (Design 1), or with an anthracycline-based chemotherapy preceding anti-HER2 therapies in combination with taxanes (Design 2), or with an anthracycline-free chemotherapy (Design 2B). Radiotherapy and/or endocrine therapy, if indicated, were given as per local guidelines and concomitantly with anti-HER2 therapies after the end of the treatment with chemotherapy. Institutional review boards at each participating center approved the ALTTO trial protocol. All patients provided written informed consent.

Study endpoints and statistical analysis

Randomization and statistical methodology were previously reported.[15] The presented analysis is descriptive and as such no *P* values are provided, but all estimates are presented with 95% confidence intervals (CIs). The primary endpoint was disease-free survival (DFS) defined as the time from randomization until the first occurrence of: (i) invasive breast cancer recurrence at any site, (ii) a second primary cancer (invasive contralateral breast cancer or non-breast malignancy) or (iii) death from any cause as the first event. Secondary endpoints included OS, defined as the time from randomization to death from any cause, time to distant relapse (TTDR), safety in general and cardiac safety.

Primary cardiac endpoints included severe symptomatic congestive heart failure class III and IV and cardiac death.

Estimation of hazard ratios (HRs) and 95% CIs used the Cox proportional hazards model stratified by hormone receptor status (two groups), nodal status (four groups) and

chemotherapy timing (two groups), totaling 16 strata. Estimation of survival functions was carried out using the Kaplan—Meier method with standard errors calculated using Greenwood's formula.

Due to changes in regulations, some data have been excluded in this final analysis: (i) all sites in China due to local regulations (441 patients; 264 censored on 1 July 2016 in DFS analysis); (ii) two sites in Thailand due to lapsed ethical consent (69 patients; 36 censored on 1 July 2016 in DFS analysis); (iii) patients not signing an informed consent form for protocol amendment 12 without reasonable explanation (651 patients; 441 censored on 1 July 2016 in DFS analysis); (iv) any data that did not have a case report form signed by the site principal investigator have also been excluded (∼1200 data points including 5 deaths, 12 recurrences and 271 visits).

The safety population includes a subset of the intention-to-treat (ITT) population receiving at least one dose of investigational targeted treatment and includes all four treatment groups.

RESULTS

Between June 2007 and July 2011, 8381 patients were accrued in the ALTTO trial (Figure 1, CONSORT flow diagram). For the current efficacy analysis, 2100 patients of the L-alone arm were removed as per protocol amendment number 10; therefore, a total of 6281 patients have been included in the efficacy analysis, of whom 2097 patients received T alone, 2093 patients received L + T and 2091 patients received T→L (Figure 1, CONSORT flow diagram). Patient and tumor characteristics were well balanced among groups and are shown in Table 1. In the ITT population, the median age was 51 years in the three groups (T, T + L, T→L), 40% of the patients had node-negative disease in the three groups (T, T + L, T→L); 57% had hormone receptor-positive disease in the T and T + L group and 58% in the T→L group.

Efficacy analysis

At a median follow-up of 9.8 years (interquartile range 6.9-10.0), the 10-year DFS was 77% (95% CI 75% to 79%) in T-alone group, 79% (95% CI 76% to 80%) in L + T group and 79% (95% CI 77% to 81%) in T→L group, with no observed differences among the three treatment groups (Figure 2A and Table 2).

DFS between treatment groups did not differ in either the hormone receptor-positive (78% in the T-alone group versus 79% in the L + T group versus 80% in the T→L group) or hormone receptor-negative (76% in the T-alone group versus 78% in the L + T group versus 78% in the T→L arm) cohorts (Table 2). No differences were observed between treatment groups in DFS also when comparing the timing of chemotherapy administration (sequentially or concomitantly) (Table 2) nor nodal status (Supplementary

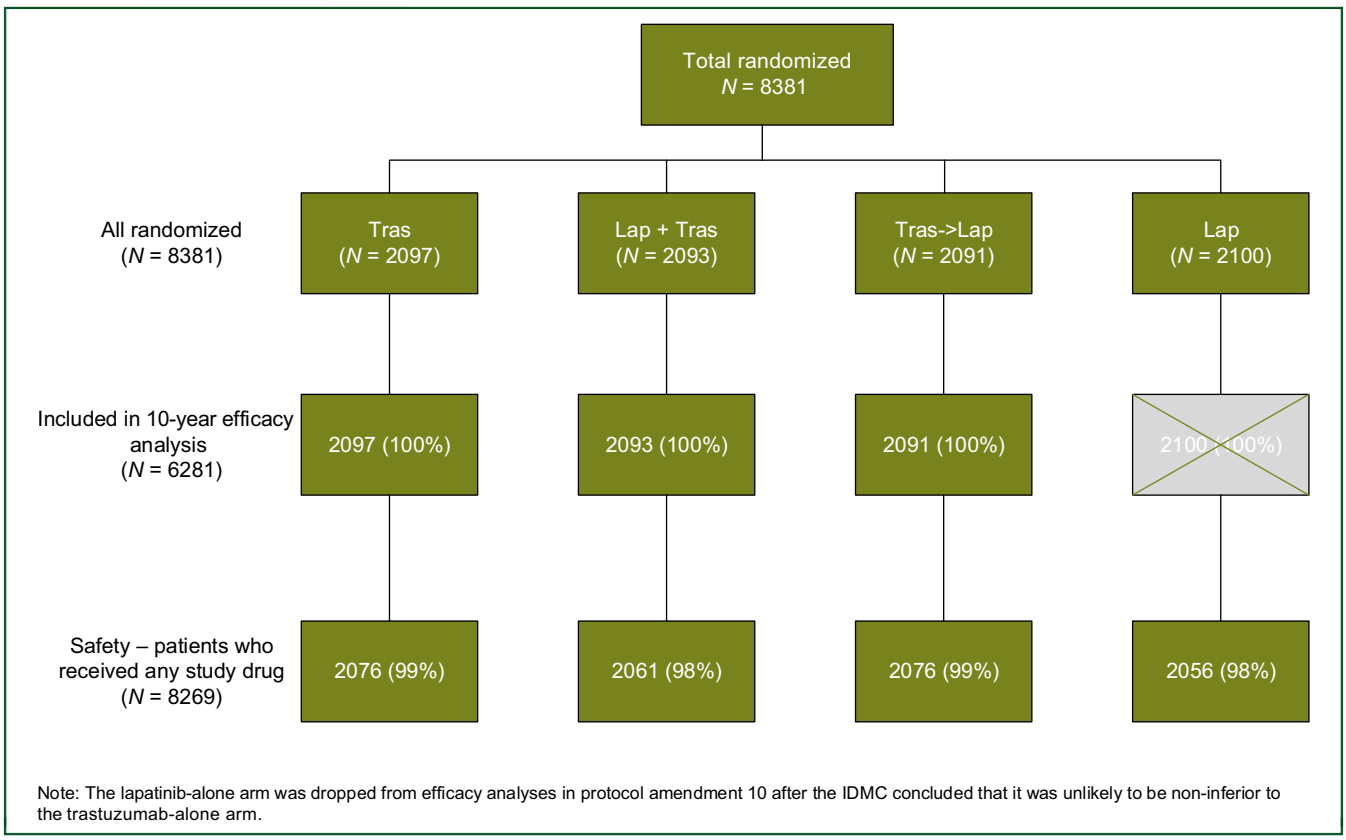

Figure 1. CONSORT diagram.
IDMC, Independent Data Monitoring Committee; Lap, lapatinib; Lap + Tras, lapatinib + trastuzumab; Tras, trastuzumab; Tras→Lap, trastuzumab followed by lapatinib.

Table 1. Baseline characteristics of the patients included in ALTTO (intention-to-treat population; *N* = 6281 patients)

Variable	T (*N* = 2097) *N* (%)	L + T (*N* = 2093) *N* (%)	T → L (*N* = 2091) *N* (%)
Region, *n* (%)			
North America (region 1)	230 (11)	233 (11)	244 (12)
South America (region 2)	113 (5)	104 (5)	113 (5)
Europe (region 3)	1118 (53)	1128 (54)	1112 (53)
Asia Pacific and South Africa (region 4)	636 (30)	628 (30)	622 (30)
Race, *n* (%)			
White	1451 (69)	1445 (69)	1454 (69)
Asian	555 (26)	546 (26)	543 (25)
Black	25 (1)	38 (1)	30 (1)
Other/missing	66 (3)	64 (3)	64 (3)
Age, *n* (%)			
Median age, years (range)	51 (18-80)	51 (22-80)	51 (22-80)
<65 years	1881 (90)	1879 (90)	1877 (90)
≥65 years	216 (10)	214 (10)	214 (10)
Menopausal status, *n* (%)			
Premenopausal	908 (43)	909 (43)	929 (44)
Postmenopausal [or male]	1189 [0] (57)	1184 [2] (57)	1162 [5] (56)
Nodal status, *n* (%)			
Not applicable (neoadj. CT)	181 (9)	168 (8)	170 (8)
Negative	844 (40)	845 (40)	842 (40)
1-3 positive nodes	603 (29)	617 (29)	617 (30)
≥4 positive nodes	469 (22)	463 (22)	462 (22)
Pathological tumor size, *n* (%)			
Not applicable (neoadj. CT)	181 (9)	168 (8)	170 (8)
≤2 cm	855 (41)	864 (41)	858 (41)
>2 cm to ≤5 cm	937 (45)	939 (45)	935 (45)
>5 cm	115 (5)	113 (5)	119 (6)
Missing	9 (<1)	9 (<1)	9 (<1)
Hormone receptor status, *n* (%)			
Positive	1200 (57)	1203 (57)	1205 (58)
Negative	897 (43)	890 (43)	886 (42)
Histologic grade, *n* (%)			
Cannot be assessed	59 (3)	79 (4)	61 (3)
Well differentiated	48 (2)	51 (2)	59 (3)
Moderately differentiated	744 (36)	774 (37)	793 (38)
Poorly differentiated	1237 (59)	1179 (57)	1171 (56)
Missing	9	10	7
Timing of chemotherapy, *n* (%)			
Sequential (design 1)	1147 (55)	1155 (55)	1143 (55)
Concurrent (design 2/2B)	950 (45)	938 (45)	948 (45)

CT, chemotherapy; neoadj., neoadjuvant; L + T, lapatinib + trastuzumab; T, trastuzumab; T→L, trastuzumab followed by lapatinib.

Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103938).

Ten-year OS rates in the ITT population were 87% (95% CI 86% to 89%) in the T-alone arm, 89% (95% CI 87% to 90%) in the L + T arm and 89% (95% CI 87% to 90%) in the T→L arm, with a L + T versus T HR of 0.85 (95% CI 0.70-1.03) and T→L versus T HR of 0.86 (95% CI 0.71-1.04) (Table 2 and Figure 2B). No evidence of differences between the three treatment groups for any of the subgroups were observed (Table 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103938).

Incidence of central nervous system (CNS) recurrence as the first site was the same in the three groups, with 48 events in the T group, 50 events in the L + T group and 52 events in the T→L group, with a 2% incidence of CNS recurrence in each group (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103938). No observed differences in the first site of DFS event were found in distant visceral recurrences (i.e. lung, liver or pleural effusion) or distant bone recurrences (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103938). TTDR was also similar in the three treatment groups (data not shown).

Safety analysis

For the safety analysis, 8269 patients were included from the four treatment groups. Overall, considering adverse events (AEs) related to study treatments, 1329 (64%) AEs in the T group, 1922 (93%) AEs in the L + T group, 1800 (87%) AEs in the T→L group and 1857 (90%) AEs in the L group were reported. Since the latest report with a median follow-up of 6.9 years, in this analysis with a median follow-up of 9.8 years, 31 additional patients with a serious adverse event (SAE) were reported (29 not related to treatment, 1 rectal cancer and 1 myocardial infarction), distributed fairly evenly across treatment groups, with 335 (16%) SAEs in the T group, 466 (23%) SAEs in the L + T group, 398 (19%) SAEs in the T→L group and 469 (23%) SAEs in the L group reported (Table 3). Across all the groups, <1% of all fatal SAEs

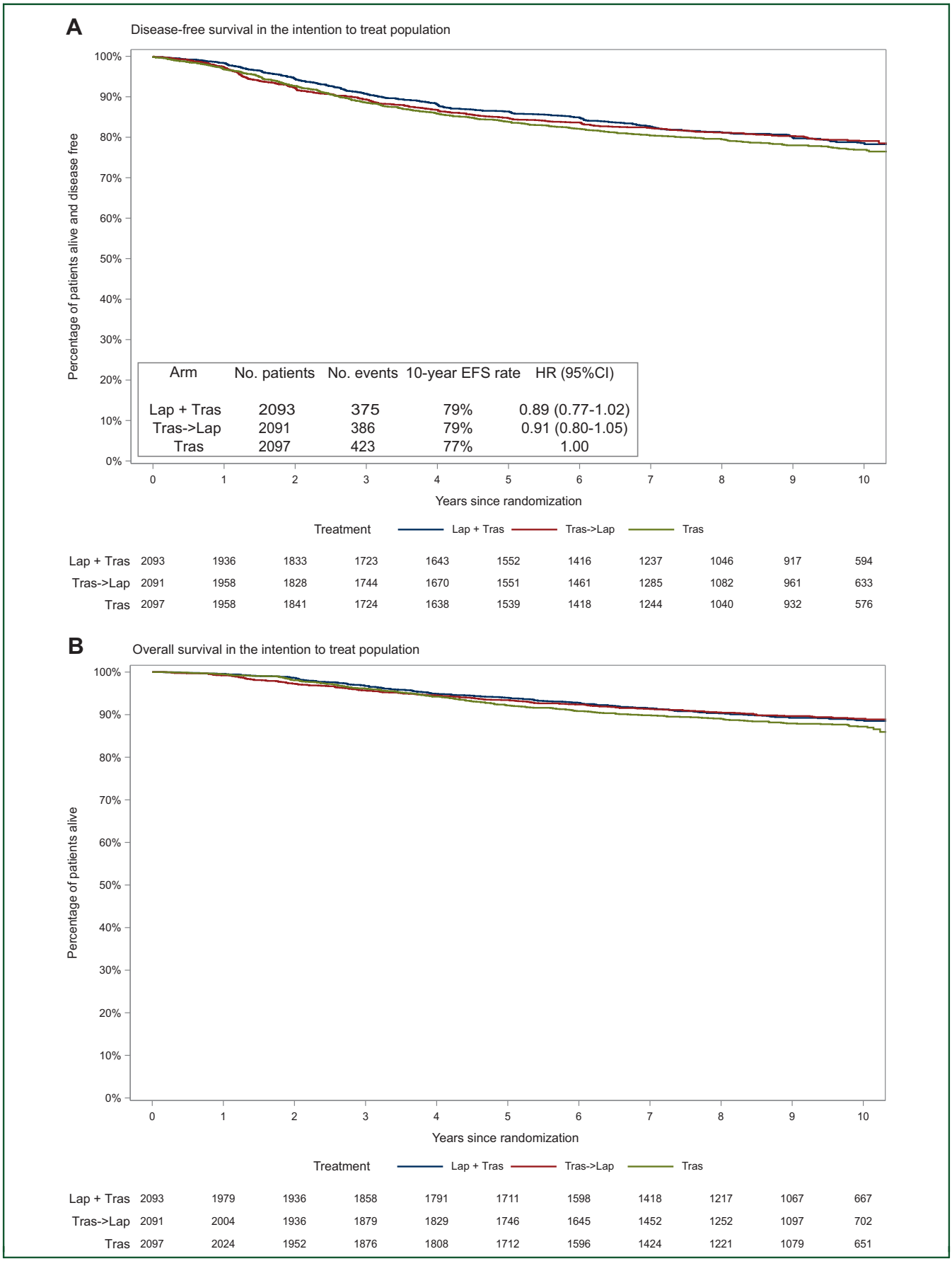

Figure 2. Disease-free and overall survival in the intention to treat population.
(A) Disease-free survival in the intention-to-treat population. (B) Overall survival.
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; Lap + Tras, lapatinib + trastuzumab; Tras: trastuzumab; Tras→Lap: trastuzumab followed by lapatinib.

Table 2. Ten-year survival outcomes in ALTTO

	10-year (%) (95%CI)	HR (95% CI)
Disease-free survival		
ITT		
T	77 (75-79)	Ref
L + T	79 (76-80)	0.89 (0.77-1.02)
T→L	79 (77-81)	0.91 (0.80-1.05)
Hormone receptor-positive		
T	78 (75-80)	Ref
L + T	79 (76-81)	0.92 (0.76-1.10)
T→L	80 (78-83)	0.88 (0.73-1.06)
Hormone receptor-negative		
T	76 (73-79)	Ref
L + T	78 (75-81)	0.85 (0.69-1.05)
T→L	78 (74-80)	0.95 (0.78-1.17)
Sequential chemotherapy		
T	74 (71-77)	Ref
L + T	76 (73-79)	0.85 (0.71-1.01)
T→L	78 (75-80)	0.85 (0.71-1.01)
Concomitant chemotherapy		
T	80 (77-83)	Ref
L + T	81 (78-84)	0.95 (0.76-1.19)
T→L	81 (78-83)	1.03 (0.82-1.28)
Overall survival		
ITT		
T	87 (86-89)	Ref
L + T	89 (87-90)	0.85 (0.70-1.03)
T→L	89 (87-90)	0.86 (0.71-1.04)
Hormone receptor-positive		
T	88 (86-90)	Ref
L + T	89 (87-91)	0.87 (0.67-1.13)
T→L	91 (89-93)	0.77 (0.58-1.00)
Hormone receptor-negative		
T	86 (83-88)	Ref
L + T	88 (85-90)	0.83 (0.63-1.10)
T→L	86 (83-89)	0.97 (0.74-1.27)
Sequential chemotherapy		
T	85 (83-87)	Ref
L + T	88 (86-90)	0.81 (0.63-1.03)
T→L	89 (86-90)	0.81 (0.64-1.04)
Concomitant chemotherapy		
T	89 (87-91)	Ref
L + T	90 (87-92)	0.93 (0.68-1.27)
T→L	90 (87-92)	0.95 (0.70-1.28)

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; ITT, intention to treat; OS, overall survival: T, trastuzumab; L + T, lapatinib + trastuzumab; T→L, trastuzumab followed by lapatinib.

were reported as related to study treatments (Table 3). One fatal SAE not related to treatment was pancreas cancer (T→L group). More treatment interruptions, dose delays and discontinuations were observed in the three experimental groups compared to T alone (Table 3).

Regarding cardiac safety, the incidence of primary cardiac events was low, with an overall incidence of 0.92% (95% CI 0.55% to 1.43%) in the T-alone group, 1.0% (95% CI 0.63% to 1.55%) in the L + T group, 0.53% (95% CI 0.26% to 0.95%) in the T→L group and 0.44% (95% CI 0.20% to 0.83%) in the L-alone group (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103938). Considering any cardiac endpoint, the T→L (2.9%) and L-alone (2.1%) groups had fewer cardiac events compared to T (4.9%) and L + T (4.0%) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103938). Most cardiac events occurred in patients treated with anthracycline-based chemotherapy (≈95%) (data not shown).

DISCUSSION

The ALTTO trial was the first randomized trial testing dual anti-HER2 blockade in patients with HER2-positive early breast cancer. At a median follow-up of 9.8 years, DFS, TTDR and OS were similar in the three treatment groups. Although superiority of L + T could not be demonstrated, the data are consistent with other studies that have demonstrated superiority of dual anti-HER2 blockade.[17] In addition, the EXTENET trial showed that extending the duration of anti-HER2 drugs (1 year of trastuzumab followed by 1 year of neratinib) improves outcomes in patients with hormone receptor-positive early breast cancer.[18-20] The failure of ALTTO and the success of a similar approach in other studies might depend on differences in the statistical assumptions.[21,22]

The rate of CNS events as the first site of distant relapse remains low in all groups (2%) and is similar when considering CNS at any time (beyond first non-CNS distant relapse; 4%-5% in each group, data not shown).

The concept of dual anti-HER2 blockade with T + L or pertuzumab improved pCR in several neoadjuvant trials.[10,12,23-25] In the adjuvant setting, the addition of pertuzumab to T and chemotherapy improved invasive DFS in APHINITY in patients with node-positive disease, independently from hormone receptor status.[7]

At 10 years, 21%-23% of patients still experience a survival event (relapse or death), demonstrating the continued need to improve adjuvant treatment for some patients. Today, new approaches such as the use of neoadjuvant therapies in patients with node-positive disease or tumor ≥2 cm to reach pCR have changed the treatment landscape in this population. Equally important is the rescue of patients with residual disease after neoadjuvant therapies, for whom we have approval for trastuzumab emtansine.[26,27] However, new anti-HER2 molecules are currently being tested against or in combination with trastuzumab emtansine [e.g. trastuzumab deruxtecan (NCT04622319) and tucatinib (NCT04457596), respectively].

Unfortunately, since the approval of adjuvant trastuzumab in 2006 and adjuvant pertuzumab and trastuzumab in 2017, we still lack validated biomarkers that could predict the benefit (or lack thereof) of anti-HER2 therapies. Identifying patients who would not benefit from these therapies would avoid unnecessary toxicities (side-effects and finances). More work is needed in this area since new drugs with different toxicity profiles are currently being tested in this scenario (NCT04622319, NCT04457596).

HER2-positive breast cancer seems to have a non-inflamed tumor microenvironment with low infiltration of tumor-infiltrating lymphocytes (TILs).[28] HER2 signaling inhibits Fin responses and down-regulates interferon regulatory factors and inflammatory chemokine production via the PI3K-AKT pathway, which results in the reduction of effector CD8+ T cells and a decrease in the major histocompatibility complex class I expression.[29] In addition, HER2 amplification also causes loss of phosphorylation of TANK-binding kinase 1 (TBK1) and reduces stimulator of

Table 3. Overall safety in the safety population of the ALTTO trial (N = 8269 patients)

	T (N = 2076) N (%)	L + T (N = 2061) N (%)	T→L (N = 2076) N (%)	L (N = 2056) N (%)
Any AE	1835 (88)	1979 (96)	1956 (94)	1964 (96)
AEs related to study treatment	1329 (64)	1922 (93)	1800 (87)	1857 (90)
AEs leading to permanent discontinuation	171 (8)	481 (23)	261 (13)	317 (15)
AEs leading to dose reductions	81 (4)	413 (20)	275 (13)	448 (22)
AEs leading to dose interruptions/delays	419 (20)	945 (46)	668 (32)	821 (40)
Any SAE	335 (16)	466 (23)	398 (19)	469 (23)
SAEs related to study treatment	116 (6)	278 (13)	191 (9)	275 (13)
Fatal SAEs	19 (<1)	21 (1)	20 (<1)	23 (1)
Fatal SAEs related to study treatment	4 (<1)	4 (<1)	3 (<1)	4 (<1)

AE, adverse event; L, lapatinib alone; L + T, lapatinib + trastuzumab; SAE, serious adverse event; T, trastuzumab; T→L, trastuzumab followed by lapatinib.

interferon genes (STING) signaling, diminishing the interferon and antitumor immune responses.[29]

It has been demonstrated in the neoadjuvant setting that higher levels of TILs and/or immune-activated RNA signatures are associated with more pCR rates as well as with a better outcome (DFS).[30] In the adjuvant setting, in patients treated in the FinHER trial, there was an association between levels of TILs and an increased trastuzumab benefit (less distant metastases).[31] The NRG/NSABP B-31 trial and the Short-HER trial also demonstrated an association of TILs and improved outcomes, but not the NCCTG-N9831 trial.[32-34] In the APHINITY trial a greater benefit in terms of invasive DFS from dual blockade was observed in tumors with TILs (>75%) and T-cell-related genes.[35]

In terms of safety, we observed more treatment interruptions, dose delays and discontinuation in the three experimental groups compared to T alone. In terms of cardiac safety, ALTTO showed a low rate of cardiac events in this patient population, which was mostly treated with anthracycline-based chemotherapy (≈95%). Interestingly, the two groups with short or no exposure to trastuzumab (L and T→L) had significantly fewer secondary cardiac events compared to trastuzumab for 1 year. This is in line with results of the PERSEPHONE trial which demonstrated less cardiotoxicity with 6 versus 12 months of adjuvant T.[36]

Conclusions

With a longer follow-up, no significant improvement was observed in DFS in patients treated with dual anti-HER2 blockade with lapatinib + trastuzumab compared to trastuzumab alone. The 10-year survival rates for the combination group are consistent with other studies that have explored dual anti-HER2 therapy.

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