

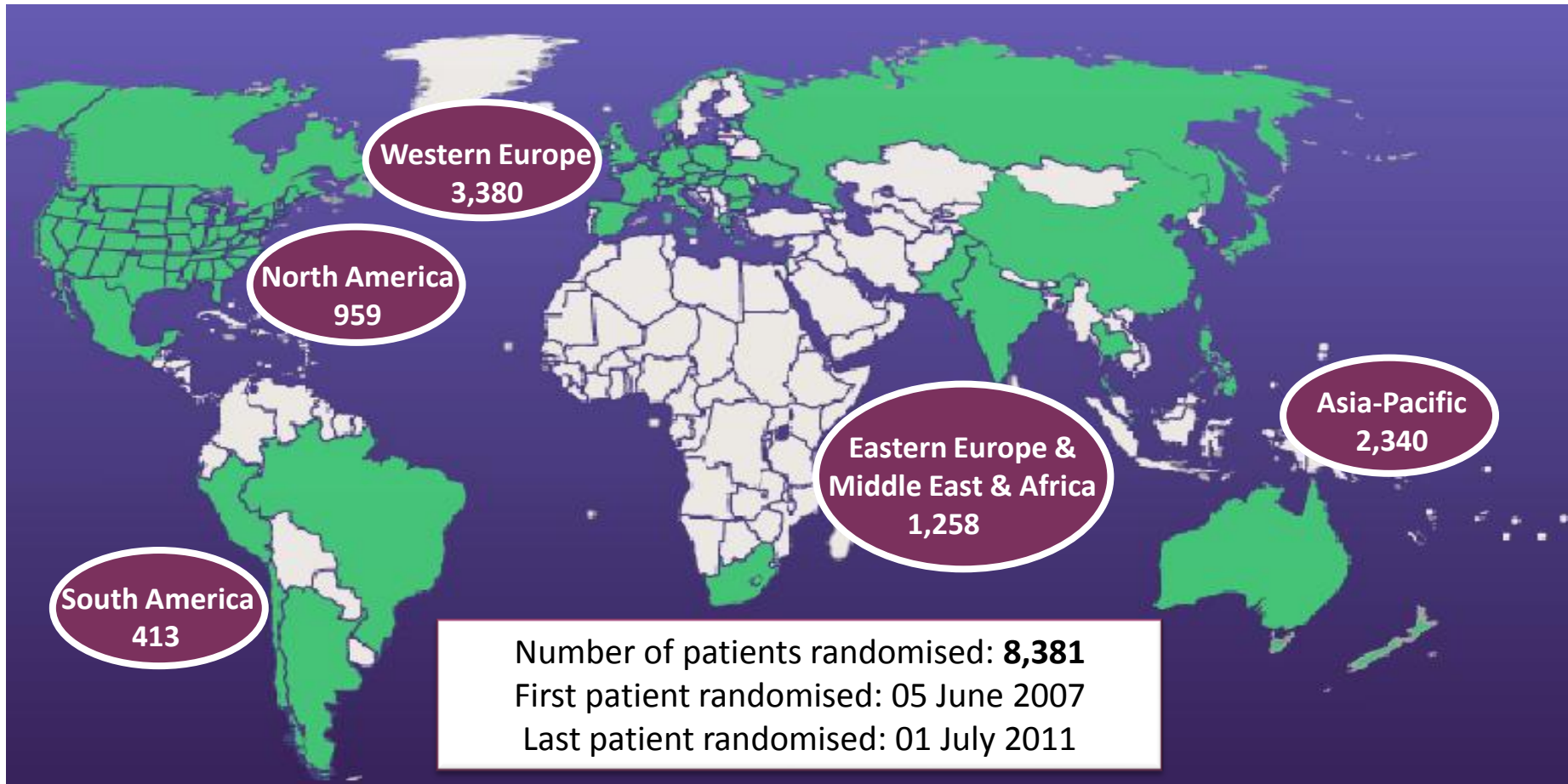


Results of the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) in the adjuvant treatment of HER2-positive early breast cancer (EBC)

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On Behalf of the ALTTO Study Team



ALTTO Recruitment



ALTO STUDY DESIGN

Anti-HER2 therapy: 4 groups assigned by randomization

Trastuzumab (T) x 52 weeks

Lapatinib (L) x 52 weeks

T x 12 wks ↔ L x 34 weeks
6 weeks

Trastuzumab and Lapatinib x 52 weeks

3 modalities of adjuvant CT administration per physician's choice

Design 1

Chemotherapy

12 to 18 weeks

Anti-HER2 therapy

52 weeks



Design 2a

Anthracycline

9 to 12 weeks

Taxane

12 weeks

Anti-HER2 therapy

52 weeks



Design 2b

Docetaxel + Carboplatin

18 weeks

Anti-HER2 therapy

52 weeks



* R: refers to the timing of randomization

ALTO Endpoints

- **Primary Endpoint:** Disease-free survival (DFS)
 - Invasive breast cancer recurrence at any site
 - 2nd primary cancer (invasive contralateral breast cancer or non-breast malignancy)
 - Death from any cause as first event
- **L + T vs. T and T → L vs. T comparisons**
- **Focus on L arm**
 - **L vs. T** (overall and within hormone-receptor subgroups)
 - **Addition of T in the L alone arm** (exploratory)

Other ALTTO Endpoints

- **Secondary Endpoints:**
 - Overall survival (OS)
 - Cumulative incidence of brain metastases
 - Cardiac safety
 - Safety in general
 - Time to recurrence (TTR)
 - Time to distant recurrence (TTDR)
 - cMYC, PTEN, p95 HER2

Statistical Considerations

- Target enrollment of at least 8,000 patients (actual 8,381 patients)
- Primary analysis triggered by protocol-specified 4.5 yrs median follow-up
- **First interim efficacy analysis (IDMC on 18th August 2011)**
 - Comparison of lapatinib alone vs. trastuzumab crossed the futility boundary (observed HR 1.52, expected HR for non-inferiority 1.16)
 - » Patients free of disease were offered to switch to trastuzumab
- **ITT population for lapatinib vs. trastuzumab comparison shown here**

ALTO CONSORT Table

	L + T	T → L	L	T	Total
ITT* Population	2,093 (100%)	2,091 (100%)	2,100 (100%)	2,097 (100%)	8,381 (100%)
PP* Population T → L vs. T	0	1,696 (81%)	0	2,024 (97%)	3,720 (89%)
Safety Population	2,061 (98%)	2,076 (99%)	2,057 (98%)	2,076 (99%)	8,270 (99%)

*ITT: intention-to-treat; PP: per protocol population

Results

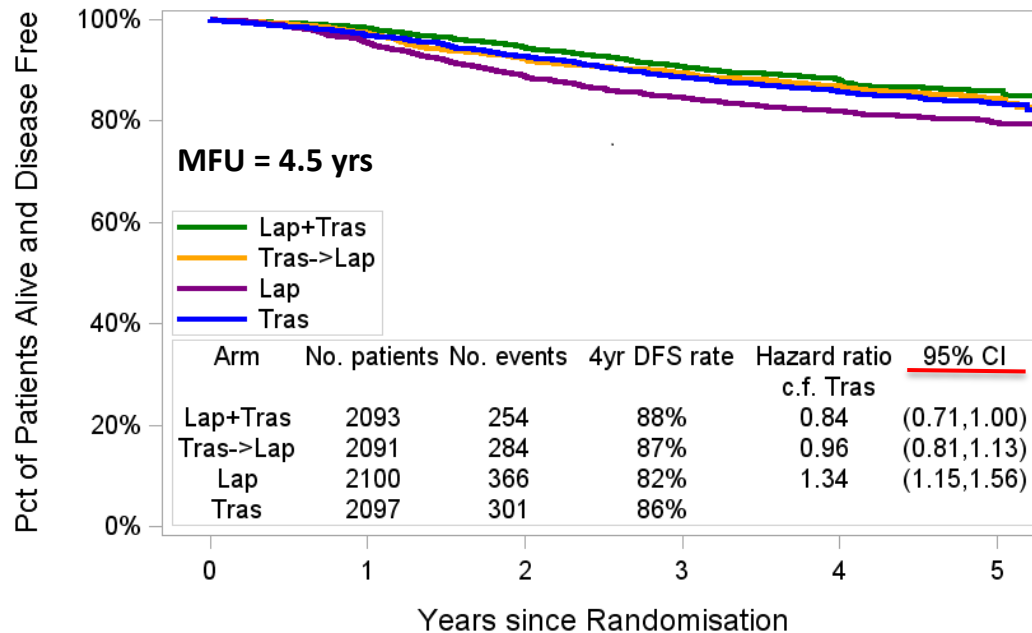
Distribution of the Stratification Factors by Treatment Arm

	L + T (N = 2,093)	T → L (N = 2,091)	L (N = 2,100)	T (N = 2,097)
Hormone Receptor Status				
Positive	1,203 (57%)	1,205 (58%)	1,197 (57%)	1,200 (57%)
Negative	890 (43%)	886 (42%)	903 (43%)	897 (43%)
Timing of chemotherapy				
Sequential (Design 1)	1,155 (55%)	1,143 (55%)	1,168 (56%)	1,147 (55%)
Concurrent (Design 2 and 2B)	938 (45%)	948 (45%)	932 (44%)	950 (45%)
Lymph Node Status				
Not applicable (neoadjuvant chemo)	168 (8%)	170 (8%)	167 (8%)	181 (9%)
Node negative	845 (40%)	842 (40%)	841 (40%)	844 (40%)
1-3 positive nodes	617 (29%)	617 (30%)	620 (30%)	603 (29%)
≥ 4 positive nodes	463 (22%)	462 (22%)	472 (22%)	469 (22%)

Distribution of Patient Characteristics by Treatment Arm

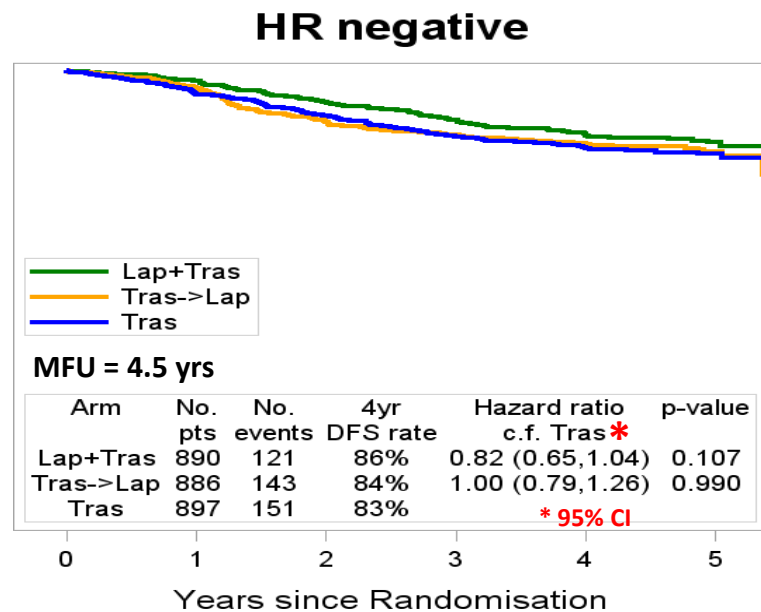
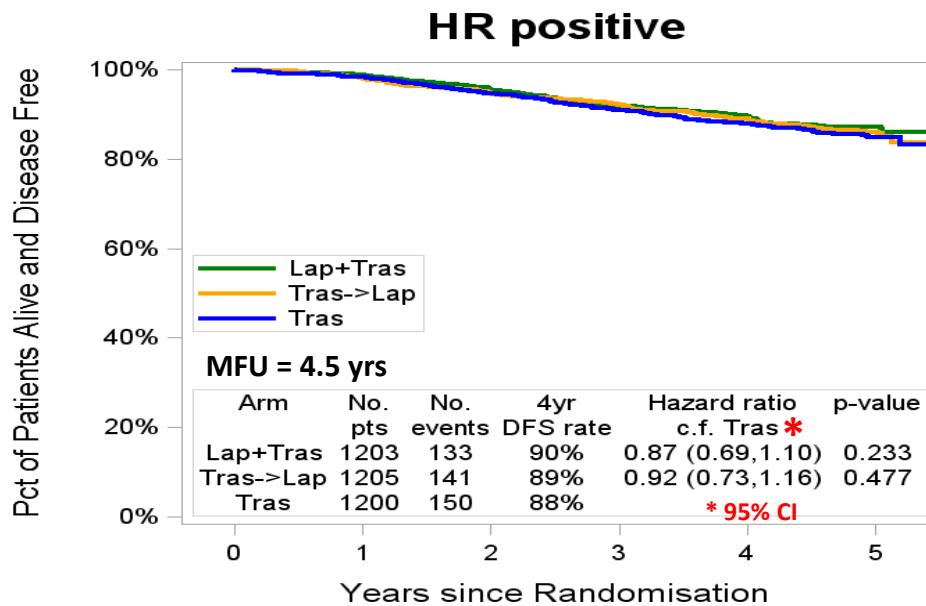
	L + T (N = 2,093)	T → L (N = 2,091)	L (N = 2,100)	T (N = 2,097)
Menopausal Status				
Premenopausal	908 (43%)	929 (44%)	891 (42%)	908 (43%)
Postmenopausal or male	1,185 (57%)	1,162 (56%)	1,208 (58%)	1,189 (57%)
Pathological primary tumor size - largest diameter of invasive component				
Not applicable (neoadjuvant chemo)	168 (8%)	170 (8%)	167 (8%)	181 (9%)
≤ 2cm	863 (41%)	856 (41%)	866 (41%)	854 (41%)
> 2cm to ≤ 5cm	937 (45%)	928 (45%)	938 (45%)	933 (45%)
> 5cm	113 (5%)	117 (6%)	119 (6%)	114 (5%)
Histologic grade				
Gx: Differentiation cannot be assessed	79 (4%)	61 (3%)	58 (3%)	59 (3%)
G1: Well differentiated	51 (2%)	59 (3%)	60 (3%)	48 (2%)
G2: Moderately differentiated	774 (37%)	793 (38%)	794 (38%)	744 (36%)
G3: Poorly differentiated/undifferentiated	1,179 (57%)	1,171 (56%)	1,183 (56%)	1,237 (59%)

Disease-free Survival (DFS) Analysis



Lap+Tras	2093	1938	1832	1672	1256	474
Tras->Lap	2091	1957	1822	1684	1261	476
Lap	2100	1844	1678	1519	1122	428
Tras	2097	1959	1838	1658	1246	448

DFS BY HORMONE RECEPTOR STATUS



Lap+Tras	1203	1122	1066	972	738	278
Tras->Lap	1205	1137	1081	1000	734	288
Tras	1200	1135	1070	968	722	260

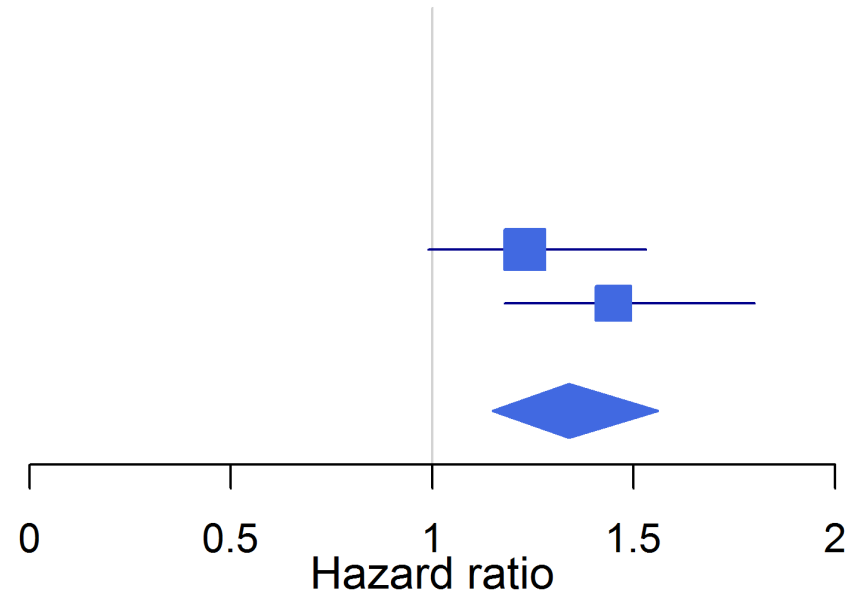
Lap+Tras	890	816	766	700	518	196
Tras->Lap	886	820	741	684	527	188
Tras	897	824	768	690	524	188

Interaction tests $p = 0.70$ L + T

$p = 0.60$ T \rightarrow L

Disease-free Survival (DFS) Analysis by Hormone Receptor Status (L vs. T)

Hormone receptor status	No. patients	Hazard ratio	95% CI
Positive	2397	1.23	0.99-1.53
Negative	1800	1.45	1.18-1.80
Overall	4197	1.34	1.15-1.56



Addition of Trastuzumab in the Lapatinib Alone Arm: Exploratory Analysis

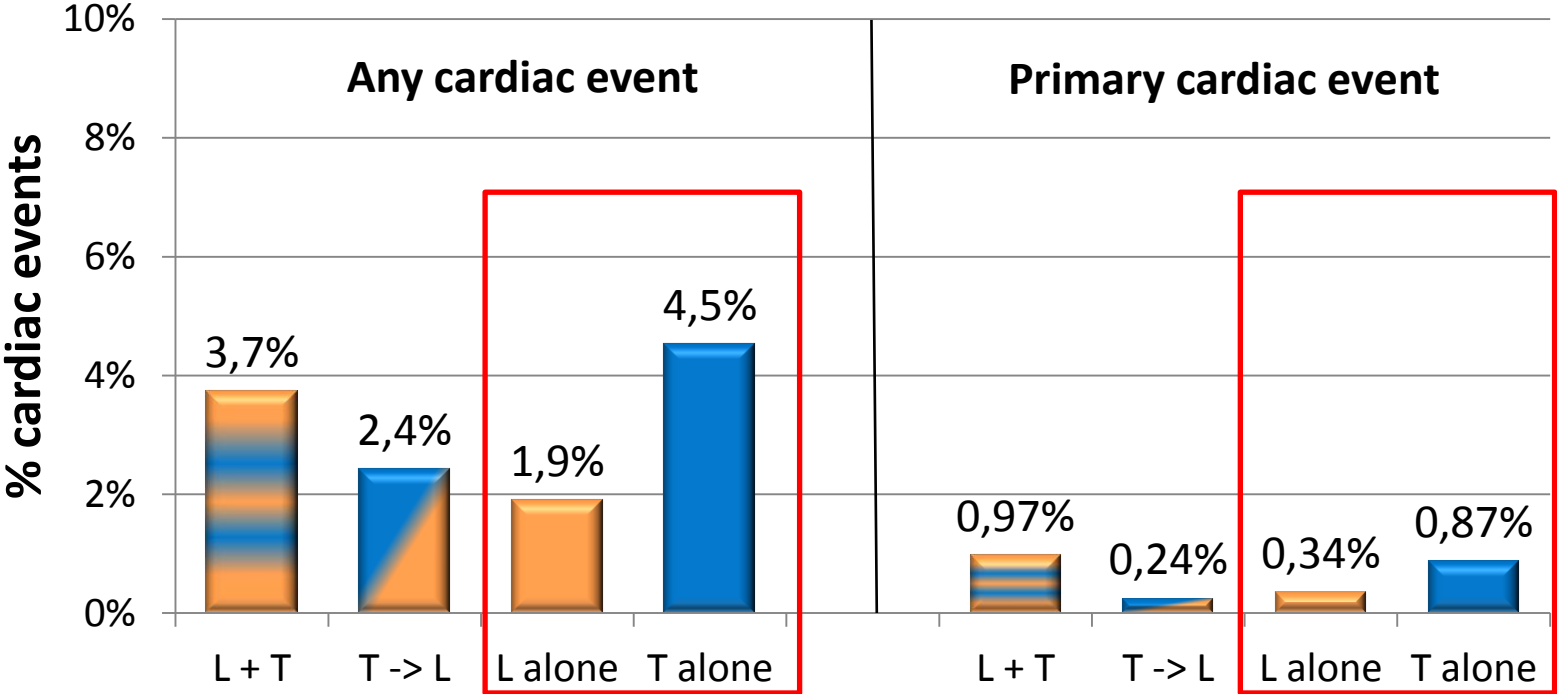
- 2,100 patients randomised to Lapatinib (L) alone
- 1,087 (52%) received at least one dose of trastuzumab (T) prior to a DFS event
 - 248 received T before 1 Oct 2011
 - 839 received T after 1 Oct 2011 (of 1,627 event-free and on study)
- 366 patients in the L alone arm had a DFS event
 - 305 of 1,013 patients who did not receive any T
 - 61 of 1,087 patients who received at least one dose of T
- Time dependent Cox model of DFS:
 - Hazard ratio = **0.67**, 95% CI (0.49-0.91)

Patients who received trastuzumab had a 33% reduction in the hazard of a DFS event.

Sites of First Recurrence

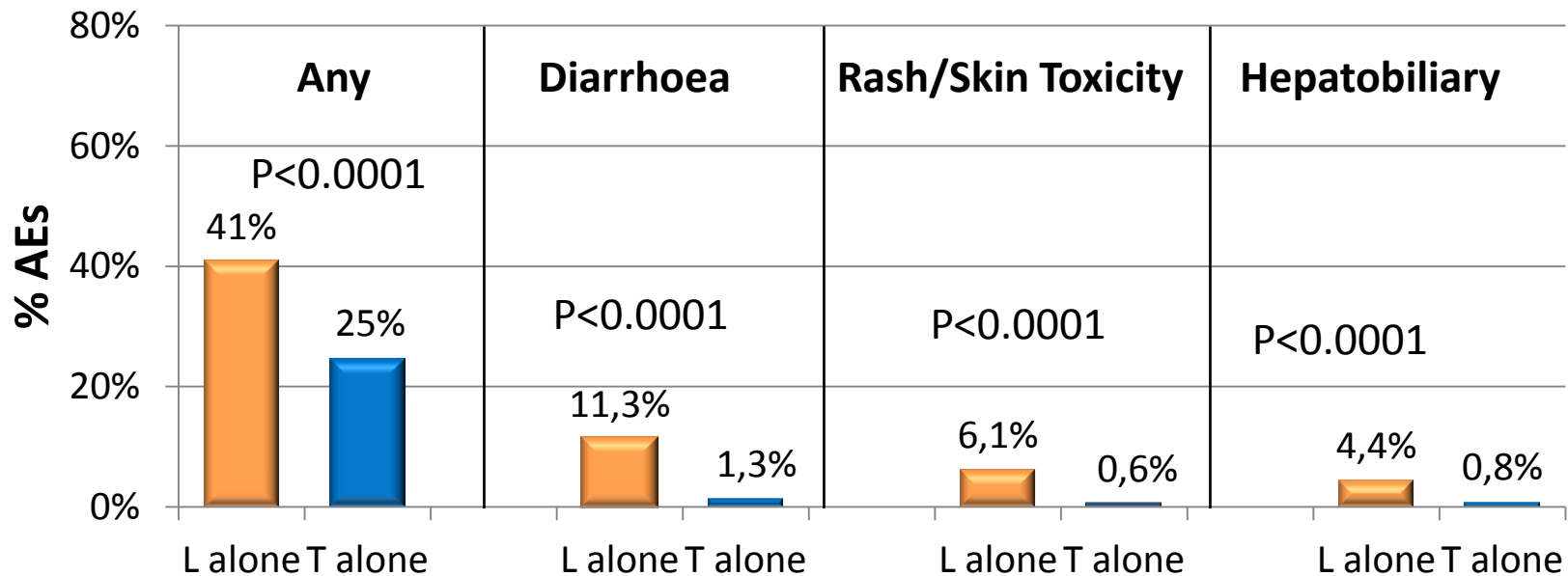
Event	L + T (N = 2,093)	T -> L (N = 2,091)	L alone (N = 2,100)	T alone (N = 2,097)
Local	23 (1%)	25 (1%)	27 (1%)	40 (2%)
Regional	3 (<1%)	10 (<1%)	11 (1%)	9 (<1%)
Distant				
Soft tissue	6 (<1%)	17 (<1%)	26 (1%)	21 (1%)
Skeletal	31 (1%)	39 (2%)	47 (2%)	36 (2%)
Central nervous system	41 (2%)	48 (2%)	50 (2%)	40 (2%)
Other visceral site	79 (4%)	84 (4%)	139 (7%)	93 (4%)
Contralateral breast cancer	21 (1%)	19 (<1%)	9 (<1%)	14 (<1%)
2 nd non-breast cancer	41 (2%)	28 (1%)	36 (2%)	34 (2%)
Death without recurrence	9 (<1%)	14 (<1%)	20 (1%)	13 (<1%)
Total	254 (12%)	284 (14%)	366 (17%)	301 (14%)

Cardiac Safety

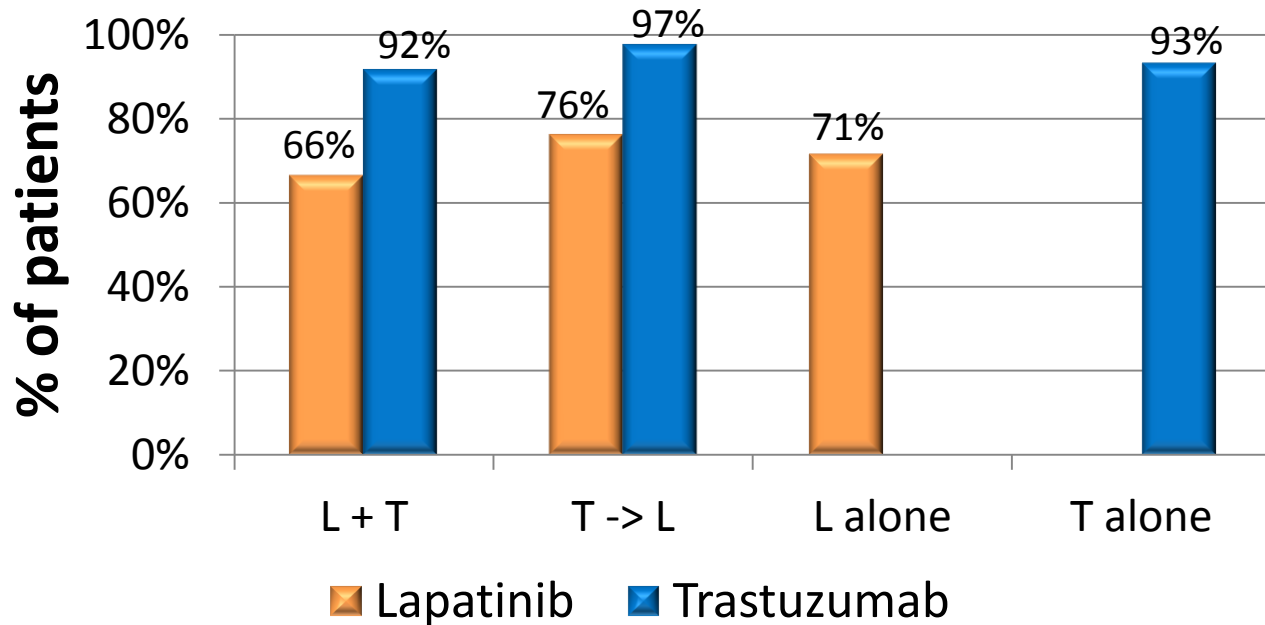


***Primary CE:** cardiac death or severe CHF NYHA Class III-IV; **Secondary CE:** asymptomatic (NYHA I) or mildly symptomatic (NYHA II) significant confirmed drop in LVEF. A significant LVEF drop is defined as an absolute decrease of >10 points below the baseline LVEF **and** to <50%

Main Differences in Grade 3-4 AEs by Treatment Arm



Proportion of Patients Receiving $\geq 85\%$ of the Planned Dose of Anti-HER2 Drugs



Conclusions (I)

- **The event rate was lower than anticipated: 555 DFS events for the L + T vs. T comparison at 4.5 years median follow-up instead of 850 target.**
- **The ALTTO trial did not meet its endpoints (DFS): Neither the L + T vs. T comparison nor the T → L vs. T comparison.**
 - **4-year DFS 88% vs. 86% for L + T vs. T (HR 0.84; 97.5%CI 0.70-1.02)**
 - **4-year DFS 87% vs. 86% for T → L vs. T (HR 0.93; 97.5%CI 0.76-1.13)**
- **The doubling in pCR observed with L + T in NeoALTTO did not translate into improved survival outcomes in ALTTO at 4.5 years median follow-up.**

Conclusions (II)

- **Trastuzumab confers a better disease-free and overall survival outcome compared to lapatinib**
 - 4-yr DFS 82% vs. 86% for L vs. T (HR **1.34**; 95% CI 1.15-1.56)
 - 4-yr OS 93% vs. 94% for L vs. T (HR **1.36**; 95% CI 1.09-1.72)
- **Patients assigned to lapatinib alone who received trastuzumab had a reduced risk of a DFS event**
 - HR **0.67**; 95% CI 0.49-0.91 (time-dependent Cox model of DFS)
 - Post-hoc analysis
- **Lapatinib did not appear to decrease the rate of CNS as first site of metastases (2% of cases in all arms)**

Conclusions (III)

- **Lapatinib is associated with significant increase in AEs of special interest compared with trastuzumab alone: diarrhoea, hepatobiliary, and rash/skin toxicity**
- **Cardiac toxicity was lower in lapatinib arm compared to trastuzumab although remained low in all treatment arms**
- **Follow-up in ALTTO will continue – a protocol-specified updated efficacy analysis is planned in 2 yrs**
- **Extensive translational correlative studies ongoing**

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<u>BIG Groups</u>	
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SWOG	

Other Groups

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