BIG
Breast International Group

ALTTO
Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

Alliance for Clinical Trials in Oncology

Disease-free survival (DFS) in the lapatinib alone arm and expanded 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

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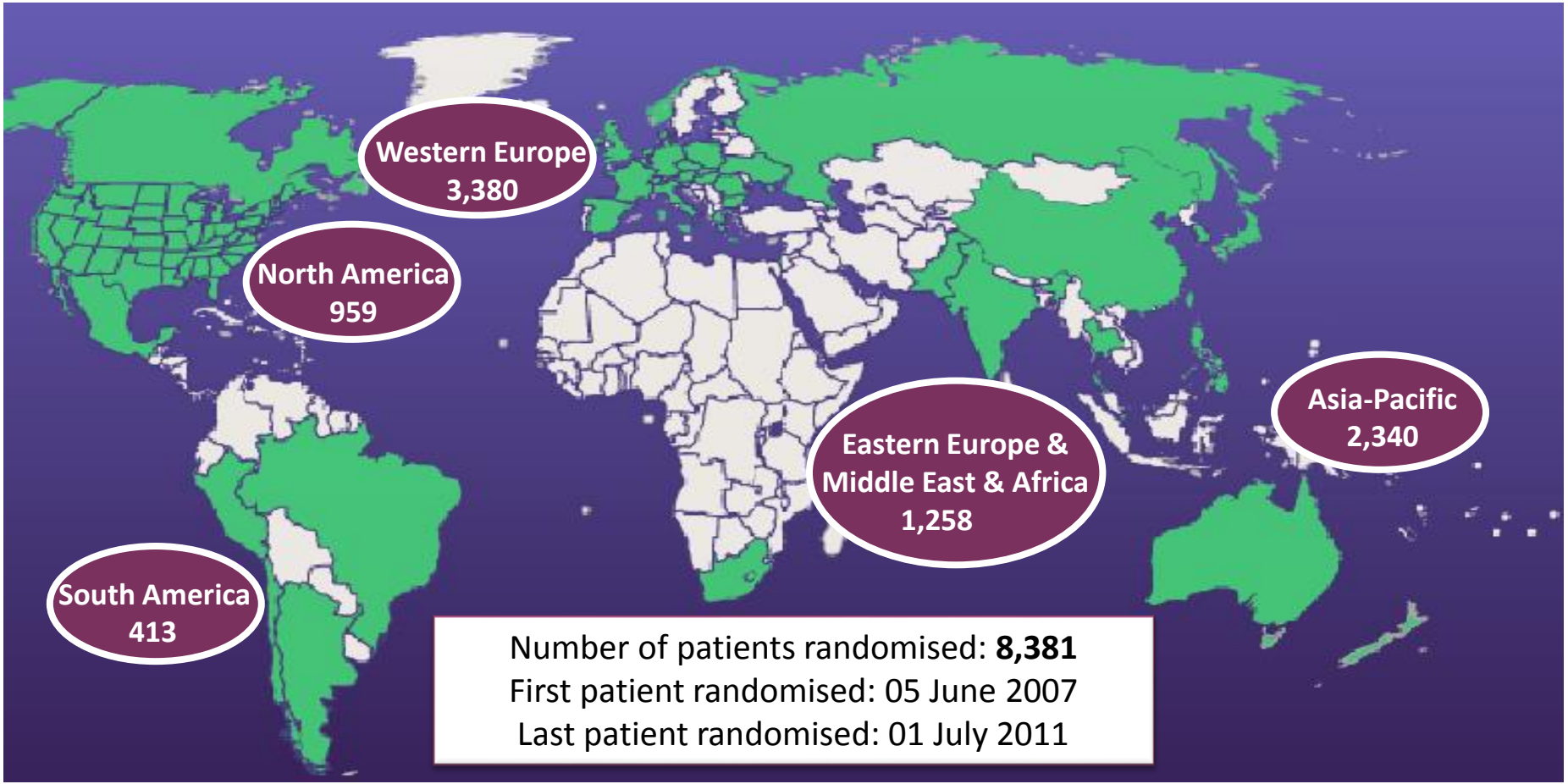
National Cancer Institute

Disclosures

Edith A. Perez, MD:

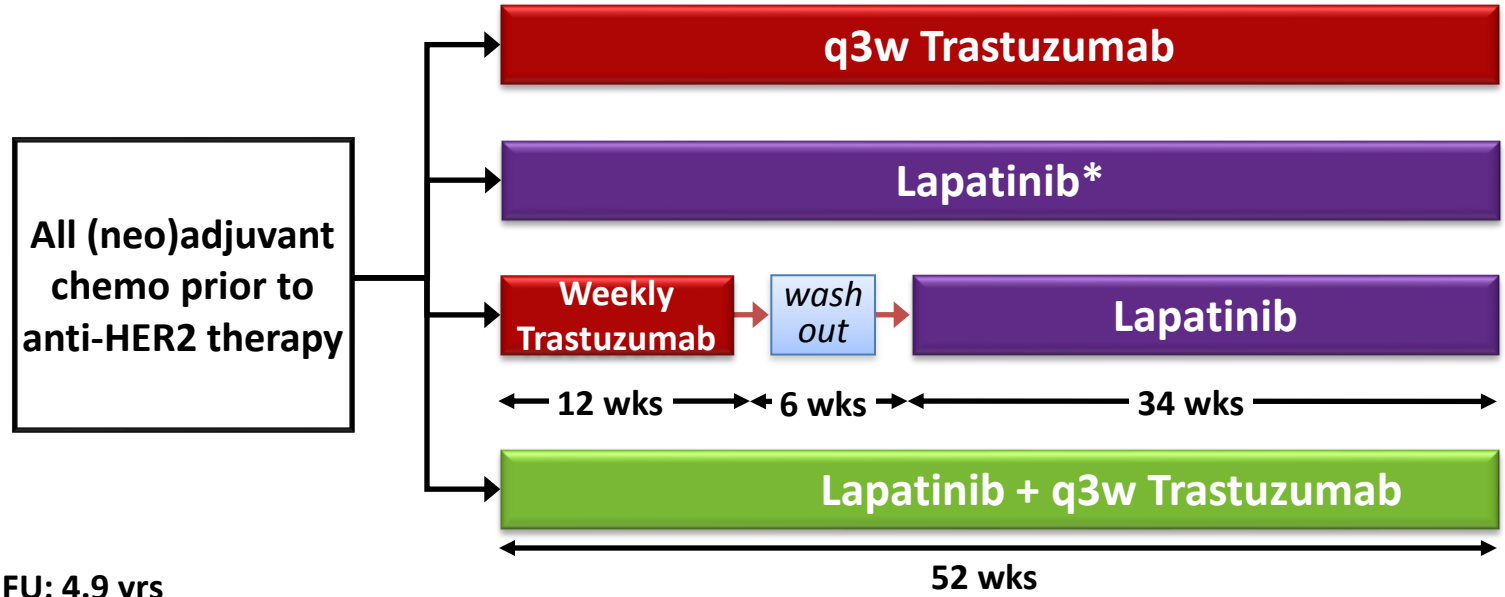
- **Research grants to Mayo Clinic:** most companies, including GSK
- **Consultant (unpaid):** various pharmaceutical and diagnostic medical companies

ALTTO Recruitment



Number of patients randomised: **8,381**
First patient randomised: 05 June 2007
Last patient randomised: 01 July 2011

Design 1: Sequential Anti-HER2 Therapy After all Chemotherapy (N= 4,613)

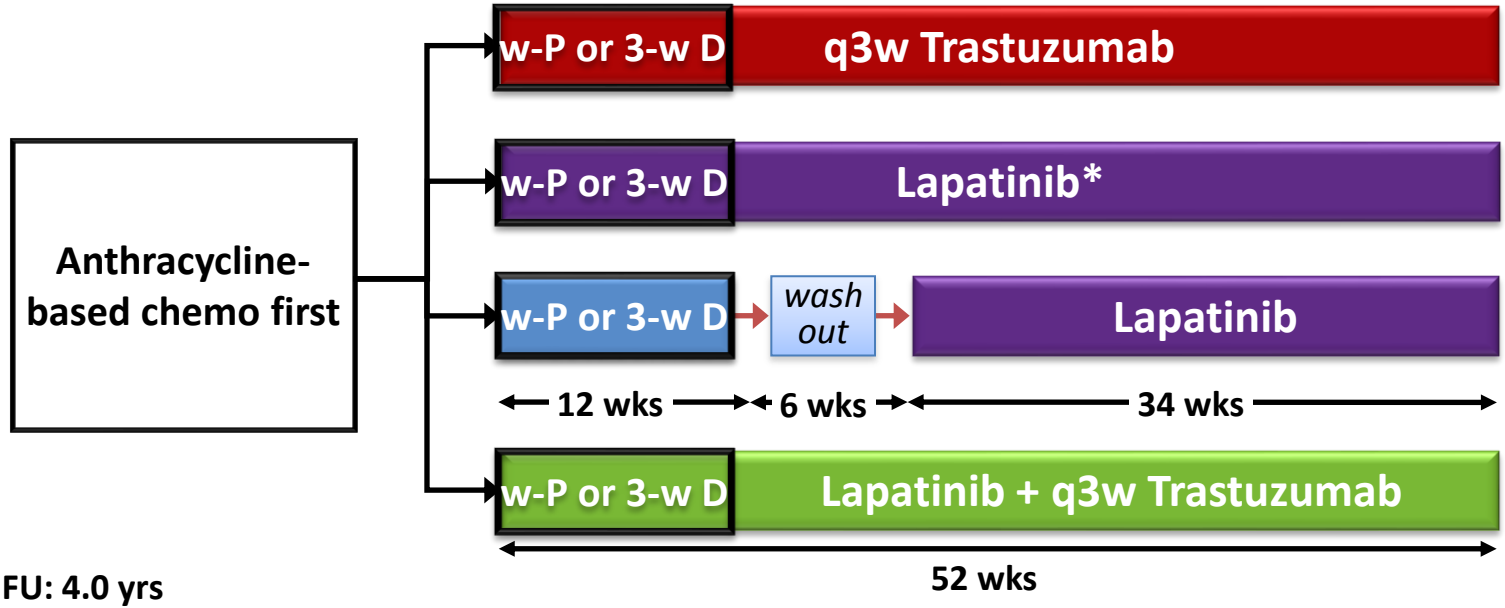


median FU: 4.9 yrs

All patients: radiotherapy, if indicated (concomitant with targeted therapy)
Hormone receptor-positive patients: endocrine therapy for at least 5 yrs
**The L alone arm was closed on 18 Aug 2011 following IDMC recommendation*

Tras alone: 8 mg/kg → 6 mg/kg iv, q21d
Lap alone: 1500 mg po qd
Tras → Lap: T 4 mg/kg → 2 mg/kg iv q7d; L 1500 mg po qd
Tras + Lap: T 8 mg/kg → 6 mg/kg iv, q21d; L 1000 mg po qd

Design 2: Concurrent Anti-HER2 Therapy After Anthracycline-based Chemotherapy (N= 3,337)

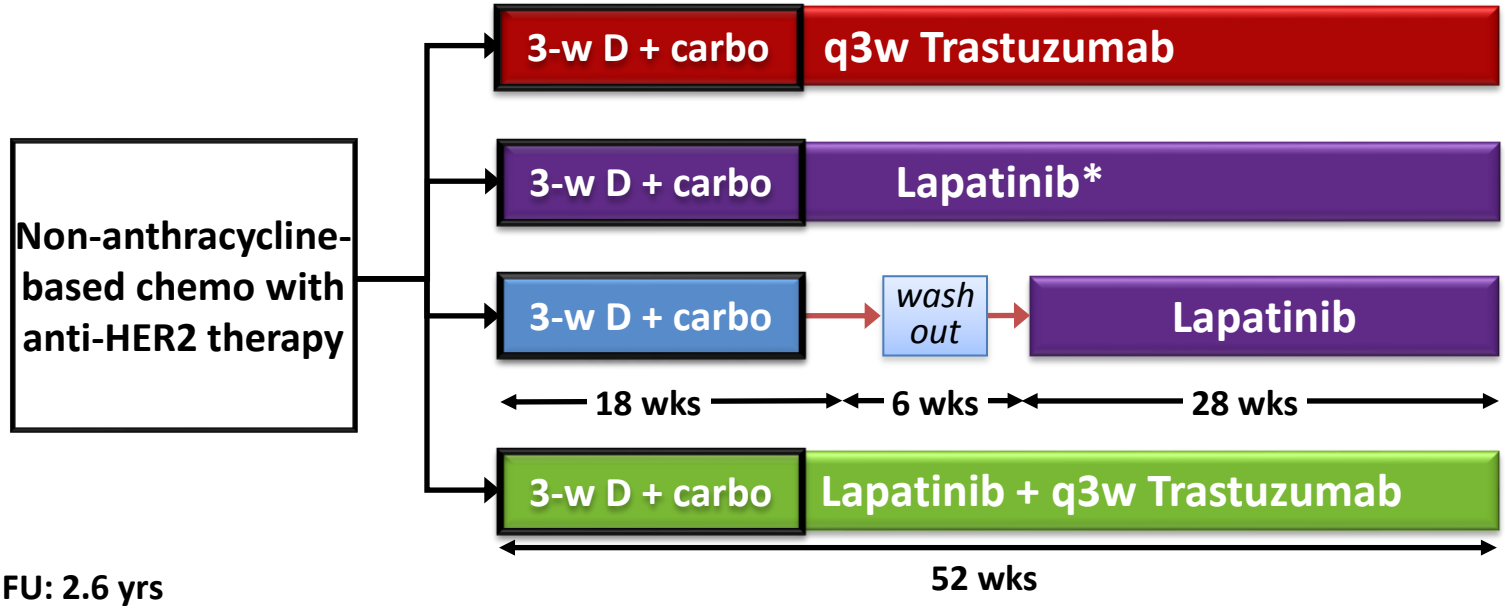


median FU: 4.0 yrs

w-P: weekly paclitaxel (80 mg/m^2); 3-w D: q3w docetaxel (75-100 mg/m^2)
All patients: radiotherapy, if indicated (concomitant with targeted therapy)
Hormone receptor-positive patients: endocrine therapy for at least 5 yrs
**The L alone arm was closed on 18 Aug 2011 following IDMC recommendation*

Tras alone: 4 mg/kg → 2 mg/kg iv, q7d → 6 mg/kg iv, q21d
Lap alone: 750 mg po qd → 1500 mg qd
Tras → Lap: T 4 mg/kg → 2 mg/kg iv q7d; L 1500 mg po qd
Tras + Lap: T 4 mg/kg → 2 mg/kg iv, q7d → 6 mg/kg iv, q21d; L 750 mg po qd → 1000 mg qd

Design 2B: Concurrent Anti-HER2 Therapy With a Non-anthracycline Chemotherapy (N= 431)



median FU: 2.6 yrs

3-w D: q3w docetaxel (75 mg/m^2); carbo: carboplatin (AUC 6)
All patients: radiotherapy, if indicated (concomitant with targeted therapy).
Hormone receptor-positive patients: endocrine therapy for at least 5 yrs
**The L alone arm was closed on 18 Aug 2011 following IDMC recommendation*

Tras alone: 4 mg/kg → 2 mg/kg iv, q7d → 6 mg/kg iv, q21d
Lap alone: 750 mg po qd → 1500 mg qd
Tras → Lap: T 4 mg/kg → 2 mg/kg iv q7d; L 1500 mg po qd
Tras + Lap: T 4 mg/kg → 2 mg/kg iv, q7d → 6 mg/kg iv, q21d; L 750 mg po qd → 1000 mg qd

ALTTO 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 previously presented (Piccart M, et al. ASCO 2014)
- **Presented here (Perez EA, et al. ESMO 2014): Focus on L arm**
  - **L vs. T** (overall and within hormone-receptor subgroups)
  - **Addition of T in the L alone arm** (exploratory)
  - **Other data**

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

* Also presented here at ESMO

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 as of October 2011
- **ITT population for lapatinib vs. trastuzumab comparison shown here**

ALTTO 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

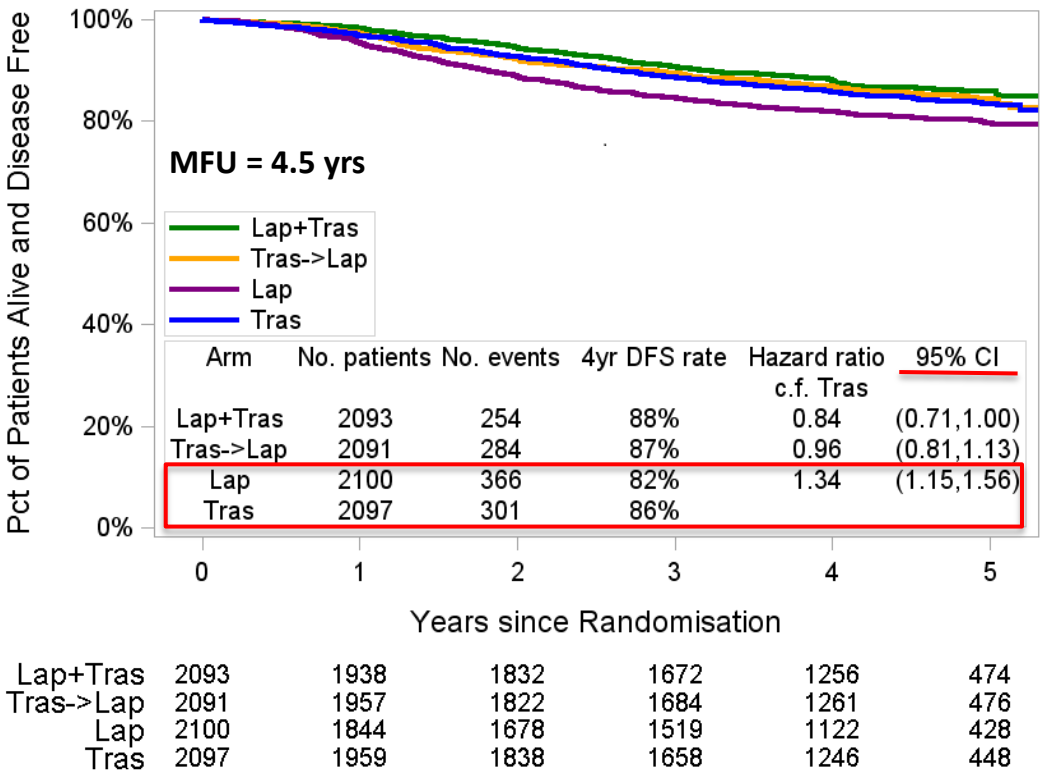
Distribution of the Stratification Factors by Treatment Arm

	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

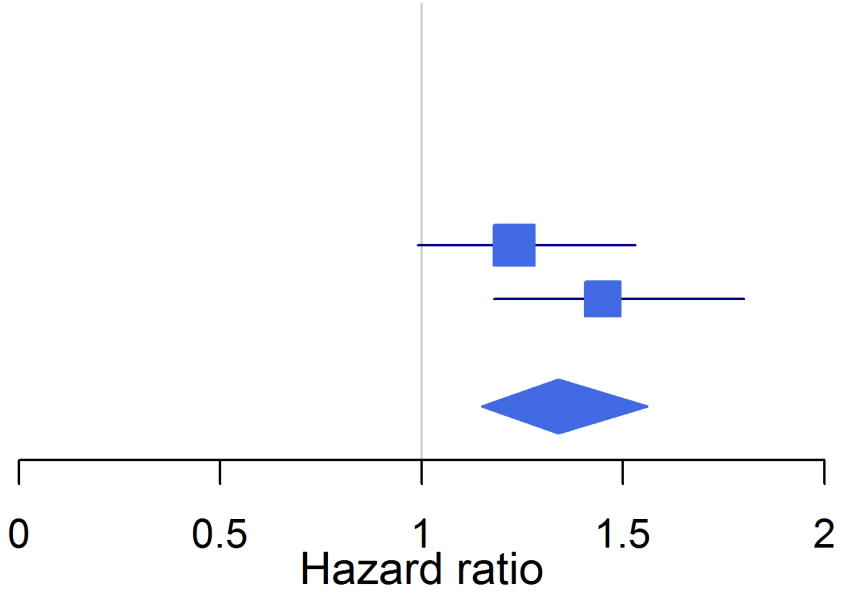


Arm	No. patients	No. events	4yr DFS rate	Hazard ratio c.f. Tras	95% CI
Lap+Tras	2093	254	88%	0.84	(0.71,1.00)
Tras->Lap	2091	284	87%	0.96	(0.81,1.13)
Lap	2100	366	82%	1.34	(1.15,1.56)
Tras	2097	301	86%		

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

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**

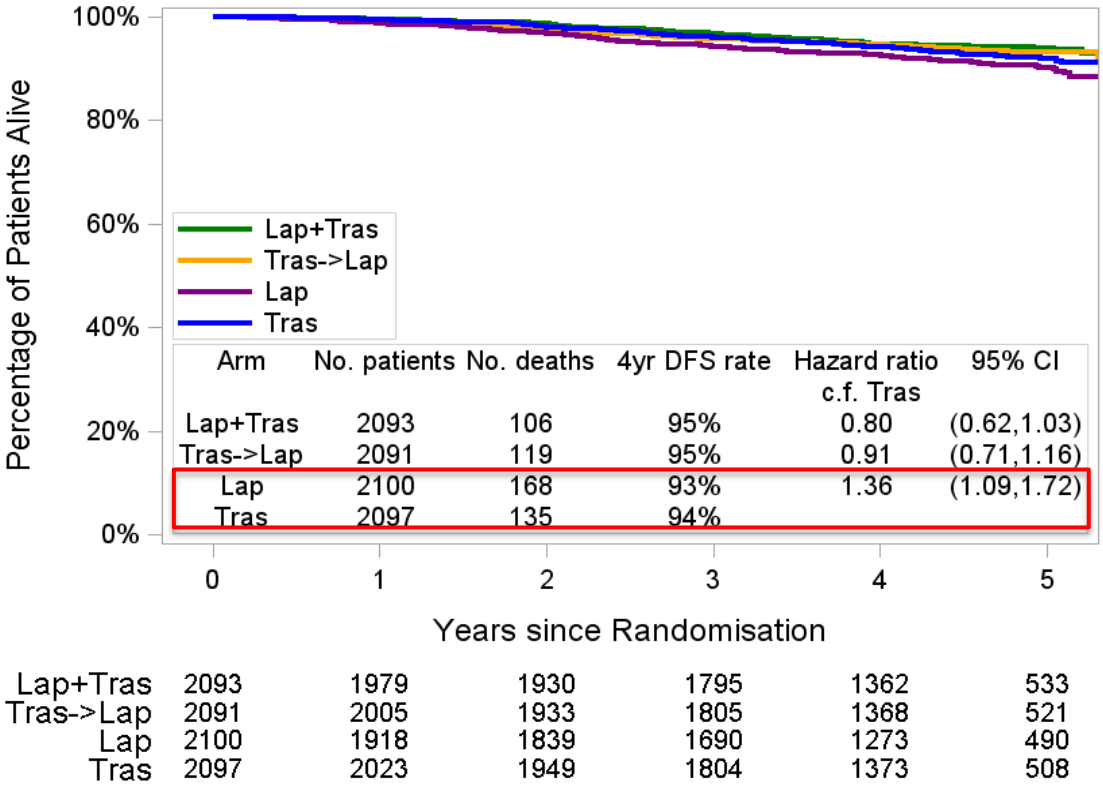


Addition of Trastuzumab in the Lapatinib Alone Arm: Exploratory Analysis

- 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.

Overall Survival (OS) Analysis



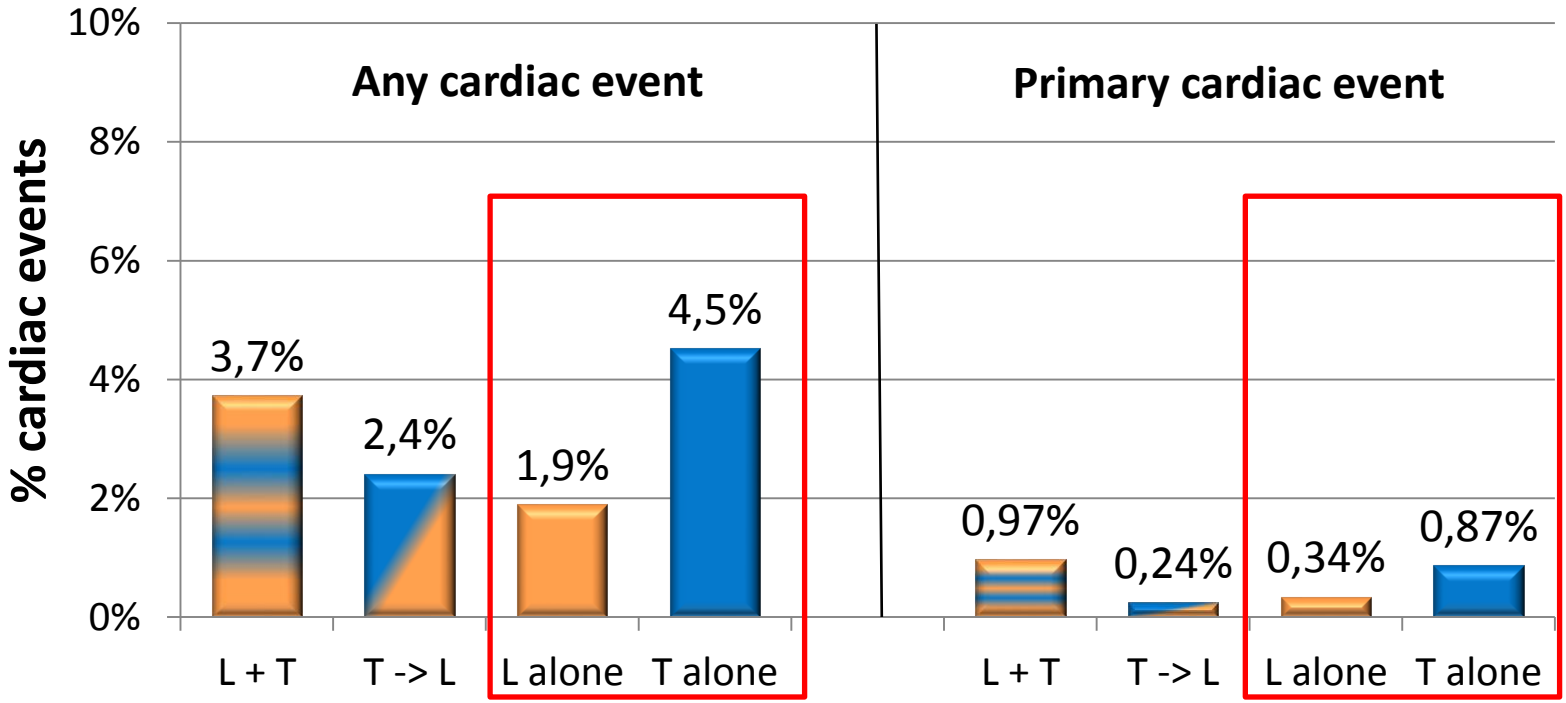
Arm	No. patients	No. deaths	4yr DFS rate	Hazard ratio c.f. Tras	95% CI
Lap+Tras	2093	106	95%	0.80	(0.62,1.03)
Tras->Lap	2091	119	95%	0.91	(0.71,1.16)
Lap	2100	168	93%	1.36	(1.09,1.72)
Tras	2097	135	94%		

Lap+Tras	2093	1979	1930	1795	1362	533
Tras->Lap	2091	2005	1933	1805	1368	521
Lap	2100	1918	1839	1690	1273	490
Tras	2097	2023	1949	1804	1373	508

Sites of First Recurrence

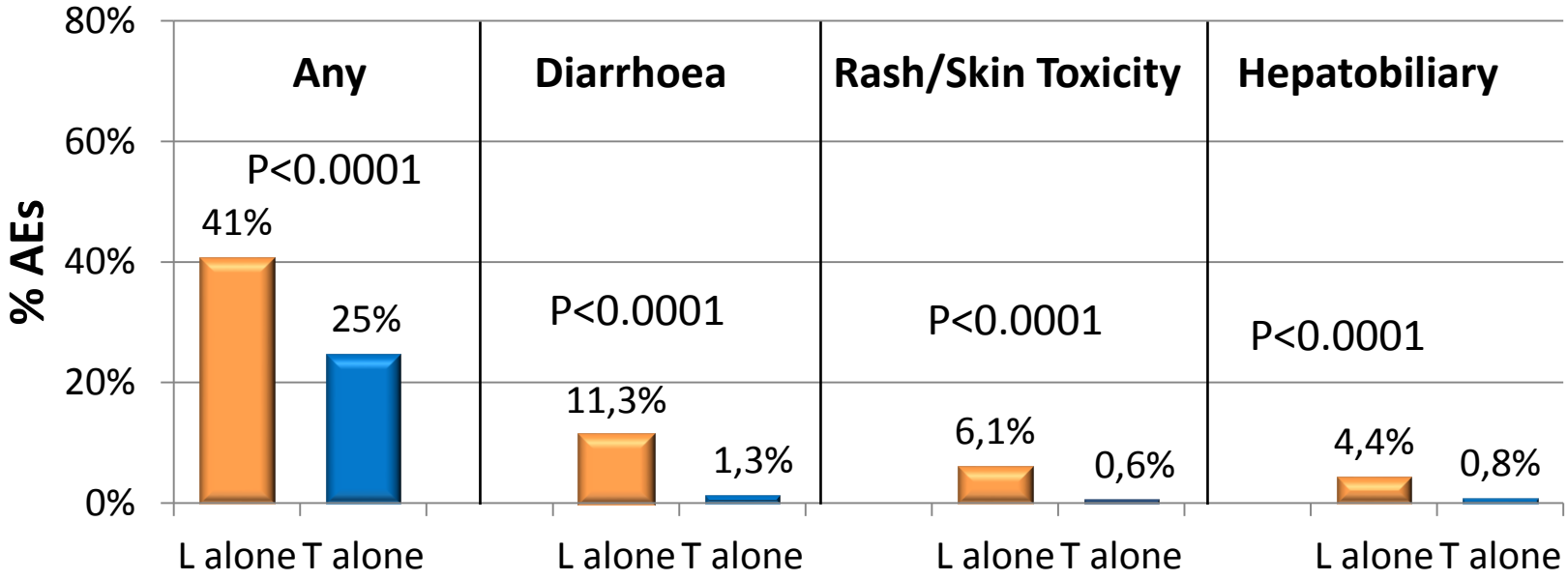
Event	L + T (N = 2,093)	T -> L (N = 2,091)	L alone (N = 2,100)	T alone (N = 2,097)
Local	23 (1%)	25 (1%)	27 (1%)	40 (2%)
Regional	3 (<1%)	10 (<1%)	11 (1%)	9 (<1%)
Distant				
Soft tissue	6 (<1%)	17 (<1%)	26 (1%)	21 (1%)
Skeletal	31 (1%)	39 (2%)	47 (2%)	36 (2%)
Central nervous system	41 (2%)	48 (2%)	50 (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%)
2nd 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

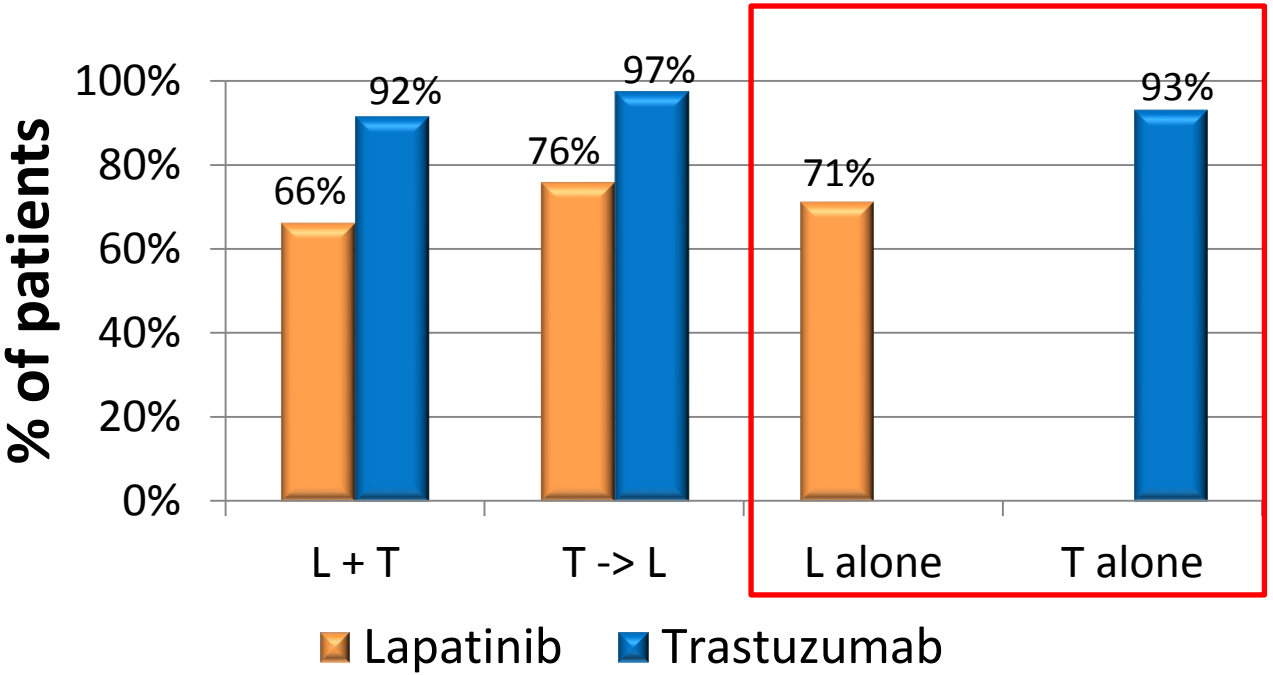


***Primary CE:** cardiac death or severe CHF NYHA Class III-IV; **Secondary CE:** asymptomatic (NYHA I) or mildly symptomatic (NYHA II) significant confirmed drop in LVEF. A significant LVEF drop is defined as an absolute decrease of >10 points below the baseline LVEF **and** to <50%

Main Differences in Grade 3-4 AEs by Treatment Arm



Proportion of Patients Receiving ≥85% of the Planned Dose of Anti-HER2 Drugs



Conclusions (1)

- **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 (2)

- **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**

Acknowledgements

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Sponsors: GlaxoSmithKline LLC; NCI (US)
Trial design/ day-to-day supervision Executive Committee Members and Joint Study Management Team Members
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