Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study

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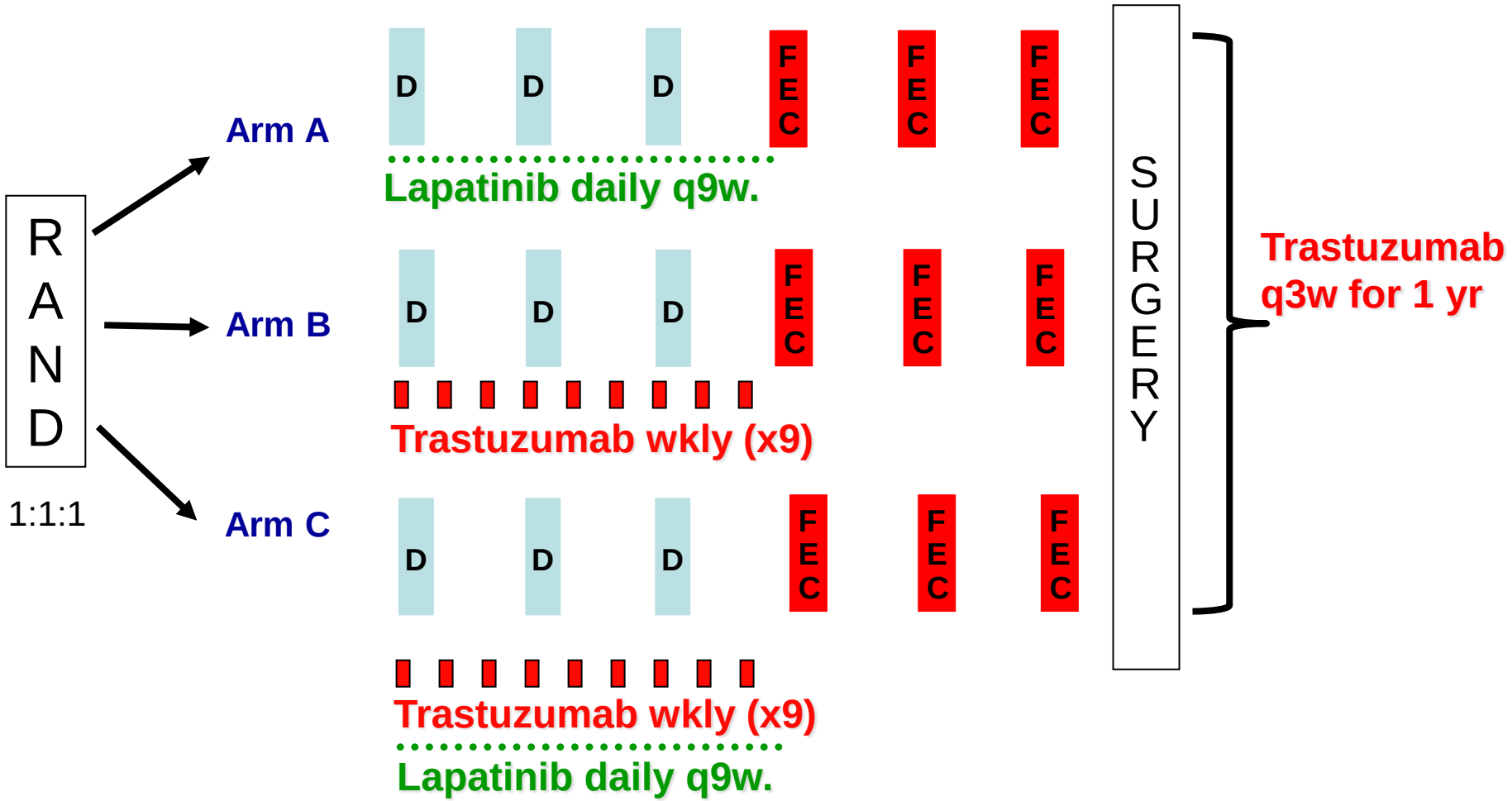
* On behalf of the EORTC Breast Cancer Group

Background

- 20-30% of patients (HER2 positive tumours) treated in the neoadjuvant setting relapse within 3 years despite trastuzumab (1, 2)
- Dual antiHER2 blockade is a promising strategy
- Five trials evaluated dual anti-HER2 blockade with lapatinib (L) and trastuzumab (T) in combination with paclitaxel based chemotherapy (3-7). They demonstrate:
  - Increased pCR% with dual blockade
  - But at cost of significant toxicity
- Hypothesis
  - Toxicity might be due to a specific PK interaction between lapatinib and **paclitaxel**

→ We embarked in this non comparative randomised phase II
- with L and T combined with **docetaxel** upfront followed by FEC.

Design



D: docetaxel
FEC: 5FU, Epi, cyclo.
Lapa: 1000mg day (arms A and C)

Post-opereative endocrine and radiation therapy according to local guidelines

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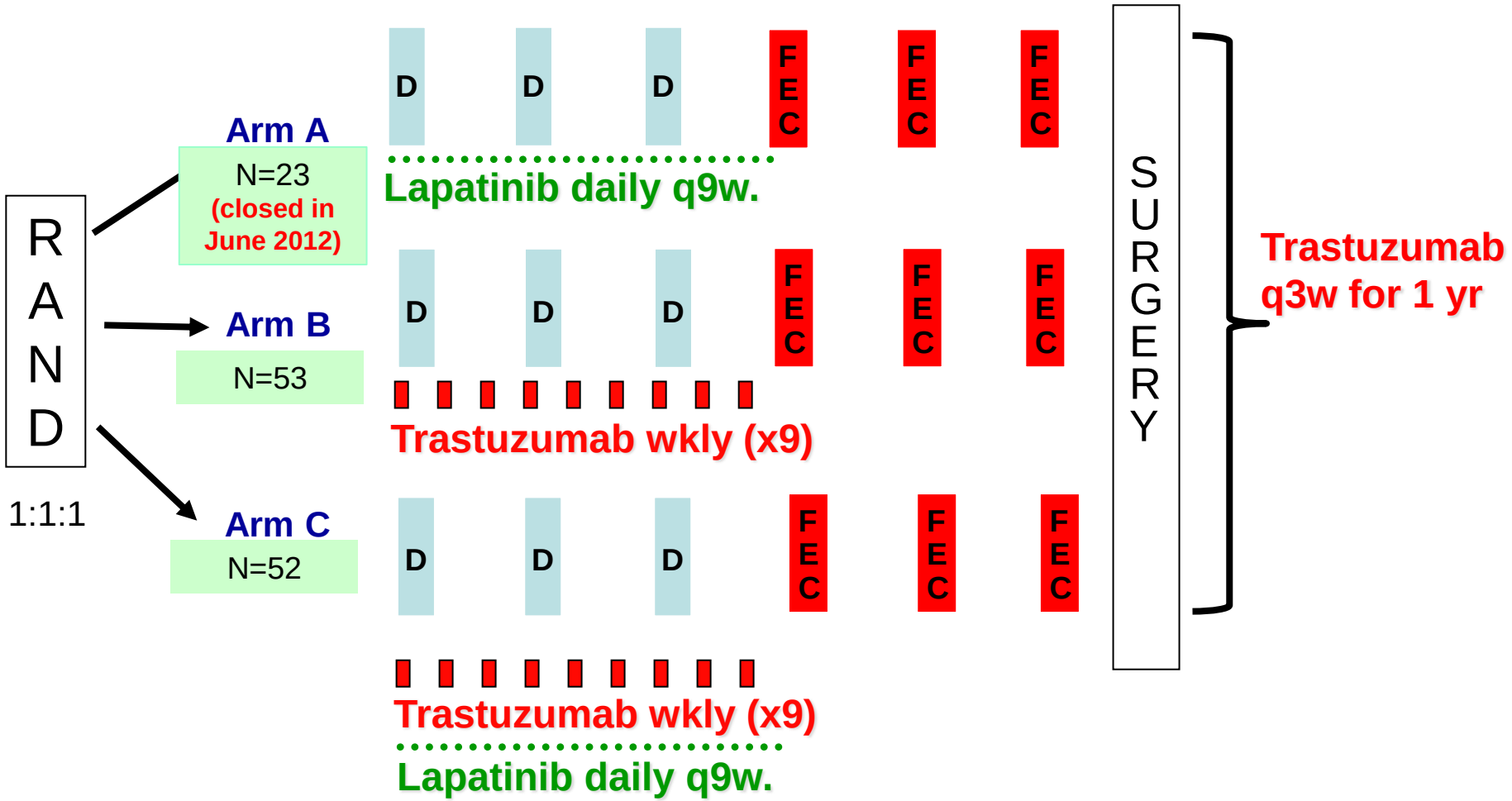

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Post-opereative endocrine and radiation therapy according to local guidelines

Key inclusion criteria

- Age 18-70 years
- Histologically confirmed invasive breast cancer:
  - Either Large operable: cT2, cT3
  - Or locally advanced or inflammatory: cT4 any N, any cT, N2 or N3
- M0
- HER2 positivity (either IHC3+ or FISH+)
- Three biopsies before inclusion (mandatory for translational research)
- WHO PS 0-2
- Adequate baseline cardiac evaluation
- Normal organ and marrow function
- Written informed consent

Study objective

- Objective
  - To assess the toxicity and activity of the combination of docetaxel with lapatinib or trastuzumab or both, followed by anthracycline-based chemotherapy.
- Primary endpoint
  - Pathological complete response (pCR) rates in the breast (DCIS allowed)
- Secondary endpoints
  - Tolerabilty (NCI-CTC v 3.0)
  - Response rate (RECIST v 1.0)
  - Rate of breast conserving surgery
  - Translational research
- Exploratory analysis
  - pCR rates in the breast and nodes
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Statistical analysis

- One-stage Fleming design for each of the L containing experimental arms (T arm as a reference).
- Type I error 10%
- **For a null hypothesis of a 40% pCR rate and an alternative hypothesis of a 60% pCR rate, 50 eligible patients needed to be treated in each arm to have a 92.5% power.**
- An experimental arm was deemed interesting for further research if at least 25 pCR out of 50 treated eligible patients are observed. This decision rule corresponded to rejecting the null hypothesis.
- When the lapatinib monotherapy arm was closed prematurely, the statistical plan was not altered for the 2 remaining arms.

Patient and tumour characteristics

	Lapatinib group N=23	Trastuzumab group N=53	Combination group N=52
Median age, years (range)	49.9 (27.3 - 68.5)	47 (25.3 - 68.9)	49.4 (27.3 – 70.8)
Tumour category			
Locally advanced or inflammatory	26.1%	20.8%	21.2%
Large operable	73.9%	79.2%	78.8%
Clinical tumour status			
T0	0.0%	0.0%	1.9%*
T1	4.3%	0.0%	0.0%
T2	47.8%	45.3%	53.8%
T3	34.8%	35.8%	25.0%
T4	13.0%	18.9%	17.3%
Missing	0.0%	0.0%	1.9%**
Clinical nodal status			
N0	30.4%	32.1%	36.5%
N1	56.5%	60.4%	55.8%
N2	8.7%%	5.7%	5.8%
N3	4.3%	1.9%	1.9%
Hormone-receptor status			
Negative	34.8%	49.1%	50%
Positive	65.2%	50.9%	48.1%
Missing	0.0%	0.0%	1.9%

* The nodal status for the 1 patient with tumour status T0 was N2

** Data are missing for one ineligible patient in the combination group.

D: docetaxel; L: lapatinib; T: trastuzumab; FEC: fluorouracil, epirubicin, cyclophosphamide.

Safety: worst grade 3 or 4 AEs during treatment

	Lapatinib group N = 22 N (%)		Trastuzumab group N = 53 N (%)		Combination group N = 50 N (%)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	3 (13.6)	7 (31.8)	7 (13.2)	15 (28.3)	4 (8.0)	19 (38.0)
Febrile neutropenia	3 (13.6)	2 (9.1)	8 (15.1)	0	4 (8.0)	1 (2.0)
Diarrhea	2 (9.1)	0	1 (1.9)	0	9 (18.0)	0
Infection other	2 (9.1)	0	2 (3.8)	0	4 (8.0)	0
Hepatic	0	0	0 (0.0)	1 (1.9)	4 (8.0)	0
Skin disorder	0	0	2 (3.8)	0	3 (4.0)	0
Other	0	0	2 (3.8)	0	3 (6.0)	0
Fatigue	2 (9.1)	0	2 (3.8)	0	0 (0.0)	0
Nausea	2 (9.1)	0	2 (3.8)	0	0	0
Pain	0	0	1 (1.9)	0	2 (4.0)	0
Allergic reaction/ hypersensitivity	0	0	1 (1.9)	0	1 (2.0)	0
Anemia	0	0	1 (1.9)	0	1 (2.0)	0

Cardiac investigations (worst results during treatment)

	Lapatinib group	Trastuzumab group	Combination group
	N = 22 *N (%)*	N = 53 *N (%)*	N = 50 *N (%)*
Clinical heart failure worst NYHA class on study			
no symptoms	20 (90.9)	49 (92.5)	40 (80.0)
I	0 (0.0)	0 (0.0)	0 (0.0)
II	1 (4.5)	0 (0.0)	0 (0.0)
III	0 (0.0)	0 (0.0)	0 (0.0)
IV	0 (0.0)	0 (0.0)	0 (0.0)
patient off study cycle 1	1 (4.5)	0 (0.0)	8 (16.0)
missing	0 (0.0)	4 (7.5)	2 (4.0)
Absolute drop ≥ 15% in LEVF from baseline			
no	21 (95.5)	48 (90.6)	36 (72.0)
yes	0 (0.0)	0 (0.0)	3 (6.0)
patient off study cycle 1	1 (4.5)	0 (0.0)	8 (16.0)
missing	0 (0.0)	5 (9.4)	3 (6.0)
Absolute drop ≥ 5% below LLN			
no	20 (90.9)	48 (90.6)	39 (78.0)
yes	1 (4.5)	0 (0.0)	0 (0.0)
patient off study cycle 1	1 (4.5)	0 (0.0)	8 (16.0)
missing	0 (0.0)	5 (9.4)	3 (6.0)

NYHA: New York Heart Association; LEVF: Left Ventricular Ejection Fraction; LLN: Lower Limit Normal.

Treatment compliance and reason for discontinuation of neo-adjuvant protocol therapy

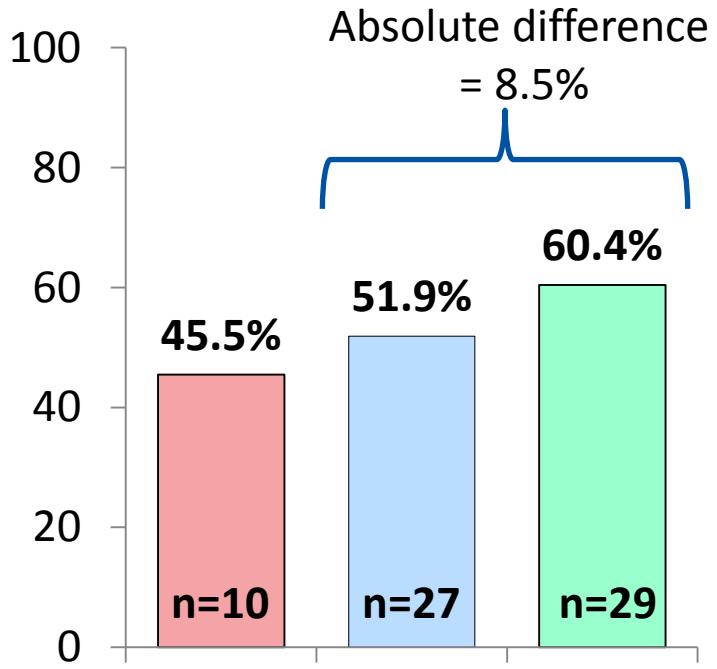
	Lapatinib group N = 22 N (%)	Trastuzumab group N = 53 N (%)	Combination group N = 50 N (%)
Completed per protocol	21 (95.5)	48 (90.6)	37 (74.0)
Not completed per protocol	1 (4.5)	5 (9.4)	13 (26.0)
Major reason for protocol discontinuation (medical review)			
Adverse events (total)	1 (4.5)	3 (5.6)	10 (20)
Diarrhoea	1	1	4
Hepatic	0	0	3
Skin disorder	0	0	1
Shingles	0	1	0
Myositis	0	1	0
allergic reaction	0	0	1
LVEF decrease	0	0	1
Subject decision	0	1 (1.9)	0
Protocol violation*	0	1 (1.9)	0
Other **	0	0	3 (6)

* Trastuzumab loading dose was given twice.

** 2 patients = Anti-HER2 therapy was stopped in two patients since the tumour was defined as HER2-negative after reassessment at the treating centre; 1 patient = No 2nd cycle of chemotherapy (FEC) given because of influenza.

Efficacy: pathological response (n=122)

Breast pCR



	L Group	T Group	Comb Group
	n=22	n=52	n=48
80% CI (2 sided)	0.31-0.61	0.42-0.62	0.50-0.70
P-value	0.376	0.054	0.003

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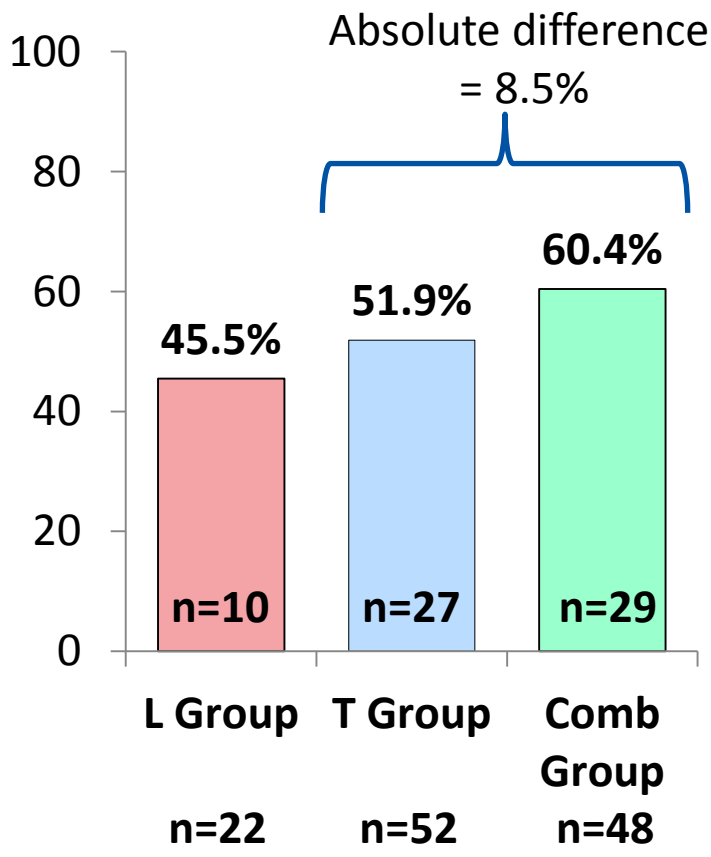

	L Group	T Group	Comb Group
	n=22	n=52	n=48
80% CI (2 sided)	0.31-0.61	0.42-0.62	0.50-0.70
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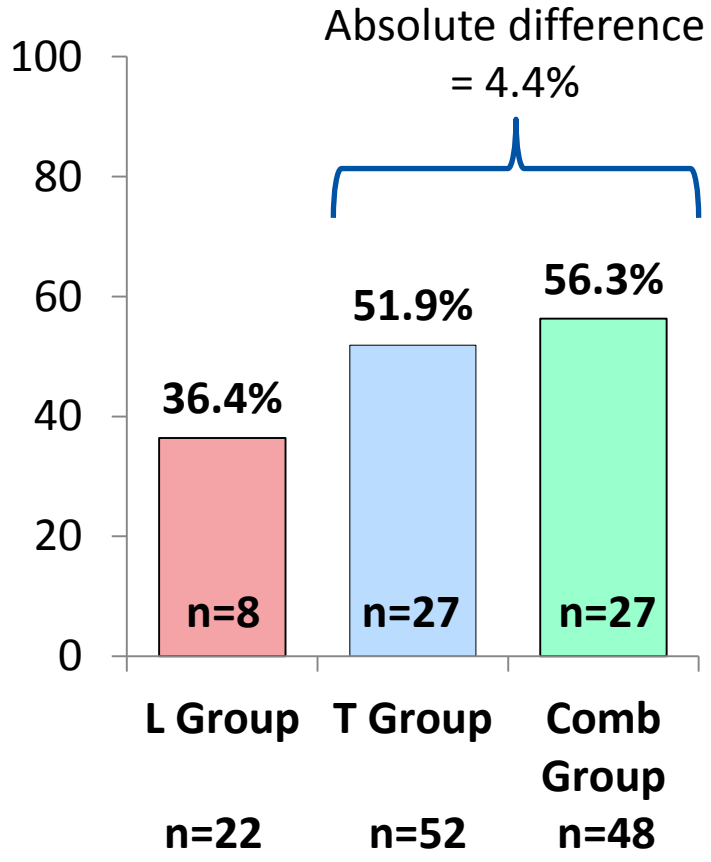
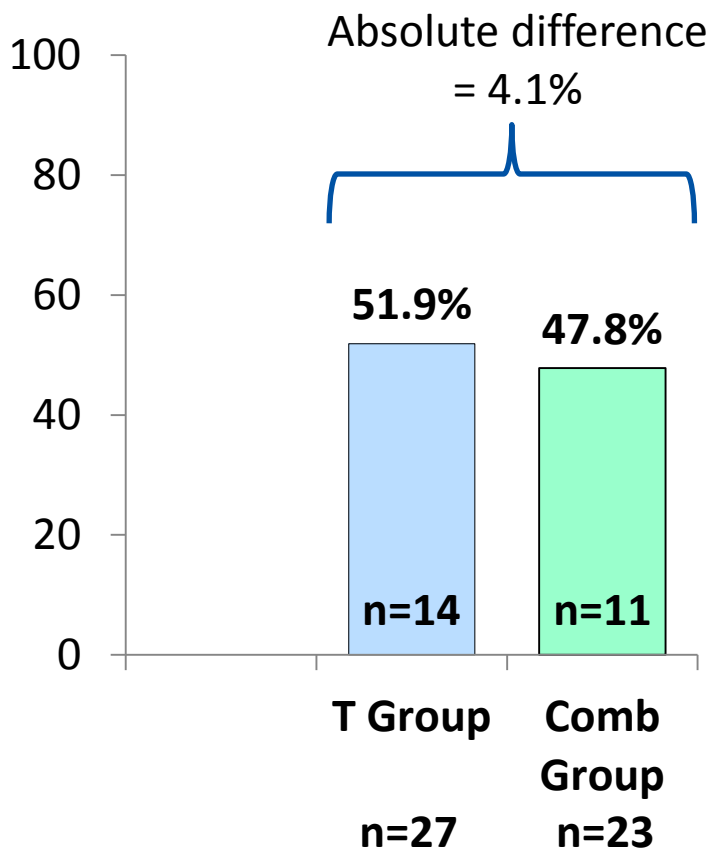
Breast and nodes pCR



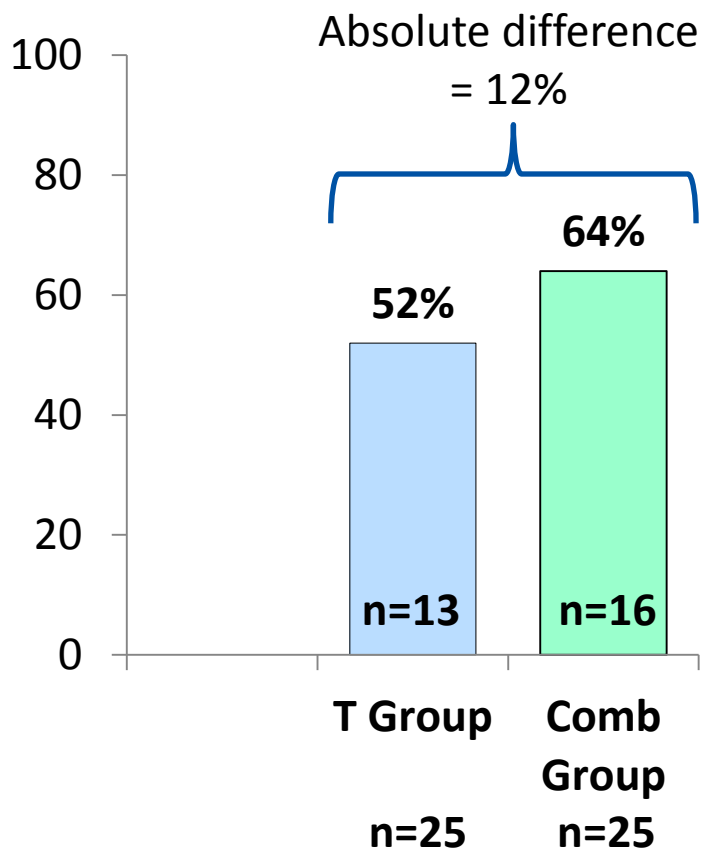
	L Group	T Group	Comb Group
	n=22	n=52	n=48

Efficacy: breast and nodes pCR by HR status (*)

HR positive



HR negative



(*) Lapatinib group results are not presented since the numbers are small

Conclusion (1)

- This study demonstrates a numerically greater rate of complete pathological responses in favour of double anti-HER2 blockade
  - 8.5% increase (from 51.9% to 60.4%) using pCR definition in breast
  - 4.4% increase (from 51.9% to 56.3%) using pCR definition in both breast and nodes
- From a strictly statistical view point, these data allow a rejection of the null hypothesis with the combination arm. However from a clinical perspective this modest increase in pCR comes with additional toxicity.
- Our results suggest that the use of docetaxel rather than paclitaxel may not reduce toxicity: in the combination group
  - 26% of patients did not complete protocol therapy as planned
  - 18% presented at least one episode of grade 3 diarrhoea.

Conclusion (2)

- Using the definition of pCR in both breast and nodes, the pCR rates for the L, T and combination groups respectively are similar in our trial and in the 3 trials with a **"pragmatic"** design reported (CHERLOB, LPT, NSABP-B41)

- A meta-analysis of neoadjuvant trials with double HER2 blockade may be useful to better take in consideration the heterogeneity of HER2 positive breast cancer and to understand the differences in pCR rates between treatment groups and long-term outcomes.

Guarneri V. et al JCO 2012; Holmes F. et al ASCO 2011; Robidoux A. et al Lancet Oncol 2014

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