LAPATINIB VS TRASTUZUMAB IN COMBINATION WITH NEOADJUVANT ANTHRACYCLINE-TAXANE-BASED CHEMOTHERAPY: PRIMARY EFFICACY ENDPOINT ANALYSIS OF THE GEPARQUINTO STUDY (GBG 44)

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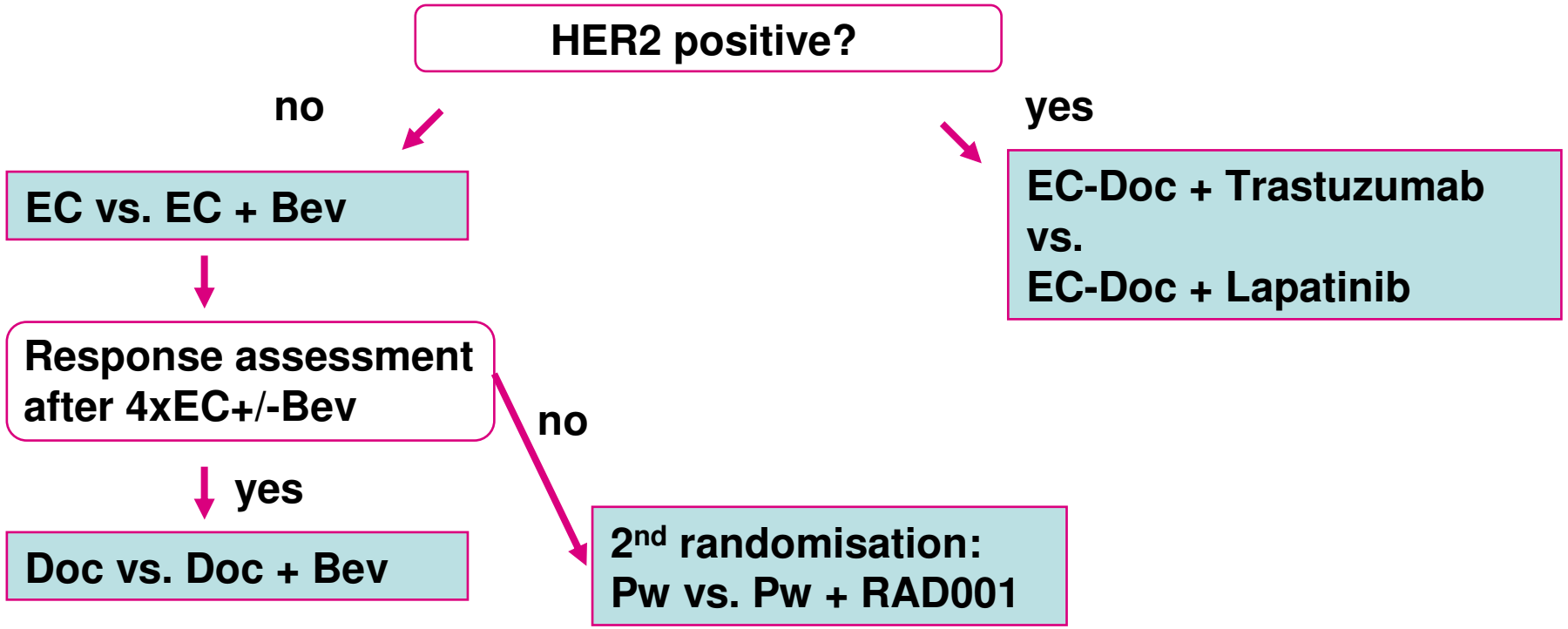
Geparquinto – Decision Tree

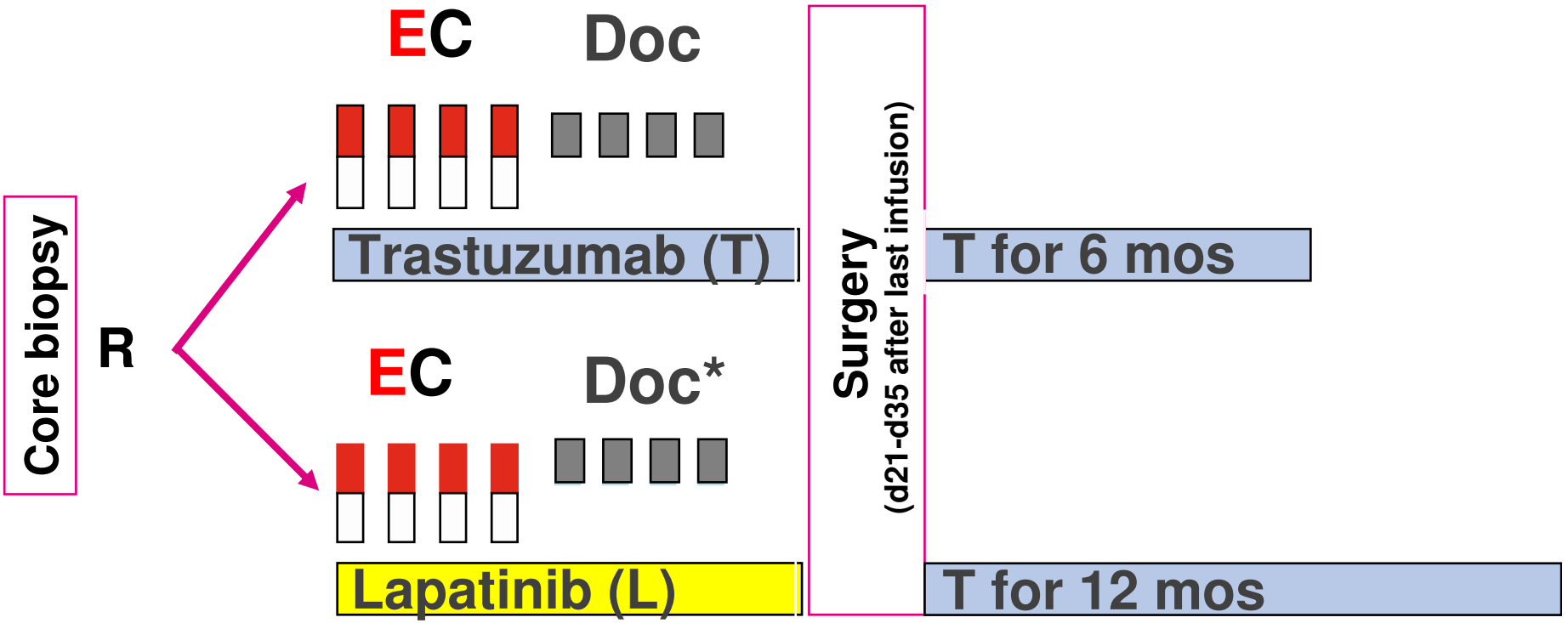


Introduction

- The tyrosine-kinase inhibitor lapatinib (L) has shown to improve efficacy of cytotoxic and endocrine treatment in patients with HER2-positive metastatic breast cancer.[1,2]
- Improved pathological complete response (pCR) rates were demonstrated by adding trastuzumab (T) to neoadjuvant chemotherapy.[3,4]
- The GeparQuinto trial was designed to compare the effects of L vs. T on pCR when given simultaneously to chemotherapy in untreated patients with early or locally advanced HER2-positive primary breast cancer.

[1]Cameron BCRT 2008
[2]Johnston J Clin Oncol 2009
[3]Gianni L, Lancet 2010
[4]Untch M, SABCS 2010

HER2-positive Part



E; Epirubicin 90 mg/m²
C: Cyclophosphamide 600 mg/m²
Doc: Docetaxel 100mg/m² *+ G-CSF

T: Trastuzumab 6 (8) mg/kg
L: 1000-1250 mg/d p.o.
(all 3 week cycles)

GEPAR quinto

Eligibility Criteria*

- untreated, uni-/ bilateral , primary breast carcinoma
- HER2-positive by local pathology (IHC Score 3+ or FISH pos.)
- breast lesion ≥ 2 cm by palpation or ≥ 1 cm by ultrasound.
- tumor stages (M0):
  - cT4 or cT3,
  - cT2 if HR- or cN+,
  - cT1 if HR- or pN_{SLN}+.
- normal organ function (incl. LVEF ≥55%).

*for details see: von Minckwitz et al, Ann Oncol 2010

Objectives

Primary:

- **pCR rates of neoadjuvant EC-Doc with either trastuzumab or lapatinib in HER2-positive, untreated primary breast cancer**

Secondary:

- **other pCR definitions**
- **breast conservation rate**
- **compliance and toxicity**
- **efficacy in stratified subgroups**
- **clinical response rates of breast and lymph-nodes**
- **disease-free and overall survival**
- **prediction by pre-defined molecular markers**

Statistics and pCR assessment

Sample size calculation:

- assumed pCR rate for EC-Doc+T: 26.0% (GeparQuattro[1])
- expected pCR rate for EC-Doc+L: 37.0% (odds ratio 1.67)
- sample size: 594 patients (2-sided, $\alpha = 0.05$, $\beta = 0.20$)

pCR definition:

- no microscopic evidence of residual viable tumor cells (invasive or non-invasive) in any resected specimens of the breast and axillary nodes (ypT0, ypN0)[1,2]
- all histology reports centrally reviewed

[1]Untch et al, J Clin Oncol 2010
[2]von Minckwitz et al, J Clin Oncol 2005 + 2010

Conclusions from run-in phase
(N=60)

- **Neutropenia Grade III/IV in 82%**
  - → **G-CSF made obligatory together with docetaxel**
- **Treatment discontinuations in 34.5%**
  - → **Lapatinib dose reduced from 1250 to 1000 mg/d**
- **Diarrhea Grade III/IV in 6.9%**
  - → **Loperamide given as stand-by medication**

***von Minckwitz, M. Untch et al, Ann Oncol 2010**

Flow of Patients

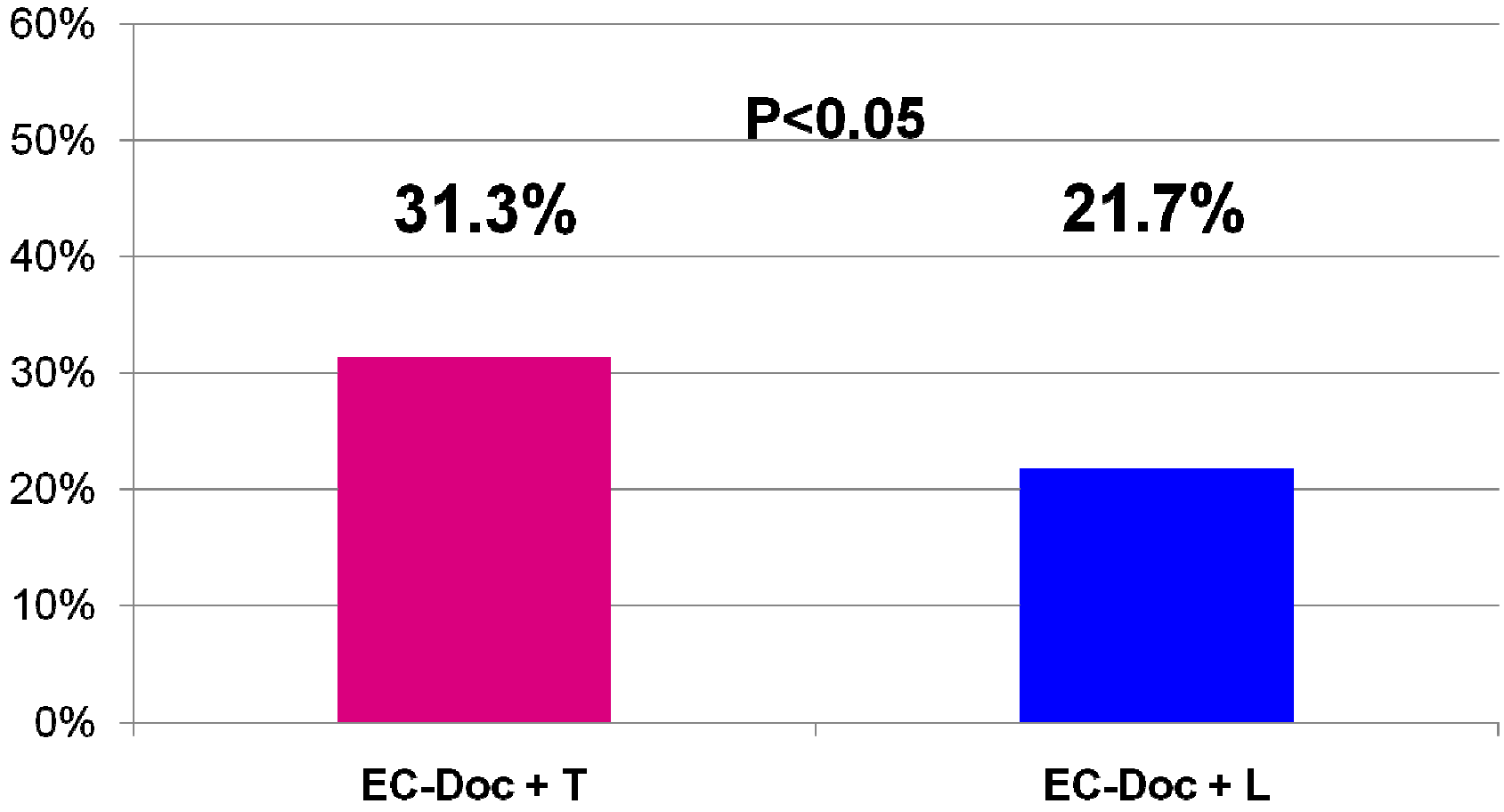
(N=620)

	EC-Doc + T	EC-Doc + L
	N	N
Randomized	**309**	**311**
Started treatment	**307**	**308**
	%	%
Discontinued CT + T/L	**10.0**	**16.0**
➢ AE during EC	0.4	0.7
➢ AE during Doc	4.2	5.5
➢ patient's wish	2.5	4.4
➢ investigator's decision	2.5	4.7
➢ progressive disease	0.4	0.7
➢ death	0	0
Discontinued only T / L	**3.1**	**7.0**

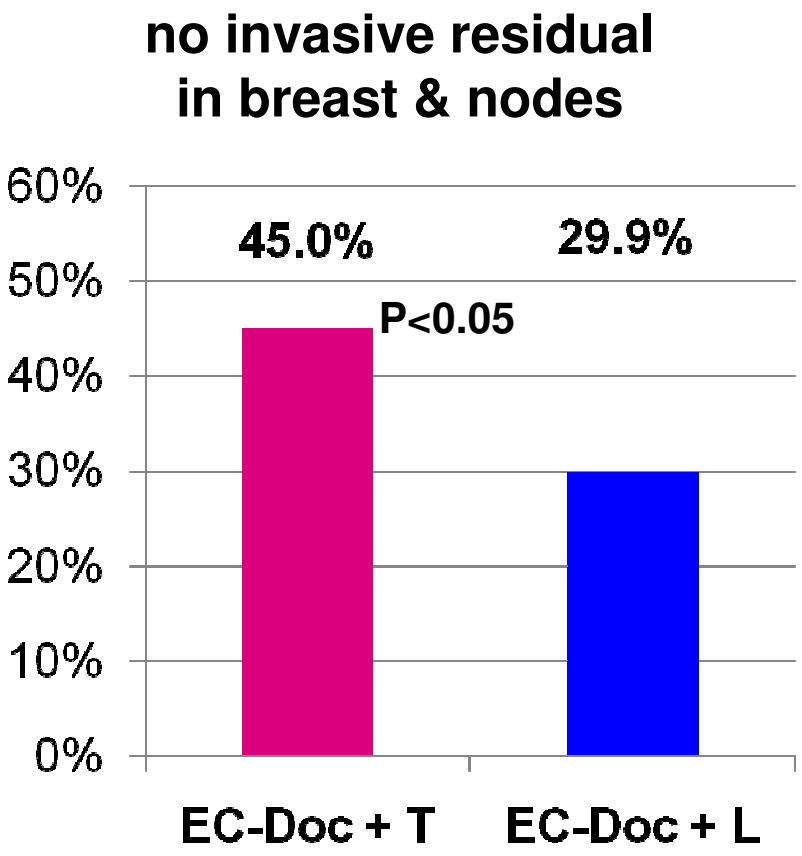
Tumor Characteristics

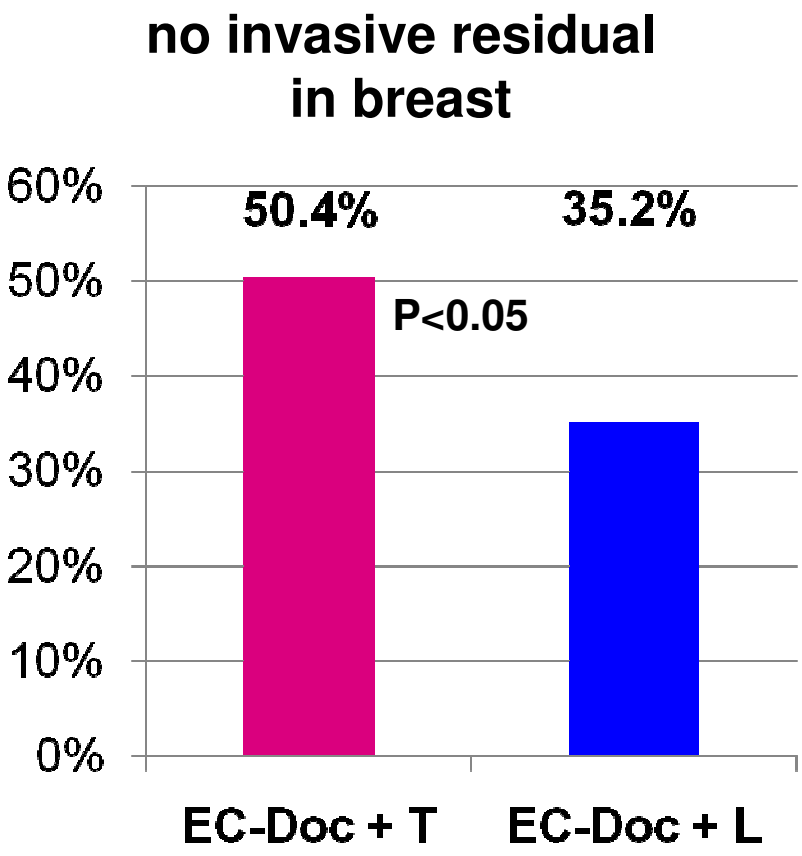
(% patients)	EC-Doc+T	EC-Doc+L
age (median years)	49	50
palpable T-size (median cm)	4.0	4.0
	%	%
cT 4	18.9	17.7
multifocal / -centric	26.5	29.3
cN +	69.4	69.0
lobular type	3.6	1.9
grade 3	45.9	49.0
ER and PR negative	42.7	44.4
HER2-negative	0	0

pCR
(no invasive/non-invasive residual in breast & nodes based on central pathology report review)

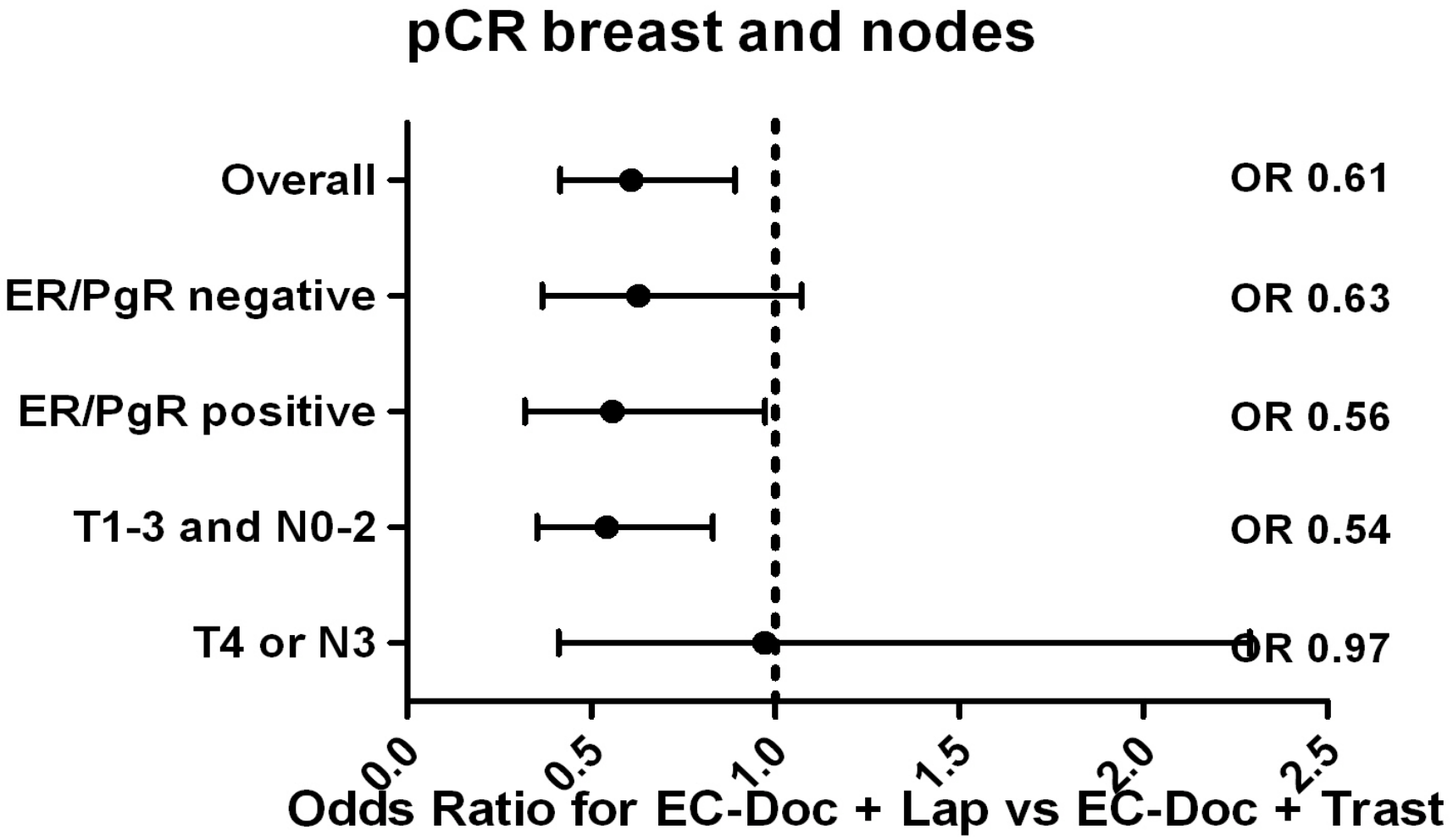


pCR rates according to other definitions

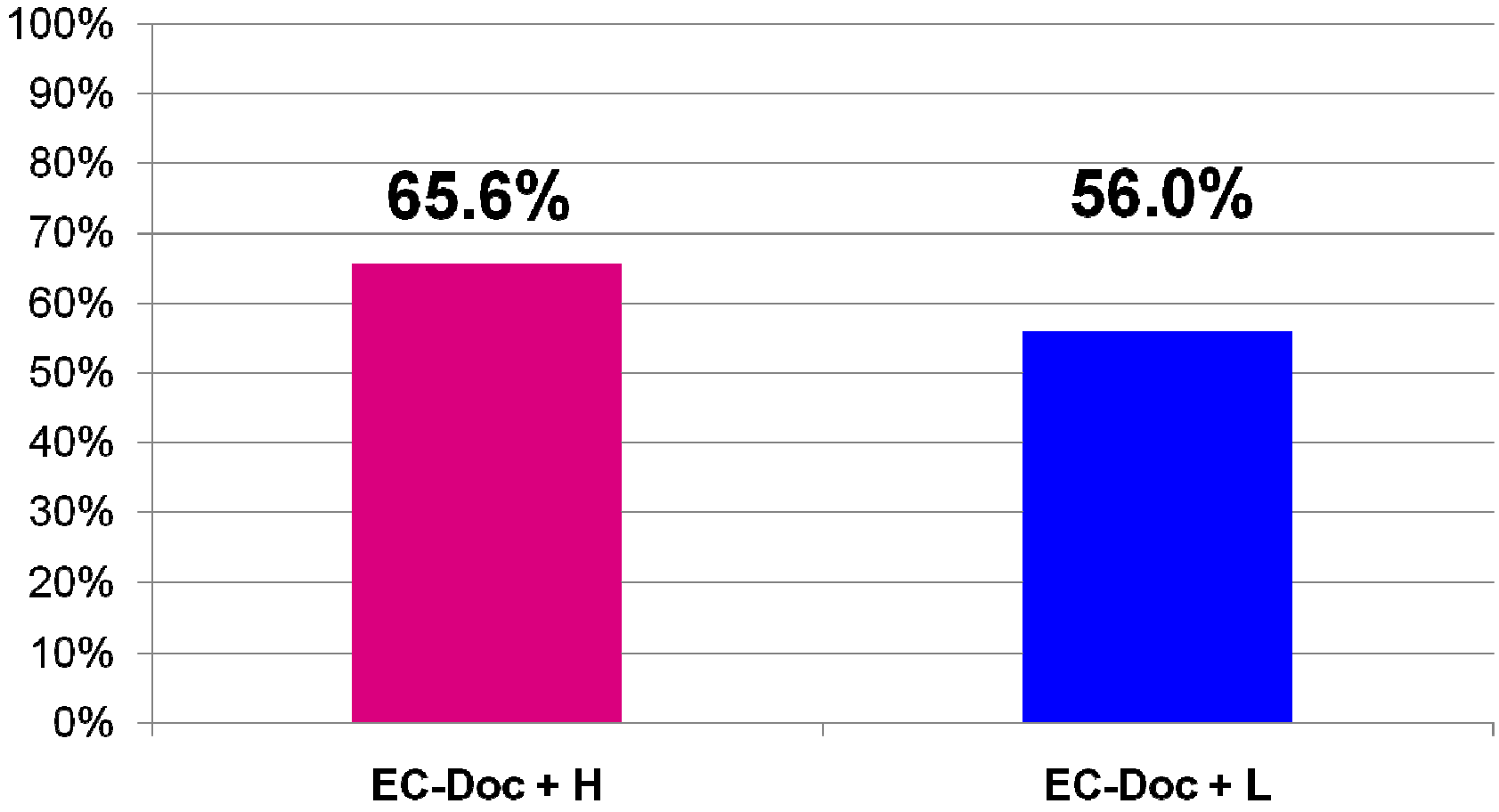




pCR according to subtypes
(predefined and stratified)



Breast Conservation Rate



SAE‘s

(absolute numbers* as of Dec., 1st 2010)

SOC	Term	EC + T	EC + L	Doc + T	Doc + L
1	Infections	5	6	6	6
3	Blood	12	17	11	12
4	Immune system	1	2	0	0
7	Psychiatric	3	2	1	1
8	Nervous system	2	3	4	1
9	Eye	1	0	0	0
11	Cardiac	0	1	3	2
12	Vascular	3	6	2	0
13	Respiratory	4	0	0	0
14	Gastrointestinal	9	9	4	6
16	Skin	1	1	2	4
17	Musculo-skeletal	0	2	2	5
20	Reproductive	0	1	0	0
22	General disorders	1	4	7	9
23	Laboratory invest.	0	1	2	0
24	Injury	0	0	1	1
	Total	**42**	**55**	**45**	**47**
	(% of N=310)	**(13.5)**	**(17.7)**	**(14.5)**	**(15.2)**

*multiple SAE‘s for same event per patient were possible

Conclusions

- **Anthracycline-taxane based CT + trastuzumab achieved a pCR (ypT0/is ypN-/+) rate of 50% in unselected locally HER2-positive patients, confirming our previous findings (TECHNO, GeparQuattro).**
- **CT + lapatinib resulted in a significant lower pCR rate of 35%.**
- **Compliance of lapatinib with EC and Docetaxel was lower than with trastuzumab.**
- **Results should be seen in the context of other studies like Neo-ALTTO, which uses a higher dose of lapatinib (1500 mg/d) but a shorter treatment duration.**

Slides can be downloaded from www.germanbreastgroup.de

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