NEOADJUVANT CHEMOTHERAPY WITH OR WITHOUT BEVACIZUMAB: PRIMARY EFFICACY ENDPOINT ANALYSIS OF THE GEPARQUINTO STUDY (GBG 44)

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for the

GBG/AGO-B study groups

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BREAST STUDY GROUP

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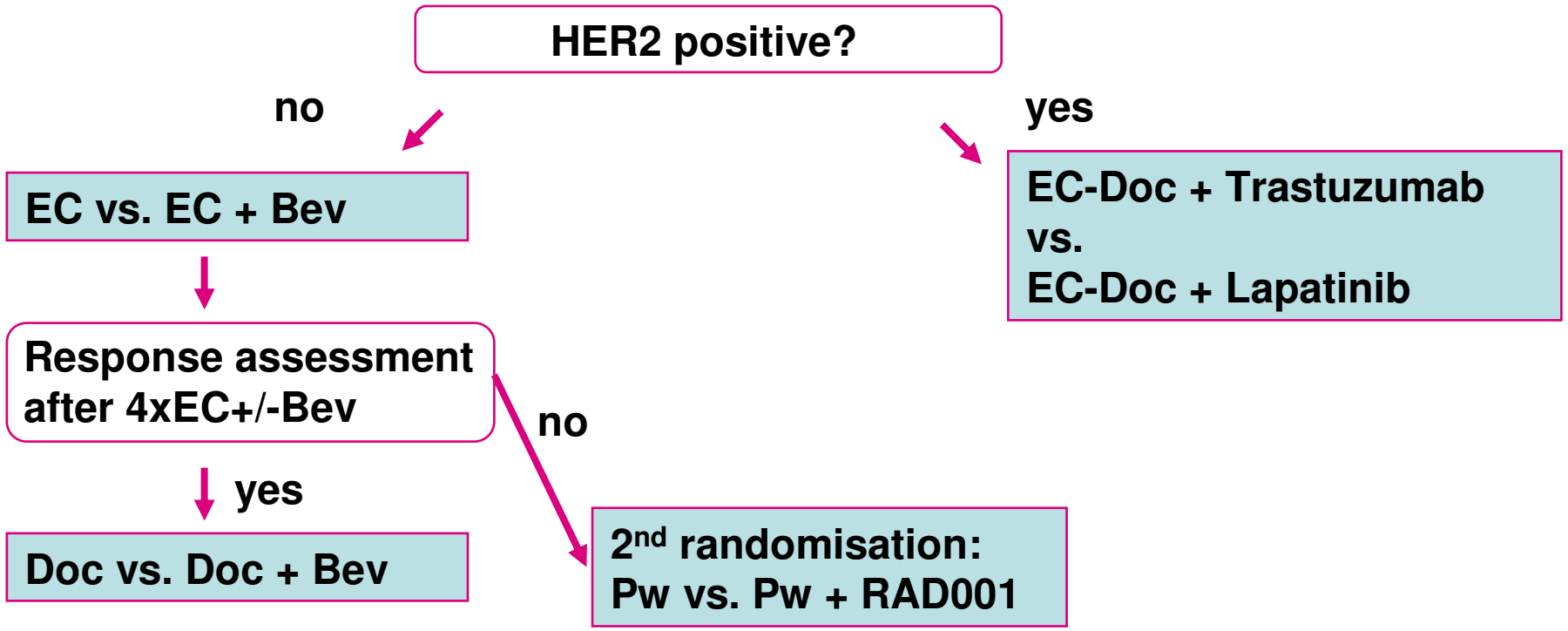
Geparquinto – Decision Tree



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Introduction

- **Bevacizumab (Bev), a monoclonal antibody, inhibits vascular endothelial growth factor (VEGF), a key mediator of angiogenesis.[1]**
- **In 3 first-line metastatic studies and in a pooled analysis Bev showed a significant overall response and PFS advantage, but no OS difference.[2,3,4,5]**
- **The GeparQuinto trial is the first randomized, phase III trial investigating the effect of Bev plus chemotherapy in early or locally advanced breast cancer.**

[1]Folkman J, NEHM 1971, [2] Miller K, NEJM 2007, [3]Miles D, J Clin Oncol 2010,
[4]Robert N, ASCO 2009, [5]O'Shaugnessy J, ASCO 2010

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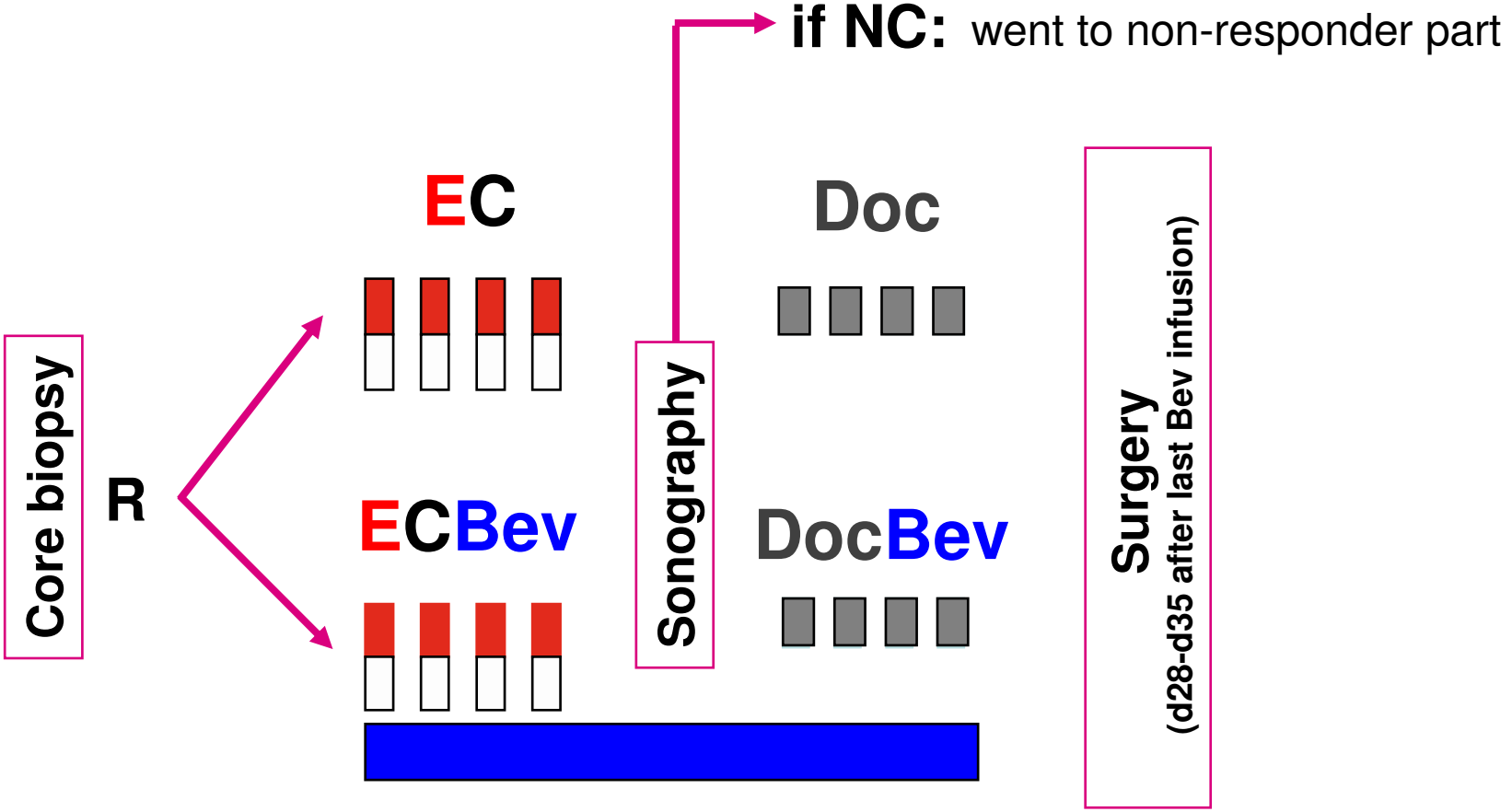
HER2-negative Part



E: Epirubicin 90 mg/m²
C: Cyclophosphamide 600 mg/m²
Doc:Docetaxel 100mg/m²
Bev: Bevacizumab 15 mg/kg
(all 3 week cycles)

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Objectives

Primary:

- **pCR rate defined as no invasive or non-invasive residual viable tumor cells in any resected specimens of the breast and axillary nodes (ypT0, ypN0) [1,2]**

Secondary:

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

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

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Eligibility Criteria*

- untreated, uni- / bilateral, primary breast carcinoma
- HER2-negative by local pathology (IHC Score 0-1 or FISH neg.)
- 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 pNSLN+
- normal organ function (incl. LVEF ≥55%)

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*von Minckwitz et al, Ann Oncol 2010

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Statistics and pCR Assessment

Sample size calculation:

- **assumed pCR rate for EC-Doc: 14.0% (GeparDuo[1])**
- **expected pCR rate for EC-Doc + Bev: 18.9% (odds ratio 1.43)**
- **sample size: 1876 patients (2-sided, $\alpha = 0.05$, $\beta = 0.20$)**
- **32% of patients were expected not having a sonographic response after 4 cycles (based on GeparQuattro[2]) and were considered as having no pCR.**

Quality assurance:

- **all histology reports centrally reviewed**

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Flow of Patients

(N=1948)

	EC-Doc	EC-Doc+Bev
	N	N
Randomized	974	974
Started treatment	968	959
	%	%
Discontinued CT±Bev	36.1	30.5
➢ No response after 4xEC±Bev	24.2	16.9
➢ Other reasons	11.9	13.6
➢ AE during EC	0.1	0.3
➢ AE during Doc	3.3	6.4
➢ investigator‘s decision	4.5	2.7
➢ patient’s wish	1.5	3.1
➢ progressive disease	2.1	1.0
➢ Death (reason unknown)	0.1	0
Discontinued only Bev	n.a.	4.1

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Patients & Tumor Characteristics

	EC-Doc	EC-Doc+Bev
age (median yrs)	48	49
palpable T-size (median cm)	4.0	4.0
	%	%
cT 4	12.3	12.2
multifocal / -centric	23.0	23.8
cN +	58.0	59.6
lobular type	10.9	10.6
grade 3	42.8	43.9
ER and PR negative	35.0	35.0
HER2-positive	0	0

SAE‘s

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

	EC	EC + Bev	Doc	Doc + Bev
Total	**115**	**153**	**126**	**225**
(% of N=974)	**(11.8)**	**(15.7)**	**(12.9)**	**(23.1)**

Events with mayor numerical differences between arms:

febrile neutropenia	**13**	**27**	**25**	**52**
nausea	**7**	**14**		
mucositis			**3**	**37**
reduced general condition			**6**	**15**
wound healing			**0**	**5**

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

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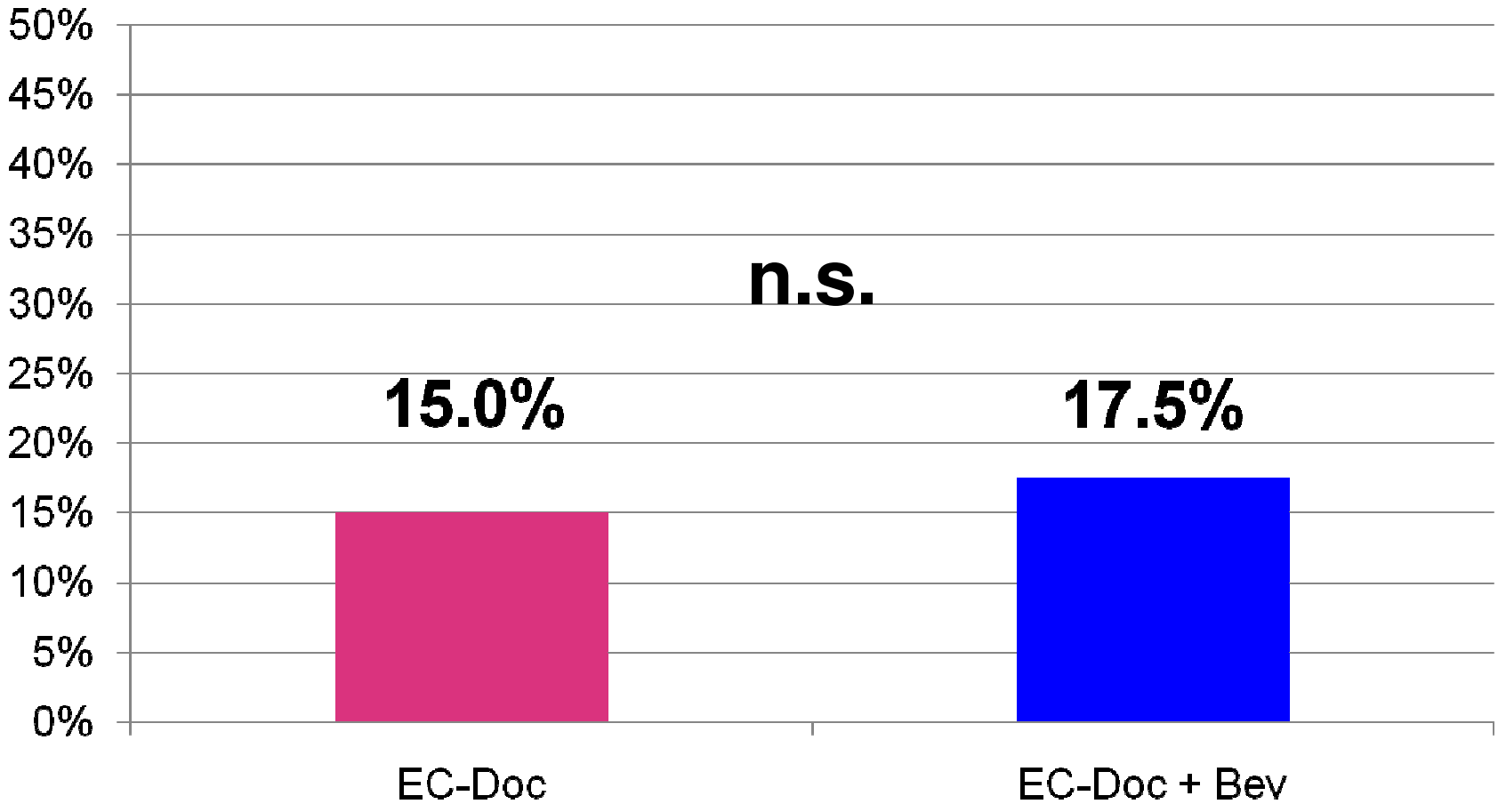
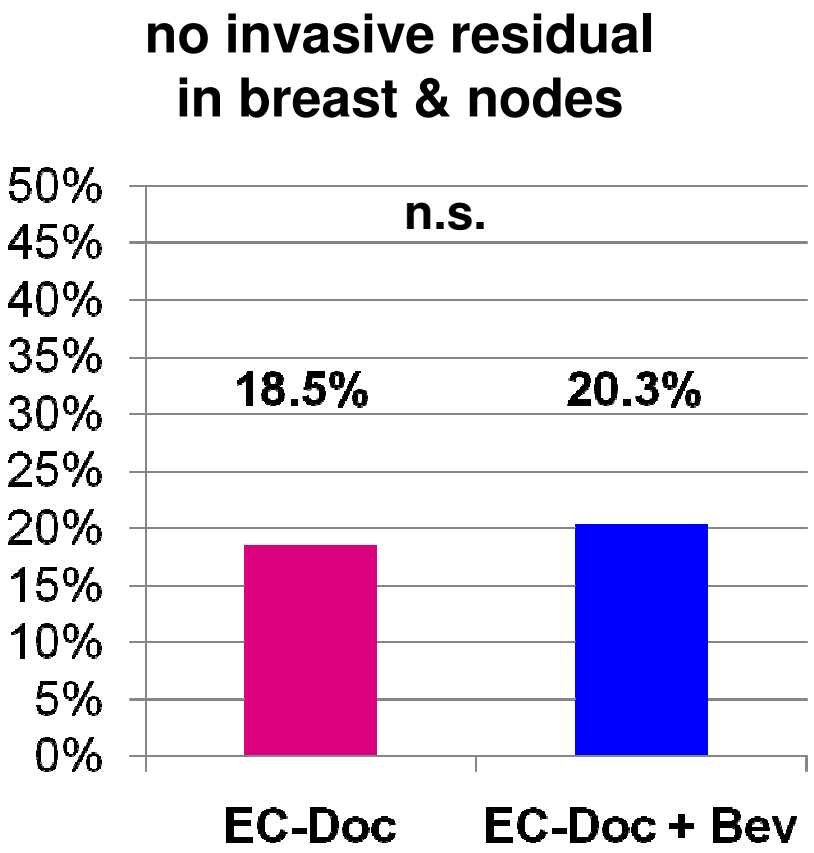
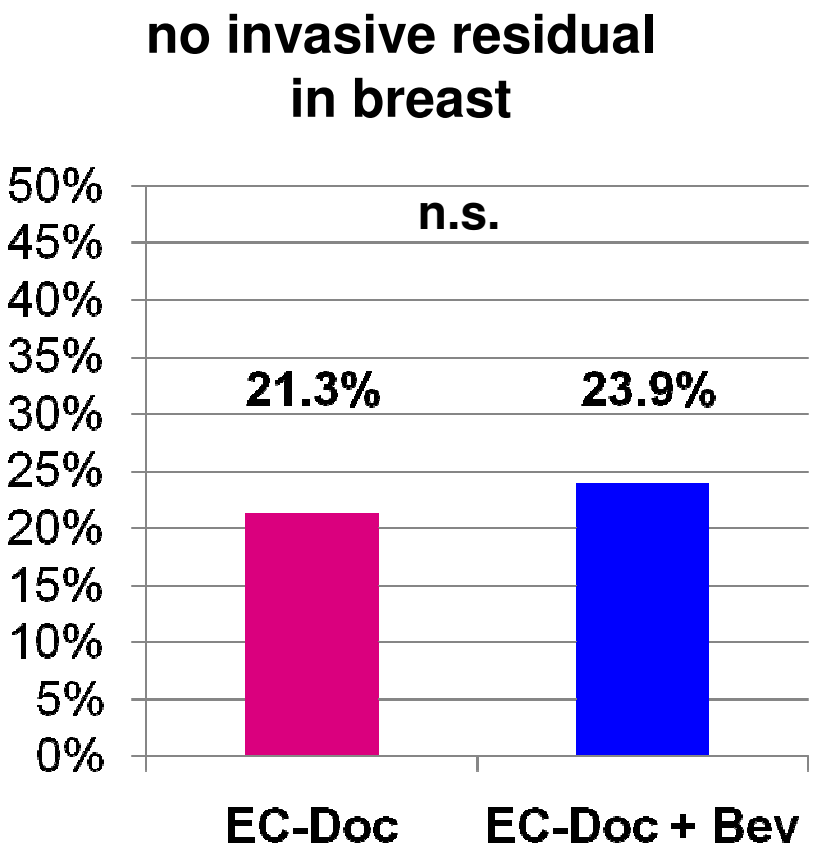
pCR

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



pCR Rates According to Other Definitions





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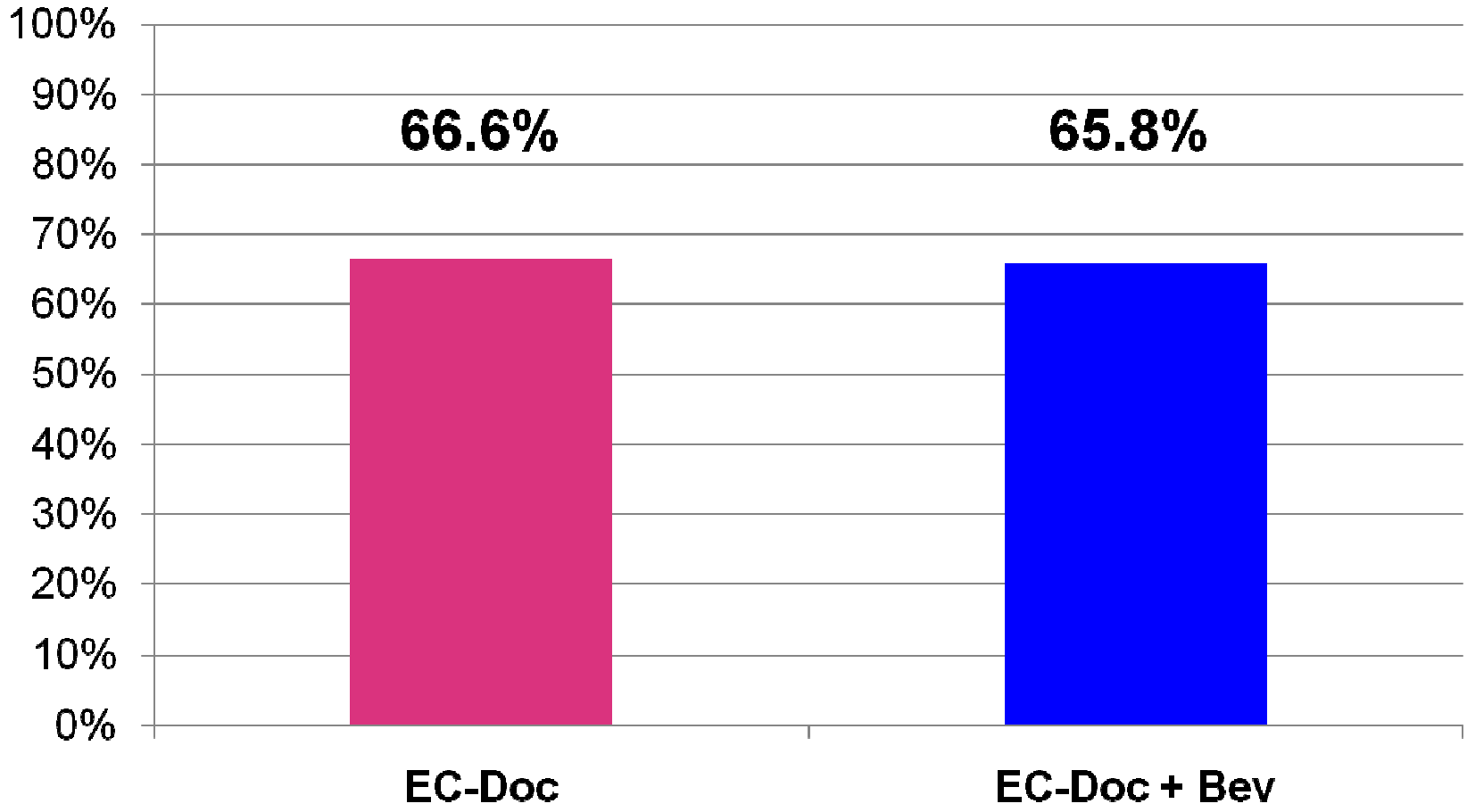
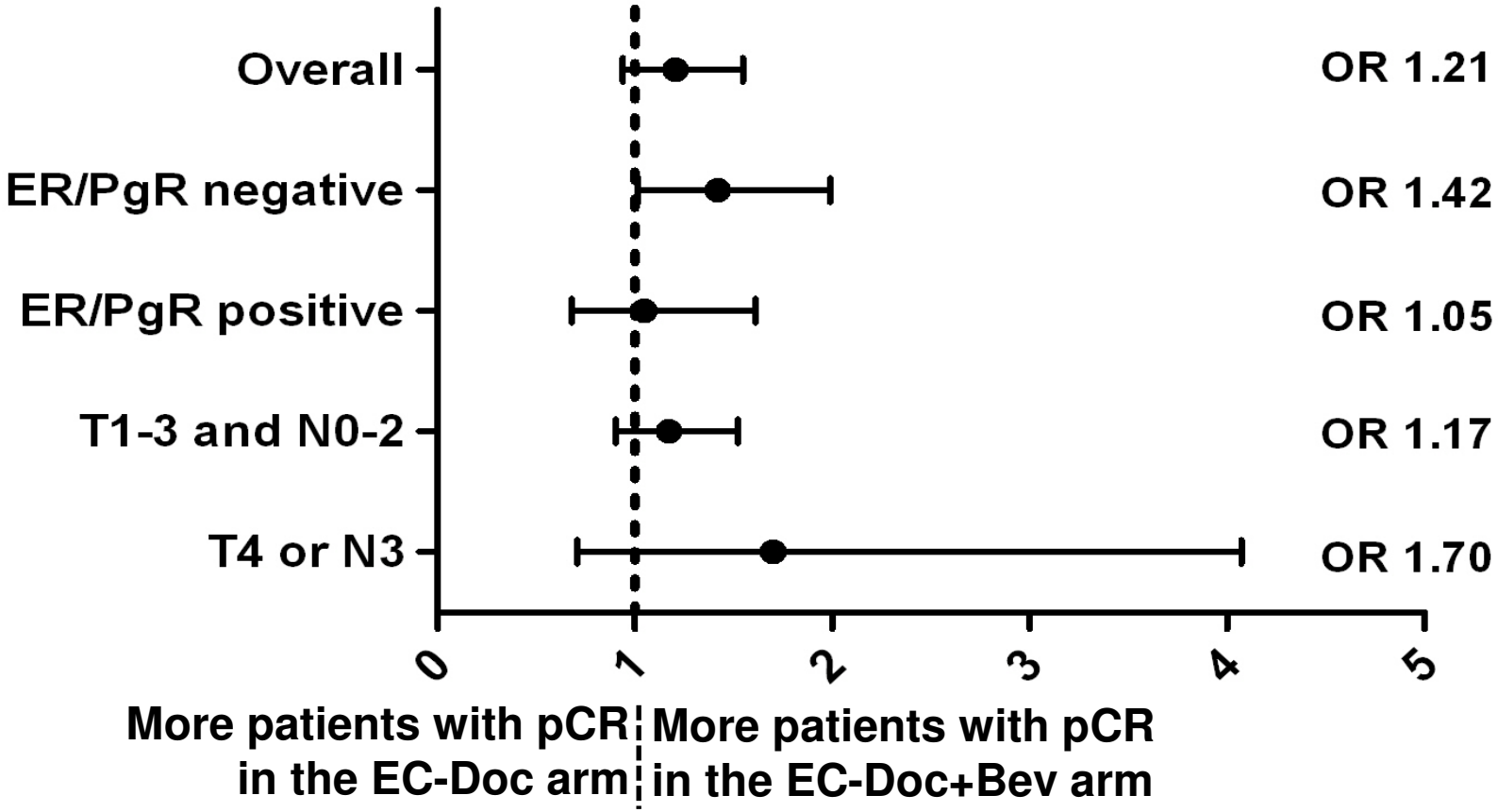
Breast Conservation Rate



pCR According to Subtypes
(predefined and stratified)



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Conclusions

- **Addition of bevacizumab to neoadjuvant chemotherapy does not increase pCR rate significantly.**
- **Positive effect of Bev might have been driven solely by the triple-negative stratum.**
- **A large biomarker program will try to identify other subgroups with higher benefit from Bev.**
- **Toxicity increased especially by adding Bev to Doc_{100}, but compliance appeared similar between the two arms.**
- **Ongoing studies (e.g. NSABP B-40, Beatrice) and long-term survival have to be awaited before drawing definite conclusions.**

Slides can be downloaded from www.germanbreastgroup.de

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