



GeparOLA - GBG 90

A Randomized Phase II Trial to Assess the Efficacy of Paclitaxel and Olaparib in Comparison to Paclitaxel and Carboplatin Followed by Epirubicin and Cyclophosphamide as Neoadjuvant Chemotherapy in Patients with HER2 Negative Early Breast Cancer and Homologous Recombination Deficiency

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-This is a joint study by GBG and AGO-B-



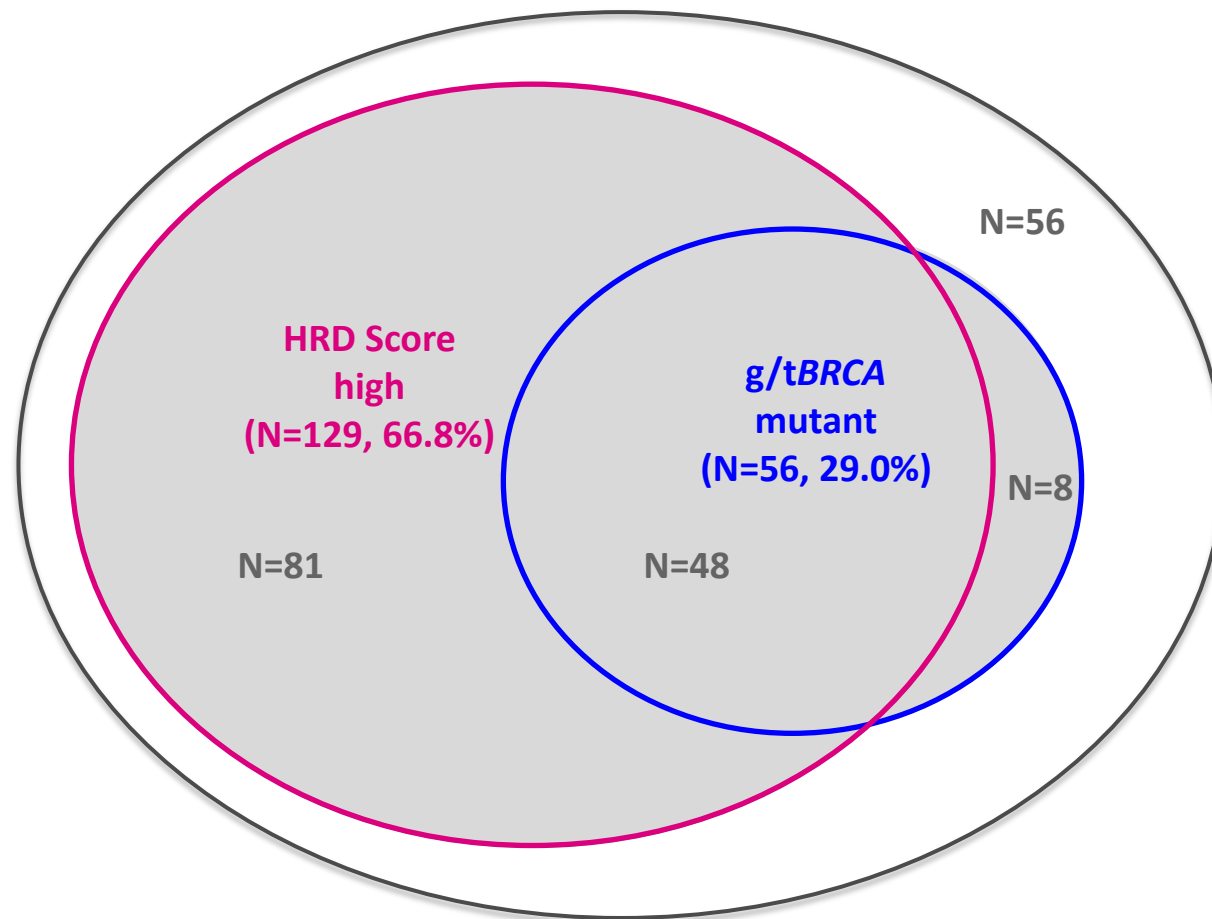
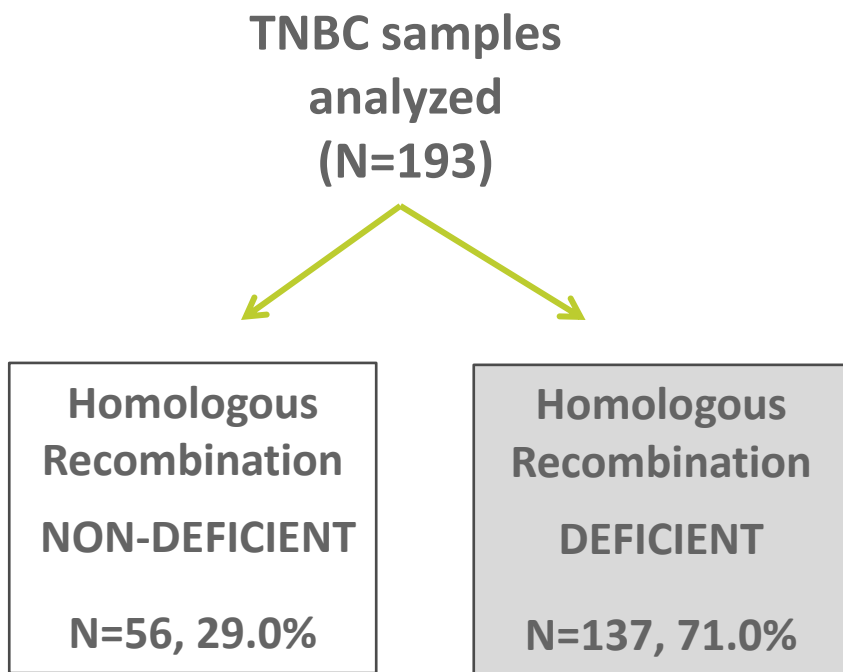
- The efficacy and toxicity of olaparib in early breast cancer (BC) patients with homologous recombination deficiency (HRD) is not well described.
- Carboplatin increased the pathological complete response (pCR) rate in triple negative breast cancer (TNBC) patients (GeparSixto, CALBG 40603, BrighTNESS).^{1,2,3}
- pCR (ypT0/is ypN0) rates were even higher in patients with *gBRCA* 1/2 mutations (65%) and HRD score high (63%).^{4,5}
- The TNT study showed a doubling in objective response rate (68% versus 33%) for patients with *gBRCA* 1/2 mutations receiving carboplatin vs docetaxel.⁶
- The BrighTNESS study could show an improved rate of pCR with the addition of veliparib and carboplatin relative to control (53% vs. 31%), but not compared to the addition of carboplatin (53% vs. 58%).³

¹von Minckwitz G et al. Lancet Oncol 2014; ²Sikov WM et al. J Clin Oncol 2015; ³Loibl S et al. Lancet 2018. ⁴Hahnen E et al. JAMA Oncol 2017; ⁵Loibl S et al. Ann Oncol 2018; ⁶Tutt A et al. Nat Med 2018;



Overlap of HRD-Score and g/tBRCA Mutation

GeparSixto Study

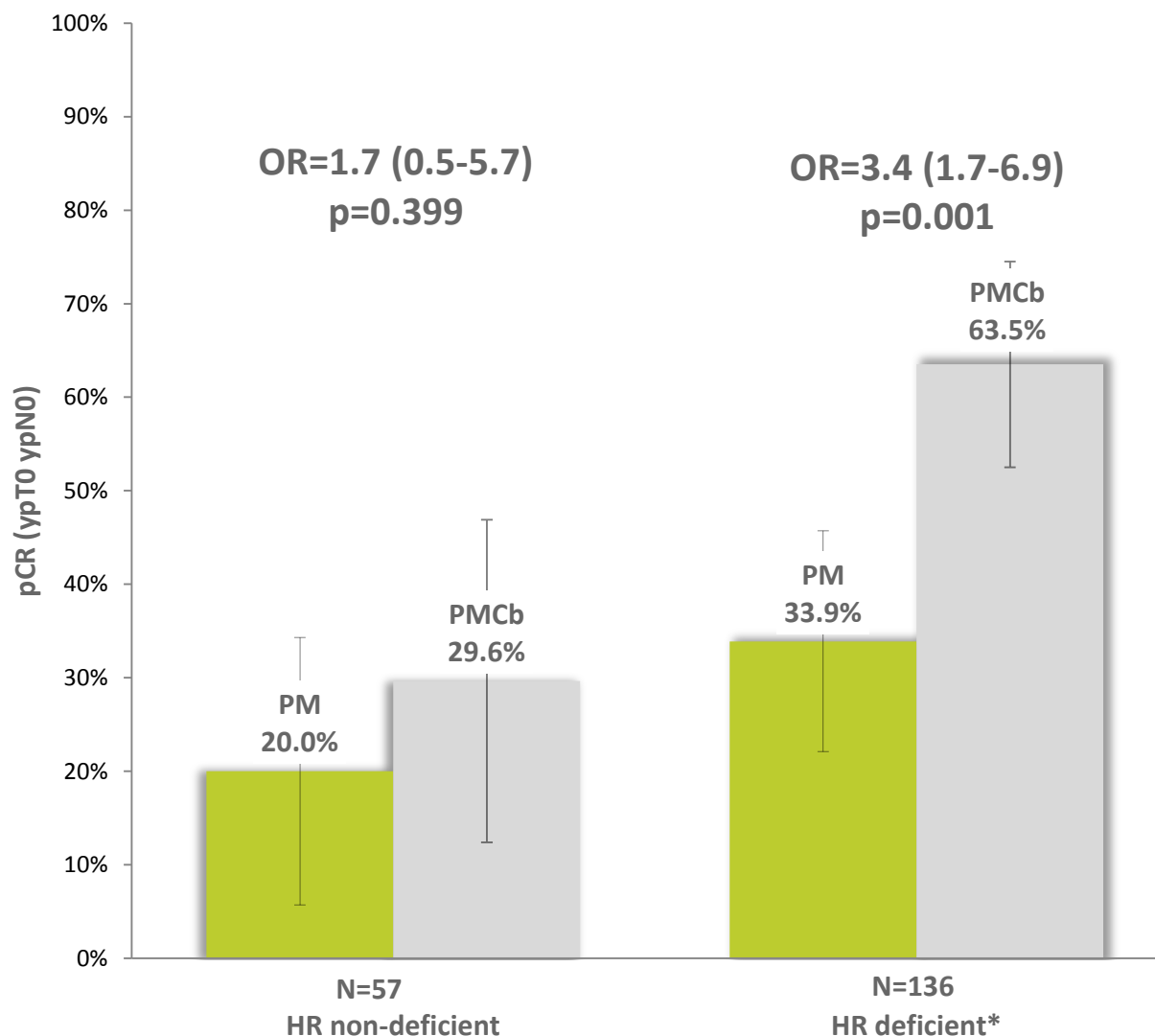


Adapted from Loibl S et al. Ann Oncol 2018.



Response TNBC by HRD Status

GeparSixto Study



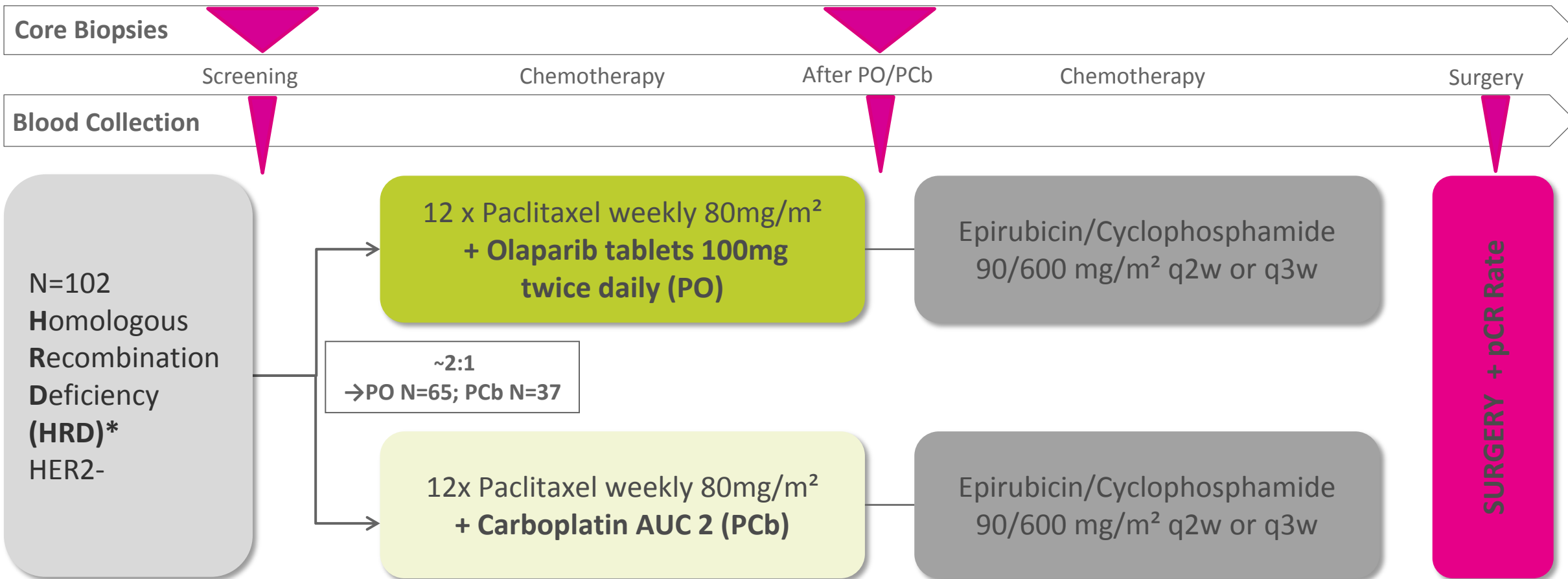
* HR deficiency was defined as either a high HRD score or *tBRCA* mutation

■ Paclitaxel 80 mg/m²/ nonpegylated liposomal doxorubicin 20 mg/m² q1w/ bevacizumab 15mg/kg q3wk (PM)

■ Paclitaxel 80 mg/m² / nonpegylated liposomal doxorubicin 20 mg/m² q1w/ bevacizumab 15mg/kg q3wk **plus carboplatin AUC2 q1wk (PMCb)**

Adapted from Loibl S et al. Ann Oncol 2018.

GeparOla Study Design



Stratification Factors:

- Age (<40 years vs >= 40 years)
- Hormone Receptor Status (HR+ vs HR-)

* Patients with either a known somatic or germline *BRCA1/2* mutation or HRD score¹ high

¹Timms et al. Breast Cancer Res 2014



Primary Objective and Endpoint:

- To assess the pathological complete response (**ypT0/is ypN0**) rate of neoadjuvant treatment of olaparib and paclitaxel followed by epirubicin and cyclophosphamide (PO→EC) in patients with early BC and HR deficient tumors (defined as either *tBRCA1/2* mutation and/or HRD score high and/or known *gBRCA* mutation).

Main Secondary Objectives and Endpoints:

- pCR rate (ypT0/is ypN0) of patients receiving paclitaxel and carboplatin followed by EC (PCb→EC)
- pCR rate (ypT0/is ypN0) in stratified subgroups
- pCR rates according to different pCR definitions: ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT_(any) ypN0
- pCR rate in HRD Score high with vs without *tBRCA* mutation
- Clinical response rate
- Breast conservation rate
- Toxicity and compliance
- Immune- and biomarker



- A pCR rate in the PO→EC arm of 55% or lower should be excluded with $\alpha=0.1$ to support a subsequent phase III study.
- Assuming a pCR rate of 70% in PO→EC arm, 65 patients are needed for two-sided one group χ^2 -test to exclude a pCR rate of 55% or lower.
- No formal comparison between the two arms was planned.
- Since pCR rate in the PCb→EC arm is expected to be 50% - 60%, inclusion of 37 patients will provide a point estimate with a 90% CI of 27% width.
 - CALGB 40603 study: pCR rate of 49%; 3 weekly carboplatin combination; unselected patients with TNBC¹
 - GeparSixto study: pCR rate of 65%; weekly carboplatin combination; *BRCA* carriers with TNBC²
- It was planned to recruit 102 (65+37) eligible patients into this study.

¹von Minckwitz G et al. Lancet Oncol 2014; ²Sikov WM et al. J Clin Oncol 2015

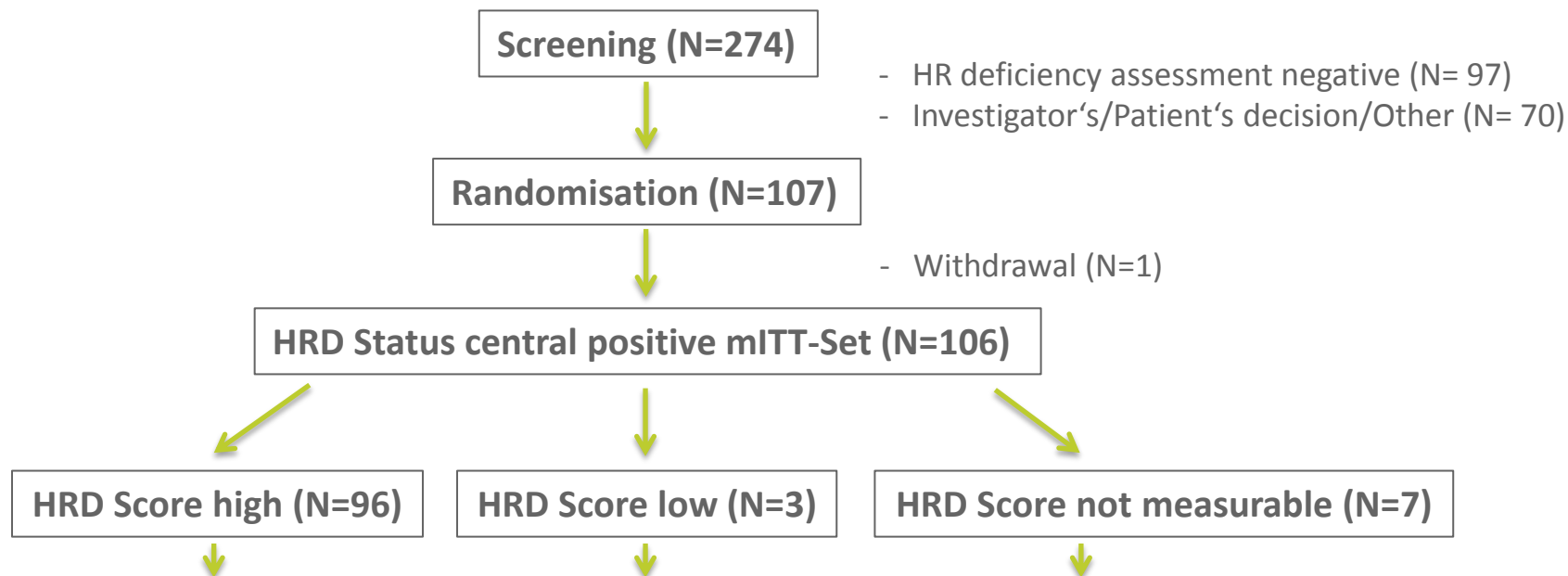
- **Primary HER2-negative carcinoma of the breast**
- **Patients must be in the following stages of disease:**
 - cT2 - cT4a-d or
 - cT1c and cN+ or
 - cT1c and pN_{SLN}+ or
 - cT1c and ER-neg and PgR-neg or
 - cT1c and Ki-67>20%
- **Central testing of ER, PgR, HER2 status, Ki-67**
- **Centrally confirmed tumor Homologous Recombinant Deficiency**
 - tBRCA mutated and/or HRD score high
 - Patients with known gBRCA and/or tBRCA status could be enrolled prior to the central test results available
- **No prior use of a PARP-inhibitor**



Main Baseline Characteristics

	PO→EC N=69 N (%)*	PCb→EC N=37 N (%)*	Overall N=106 N (%)*
Age (years), median (range)	48.0 (25.0, 71.0)	45.0 (26.0, 67.0)	47.0 (25.0, 71.0)
Pre-/perimenopausal	41 (59.4)	25 (67.6)	66 (62.3)
cT1	25 (36.8)	13 (35.1)	38 (36.2)
cT2	41 (60.3)	23 (62.2)	64 (61.0)
cT3	2 (2.9)	1 (2.7)	3 (2.9)
cN+	17 (24.5)	16 (45.7)	33 (31.8)
ER and/or PgR positive**	19 (27.5)	10 (27.0)	29 (27.4)
HER2-negative**	69 (100.0)	37 (100.0)	106 (100.0)
G3	58 (84.1)	34 (91.9)	92 (86.8)
Ki-67 > 20%**	63 (91.3)	32 (86.5)	95 (89.6)

* valid percent; ** central testing



tBRCA	HRD Score high N (%)	HRD Score low N (%)	HRD Score not measurable* N (%)
Mutated	49 (46.2)	3 (2.8)	3 (2.8)
Intact	46 (43.4)	0 (0.0)	0 (0.0)
Not measurable*	1 (0.9)	0 (0.0)	4 (3.8)**

■ Eligible patients
 * Insufficient quality or quantity of DNA
 ** Eligibility criteria: gBRCA local positive



Discontinuations

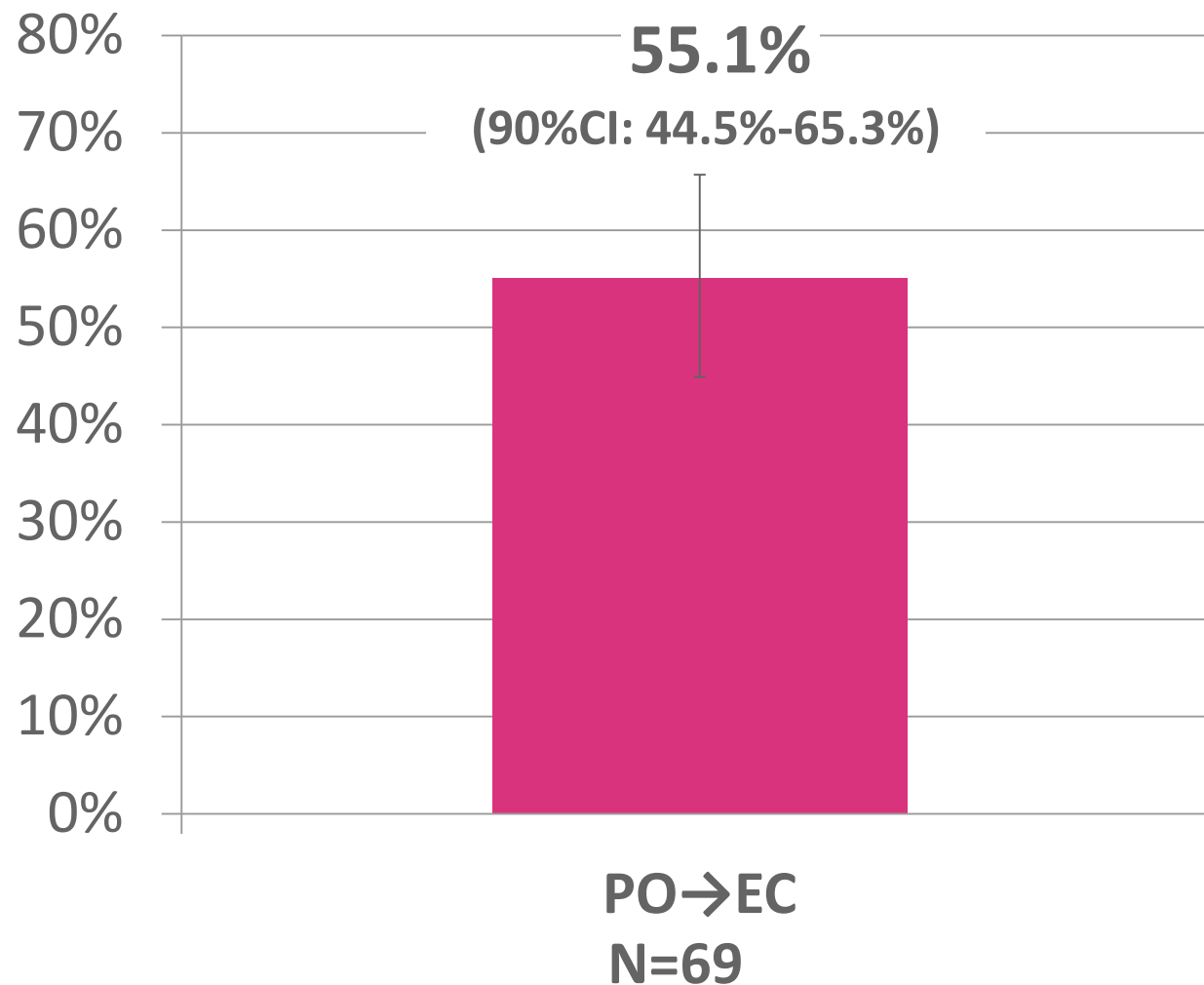
	PO→EC N=69 N (%)	PCb→EC N=37 N (%)	Overall N=106 N (%)
Completed all treatments	52 (75.4)	24 (64.9)	76 (71.7)
Discontinued Paclitaxel + Carboplatin/Olaparib	6 (8.7)	6 (16.2)	12 (11.3)
Local progression	2 (2.9)	0 (0.0)	2 (1.9)
Adverse event	2 (2.9)	5 (13.5)	7 (6.6)
Patient's / Investigator's decision	2 (2.9)	1 (2.7)	3 (2.8)
Never received EC	11 (15.9)	8 (21.6)	19 (17.9)
Local progression	2 (2.9)	0 (0.0)	2 (1.9)
Adverse event	0 (0.0)	1 (2.7)	1 (0.9)
Patient's / Investigator's decision	9 (13.0)	6 (16.2)	15 (14.1)
Discontinued EC	3 (4.3)	3 (8.1)	6 (5.7)
Local progression	1 (1.4)	0 (0.0)	1 (0.9)
Adverse event	0 (0.0)	2 (5.4)	2 (1.9)
Patient's / Investigator's decision	2 (2.8)	1 (2.7)	3 (2.8)

	PO→EC N=69	PCb→EC N=37
Total No of SAEs	11	37
Pts with at least 1 SAE	9 (13.0%)	19 (51.3%)
01. Infections and infestations	4	2
03. Blood and lymphatic system disorders	3	25
04. Immune system disorders	0	1
06. Metabolism and nutrition disorders	0	1
08. Nervous system disorders	0	1
14. Gastrointestinal disorders	2	3
15. Hepatobiliary disorders	1	1
22. General disorders	1	2
24. Injury, poisoning and procedural complications	0	1

- **No fatal SAEs or SUSARs occurred**

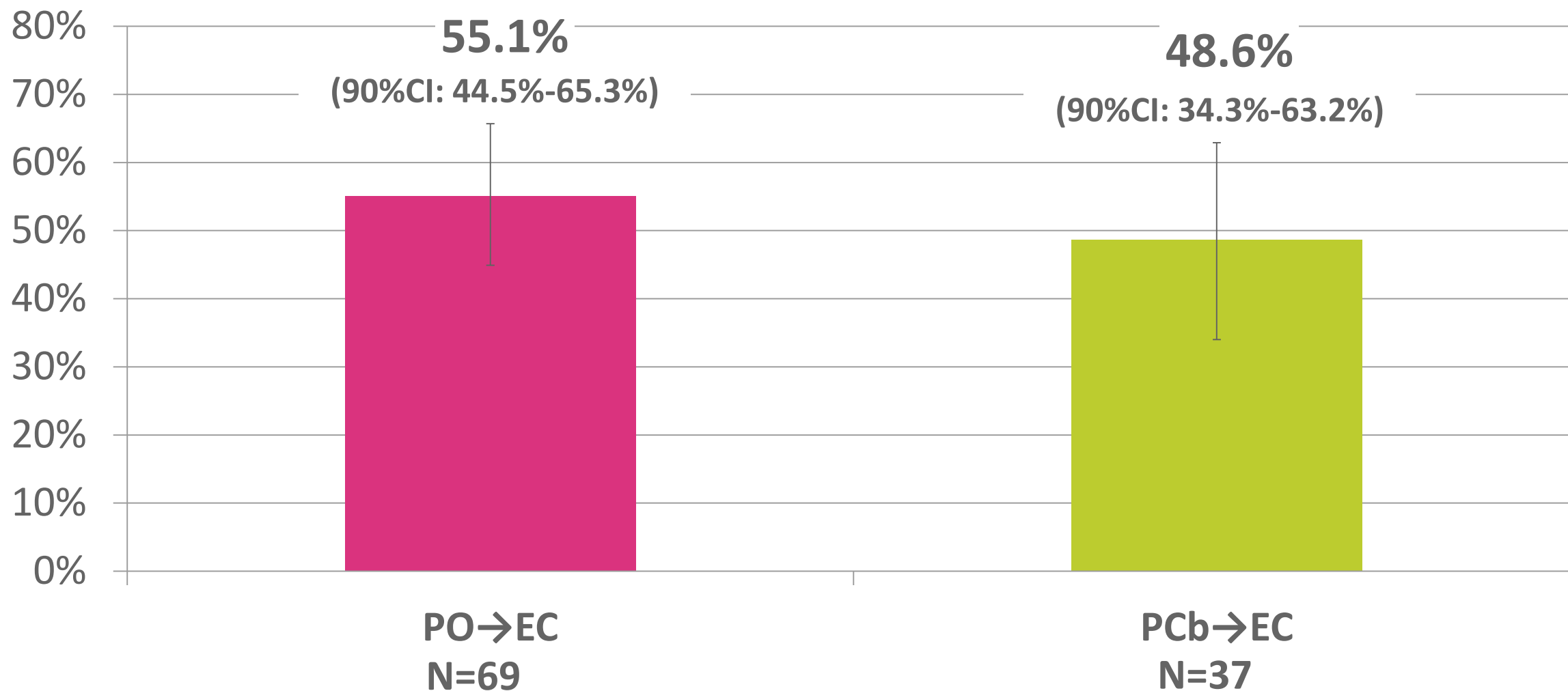


Primary Endpoint – pCR ypT0/is ypN0





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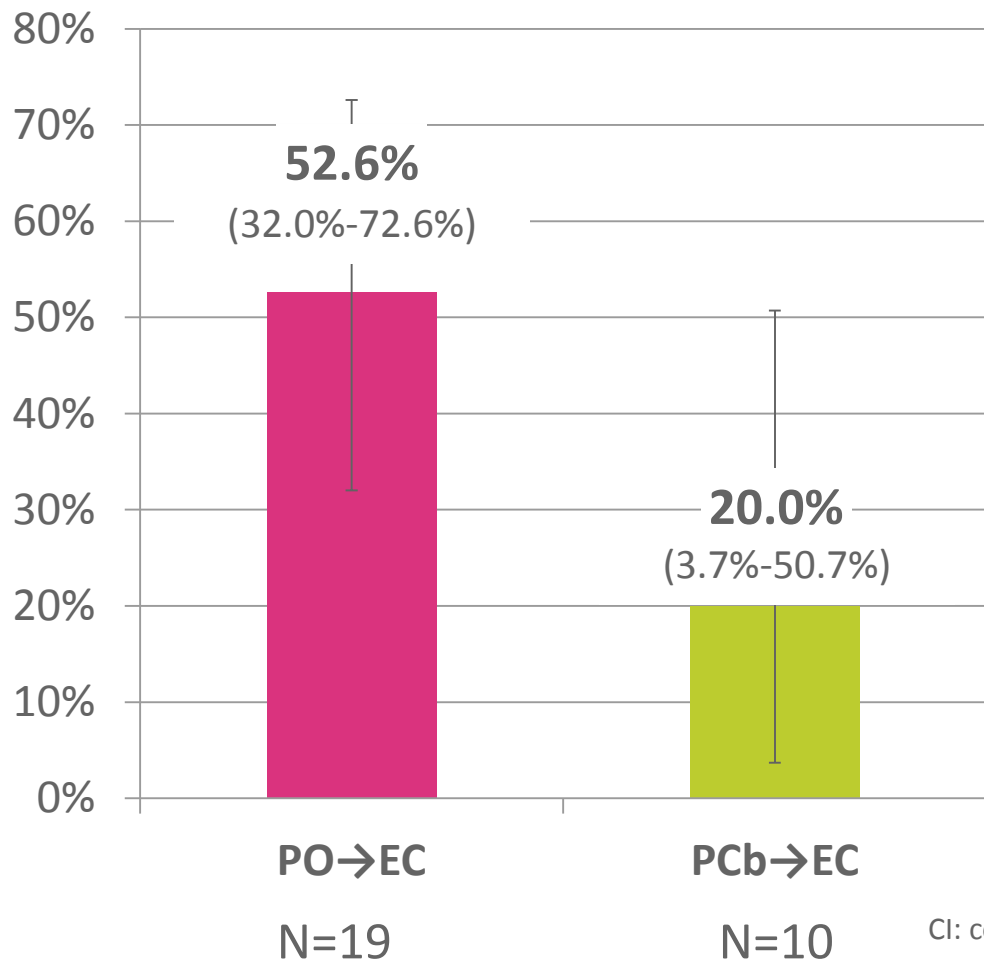


Predefined Subgroup Analysis (ypT0/is ypN0)

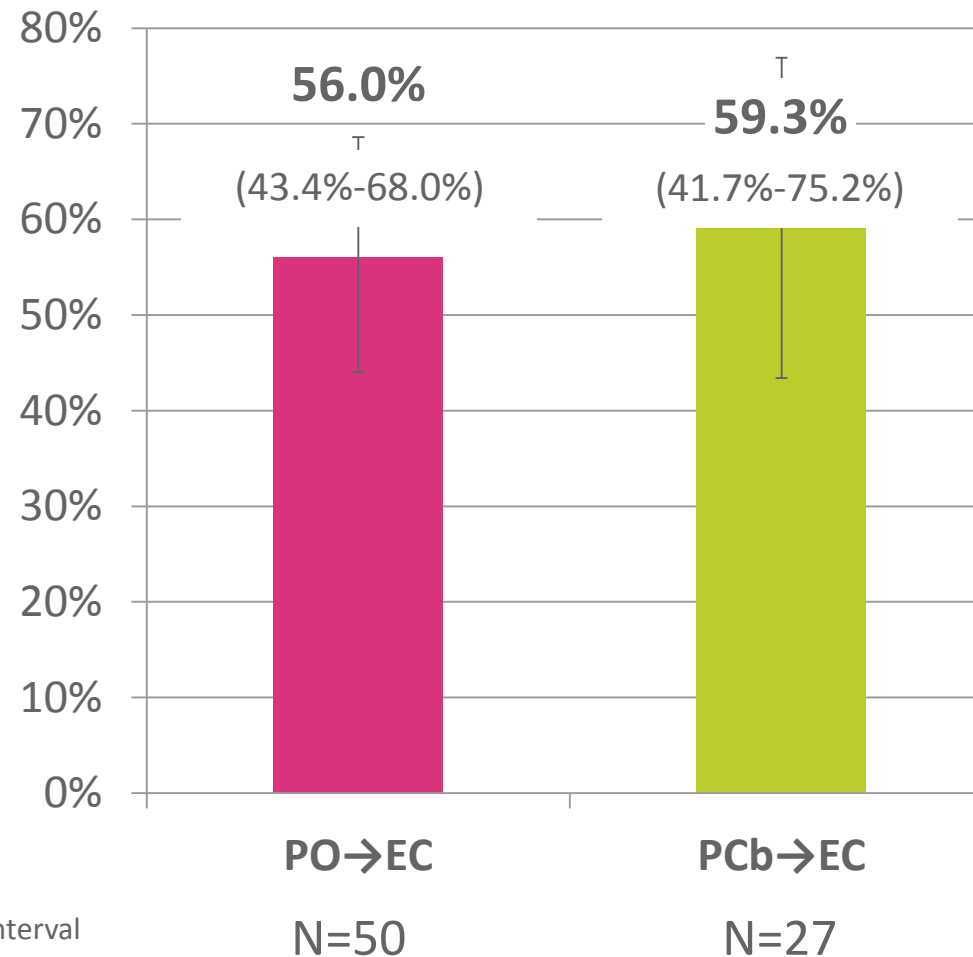
Hormone Receptor Status



pCR rates and 90% CI in HR+ pts. (N=29)



pCR rates and 90% CI in HR- pts. (N=77)



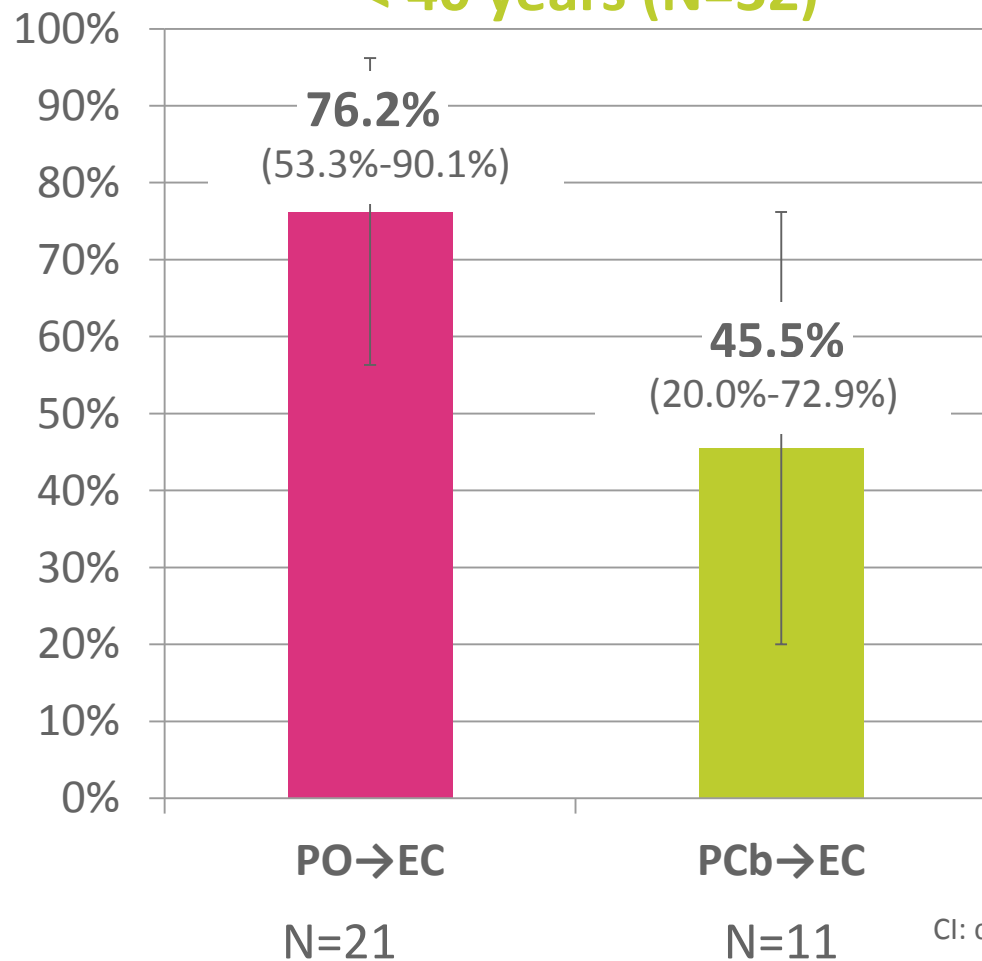


Predefined Subgroup Analysis (ypT0/is ypN0)

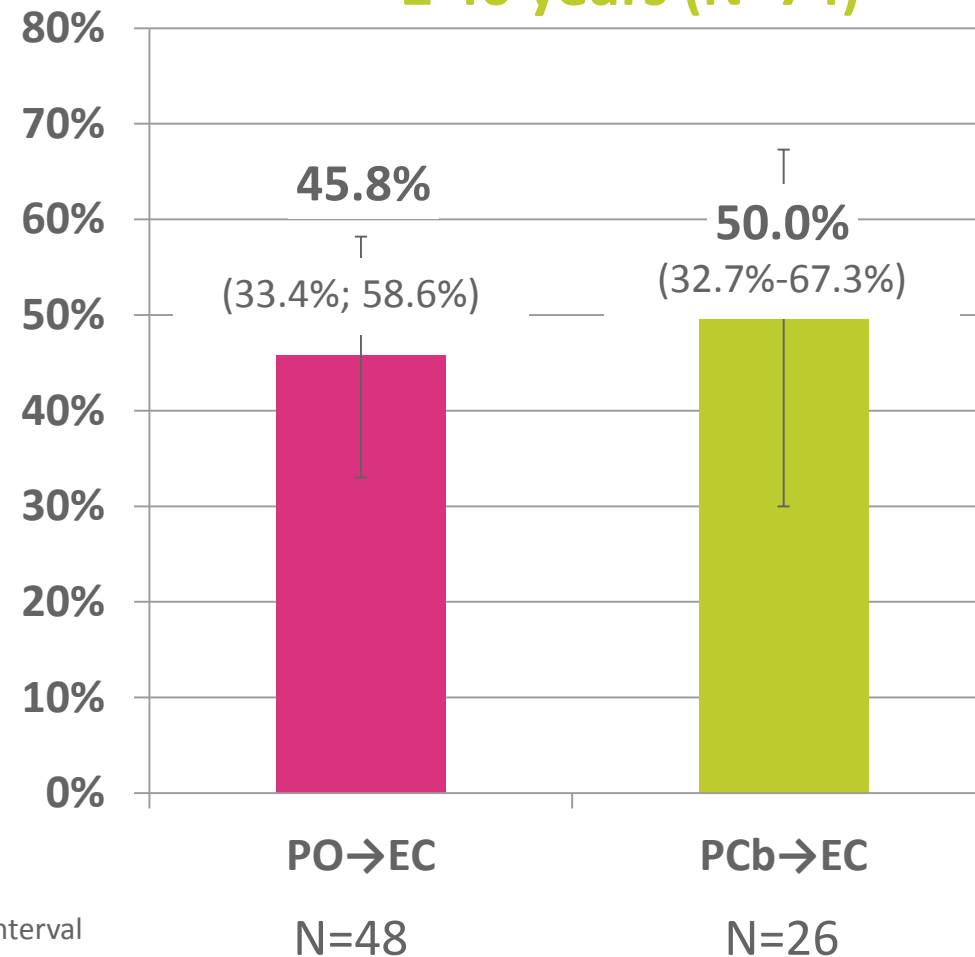


Age

pCR rates and 90% CI in pts.
< 40 years (N=32)



pCR rates and 90% CI in pts.
≥ 40 years (N=74)



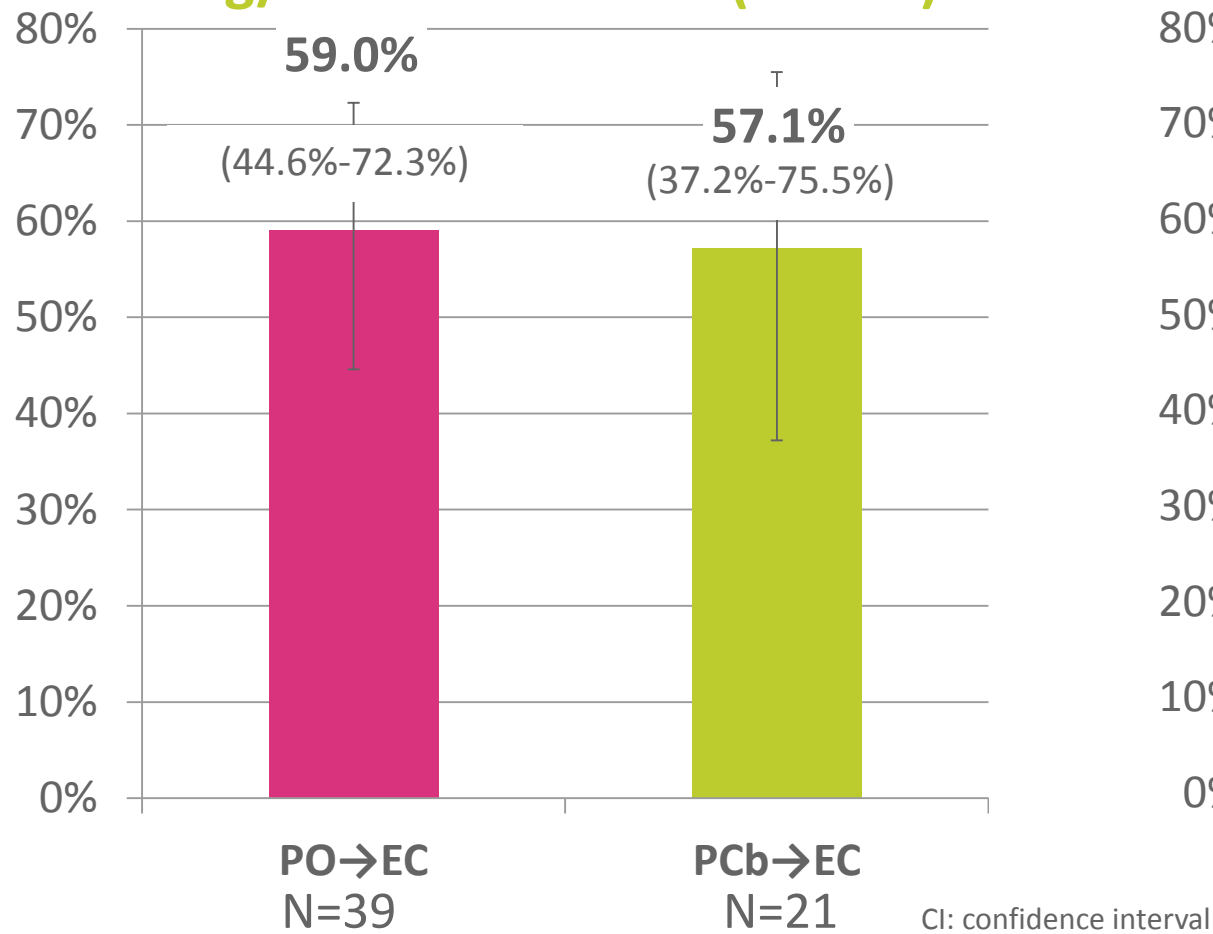


Predefined Subgroup Analysis (ypT0/is ypN0)

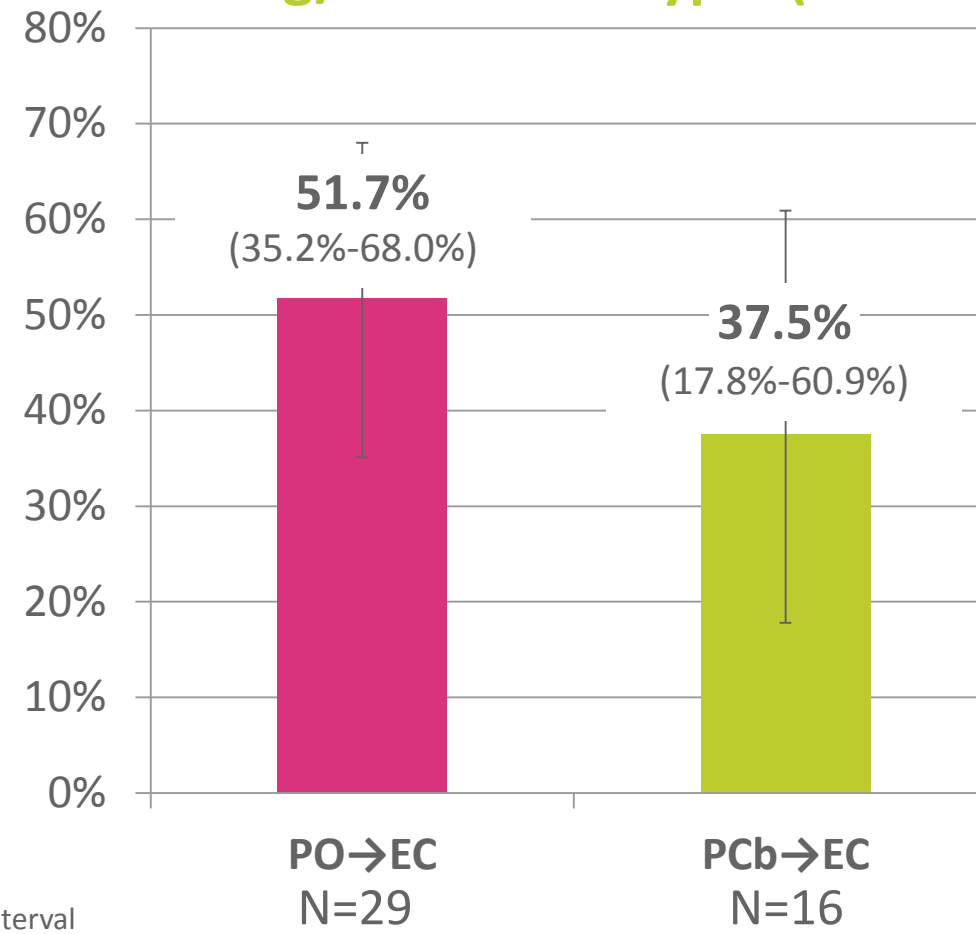
BRCA Mutation



pCR rates and 90% CI in pts. with g/tBRCA Mutation (N=60*)



pCR rates and 90% CI in pts. with g/tBRCA wildtype† (N=45*)



*One patient without tBRCA result due to insufficient quantity of DNA→HRD Score high
† HRD Score high



- GeparOLA investigates the addition of olaparib to paclitaxel as part of a neoadjuvant therapy in HER2 negative early breast cancer with HRD (t/gBRCA1/2 mutation and/or HRD Score high).
- Addition of olaparib to paclitaxel was well tolerated.
- GeparOLA could not exclude a pCR rate of $\leq 55\%$ in the PO arm:
 - pCR rate was 55.1% (90% CI: 44.5%-65.3%)
- Subgroup analyses are hypothesis generating and need further confirmation:
 - patients with HR+ tumors (pCR rate PO 52.6% vs. PCb 20.0%)
 - patients <40 years (pCR rate PO 76.2% vs. PCb 45.5%)
 - HRD score high, BRCA1/2 wildtype patients (pCR rate PO 51.7% vs. PCb 37.5%)
- Olaparib as part of a neoadjuvant therapy should be further investigated in pts. with HRD.
- Further exploratory and translational research is ongoing.

- All patients and their families
- All participating sites

External Partners

Cooperating partners

Central Pathology:

Carsten Denkert
Wolfgang Schmidt
Peggy Wolkenstein
Britta Beyer



HRD- Testing

Financial and Drug Support

Cryostorage Biomaterial

Patient Self-Registry

GBG

Members of the Subboard GBG and AGO-B

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Bärbel Felder
Stefanie Lettkemann

Datamanagement:

Sabine Kleinfeld

Medical Department:

Sabine Seiler
Jenny Furlanetto



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Backup Material

- Test is utilizing Illumina HiSeq next generation sequencing (paraffin embedded tumor tissue)
- Myriad myChoice[®] HRD includes the following components:

1. HDR Score = Genomic Instability Status assay

- NGS test → comprehensive signature for HRD by testing genome-wide single nucleotide variants in DNA
- determined by measuring several elements including
 - loss of heterozygosity (LOH)
 - telomeric allelic imbalance (TAI)
 - large-scale state transitions (LST)

2. tBRCA1/2 sequence analysis

3. tBRCA1/2 large rearrangement analysis

myChoice [®] HRD Result →HRD Status	Genomic Instability Status →HDR Score	tBRCA1/2 Mutation Status
Positive	Negative/Low	Positive
Positive	Positive/High	Negative
Positive	Inconclusive or Incomplete	Positive
Positive	Positive/High	Inconclusive or Incomplete

Myriad myChoice[®] HRD Technical Specifications; Effective Date: June 2017

Predefined Analysis mITT ypT0/is ypNany



ypT0/is ypN any- Pathological Complete Response

