Prediction of pathological complete response (pCR) by Homologous Recombination Deficiency (HRD) after carboplatin-containing neoadjuvant chemotherapy in patients with TNBC – Results from GeparSixto.

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for the

GBG/AGO-B study groups

Introduction

- We previously showed that adding carboplatin to paclitaxel/liposomal doxorubicin/bevacizumab (PM) can improve the pathological complete response (pCR) rate in patients with TNBC at the cost of added toxicity[1]
- Tumors with decreased DNA repair capacity, e.g. due to mutations of *BRCA* 1 or 2, are expected to show high sensitivity to DNA damaging agents[2,3,4]
- DNA repair capacity can be measured by a Homologous Recombination Deficiency (HRD) assay[5]
- We examined whether the HRD assay can predict the effect of chemotherapy with or without carboplatin in patients with TNBC

[1]von Minckwitz G, Lancet Oncol 2014, [2]Byrski T, JCO 2010, [3]Kern P, Chemother 2013, [4]von Minckwitz G, ASCO 2014 [5]Telli M, JCO 2015

Main Study Design

N=595

centrally confirmed TNBC or HER2-positive breast cancer

cT2, cT3, or cT4a-d or cT1 and cN+ or pN_{SLN}+

R

PM

PMCb

Surgery

Paclitaxel 80 mg/m² q1w

Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w

Carboplatin AUC 1.5-2* q1w

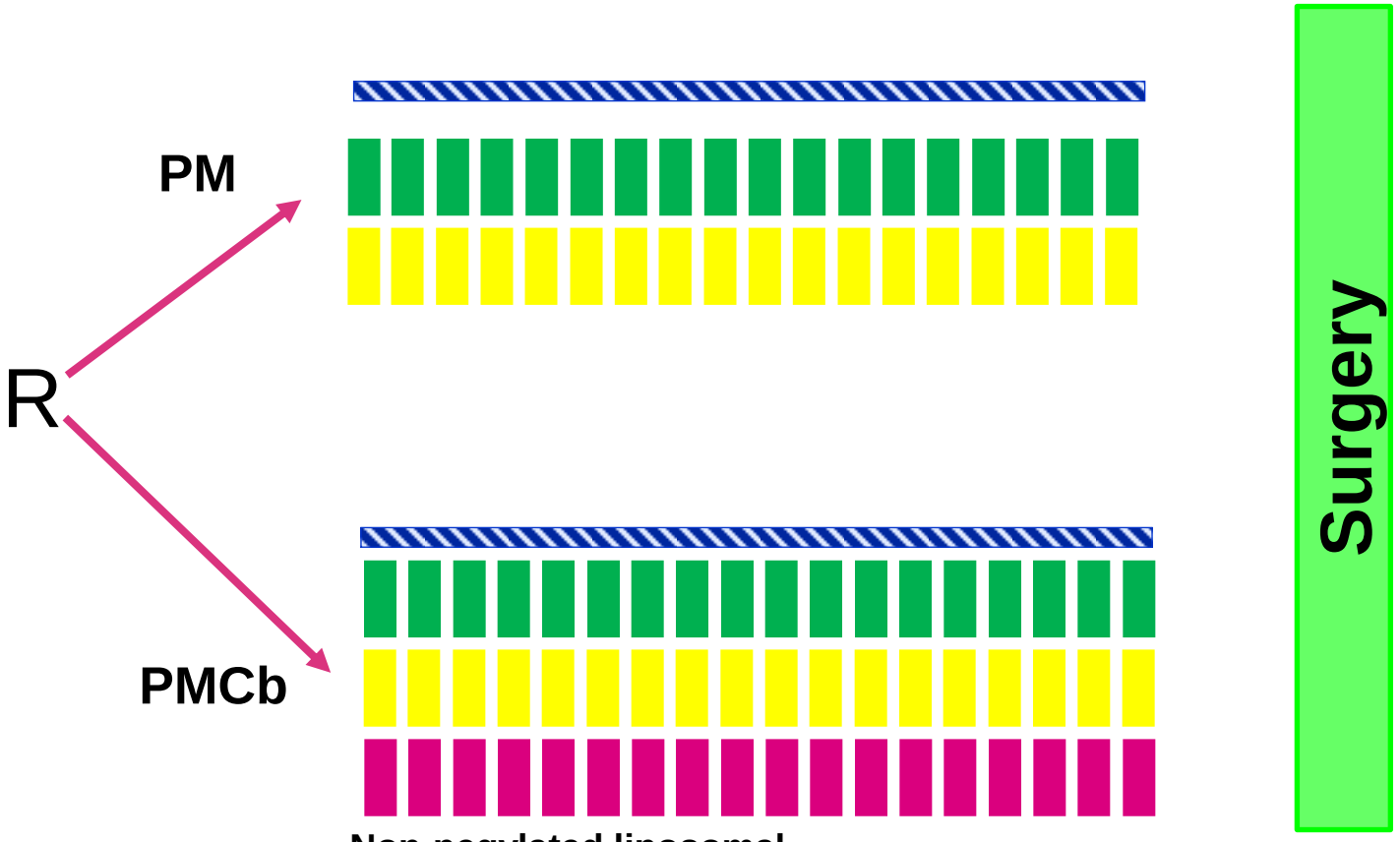
*reduced from AUC 2 to AUC 1.5 after enrolment of 330 patients

von Minckwitz et al. Lancet Oncology, May 2014

Therapy in TNBC Subgroup

N=315

centrally confirmed TNBC



Paclitaxel 80 mg/m² q1w

Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w

Carboplatin AUC 1.5-2 q1w

Bevacizumab 15 mg/kg q3w

von Minckwitz et al. Lancet Oncology, May 2014

Definitions

- gm*BRCA* = deleterious mutation of *BRCA*1 or *BRCA*2 in the germline
- *tmBRCA* = deleterious mutation of *BRCA*1 or *BRCA*2 in the tumor
- *HRD score* = LOH score + TAI score + LST score
- HRD score ranges from 0-100. High HRD score was predefined as ≥42
- *HR deficient* = either a high HRD score or tumor *BRCA* mutation
- ypT0/is ypN0 defined as primary, ypT0 ypN0 as secondary endpoint

LOH Score = number of Loss Of Heterogeneity regions longer than 15 Mb but shorter than the length of a whole chromosome (Abkevich, 2012),
TAI Score = number of telomeric region imbalances which extend to the subtelomere but do not cross the centromere (Birkbak, 2012)
LST Score = number of chromosomal breaks between adjacent regions longer than 10 Mb after filtering out regions shorter than 3 Mb (Popova, 2012)

Flow of Patients

Patients in GeparSixto (N=595)

↓ - N=280 HER2-positive tumor

Patients with TNBC (N=315)

↓
- No samples available (N=58)
- DNA yield <10 ng (N=8)
- HR deficiency assessment failed (N=56)

HR deficiency assessed (N=193)

↓

	gBRCA		
t*BRCA*	intact	mutated	not assessed
mutated	16 (11.3%)	33 (94.3%)	5
intact	121 (85.2%)	2 (5.7%)	11
not assessed	5 (3.5%)	0	0

Flow of Patients

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- N=280 HER2-positive tumor

Patients with TNBC (N=315)

- No samples available (N=58)
- DNA yield <10 ng (N=8)
- HR deficiency assessment failed (N=56)

HR deficiency assessed (N=193)

	HRD score		
t*BRCA*	low	high	not measured
mutated	3	47	4
intact	55	79	n.a.
not assessed	2	3	n.a.

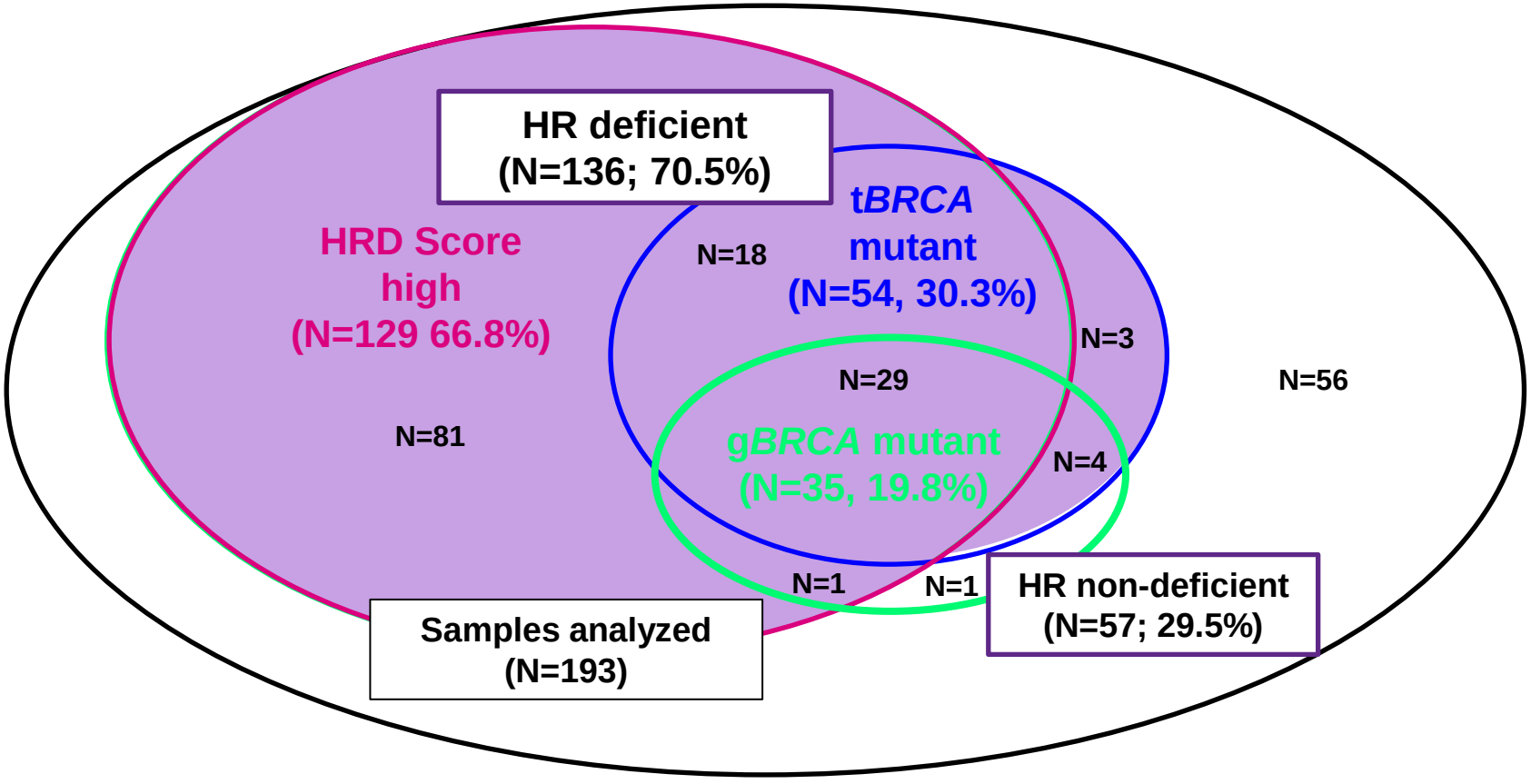
Treated with PM (n=92)

- HR deficient (N=62; 67.4%)
- HR non-deficient (N=30; 32.6%)

Treated with PMCb (N=101)

- HR deficient (N=74; 73.3%)
- HR non-deficient (N=27; 26.7%)

Overlap of HR Deficiency and BRCA Mutations



HR Deficiency in Correlation with other Markers

Parameter		HR non-deficient	HR deficient	p-value
age	<50	25 (21%)	92 (79%)	0.003
	>=50	32 (42%)	44 (58%)	
cT	cT1	10 (23%)	33 (77%)	0.348
	cT2-4	47 (31%)	103 (69%)	
cN	negative	24 (22%)	85 (78%)	0.005
	positive	32 (42%)	44 (58%)	
Grading	G1+2	16 (32%)	34 (68%)	0.719
	G3	41 (29%)	102 (71%)	
Ki67	<60%	23 (37%)	40 (63%)	0.178
	>=60%	34 (26%)	96 (74%)	
Lymphocyte predominant BC	No	43 (30%)	102 (70%)	1.000
	yes	14 (29%)	34 (71%)	
gm*BRCA*	no	54 (38%)	88 (62%)	<.001
	yes	1 (3%)	34 (97%)	
Family risk*	no	41 (38%)	68 (62%)	0.007
	yes	12 (18%)	55 (82%)	

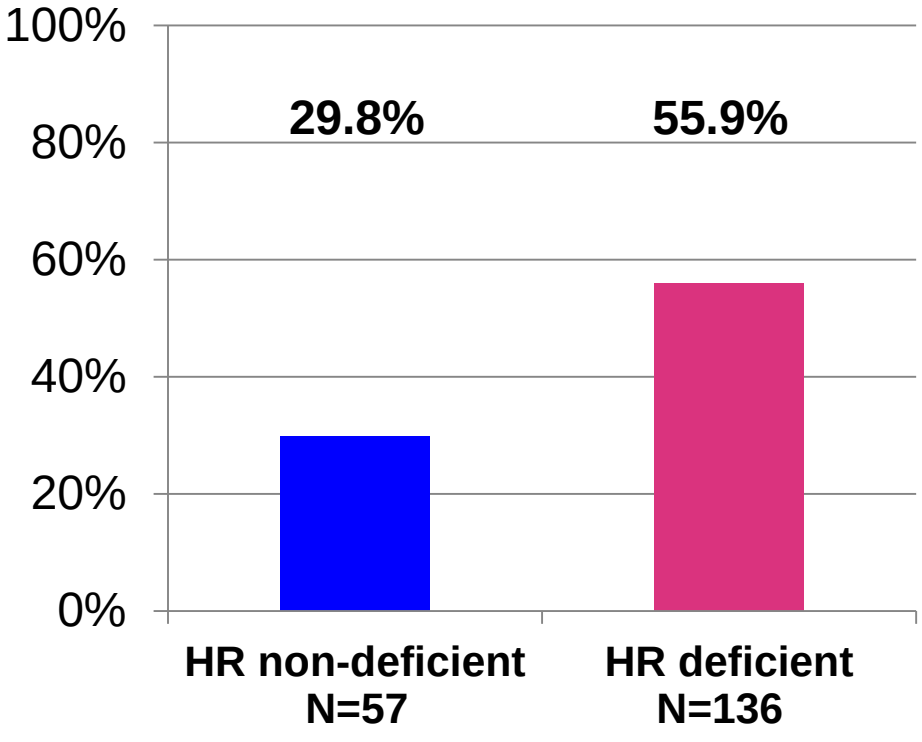
*assessed by a checklist of the German BRCA consortium to identify women at risk for germline alterations of >10%

pCR Rates by HR Deficiency

(treatment arms combined)

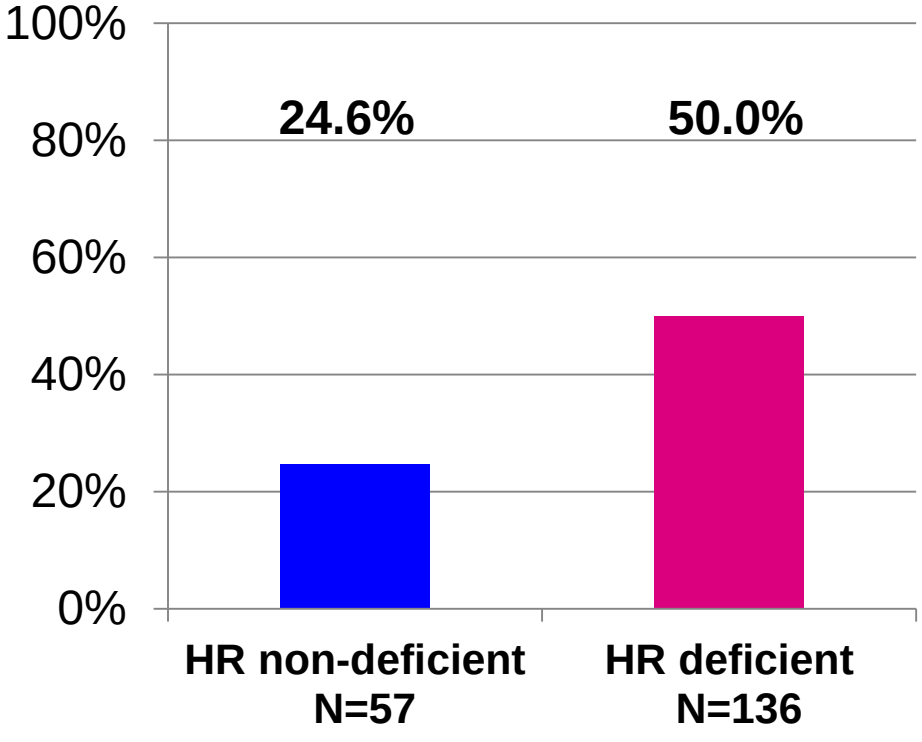
ypT0/is ypN0

OR 2.98 (1.54-5.77)
P<0.001



ypT0 ypN0

OR 3.07 (1.54-6.13)
P<0.001



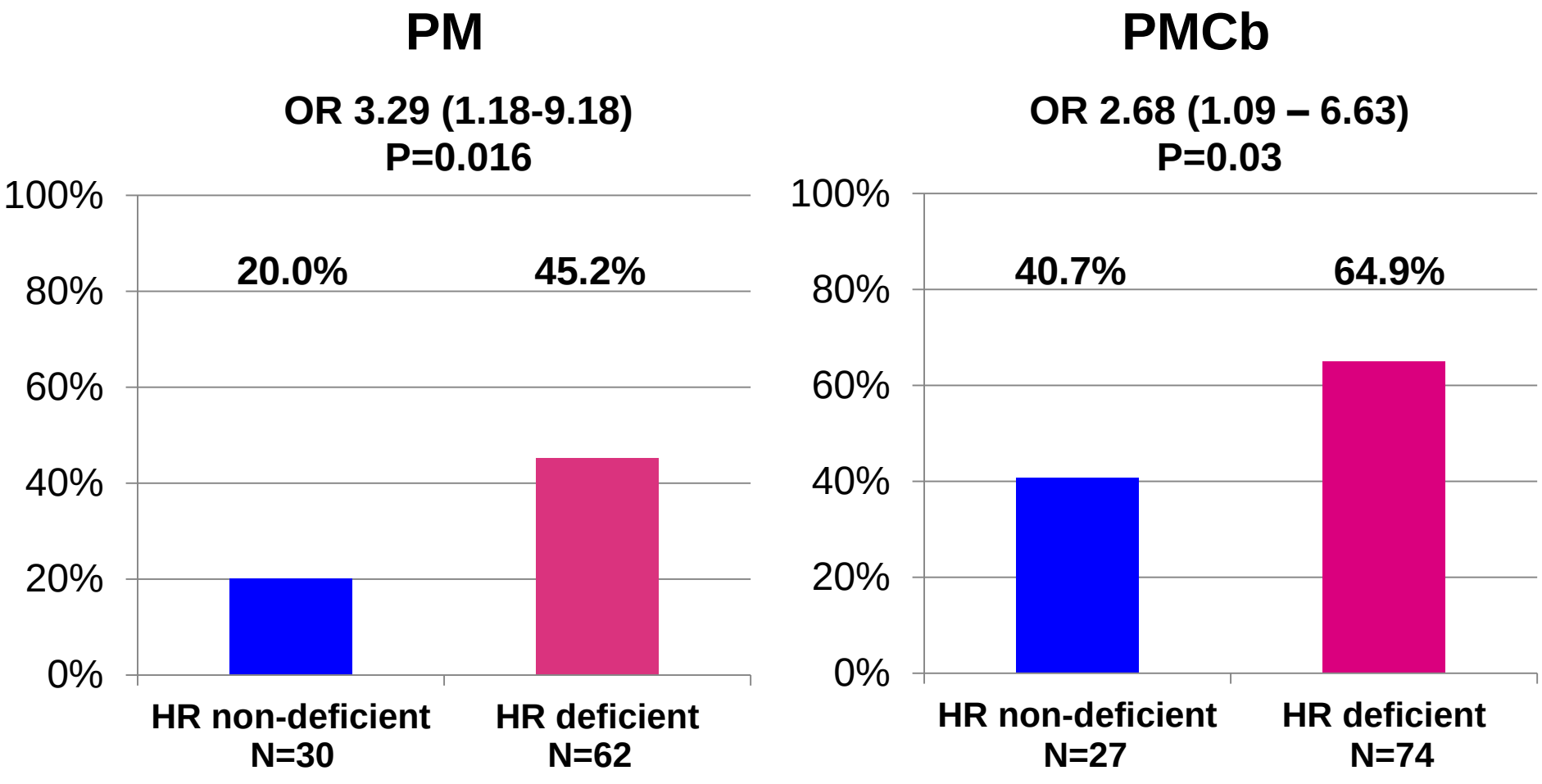
Multivariate Logistic Regression Model Comparing HR Deficiency with Established Markers

(treatment arms combined, ypT0/is ypN0)

Parameter	*Effect*	*odds ratio*	*95% CI*	*LR p-value*
HR deficient	yes vs no	**2.506**	**(1.243, 5.051)**	**0.009**
cN	positive vs negative	**0.482**	**(0.255, 0.908)**	**0.023**
Lymphocyte pre-dominant BC.	yes vs no	**2.567**	**(1.229, 5.360)**	**0.010**

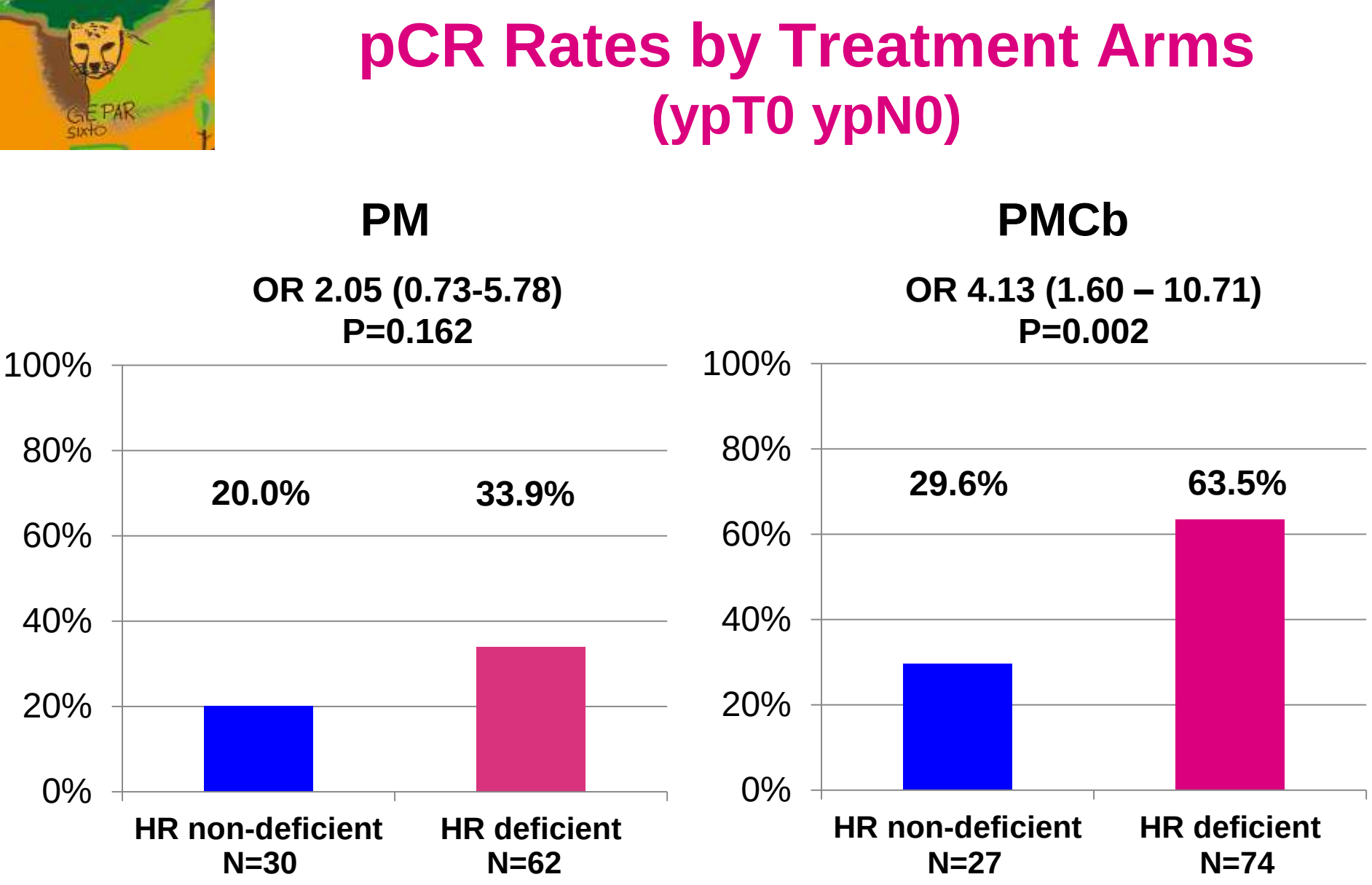
Variables age, tumor size, grading, Ki67, gm*BRCA* and family history did not contribute significantly to the regression model und thus were omitted.

pCR Rates by Treatment Arms
(ypT0/is ypN0)



Test for interaction p=0.769

pCR Rates by Treatment Arms (ypT0 ypN0)

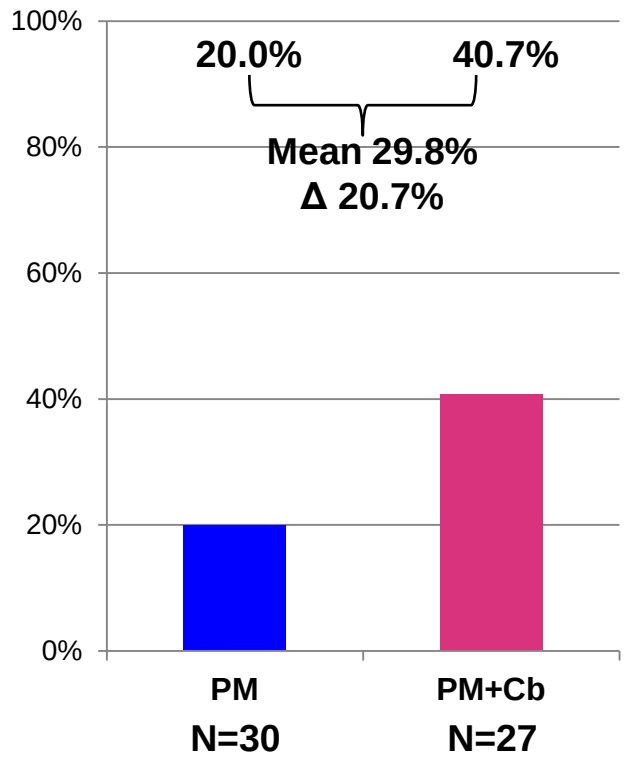


Test for interaction p=0.327

pCR Rates by Treatment and According to HR Deficiency Status (ypT0/is ypN0)

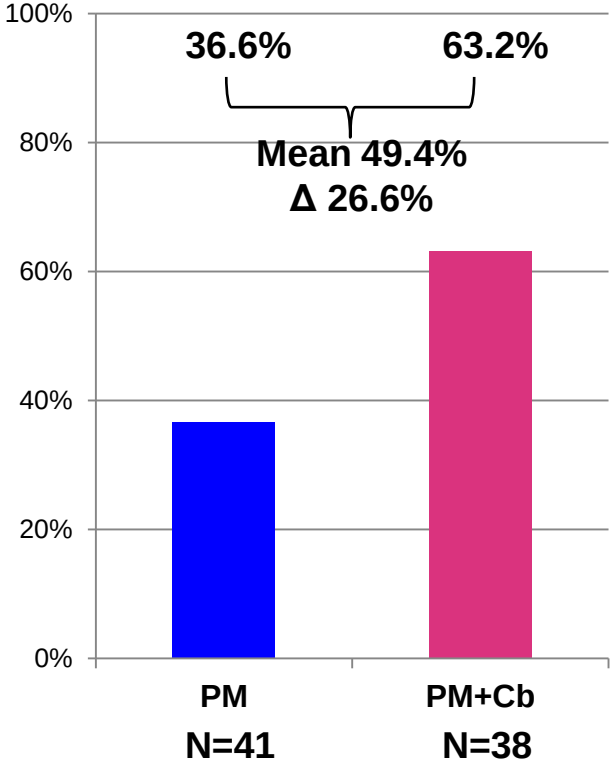
HR non-deficient

OR 2.75 (0.85-8.94)
P=0.086



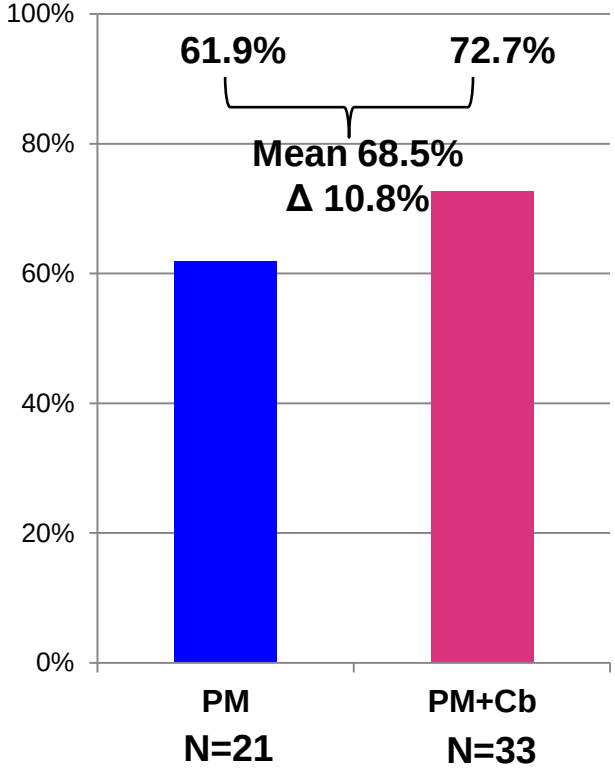
HRD score high tBRCA intact

OR 2.97 (1.19-7.42)
P=0.018



tBRCA mutant

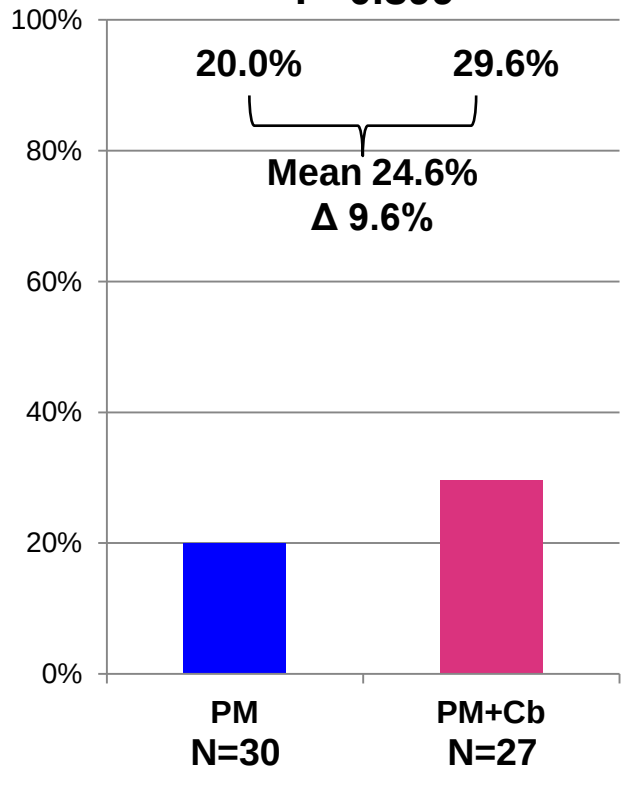
OR 1.64 (0.51-5.27)
P=0.406



pCR Rates by Treatment and According to HR Deficiency Status (ypT0 ypN0)

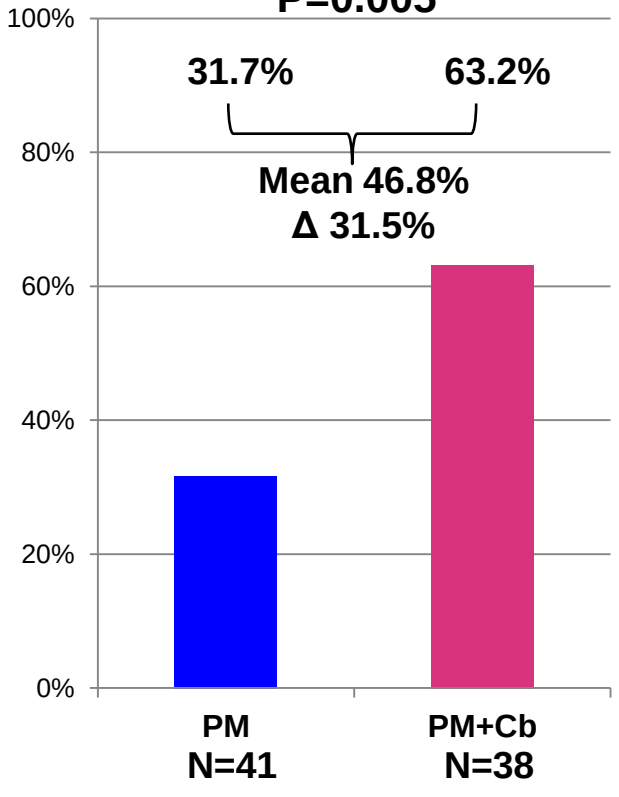
HR non-deficient

OR 1.68 (0.50-5.69)
P=0.399



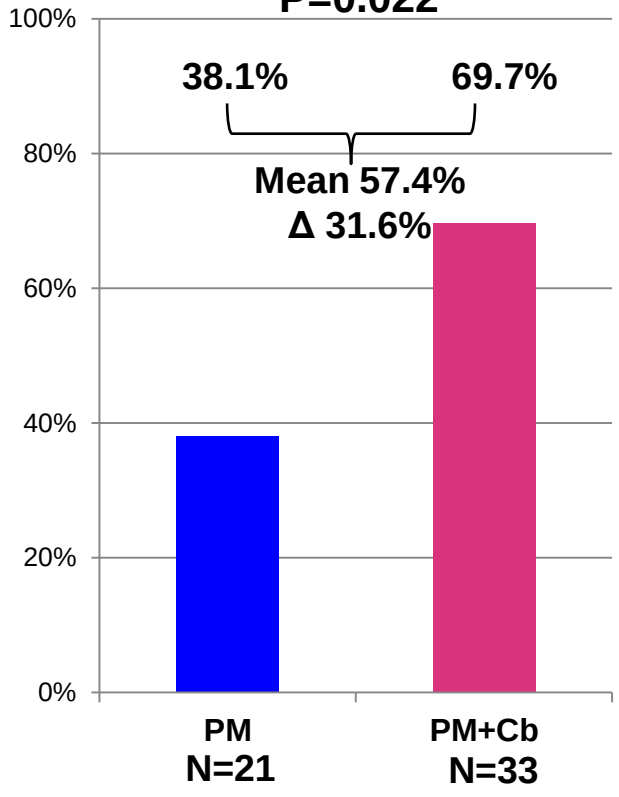
HRD score high tBRCA intact

OR 3.69 (1.46-9.37)
P=0.005



tBRCA mutant

OR 3.74 (1.18-11.82)
P=0.022



Conclusion

- **Patients with TNBC were found to have HR deficient tumors in 70.5%, t*BRCA* mutations in 30.3%, and g*BRCA* in 19.8%.**
- **HR deficiency in TNBC is an independent predictor of high pCR rates to neoadjuvant PM+/-Cb.**
- **Higher pCR (ypT0 ypN0) rates were observed with carboplatin added to PM in patients with**
  - **tm*BRCA* tumors (OR 3.74, p=0.022)**
  - **high HRD scores in t*BRCA*-intact tumors (OR 3.69, p=0.005)**
  - **but not with HR-non-deficient tumors (OR 1.68, p=0.399).**

  However, results using ypT0/is ypN0 as an endpoint are inconsistent and a formal interaction between HR deficiency and carboplatin could not be shown.
- **Results have to be confirmed by other studies (e.g. CALBG 40603) and set into context with survival data (expected for end of 2015).**

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Slides can be downloaded from www.gbg.de.

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